A Phase 1b, Multicenter, Randomized, Placebo-Controlled, Double-Blind Study, followed by an Open-Label Extension, to Determine the Safety, Pharmacokinetics, and Pharmacodynamics of DNL343 in Participants with Amyotrophic Lateral Sclerosis

Published: 15-06-2021
Last updated: 14-03-2025

Primary• To investigate the safety and tolerability of multiple oral doses of DNL343 in participants with ALSSecondary• To characterize the PK of DNL343 in plasma following single and multiple oral doses• To characterize the concentration of DNL343...

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

Summary

ID

NL-OMON56265

Source
ToetsingOnline

Brief title
DNL343 in participants with ALS

Condition

- Neuromuscular disorders

Synonym
ALS, Amyotrophic Lateral Sclerosis

Research involving
Human

Sponsors and support

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

Intervention

Keyword: ALS, DNL343, PD, PK

Outcome measures

Primary outcome

Incidence of treatment-emergent adverse events (TEAEs) throughout the

double-blind period

Secondary outcome

• DNL343 PK parameters, including, but not limited to, maximum concentration

(Cmax), time to reach maximum concentration (tmax), trough concentration

(Ctrough), and area under the concentration-time curve from time zero to 24

hours (AUC0-24)

• CSF-to-plasma concentration ratio

Study description

Background summary

This is a Phase 1b study in > 30 and <= 45 participants with ALS that will enable clinical development of DNL343 in ALS, a disease in which inhibition of the ISR may provide therapeutic benefit. The principal aim of this study is to investigate the safety and tolerability of DNL343 when administered orally as multiple doses to participants with ALS. The study will also explore the PK and PD of DNL343, to determine whether DNL343 affects biomarkers related to neurodegeneration and ALS pathophysiology (including ISR genes and proteins) at exposures predicted to provide clinical efficacy based on animal models. The

data from this study will inform dose selection for participants with ALS and the design of future clinical studies.

Study objective

Primary
• To investigate the safety and tolerability of multiple oral doses of DNL343 in participants with ALS

Secondary
• To characterize the PK of DNL343 in plasma following single and multiple oral doses
• To characterize the concentration of DNL343 in cerebrospinal fluid (CSF) following multiple oral doses

Study design

Up to 45 participants with ALS will be randomly assigned in a 1:1:1 ratio to receive DNL343 100 mg, DNL343 200 mg, or placebo once daily (QD) (powder-in-capsules and when available granules-in-capsule formulation) for 28 days in addition to standard-of-care treatments during the double-blind period of the study. A minimum of approximately 30 participants will be required to complete the double-blind period. Following the double-blind period, eligible participants will have the option to continue into an OLE period, during which they will receive DNL343 200 mg QD for <= 18 months. The DNL343 dose of 200 mg QD in the OLE period may be reduced based on the safety and tolerability of DNL343 in the double-blind period or OLE period of the study.

Intervention

• Study interventions: DNL343 and matching placebo (as powder-in-capsules and when available granules-in-capsules or granules either reconstituted in water for oral or feeding tube administration or coadministered with soft food)
• Proposed doses: 100 and 200 mg QD for double-blind treatment period; 200 mg QD for OLE treatment period
• Administration route: Oral or feeding tube

Study burden and risks

The benefit and risks of DNL343 treatment in participants with ALS have not been established. Based on the mechanism of action of DNL343, inhibition of the ISR may provide therapeutic benefit to participants with ALS. The risks of DNL343 treatment are based on extensive evaluation in nonclinical studies and evaluation in clinical studies in approximately 85 to 87 healthy participants to characterize the safety profile. The potential risks of participation in the current study are primarily those associated with adverse reactions to the

study intervention and study procedures.

Contacts

Public
Denali Therapeutics Inc

Oyster Point Blvd. 161
South San Francisco CA 94080
US
Scientific
Denali Therapeutics Inc

Oyster Point Blvd. 161
South San Francisco CA 94080
US

Trial sites

Listed location countries

Netherlands

Eligibility criteria

Age
Adults (18-64 years)
Elderly (65 years and older)

Inclusion criteria

Participants must satisfy all of the following criteria for study entry:
1. Women of non-childbearing potential and men, aged 18 to 80 years, inclusive
2. BMI of 18 to 35 kg/m2
3. Willing and able to give informed consent (via legally authorized representative is acceptable) for study participation
4. Able to communicate with the investigator and staff
5. Willing and able to comply with the requirements of the study, including scheduled visits, study restrictions, laboratory tests, and all other study procedures

6. Women must have been surgically sterilized (hysterectomy, bilateral oophorectomy, or bilateral tubal ligation; proper documentation required) >= 3 months prior to dosing (Essure*fallopian tube coil placement is not accepted as surgical sterilization because of the high failure rate), or be postmenopausal (amenorrheic for >= 12 consecutive months before dosing, with a follicle-stimulating hormone [FSH] level of > 40 IU/L at screening).
7. For men: When engaging in sex with a woman of childbearing potential (WOCBP), both the male participant and his female partner must use highly effective contraception consisting of two forms of birth control, one of which must be a male barrier method such as a latex or polyurethane condom, from the start of dosing, throughout the study period, and for 90 days after the final administration of study intervention. See Section 10.6 of the protocol for contraceptive guidance for female partners.
8. For men: The participant must not donate sperm at any time from the start of dosing, throughout the study period, and for 90 days after the final administration of study intervention.
9. Diagnosis of laboratory-supported probable, probable, or definite (sporadic or familial) ALS according to the El Escorial World Federation of Neurology revised research diagnostic criteria (Ludolph et al. 2015)
10. Years since symptom onset as follows:
a. <= 3 years (approximately 80% or more of the study population)
b. > 3 to <= 4 years (limited to approximately <= 20% of the study population)
11. SVC > 50% predicted, measured within 28 days of screening (forced vital capacity at screening also acceptable)
12. If participant is taking locally approved ALS treatments, the following guidelines must be met:
a. If the participant is taking riluzole, doses must be stable for >= 42 days prior to the first dose of study intervention; participant is expected to stay on a stable regimen throughout the double-blind period of the study. Participants who initiated or changed medication doses within 42 days prior to the planned first dose of study intervention may be rescreened after dose stabilization.
b. If the participant is taking any other locally approved ALS treatment besides riluzole (e.g., edaravone), doses must be stable for >= 21 days prior to the first dose of study intervention; the participant is expected to stay on a stable regimen throughout the double-blind period of the study. For edaravone, stable treatment regimen means completion of at least the first 14 days of treatment during the first treatment cycle with intent to continue treatment cycles during the double-blind period. Participants who initiated or changed medication doses within 21 days prior to the planned first dose of study intervention may be rescreened after dose stabilization.
13. Doses of other chronic prescription medications must be stable for 14 days prior to the first dose of study intervention; participant is expected to stay on a stable regimen throughout the double-blind period of the study. Participants who initiated or changed medication doses within 14 days prior to the planned first dose of study intervention may be rescreened after dose stabilization.

14. For the double-blind period of the study, participant must be able to swallow the study intervention capsules.
15. For the OLE period of the study, participants may participate only if they have completed the double-blind treatment period up to Day 28 and the Final Study Treatment visit (Day 28) procedures, have no unresolved TEAEs of clinical concern, and continue to meet the study eligibility criteria (except for requirement of symptom onset < 3 years and able to swallow study intervention capsules) at the time of entry in the OLE period

Exclusion criteria

Participants who meet any of the following criteria will be excluded from study entry:
1. Any history of unstable or poorly controlled psychiatric, endocrine, pulmonary, cardiovascular, gastrointestinal, hepatic, pancreatic, renal, metabolic, hematologic, immunologic, or allergic disease, or other major disorders. Well-controlled conditions are permitted if investigator and Sponsor agree.
2. Positive serum pregnancy test or currently lactating or breastfeeding
3. History of malignancy within 5 years, except fully resected basal cell carcinoma or other malignancies at low risk of recurrence, depending on investigator and Medical Monitor agreement
4. History of clinically significant neurologic disorders other than ALS, including stroke, significant cognitive impairment, or seizure within 5 years of the first dose of study intervention, or head trauma with loss of consciousness, documented by a physician, within 1 year of the first dose of study intervention
5. History of serious adverse reaction or serious hypersensitivity to two or more drug classes or clinically significant history of previous allergy or hypersensitivity to DNL343 or any of the excipients contained within theDNL343 drug product
6. History of clinically significant hypersensitivity to local anesthetics that may be used for LP (e.g., lidocaine)
7. Have criteria that would preclude an LP, such as a local infection at the site of the LP, < 100 GI/L(100,000/mm3) platelets or clinically significant coagulation abnormality or significant active bleeding, or treatment with an anticoagulant or more than two antiplatelet agents
8. History of clinically significant back pathology and/or back injury (e.g., degenerative disease, spinal deformity, or spinal surgery) or severe respiratory compromise that may predispose to complications or technical difficulty with LP. Participants with ALS who cannot tolerate lumbar punctures in the prone or lateral recumbent position due to respiratory difficulties may undergo the procedure in an upright sitting position if the position resolves respiratory distress.
9. Current significant psychiatric disorder, suicidal ideation in the previous

6 months as assessed by the Baseline/Screening version of the C-SSRS (a *yes* response to question 1 or 2 on the Suicidal Ideation section may be acceptable pending investigator and Sponsor Medical Monitor agreement and Intensity of Ideation scores are 2 or lower), or a lifetime suicide attempt (a *yes* response to question 4 or 5 on the Suicidal Ideation section or an Intensity of Ideation score of 4 or 5) at screening. A lifetime suicide attempt or score of 4 or 5 on the Intensity of Ideation > 5 years may be allowed pending investigator and Sponsor review.
10. History of alcoholism, drug abuse, or drug addiction in the previous 12 months Note: Participants who test positive for drugs included in the urine drug screen (see Section 10.2) may be enrolled at the investigator*s discretion.
11. Evidence of hepatic impairment, including alanine aminotransferase (ALT) or aspartate aminotransferase(AST) > 3 x the upper limit of normal (ULN) or bilirubin > 1.5×ULN at screening or baseline. Patients with Gilbert*s syndrome without evidence of hepatic impairment may be enrolled.
12. History of clinically significant renal impairment or an estimated glomerular filtration rate (eGFR) < 60mL/min/1.73 m2 at screening, as estimated with the Chronic Kidney Disease Epidemiology Collaboration (CKD-EPI) equation
13. Other clinical laboratory test values outside of the normal range at screening or baseline, unless assessed by the investigator as clinically nonsignificant values
14. 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) (see Section 10.2 of the protocol)
15. Supine SBP < 90 or > 160 mm Hg, supine diastolic blood pressure (DBP) < 40 or > 95 mm Hg, HR < 40 or >110 beats per minute (bpm), or elevated body temperature (>= 100.4°F [38°C]) at screening or baseline. BP and HR measurements may be repeated once if initial measurements are considered to be atypical for participant. Participants with controlled hypertension on a stable medical regimen for > 30 days may be enrolled pending investigator discretion.
16. History or presence of a clinically significant ECG abnormality, including, but not limited to, complete left bundle branch block, second- or third-degree heart block, clinically significant
T wave abnormalities, or other abnormalities that, in the investigator*s opinion, put the participant at risk and/or preclude accurate interpretation of cardiac intervals (e.g., PR, QT, QRS)
17. QT interval corrected for heart rate by Fridericia*s method (QTcF) > 450 ms in male participants, > 470 ms in female participants, or QRS > 120 ms demonstrated in >=2 ECGs recorded > 30 minutes apart. ECG abnormalities due to right bundle branch block and absence of other significant cardiac disease or due to pacemaker may be acceptable pending investigator and Sponsor Medical Monitor agreement.
18. Participation in any other investigational drug trial or use of investigational drug (within 42 days [or 6 months for biologics] before the first dose of study intervention and thereafter). Participants who participated

in another trial or used investigational drugs within 42 days (or 6 months for biologics) before the first dose of study intervention may be rescreened after this window has elapsed. Participants who participated in experimental gene therapy or cell therapy at any time are excluded from this study.
19. Use of prescription or over-the-counter (OTC) medications (including herbal medicines such as St. John*s wort) that are moderate or strong CYP3A4/5 inducers or inhibitors within 7 days or 5 half-lives (whichever is longer) of the first dose administration or anticipated use during the study treatment period (see Section 6.5.1 of the protocol)
Note: Non systemic medications (e.g., topical medications unlikely to achieve meaningful plasma exposure),subcutaneous lidocaine, paracetamol/acetaminophen, caffeine for treatment of post-LP headache, and medications needed to treat AEs and medical emergencies are permitted. Other medications may be permitted with joint agreement of the investigator and Sponsor.
20. Use of prescription or OTC medications that are sensitive CYP3A4/5 substrates with a narrow therapeutic index within 7 days or 5 half-lives (whichever is longer) of the first dose administration or anticipated use during the study treatment period (see Section 6.5.1 of the protocol)
21. Use of prescription or OTC medications that are substrates for BCRP, OATP1B1, or OAT3 transporters and have a narrow therapeutic index within 7 days or 5 half-lives (whichever is longer) of the first dose administration or anticipated use during the study treatment period (see Section 6.5.1)
22. Use of any medications known to lower seizure threshold or increase seizure risk (e.g., antipsychotics) within 7days or 5 half-lives (whichever is longer) of the first dose administration or anticipated use during the study treatment period (see Section 6.5.1 of the protocol)
23. Any surgical or medical condition affecting drug absorption (e.g., gastrectomy)
24. Donation or loss of > 500 mL whole blood within 30 days before entry in the treatment period
25. Hospitalization during the 4 weeks prior to screening. Participants who were hospitalized within 4 weeks of screening may be rescreened after this window has elapsed.
26. Employees 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
27. Any ot

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):	11-08-2021
Enrollment:	15
Type:	Actual

Medical products/devices used

Registration:	No
Product type:	Medicine
Brand name:	DNL343
Generic name:	NA

Ethics review

Approved WMO Date:	15-06-2021
Application type:	First submission
Review commission:	BEBO: Stichting Beoordeling Ethiek Bio-Medisch Onderzoek (Assen)
Approved WMO Date:	07-07-2021
Application type:	First submission
Review commission:	BEBO: Stichting Beoordeling Ethiek Bio-Medisch Onderzoek (Assen)
Approved WMO Date:	08-08-2021
Application type:	Amendment
Review commission:	BEBO: Stichting Beoordeling Ethiek Bio-Medisch Onderzoek (Assen)

Approved WMO Date:	16-08-2021
Application type:	Amendment
Review commission:	BEBO: Stichting Beoordeling Ethiek Bio-Medisch Onderzoek (Assen)
Approved WMO Date:	17-09-2021
Application type:	Amendment
Review commission:	BEBO: Stichting Beoordeling Ethiek Bio-Medisch Onderzoek (Assen)
Approved WMO Date:	20-10-2021
Application type:	Amendment
Review commission:	BEBO: Stichting Beoordeling Ethiek Bio-Medisch Onderzoek (Assen)
Approved WMO Date:	10-03-2022
Application type:	Amendment
Review commission:	BEBO: Stichting Beoordeling Ethiek Bio-Medisch Onderzoek (Assen)
Approved WMO Date:	16-04-2022
Application type:	Amendment
Review commission:	BEBO: Stichting Beoordeling Ethiek Bio-Medisch Onderzoek (Assen)
Approved WMO Date:	22-04-2022
Application type:	Amendment
Review commission:	BEBO: Stichting Beoordeling Ethiek Bio-Medisch Onderzoek (Assen)
Approved WMO Date:	23-08-2022
Application type:	Amendment
Review commission:	BEBO: Stichting Beoordeling Ethiek Bio-Medisch Onderzoek (Assen)
Approved WMO Date:	18-11-2022
Application type:	Amendment

Review commission:	BEBO: Stichting Beoordeling Ethiek Bio-Medisch Onderzoek (Assen)
Approved WMO Date:	01-02-2023
Application type:	Amendment
Review commission:	BEBO: Stichting Beoordeling Ethiek Bio-Medisch Onderzoek (Assen)
Approved WMO Date:	02-02-2023
Application type:	Amendment
Review commission:	BEBO: Stichting Beoordeling Ethiek Bio-Medisch Onderzoek (Assen)
Approved WMO Date:	28-11-2023
Application type:	Amendment
Review commission:	BEBO: Stichting Beoordeling Ethiek Bio-Medisch Onderzoek (Assen)
Approved WMO Date:	05-12-2023
Application type:	Amendment
Review commission:	BEBO: Stichting Beoordeling Ethiek Bio-Medisch Onderzoek (Assen)
Approved WMO Date:	30-04-2024
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	EUCTR2021-001766-37-NL
ClinicalTrials.gov	NCT05006352
CCMO	NL77969.056.21