A Phase 1/2, Multicenter, Open-Label Study to Determine the Safety, Pharmacokinetics, and Pharmacodynamics of DNL310 in Pediatric Participants with Hunter Syndrome

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This study has been transitioned to CTIS with ID 2023-508619-22-00 check the CTIS register for the current data. The primary objective of the study is the following:• To characterize the safety and tolerability of DNL310 in pediatric subjects with...

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

Summary

ID

NL-OMON54074

Source
ToetsingOnline

Brief title
DENA211102_DNL310 in Pediatric Participants with Hunter Syndrome

Condition

- Other condition
- Metabolic and nutritional disorders congenital

Synonym
Hunter syndrome, mucopolysaccharidosis type II (MPS II)

Health condition

Lysosomal Storage Diseases, Neurologic Manifestations, Nervous System Diseases

Research involving
Human

Sponsors and support

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

Intervention

Keyword: Hunter Syndrome, MPS II, nMPS II

Outcome measures

Primary outcome

- Incidence and severity of treatment-emergent adverse events (TEAEs) at 24 weeks, 104 weeks, 261 weeks, and across study

- Change from baseline in safety laboratory values, vital sign measurements, electrocardiogram (ECG) findings, urine total glycosaminoglycan (GAG) levels, and physical and neurological assessments at 24 weeks, 104 weeks, 261 weeks, and across study

- Incidence and severity of infusion-related reactions (IRRs) at 24 weeks, 104 weeks, 261 weeks, and across study

- Change from baseline in concomitant medication at 24 weeks, 104 weeks, 261 weeks, and across study

Secondary outcome

- Percent change from baseline in cerebrospinal fluid (CSF) of heparan sulfate [Time Frame:24 weeks]

- Participants with improvement in individual disease progression in the Vineland Adaptive Behavior Scale Adaptive Behavior Composite (ABC) score [Time Frame: 49 weeks]

- Participants with improvement in individual disease progression in theVineland Adaptive Behavior Scale subdomain scores at week 49 [Time Frame: 49 weeks]

- To characterize the CNS effects of DNL310 on adaptive behaviors as assessed by the Vineland Adaptive Behavior Scale [Time Frame: 49 weeks]

- PK parameter: Maximum observed concentration (Cmax) of DNL310 in serum [Time Frame: 24 weeks]

- PK parameter: Trough concentration (Cmin) of DNL310 in serum [Time Frame: 24 weeks]

- PK parameter: Time to maximum observed concentration (tmax) of DNL310 in serum [Time Frame: 24 weeks]

- PK parameter: Area under the concentration-time curve from time zero to the time of last quantifiable concentration (AUClast) of DNL310 in serum [Time Frame: 24 weeks]

- PK parameter: Area under the concentration-time curve from time zero to infinity (AUC*) of DNL310 in serum [Time Frame: 24 weeks]

- PK parameter: Area under the concentration-time curve over a dosing interval (AUC*) of DNL310 in serum [Time Frame: 24 weeks]

- PK parameter: Apparent terminal elimination half-life (t*) of DNL310 in serum [Time Frame: 24 weeks]

- Characterization of immunogenicity of DNL310 in serum, as measured by the incidence of anti-drug antibodies (ADAs) relative to baseline

[Time Frame: 24 weeks]

- Percent change from baseline in urine concentration of heparan sulfate (HS)

[Time Frame: 24 weeks]

- Participants with liver volume in the normal range [Time Frame: 24 weeks and 49 weeks]

- Percentage change form baseline in liver volume [Time Frame: 24 weeks and 49 weeks]

Study description

Background summary

"Mucopolysaccharidosis type II (MPS II or Hunter Syndorme), is a rare genetic condition that occurs almost exclusively in boys. MPS II is caused by lack of an enzyme resulting in accumulation of certain sugars in the body, causing abnormalities in many organs, including the skeleton, heart, and respiratory systems. In severe cases, this leads to early death.

There is no cure for MPS II. Approved enzyme replacement therapies (ERT) may improve some symptoms of MPS II, especially if started early in the disease. However, as standard-of-care ERT cannot cross the blood-brain barrier, it does not treat the cognitive impairment in patients with central nervous system (CNS) symptoms. There is still a high, unmet medical need for improved treatment of MPS II."

This Phase 1/2 study in pediatric subjects with Hunter syndrome is the first clinical investigation of DNL310. DNL310 is an intravenous (IV) ERT designed to deliver IDS enzyme to both the CNS and peripheral tissues. This study will evaluate the safety, PK, and pharmacodynamics (PD) of DNL310, as well as explore its potential clinical efficacy.

The aim of the study is to identify generally safe and well-tolerated doses of DNL310 that demonstrate pharmacological activity in the CNS and the periphery.

These results will be used to identify a dose to be studied in a separate efficacy and safety study.

Study objective

This study has been transitioned to CTIS with ID 2023-508619-22-00 check the CTIS register for the current data.

The primary objective of the study is the following:
• To characterize the safety and tolerability of DNL310 in pediatric subjects with MPS II (all cohorts)

The secondary objectives of the study are as follows:
• To characterize the CNS effects of DNL310 on heparan sulfate (HS) concentrations in CSF (all cohorts)
• To characterize the CNS effects of DNL310 on adaptive behaviors as assessed by the Vineland Adaptive Behavior Scale (all cohorts)
• To characterize the PK of once-weekly IV infusions of DNL310 in serum (all cohorts)
• To characterize immunogenicity of DNL310 in serum (all cohorts)
• To characterize the peripheral effects of DNL310 on HS concentrations in urine (all cohorts)
• To characterize the peripheral effects of DNL310 on liver volume as measured by MRI (Cohorts C, D, and E only)

Study design

"This is a multicenter, multiregional, open-label study to assess the safety, pharmacokinetics (PK), and pharmacodynamics (PD) of DNL310, an investigational central nervous system (CNS)-penetrant enzyme replacement therapy (ERT), designed to treat both the peripheral and CNS manifestations of Mucopolysaccharidosis type II (MPS II; Hunter syndrome).

Participants, whose physicians feel they are deriving benefit, will have the opportunity to be reconsented into a safety extension and then an open-label extension for continued evaluation."

Intervention

DNL310 (ETV:IDS) administered intravenously weekly

Study burden and risks

DNL310 is being given to humans for the first time in this study. So far, participants receiving DNL310 weekly have tolerated the study intervention well. The most frequently observed treatment-related events were

infusion-related reactions (IRRs), which is consistent with other approved ERTs.

Potential risks (based on known class effects and nonclinical data) are:

• Anti-drug antibody (ADA) formation
• Anemia (decrease in red blood cells)

Please refer to ICF Appendix D for all study related risks and discomforts.

Contacts

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Trial sites

Listed location countries

Netherlands

Eligibility criteria

Age
Adolescents (12-15 years)
Adolescents (16-17 years)
Children (2-11 years)
Babies and toddlers (28 days-23 months)
Newborns

Inclusion criteria

- Confirmed diagnosis of MPS II
- Cohort A: Participants aged >= 5 to <=10 years with neuronopathic MPS II (nMPS II)
- Cohort B: Participants aged >= 1 to <=18 years with non-neuronopathic MPS II (nnMP II), neuronopathic MPS II, or unknown phenotype
- Cohort C: Participants aged <4 years with neuronopathic MPS II (this cohort can include participants >=4 years of age if participant is a blood relative with the same genetic mutation as participant >= 4 to <=18 years of age who will be enrolled in the study)
- Cohort D: Participants aged <=18 years with nMPS II and nnMPS II and preexisting hepatomegaly who have never taken standard - of - care ERT
- Cohort E: Neuronopathic MPS II Participants aged >= 6 years at screening, nnMPS II participants < 6 or >=17 years at screening, and nMPS II participants >= 1 to <=18 years at screening who have completed at least 48 weeks in Study DNLI-E-0001
- For participants receiving intravenous iduronate 2-sulfatase (IDS) ERT, tolerated a minimum of 4 months of therapy during the period immediately prior to screening.

Exclusion criteria

- Unstable or poorly controlled medical condition(s) or significant medical or psychological comorbidity or comorbidities that, in the opinion of the investigator, would interfere with safe participation in the trial or interpretation of study assessments
- Use of any CNS-targeted MPS II ERT within 3 months before study start for participants aged >=5 years, and within 6 months before study start for participants aged <5 years.
- Use of IDS gene therapy or stem cell therapy at any time
- Clinically significant thrombocytopenia, other clinically significant coagulation abnormality, or significant active bleeding, or required treatment with an anticoagulant or more than two antiplatelet agents
- Contraindication for lumbar punctures
- Have a clinically significant history of stroke, status epilepticus, head trauma with loss of consciousness, or any CNS disease that is not MPS II-related within 1 year of screening
- Have had a ventriculoperitoneal (VP) shunt placed, or any other brain surgery, or have a clinically significant VP shunt malfunction within 30 days of screening
- Have any clinically significant CNS trauma or disorder that, in the opinion of the investigator, may interfere with assessment of study endpoints or make participation in the study unsafe

- Have clinically significant anemia

Study design

Design

Study type: Interventional

Masking:	Open (masking not used)
Control:	Uncontrolled
Primary purpose:	Treatment

Recruitment

NL

Recruitment status:	Recruiting
Start date (anticipated):	01-11-2021
Enrollment:	2
Type:	Actual

Medical products/devices used

Product type:	Medicine
Brand name:	DNL310
Generic name:	Iduronate-2-Sulfatase fused to a fc polypeptide that binds to the human transferrin receptor

Ethics review

Approved WMO Date:	09-11-2020
Application type:	First submission
Review commission:	CCMO: Centrale Commissie Mensgebonden Onderzoek (Den Haag)
Approved WMO Date:	11-05-2021
Application type:	First submission
Review commission:	CCMO: Centrale Commissie Mensgebonden Onderzoek (Den

	Haag)
Approved WMO Date:	18-06-2021
Application type:	Amendment
Review commission:	CCMO: Centrale Commissie Mensgebonden Onderzoek (Den Haag)
Approved WMO Date:	20-07-2021
Application type:	Amendment
Review commission:	CCMO: Centrale Commissie Mensgebonden Onderzoek (Den Haag)
Approved WMO Date:	06-08-2021
Application type:	Amendment
Review commission:	CCMO: Centrale Commissie Mensgebonden Onderzoek (Den Haag)
Approved WMO Date:	06-09-2021
Application type:	Amendment
Review commission:	CCMO: Centrale Commissie Mensgebonden Onderzoek (Den Haag)
Approved WMO Date:	29-11-2021
Application type:	Amendment
Review commission:	CCMO: Centrale Commissie Mensgebonden Onderzoek (Den Haag)
Approved WMO Date:	22-12-2021
Application type:	Amendment
Review commission:	CCMO: Centrale Commissie Mensgebonden Onderzoek (Den Haag)
Approved WMO Date:	21-02-2022
Application type:	Amendment
Review commission:	CCMO: Centrale Commissie Mensgebonden Onderzoek (Den Haag)
Approved WMO Date:	09-05-2022

Application type:	Amendment
Review commission:	CCMO: Centrale Commissie Mensgebonden Onderzoek (Den Haag)
Approved WMO Date:	27-06-2022
Application type:	Amendment
Review commission:	CCMO: Centrale Commissie Mensgebonden Onderzoek (Den Haag)
Approved WMO Date:	06-07-2022
Application type:	Amendment
Review commission:	CCMO: Centrale Commissie Mensgebonden Onderzoek (Den Haag)
Approved WMO Date:	23-02-2023
Application type:	Amendment
Review commission:	CCMO: Centrale Commissie Mensgebonden Onderzoek (Den Haag)
Approved WMO Date:	13-03-2023
Application type:	Amendment
Review commission:	CCMO: Centrale Commissie Mensgebonden Onderzoek (Den Haag)
Approved WMO Date:	22-05-2023
Application type:	Amendment
Review commission:	CCMO: Centrale Commissie Mensgebonden Onderzoek (Den Haag)
Approved WMO Date:	23-06-2023
Application type:	Amendment
Review commission:	CCMO: Centrale Commissie Mensgebonden Onderzoek (Den Haag)
Approved WMO Date:	31-07-2023
Application type:	Amendment
Review commission:	CCMO: Centrale Commissie Mensgebonden Onderzoek (Den Haag)

Approved WMO Date:	22-09-2023
Application type:	Amendment
Review commission:	CCMO: Centrale Commissie Mensgebonden Onderzoek (Den Haag)
Approved WMO Date:	20-12-2023
Application type:	Amendment
Review commission:	CCMO: Centrale Commissie Mensgebonden Onderzoek (Den Haag)
Approved WMO Date:	24-01-2024
Application type:	Amendment
Review commission:	CCMO: Centrale Commissie Mensgebonden Onderzoek (Den Haag)

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	CTIS2023-508619-22-00
EudraCT	EUCTR2019-004909-27-NL
ClinicalTrials.gov	NCT04251026
CCMO	NL74319.000.20