A Phase 2/3, Multicenter, Double-Blind, Randomized Study to Determine the Efficacy and Safety of Tividenofusp Alfa (DNL310) vs Idursulfase in Pediatric and Young Adult Participants With Neuronopathic or Non-Neuronopathic Mucopolysaccharidosis Type II

Published: 11-05-2022
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This study has been transitioned to CTIS with ID 2024-510990-21-00 check the CTIS register for the current data. The co-primary objectives are: To evaluate the CNS activity of DNL310 vs idursulfase as measured by the cerebrospinal fluid (CSF)...

Ethical review	Approved WMO
Status	Recruiting
Health condition type	Neurological disorders NEC
Study type	Interventional

Summary

ID

NL-OMON53946

Source
ToetsingOnline

Brief title
DNLI-E-0007

Condition

- Neurological disorders NEC

Synonym
Hunter syndrome, Mucopolysaccharidosis Type II (MPS II)

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, Mucopolysaccharidosis Type II (MPS II), nMPS II, nnMPS II

Outcome measures

Primary outcome

- Percent change from baseline in CSF HS concentration at Week 24 (Cohort A only)

- Change from baseline in the Vineland-3 8-subdomain Adaptive Behavior Raw Score (ABRS-8) at Week 96 (Cohort A)

Secondary outcome

- Change from baseline in the BSID-III cognitive raw score at Week 96 (Cohort A only)

- Change from baseline in the Vineland-3 ABC at Week 96 (Cohort A only)

- Change from baseline in serum neurofilament light chain (NfL) at Week 96 (Cohort A only)

- Change from baseline in distance walked (meters) in the 6MWT at Week 48 (Cohort B only)

- Percent change from baseline in the sum of urine HS and dermatan sulfate (DS) concentrations at Week 24 (Cohorts A and B)

- Percent change from baseline in the sum of urine HS and DS concentrations at Week 48 (Cohorts A and B)

- Liver volume within the normal range (normal vs abnormal) as measured by MRI

at Week 48 (Cohorts A and B)

- Spleen volume within the normal range (normal vs abnormal) as measured by MRI

at Week 48 (Cohorts A and B)

- Improvement in CaGI-C Overall MPS II (defined as much improved or a little

improved) at Week 48 (Cohorts A and B)

Study description

Background summary

Two IV idursulfase replacement therapies are currently marketed for the treatment of the peripheral manifestation of MPS II. Elaprase (idursulfase; Shire Human Genetic Therapies, Inc., Lexington, MA) was approved by the Food and Drug Administration (FDA) and European Medicines Agency (EMA) in 2006 and 2007, respectively, and is the standard of care worldwide (Elaprase US Prescribing Information [USPI] 2013; Elaprase Summary of Product Characteristics [SmPC] 2020; Muenzer et al. 2006). Hunterase (idursulfase-β; GCPharma, Gyeonggi-do, South Korea) has been marketed in South Korea since 2012 and was approved in China in 2020. Extensive clinical experience and clinical safety data for the administration of these IDS enzymes in MPS II patients, including children, are available. Elaprase and Hunterase do not adequately control many aspects of the disease, including skeletal, cardiac, and pulmonary involvement, and, most importantly, they do not effectively cross the blood-brain barrier (BBB).

A key area of unmet need is treatment of the CNS manifestations of MPS II disease, such as developmental delay, disruptive behaviors, and impaired cognition. Therapeutic approaches that aim to address the neurocognitive components of MPS II are under development. Two therapeutic approaches were approved in Japan in 2021: intracerebroventricular (ICV) Hunterase (idursulfase-β; Clinigen KK, Tokyo, Japan) and Izcargo* (pabinafusp alfa; JCR Pharmaceuticals Co., Ltd., Ashiya, Japan), an IV administered fusion protein consisting of human IDS and an anti-human transferrin receptor antibody that attained Sakigake designation in Japan. DNL310 represents an alternative, noninvasive approach whereby an IDS fusion protein is administered IV and carried across the BBB via endogenous receptor-mediated transport mechanisms.

This Phase 2/3, multiregional, two-arm, double-blind, randomized, active

(standard-of-care)-controlled study is designed to determine the efficacy and safety of DNL310 compared with idursulfase in pediatric participants with either nMPS II or nnMPS II. A key therapeutic hypothesis of the DNL310 program and this study is that uniform distribution of IDS throughout the brain will result in substantially better overall CNS efficacy for patients with MPS II than the current standard of care treatment, IV-delivered idursulfase, while also maintaining peripheral benefit.

Study objective

This study has been transitioned to CTIS with ID 2024-510990-21-00 check the CTIS register for the current data.

The co-primary objectives are: To evaluate the CNS activity of DNL310 vs idursulfase as measured by the cerebrospinal fluid (CSF) concentration of heparan sulfate (HS) in participants with the neuronopathic form of mucopolysaccharidosis type II (nMPS II). And to evaluate the clinical CNS efficacy of DNL310 vs idursulfase on adaptive behavior as assessed by the Vineland Adaptive Behavior Scale, Third Edition (Vineland-3), 8-subdomain Adaptive Behavior Raw Score (ABRS-8) in nMPS II participants.

The secondary objectives are: To evaluate the clinical CNS efficacy of DNL310 vs idursulfase on neurocognitive development, as assessed by the Bayley Scales of Infant and Toddler Development, Third Edition (BSID-III), cognitive domain in nMPS II participants.
To evaluate the clinical CNS efficacy of DNL310 vs idursulfase on adaptive behavior as assessed by the Vineland-3 Adaptive Behavior Composite (ABC) in nMPS II participants.
To evaluate the efficacy of DNL310 vs idursulfase on neuronal injury in nMPS II participants.
To evaluate the clinical efficacy of DNL310 vs idursulfase on physical endurance as measured by the Six-Minute Walk Test (6MWT) in participants with the non-neuronopathic form of mucopolysaccharidosis type II (nnMPS II).
To evaluate the onset and durability of peripheral efficacy of DNL310 vs idursulfase as measured by the urine concentration of total glycosaminoglycans (GAGs) by a mass-spectrometry-based detection method in nMPS II and nnMPS II participants.
To evaluate the efficacy of DNL310 vs idursulfase on liver volume and spleen volume as measured by magnetic resonance imaging (MRI) in nMPS II and nnMPS II participants.
To evaluate the parent*s/caregiver*s assessment of efficacy of DNL310 vs idursulfase as measured by the Parent/Caregiver Global Impression of Change (CaGI-C) in nMPS II and nnMPS II participants.

Study design

This is a Phase 2/3, multiregional, two-arm, double-blind, randomized, active (standard-of-care)-controlled study of the efficacy and safety of DNL310, an investigational CNS-penetrant ERT for MPS II. Approximately 54 participants aged >= 2 to under 26 years with MPS II will be enrolled in one of the two following cohorts (Cohort A or Cohort B) according to MPS II phenotype (neuronopathic vs non neuronopathic): - Cohort A: Approximately 33 participants aged >= 2 to under 6 years with nMPS II, as determined based on genetic testing (and cognitive testing or family history, as applicable), will be randomized 2:1 to receive either DNL310 or IV idursulfase through Week 96. Target enrollment is for at least 50% of the participants to be aged >= 24 and <= 48 months at randomization and for at least 70% of participants aged >48 months to have a cognitive developmental quotient (DQ) of equal to or higher than 20 as measured by the BSID-III. Randomization will be stratified by chronological age (less then or equal to 48 months or more than 48 months) and genotype (presence or absence of a known severe IDS variant [eg, whole-gene deletion or large rearrangement]). - Cohort B: Approximately 21 participants aged >= 6 to <26 years with nnMPS II, as determined based on genetic and cognitive testing, will be randomized 2:1 to receive either DNL310 or IV idursulfase through Week 48. Randomization will be stratified by chronological age (< 12 years, >= 12 years to < 17 years, or >= 17 years). The study includes a screening period of approximately 6 weeks, a baseline period of approximately 3 weeks, and a 96-week (Cohort A) or 48-week (Cohort B) postrandomization treatment period. For participants who are ERT-nai*ve or ERT-pseudo-nai*ve (ie, have no history of treatment with idursulfase), a run-in idursulfase treatment period totaling approximately 4 months (ie, 16 weeks), including an overlapping baseline period, will be included between screening and the first day of study intervention administration in the controlled treatment phase.

Intervention

Name and formulation: DNL310 is supplied in a lyophilized form and is intended to be administered intravenously after reconstitution and dilution.
Dose: 15 mg/kg dosed once per week
Route of administration: IV infusion

Control Test Product: Idursulfase is to be administered at the recommended dose (0.5 mg/kg) once per week as an IV infusion.

Study burden and risks

This is a Phase 2/3, multiregional, two-arm, double-blind, randomized, active (standard-of-care)-controlled study of the efficacy and safety of DNL310, an investigational central nervous system (CNS)-penetrant enzyme-replacement therapy (ERT) for mucopolysaccharidosis type II (MPS II). Approximately 54 participants aged >= 2 to < 26 years with MPS II will be enrolled. For all participants baseline assessments will include safety, imaging, audiology,

neurocognitive testing, and biomarker sample collections (blood, urine, and CSF). Results from the Phase 1/2 study with DNL310 (Study DNLI E 0002) informed the dosage of 15 mg/kg IV once weekly to be used in this Phase 2/3 study. These data showed that the 15-mg/kg dose provided consistent and sustained reductions in CSF HS, DS, and GM3 (lysosomal lipid) and urine GAG concentrations (see DNL310 IB Section 5.2). In order to ensure the continuation of their current treatment, participants should continue to receive prior ERT with idursulfase during the baseline period until 1 week prior to Day 1, and will receive their randomly assigned study intervention starting on Day 1 without a washout period. All study intervention infusions for this study will be administered at the study center.

Contacts

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Trial sites

Listed location countries

Netherlands

Eligibility criteria

Age
Adolescents (12-15 years)
Adolescents (16-17 years)
Adults (18-64 years)
Children (2-11 years)

Inclusion criteria

1. Participants aged >=2 to <6 years (Cohort A) or >=6 to <26 years (Cohort B).
2. Confirmed diagnosis of MPS II (for Cohort A, nMPS II; for Cohort B, nnMPS II).
3. For non-run-in Cohort A and Cohort B only: Be on maintenance enzyme replacement therapy (ERT) and have tolerated a minimum of 4 months (ie, 16 weeks) of idursulfase therapy during the period immediately prior to screening.

Exclusion criteria

1. Have a documented pathogenic or likely pathogenic variants that are known to cause developmental delay or decline, cognitive dysfunction, seizures, or other significant CNS disorders

2. Previously received an IDS gene therapy or stem cell therapy

3. Received any CNS-targeted MPS ERT within 6 months prior to screening

4. Have a contraindication for lumbar punctures and/or magnetic resonance imaging (MRIs)

5. Participated in any other investigational drug study or used an investigational drug within 60 days prior to screening or intend to receive another investigational drug during the study

Study design

Design

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

Recruitment

NL

Recruitment status:	Recruiting
Start date (anticipated):	23-02-2023
Enrollment:	3
Type:	Actual

Medical products/devices used

Registration:	No
Product type:	Medicine
Brand name:	DNL310
Generic name:	tividenofusp alfa
Product type:	Medicine
Brand name:	Idursulfase (Elaprase)
Generic name:	Purified form of the lysosomal enzyme iduronate-2-sulfatase
Registration:	Yes - NL intended use

Ethics review

Approved WMO Date:	11-05-2022
Application type:	First submission
Review commission:	METC Erasmus MC, Universitair Medisch Centrum Rotterdam (Rotterdam)
Approved WMO Date:	04-08-2022
Application type:	First submission
Review commission:	METC Erasmus MC, Universitair Medisch Centrum Rotterdam (Rotterdam)
Approved WMO Date:	05-11-2022
Application type:	Amendment
Review commission:	METC Erasmus MC, Universitair Medisch Centrum Rotterdam (Rotterdam)
Approved WMO	

Date:	29-11-2022
Application type:	Amendment
Review commission:	METC Erasmus MC, Universitair Medisch Centrum Rotterdam (Rotterdam)
Approved WMO Date:	28-04-2023
Application type:	Amendment
Review commission:	METC Erasmus MC, Universitair Medisch Centrum Rotterdam (Rotterdam)
Approved WMO Date:	06-06-2023
Application type:	Amendment
Review commission:	METC Erasmus MC, Universitair Medisch Centrum Rotterdam (Rotterdam)
Approved WMO Date:	23-06-2023
Application type:	Amendment
Review commission:	METC Erasmus MC, Universitair Medisch Centrum Rotterdam (Rotterdam)
Approved WMO Date:	11-09-2023
Application type:	Amendment
Review commission:	METC Erasmus MC, Universitair Medisch Centrum Rotterdam (Rotterdam)
Approved WMO Date:	20-11-2023
Application type:	Amendment
Review commission:	METC Erasmus MC, Universitair Medisch Centrum Rotterdam (Rotterdam)
Approved WMO Date:	19-12-2023
Application type:	Amendment
Review commission:	METC Erasmus MC, Universitair Medisch Centrum Rotterdam (Rotterdam)
Approved WMO Date:	30-07-2024
Application type:	Amendment
Review commission:	METC Erasmus MC, Universitair Medisch Centrum Rotterdam

	(Rotterdam)
Approved WMO Date:	20-09-2024
Application type:	Amendment
Review commission:	METC Erasmus MC, Universitair Medisch Centrum Rotterdam (Rotterdam)

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	CTIS2024-510990-21-00
EudraCT	EUCTR2021-005200-35-NL
CCMO	NL81027.078.22