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Study to determine the effectiveness and safety of DNL310 vs idursulfase in pediatric participants with neuronopathic or non-neuronopathic Hunter Syndrome

Submission date
28/04/2022

Recruitment status
No longer recruiting

Registration date
30/06/2022

Overall study status
Completed

Last Edited
15/11/2022

Condition category
Nutritional, Metabolic, Endocrine

[X] Prospectively registered
[_] Protocol
[_] Statistical analysis plan
[_] Results
[_] Individual participant data
[_] Record updated in last year

Plain English summary of protocol

Background and study aims
Mucopolysaccharidosis type II (MPS II or Hunter Syndrome) is a rare genetic condition that occurs almost exclusively in boys. MPS II is caused by a lack of an enzyme resulting in the accumulation of certain sugars in the body, causing abnormalities in many organs, including the skeleton, heart, and breathing 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 the 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. DNL310 is an investigational medicine (not yet approved by regulatory authorities). DNL310 will be given intravenously (into a vein) once a week. If DNL310 works as expected, it may help to reduce the CNS and physical symptoms of MPS II. The aim of this study is to assess the effectiveness and safety of DNL310 for MPS II.

Who can participate?
Patients aged 2 to 17 years with MPSII

What does the study involve?
Patients aged 2 to 6 years are randomly allocated to receive either DNL310 or idursulfase until Week 96. Participants aged 6 to 17 years are randomly allocated to receive either DNL310 or idursulfase until Week 48. During the study participants will undergo assessments which include physical exams, cognitive and behavioural assessments, blood, urine, cerebrospinal fluid analysis, hearing test, electrocardiogram, ultrasound and scales and questionnaires.

What are the possible benefits and risks of participating?
In the previous study of DNL310, the study drug was generally well tolerated by participants. The most frequently observed side effects were infusion-related reactions, which are any side effect that occurs within 24 hours of the study drug and could be related to this study drug. This

is consistent with other approved drugs of this type. As of 03/06/2021, 13 of 18 (72.2%) participants in a DNL310 study experienced reactions that were mostly mild or moderate in severity. Symptoms include:
1. Mild reactions: flushing, fever, shivering, irritability or mild pain and discomfort at the injection site
2. Moderate reactions: rash, itching, abdominal pain, or cramps, vomiting and diarrhoea
Severe reactions: sudden and severe reactions that require urgent care. Symptoms include:
1. Cardiovascular effects including cardiac arrhythmia (irregular heartbeat), shock (steep drop in blood pressure) and circulatory collapse
2. Respiratory symptoms such as shortness of breath, stridor (high-pitched musical sound), wheezing (a whistling sound in the chest that can be heard using a stethoscope), laryngeal oedema (swelling of the voice box)
3. Changes in mental status such as disorientation and unresponsiveness
4. Anaphylactic reactions
Study doctors may decide to treat participants with antihistamines, corticosteroids, or other medications just prior to beginning the study drug infusion and during/after the infusion in order to prevent or reduce any infusion-related reactions to the study drug.

Other potential side effects of DNL310 are:
1. Anaemia
2. Formation of antibodies against the study drug

Idursulfase:
1. Hypersensitivity and infusion-related reactions as detailed above
2. Vomiting
3. Rash
4. Ear infection
5. Fever
6. Pneumonia

Participants will be monitored for adverse events and serious adverse events by qualified staff at the study site throughout the study, from the signing of the consent form to the completion of study participation. These will be assessed at every site visit. It is not known if the study drug will harm an unborn baby and therefore pregnancy tests will be performed where required in female participants of childbearing capacity and all participants of reproductive capacity will be instructed to use two highly effective methods of contraception (as detailed in the patient information sheet). Females of childbearing potential will be instructed to notify the study doctor immediately if they become pregnant, and male participants will be instructed to notify the study doctor immediately if their partner becomes pregnant. There may also be potential risks and burdens from the study procedures detailed in the patient information sheet.

Where is the study run from?
Denali Therapeutics (USA)

When is the study starting and how long is it expected to run for?
May 2022 to September 2025

Who is funding the study?
Denali Therapeutics (USA)

Who is the main contact?
Jose Rodriguez, jarodriguez@dnli.com

Contact information

Type(s)
Scientific

Contact name
Dr Jose Rodriguez

Contact details
Denali Therapeutics Inc.
161 Oyster Point Boulevard
South San Francisco
United States of America
94080
+1 (0)650 580 1167
jarodriguez@dnli.com

Type(s)
Public

Contact name
Dr Jose Rodriguez

Contact details
Denali Therapeutics Inc.
161 Oyster Point Boulevard
South San Francisco
United States of America
94080
-
jarodriguez@dnli.com

Type(s)
Principal investigator

Contact name
Prof Simon Jones

Contact details
Saint Mary's Hospital
Oxford Road
Manchester
United Kingdom
M13 9WL
+44 (0)16 17012137 ext 0
simon.jones@mft.nhs.uk

Additional identifiers

Clinical Trials Information System (CTIS)
2021-005200-35

Integrated Research Application System (IRAS)
1005494

Protocol serial number
IRAS 1005494, DNLI-E-0007, CPMS 52297

Study information

Scientific Title
A Phase II/III, multicenter, double-blind, randomized study to determine the efficacy and safety of DNL310 vs idursulfase in pediatric participants with neuronopathic or non-neuronopathic mucopolysaccharidosis type II

Study objectives
Primary objectives:
1. 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)
2. 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), in nMPS II participants

Secondary objectives:
1. 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), in nMPS II participants
2. To evaluate the clinical efficacy of DNL310 vs idursulfase on physical endurance as measured by the Six-Minute Walk Test (6MWT) in participants with non-neuronopathic mucopolysaccharidosis type II (nnMPS II)
3. 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
4. To evaluate the efficacy of DNL310 vs idursulfase on liver volume and spleen volume as measured by MRI in nMPS II and nnMPS II participants
5. To evaluate the parent’s/caregiver’s assessment of the efficacy of DNL310 vs idursulfase as measured by the Parent/Caregiver Global Impression of Change (CaGI-C) in nMPS II and nnMPS II participants

Ethics approval required
Old ethics approval format

Ethics approval(s)
Approved 21/06/2022, South Central – Berkshire Research Ethics Committee (Bristol REC Centre, Temple Quay House, 2 The Square, Temple Quay, Bristol, UK, BS1 6PN; +44 (0)207 104 8178; berkshire.rec@hra.nhs.uk), ref: 22/SC/0156

Study design

Double-blind randomized controlled trial

Primary study design
Interventional

Study type(s)
Treatment

Health condition(s) or problem(s) studied
Mucopolysaccharidosis Type II [MPS II]

Interventions
Study interventions:
1. Dose of DNL310: 15 mg/kg dosed once per week as an IV infusion.
2. Idursulfase: recommended dose (0.5 mg/kg) once per week as an IV infusion.

Study cohorts and trial arm details:

Cohort A: Approximately 33 participants aged ≥2 to <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 until Week 96. Target enrollment is for at least 70% of the participants to be aged ≥24 and ≤48 months at randomization. Randomization will be stratified by chronological age (≤48 months or > 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 <17 years with nnMPS II, as determined based on genetic and cognitive testing, will be randomized 2:1 to receive either DNL310 or IV idursulfase until Week 48. Randomization will be stratified by chronological age (<12 years or ≥12 years). Dose of DNL310: 15 mg/kg dosed once per week as an IV infusion. Dose of idursulfase: recommended dose (0.5 mg/kg) once per week as an IV infusion.

Intervention Type
Drug

Phase
Phase II/III

Drug/device/biological/vaccine name(s)
DNL310, idursulfase

Primary outcome(s)
1. Cerebrospinal fluid (CSF) heparan sulfate (HS) concentration is measured via CSF samples taken at baseline and Week 24 (Cohort A only)
2. Adaptive behaviour is assessed by the Vineland-3 scale at baseline and Week 96 (Cohort A only)

Key secondary outcome(s))
1. Neurocognitive development is assessed by the Bayley Scales of Infant and Toddler Development, Third Edition (BSID-III) at baseline and Week 96 (Cohort A only)
2. Physical endurance is measured as distance walked in the 6 Minute Walk Test (6MWT) at baseline and Week 48 (Cohort B only)

3. Onset and durability of peripheral efficacy are measured by the sum of urine heparan sulfate (HS) and dermatan sulfate (DS) concentrations at baseline and Week 48 (Cohorts A and B)
4. Liver volume within the normal range (normal vs abnormal) as measured by MRI at Week 48 (Cohorts A and B)
5. Spleen volume within the normal range (normal vs abnormal) as measured by MRI at Week 48 (Cohorts A and B)
6. Parents'/caregivers' assessment of efficacy is measured by improvement in the Parent /Caregiver Global Impression Assessment (CaGI-C) Overall MPS II at Week 48 (Cohorts A and B)

Completion date
01/09/2025

Eligibility

Key inclusion criteria
1. Participants aged ≥2 to <6 years (Cohort A) or ≥6 to <17 years (Cohort B)
2. Confirmed diagnosis of MPS II (for Cohort A, nMPS II; for Cohort B, nnMPS II)
3. Be on maintenance enzyme replacement therapy (ERT) and have tolerated idursulfase for a minimum of 4 months prior to screening

Participant type(s)
Patient

Healthy volunteers allowed
No

Age group
Child

Lower age limit
2 years

Upper age limit
17 years

Sex
All

Key exclusion criteria
1. Have a documented mutation of other genes or genetic diagnosis accounting for developmental delay
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 (MRI)
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

Date of first enrolment
21/07/2022

Date of final enrolment
25/08/2023

Locations

Countries of recruitment
United Kingdom

Argentina

Australia

Belgium

Brazil

Canada

Colombia

France

Germany

Italy

Mexico

Netherlands

Spain

Sweden

Türkiye

Study participating centre
Great Ormond Street Hospital
Great Ormond Street
London
United Kingdom
WC1N 3JH

Study participating centre
St Mary's Hospital
Praed Street

London
United Kingdom
W2 1NY

Sponsor information

Organisation
Denali Therapeutics (United States)

ROR
https://ror.org/00pprn321

Funder(s)

Funder type
Industry

Funder Name
Denali Therapeutics

Results and Publications

Individual participant data (IPD) sharing plan
The data-sharing plans for the current study are unknown and will be made available at a later date. The sponsor is committed to responsible sharing of clinical data with the goal of advancing medical science and improving patient care. Independent researchers will be permitted to use anonymized data collected from participants during this study to conduct additional scientific research, which may be unrelated to the study medication. The data provided to external researchers will not include identifiable information.

IPD sharing plan summary
Data sharing statement to be made available at a later date

Study outputs

Output type	Details	Date created	Date added	Peer reviewed?	Patient-facing?
HRA research summary			28/06/2023	No	No
Study website	Study website	11/11/2025	11/11/2025	No	Yes