A multinational, open-label, randomised, controlled trial to investigate efficacy and safety of NNC0365-3769 (Mim8) in adults and adolescents with haemophilia A with or without inhibitors.

Published: 15-02-2021
Last updated: 28-09-2024

Primary objectives:- To confirm the haemostatic effect of Mim8 as treatment prophylaxis for adult and adolescent patients with haemophilia A with or without inhibitors.Secondary objectives:- To investigate safety of Mim8 prophylaxis in adults and...

Ethical review	Approved WMO
Status	Recruitment stopped
Health condition type	Coagulopathies and bleeding diatheses (excl thrombocytopenic)
Study type	Interventional

Summary

ID

NL-OMON51871

Source
ToetsingOnline

Brief title
Frontier 2

Condition

- Coagulopathies and bleeding diatheses (excl thrombocytopenic)

Synonym
blood clothing disorder, Haemophilia A

Research involving
Human

Sponsors and support

Primary sponsor: Novo Nordisk
Source(s) of monetary or material Support: Novo Nordisk

Intervention

Keyword: Haemophilia A with and without inhibitors, Mim8, NNC0365-3769

Outcome measures

Primary outcome

- Number of treated bleeds from randomisation (week 0) to end of main (Week 26) in subjects with no prophylaxis treatment (arm 1 and 2).

- Number of treated bleeds from initiation of run-in (26-52 weeks prior to week 0) to week 0 and from randomisation (week 0) to end of main (Week 26) in subjects with prophylaxis treatment (arm 3 and 4).

Secondary outcome

Number of injection site reactions:

- from randomisation (week 0) to end of main (Week 26) in all subjects receiving Mim8 (Arm 2, 3 and 4)

Occurrence of anti-Mim8 antibodies:

- from randomisation (week 0) to end of extension (Week 52) in all subjects receiving Mim8 (Arm 2, 3 and 4)

Number of treated spontaneous bleeds:

- from randomisation (week 0) to end of main (Week 26) in subjects with no prophylaxis treatment (Arms 1 and 2)

- from initiation of run-in (26-52 weeks prior to week 0) to week 0 and from randomisation (week 0) to end of main (Week 26) in subjects with prophylaxis treatment (Arms 3 and 4)

Number of treated joint bleeds:
- from randomisation (week 0) to end of main (Week 26) in subjects with no prophylaxis treatment (Arms 1 and 2)
- from initiation of run-in (26-52 weeks prior to week 0) to week 0 and from randomisation (week 0) to end of main (Week 26) in subjects with prophylaxis treatment (Arms 3 and 4)

Number of treated traumatic bleeds:
- from randomisation (week 0) to end of main (Week 26) in subjects with no prophylaxis treatment (Arms 1 and 2)
- from initiation of run-in (26-52 weeks prior to week 0) to week 0 and from randomisation (week 0) to end of main (Week 26) in subjects with prophylaxis treatment (Arms 3 and 4)

Number of target joint bleeds:
- from randomisation (week 0) to end of main (Week 26) in subjects with no prophylaxis treatment (Arms 1 and 2)
- from initiation of run-in (26-52 weeks prior to week 0) to week 0 and from randomisation (week 0) to end of main (Week 26) in subjects with prophylaxis treatment (Arms 3 and 4)

Consumption of factor product per bleed treatment (number of injections):

- from randomisation (week 0) to end of main (Week 26) in subjects with no prophylaxis treatment (Arms 1 and 2)

- from initiation of run-in (26-52 weeks prior to week 0) to week 0 and from randomisation (week 0) to end of main (Week 26) in subjects with prophylaxis treatment (Arms 3 and 4)

Change in physical function domain of PEDS-QL from randomisation (week 0) to the end of the main part (week 26) in all subjects (Arms 1, 2, 3 and 4)

Change in patient*s treatment burden using the Hemo-TEM from randomisation (week 0) to the end of the main part (week 26) in all subjects (Arms 1, 2, 3 and 4)

Change in patient*s joint pain score using Joint Pain Rating Scale from randomisation (week 0) to the end of the main part (week 26) in all subjects (Arms 1, 2, 3 and 4)

Study description

Background summary

Mim8 has been evaluated in a nonclinical programme comprising PK, toxicology, efficacy and safety pharmacology. Collectively, the nonclinical safety studies support progression of Mim8 in clinical development.
The First Human Dose (FHD) trial with Mim8, NN7769-4513, started in January 2020 and includes single ascending dose (SAD) and multiple ascending dose (MAD) parts. SAD is performed in healthy volunteers and MAD in severe haemophilia A

patients with or without FVIII inhibitors. Trial 4513 is a combined phase 1/2 trial, which aims to evaluate initial safety and clinical proof of concept and support the dose selection for NN7769-4514, the phase 3 trial in adults and adolescents.
The purpose of this pivotal phase 3 trial is to confirm efficacy and safety of Mim8 prophylaxis in a larger population of patients with haemophilia A with or without inhibitors and to support marketing authorisation.

Study objective

Primary objectives:
- To confirm the haemostatic effect of Mim8 as treatment prophylaxis for adult and adolescent patients with haemophilia A with or without inhibitors.

Secondary objectives:
- To investigate safety of Mim8 prophylaxis in adults and adolescents with haemophilia A with or without FVIII inhibitors.
- To evaluate the consumption of factor product per bleed treatment (number of injections) after Mim8 prophylaxis in adults and adolescents with haemophilia A with or without inhibitors.
- To evaluate the development of anti-Mim8 antibodies after Mim8 prophylaxis in adults and adolescents with haemophilia A with or without inhibitors.

Study design

This is a prospective, multinational, multicentre, open label phase 3 trial in haemophilia A patients with four randomised arms. The trial includes a run-in period of up to 52 weeks duration.

Patients on coagulation factor prophylaxis must continue the same drug and dosing frequency in the run-in period for at least 26 weeks before they can be randomised into the main part of the trial.
Patients not receiving prophylaxis are not required to first enter the run-in.

The main part of the trial is completed for a given patient when 26 weeks of participation (screening and run-in period not included) has been completed. After the main part of the trial, all patients will continue in the extension part of the trial and receive treatment with Mim8 for 26 weeks. Subjects in Arm 1 will be offered weekly Mim8 dosing during the extension part, and subjects in Arms 2, 3 and 4 will follow the same dosing schedule as they did in the main part. Once a patient has completed the extension part of this trial, transfer to the Open Label Extension trial NN7769-4532 will be offered. In this trial the patient will receive Mim8 prophylaxis. If a subject does not want to be transferred to trial NN7769-4532 a follow-up visit should be completed.

Intervention

Subcutaneous Mim8 injection into a skinfold.

Study burden and risks

Based on the findings from nonclinical studies, on the identified potential risks, and the possible clinical benefit in subjects with haemophilia A with or without FVIII inhibitors, it is evaluated that the anticipated benefits outweigh the potential risks of Mim8 in this phase 3 trial.

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)
Elderly (65 years and older)

Inclusion criteria

- Informed consent obtained before any trial-related activities. Trial related activities are any procedures that are carried out as part of the trial, including activities to determine suitability for the trial
- Male or female with diagnosis of congenital haemophilia A of any severity based on medical records
- Patient has been prescribed, or in need of, treatment with factor VIII or bypassing agent in the last 26 weeks prior to screening
- Age above or equal to 12 years at the time of signing informed consent. Germany, Japan and Taiwan: Local requirements apply
- Body weight above or equal to 30 kg
- Applicable to patients on emicizumab prophylaxis: patient is willing to discontinue emicizumab at the time of screening
- Applicable to patients treated with no prophylaxis prior to enrolment: 5 or more bleeds in the last 26 weeks prior to screening visit
- Applicable to patients with FVIII activity above 1% who are on prophylactic treatment: 1 or more bleeds in the last 26 weeks prior to screening visit
- Willingness and ability to comply with scheduled visits and study procedures, including the completion of diary and patient-reported outcomes questionnaires

Exclusion criteria

- Previous participation in this trial. Participation is defined as signed informed consent
- Participation in any clinical trial of an approved or non-approved investigational medicinal product, within 30 days (or 5 half-lives of the investigational medicinal product, whichever is greater) before screening
- Female who is pregnant, breast-feeding or intends to become pregnant or is of child-bearing potential and not using a highly effective contraceptive method (highly effective contraceptive measures as defined in the protocol or as required by local regulation or practice). Breast feeding is allowed only during the run-in period
- Any disorder, except for conditions associated with haemophilia A, which in the investigator's opinion might jeopardise subject's safety or compliance with the protocol
- Known or suspected hypersensitivity to trial product(s), any constituents of the product or to related products
- Receipt of gene therapy at any given time point
- Ongoing or planned immune tolerance induction (ITI) therapy
- Major surgery planned at the time of screening
- Known congenital or acquired coagulation disorders other than haemophilia A
- Hepatic dysfunction defined as aspartate aminotransferase (AST) and/or

alanine aminotransferase (ALT) above 3 times the upper limit combined with total bilirubin above 1.5 times the upper limit measured at screening
- Renal impairment defined as estimated Glomerular Filtration Rate (eGFR) below or equal to 30 ml/min/1.73 m^2 for serum creatinine measured at screening
- Previous or current thromboembolic disease or events (includes arterial and venous thrombosis including myocardial infarction, thrombotic microangiography (TMA), pulmonary embolism, cerebral
infarction/thrombosis, deep vein thrombosis, other clinically significant thromboembolic events and peripheral artery occlusion) (with the exception of previous catheter-associated thrombosis for which antithrombotic treatment is not currently ongoing) or risk of thromboembolic disease, as evaluated by investigator
- Mental incapacity, unwillingness to cooperate, or a language barrier precluding adequate understanding and cooperation
- Other conditions (e.g. autoimmune disease) or laboratory abnormality that may increase risk of bleeding or thrombosis as evaluated by the investigator

Study design

Design

Study phase:	3
Study type:	Interventional
Masking:	Open (masking not used)
Control:	Uncontrolled
Primary purpose:	Treatment

Recruitment

NL

Recruitment status:	Recruitment stopped
Start date (anticipated):	09-03-2022
Enrollment:	6
Type:	Actual

Medical products/devices used

Product type:	Medicine
Brand name:	nog niet bekend
Generic name:	NNC0365-3769 (Mim8)

Ethics review

Approved WMO Date:	15-02-2021
Application type:	First submission
Review commission:	METC Amsterdam UMC
Approved WMO Date:	03-04-2021
Application type:	Amendment
Review commission:	METC Amsterdam UMC
Approved WMO Date:	06-04-2021
Application type:	First submission
Review commission:	METC Amsterdam UMC
Approved WMO Date:	31-10-2021
Application type:	Amendment
Review commission:	METC Amsterdam UMC
Approved WMO Date:	15-11-2021
Application type:	Amendment
Review commission:	METC Amsterdam UMC
Approved WMO Date:	13-06-2022
Application type:	Amendment
Review commission:	METC Amsterdam UMC
Approved WMO Date:	24-06-2022
Application type:	Amendment
Review commission:	METC Amsterdam UMC
Approved WMO Date:	21-07-2022
Application type:	Amendment
Review commission:	METC Amsterdam UMC
Approved WMO Date:	22-07-2022

Application type:	Amendment
Review commission:	METC Amsterdam UMC
Approved WMO Date:	24-09-2022
Application type:	Amendment
Review commission:	METC Amsterdam UMC
Approved WMO Date:	23-12-2022
Application type:	Amendment
Review commission:	MEC Academisch Medisch Centrum (Amsterdam) Kamer G4-214 Postbus 22660 1100 DD Amsterdam 020 566 7389 mecamc@amsterdamumc.nl
Approved WMO Date:	19-01-2023
Application type:	Amendment
Review commission:	MEC Academisch Medisch Centrum (Amsterdam) Kamer G4-214 Postbus 22660 1100 DD Amsterdam 020 566 7389 mecamc@amsterdamumc.nl
Approved WMO Date:	24-02-2023
Application type:	Amendment
Review commission:	MEC Academisch Medisch Centrum (Amsterdam) Kamer G4-214

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Approved WMO Date:	11-06-2023
Application type:	Amendment
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Approved WMO Date:	26-06-2023
Application type:	Amendment
Review commission:	MEC Academisch Medisch Centrum (Amsterdam)
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Approved WMO Date:	22-04-2024
Application type:	Amendment
Review commission:	MEC Academisch Medisch Centrum (Amsterdam)
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Approved WMO Date:	17-06-2024
Application type:	Amendment
Review commission:	MEC Academisch Medisch Centrum (Amsterdam) Kamer G4-214 Postbus 22660 1100 DD Amsterdam 020 566 7389 mecamc@amsterdamumc.nl

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	EUCTR2020-001048-24-NL
CCMO	NL75751.018.20