Health Technology Briefing
December 2023

Mim8 for prophylaxis of haemophilia A

Company/Developer	Novo Nordisk

☒ New Active Substance ☐ Significant Licence Extension (SLE)

NIHRIO ID: 29193	NICE ID: Not available	UKPS ID: 670274

Licensing and Market Availability Plans

Currently in phase III clinical trials

Summary

Mim8 (NNC0365-3769) is in clinical development for haemophilia A with or without inhibitors. Haemophilia is a rare condition that affects the blood's ability to clot. It is usually inherited. An inhibitor is a type of antibody that prevents factor replacement treatment from working. Normally, when you cut yourself, substances in your blood known as clotting factors mix with blood cells called platelets to make your blood sticky and form a clot. This makes the bleeding stop eventually. Haemophilia A is a bleeding disorder caused by missing or defective factor VIII (FVIII), a blood clotting protein. As a result, people with haemophilia A may suffer from spontaneous or traumatic bleeds due to the missing or defective FVIII. Despite the availability of several medicinal products to prevent bleeding in haemophilia A, there are still unmet needs such as frequent injection, inability to prevent micro-bleeds, or traumatic bleedings.

Mim8 is composed of an antibody that bridges together two other clotting factors; FIXa and FX, mimicking the role that FVIII usually plays in the body. This stimulates production of thrombin, an enzyme that helps blood to clot. Mim8 is administered subcutaneously (under the skin). If licensed, Mim8 will provide an additional prophylactic option for patients with haemophilia A with or without inhibitors.

Proposed Indication

Prophylaxis of bleeding episodes in people with haemophilia A with or without inhibitors.[1]

Technology

Description

Mim8 (NNC0365-3769) is a novel, next-generation FVIII mimetic bispecific antibody with anti-activated factor IX (FIXa) and anti-factor X (FX) arms that potently stimulates FX activation resulting in efficacious haemostasis in vitro and in vivo. Mim8 has a high potency, good pharmacokinetic parameters, minimal target binding in the blood, and good biophysical properties.[2] Mim8 is a fully human, bispecific antibody that mimics activated factor VIII (FVIIIa) function by bridging FIXa and FX on the phospholipid surface of activated platelets, enhancing the proteolytic activity of FIXa, and thus facilitating effective FX activation.[3]

Mim8 is in clinical development for the prophylactic treatment of patients with haemophilia A with or without inhibitors. In the phase III clinical trial (FRONTIER 2; NCT05053139), adults and adolescents receive Mim8 subcutaneously (SC), once-weekly, or once-monthly.[1]

Key Innovation

The needs of each person living with haemophilia are individual, complex, and changing.[4] When people are exposed to factor concentrates to replace the clotting factor (FVIII or FIX) that they are missing or have in an altered form, their immune system may see it as a foreign protein and develop neutralizing allo-antibodies called inhibitors against it. This then makes factor concentrate replacement ineffective for the treatment or prevention of bleeds.[5] The prevention and treatment of bleeds with factor VIII (FVIII) replacement products have greatly improved the quality of care for patients with haemophilia A. However, development of neutralizing antibodies, or inhibitors, against infused factor remains a challenging complication of haemophilia treatment.[6] Mim8 is in development to be used once weekly, once every two weeks or once-monthly (SC administration) by haemophilia A patients, whereas current prophylactic options are usually administered intravenously, three to four times weekly.[7,8] SC administration has proven to be effective, safe, well-tolerated, generally preferred by patients and healthcare providers and results in reduced drug delivery-related healthcare costs and resource use .[9]

If licensed, Mim8 will offer an additional prophylactic therapy option in patients with haemophilia A with or without inhibitors.

Regulatory & Development Status

Mim8 does not currently have Marketing Authorisation in the EU/UK for any indication.

Mim8 is not currently in phase II or III development for any other indications.[10]

Patient Group

Disease Area and Clinical Need

Haemophilia is usually an inherited bleeding disorder in which the blood does not clot properly. This can lead to spontaneous bleeding as well as bleeding following injuries or surgery. Blood contains many proteins called clotting factors that can help to stop bleeding. People with haemophilia have low levels of

either factor VIII (haemophilia A) or factor IX (haemophilia B).[11] Although it is passed down from parents to children, about one third of cases found have no previous family history.[12] The gene change is on the X chromosome. It can be carried by either the mother or father, or both.[13] The biggest risk factor for haemophilia is to have family members who also have the disorder. Males are much more likely to have haemophilia than females. Some people develop haemophilia with no family history of the disorder, this is called acquired haemophilia. Acquired haemophilia can be associated with pregnancy, autoimmune conditions, cancer, multiple sclerosis, and drug reactions.[14] Approximately 30% of patients with severe haemophilia A will develop inhibitors.[6] The symptoms of haemophilia can be mild to severe, depending on the level of clotting factors present. The main symptom is bleeding that does not stop. People with haemophilia may have nosebleeds that take a long time to stop, bleeding from wounds that lasts a long time, bleeding gums, skin that bruises easily, pain and stiffness around joints, such as elbows, because of internal bleeding.[15]

About 6,000 people in the UK have haemophilia. Most are males because of the way the condition is inherited.[16] In the UK, the prevalence of haemophilia A is between 1 in 5,000 and 1 in 10,000 males.[17] In England, in 2021-22, there were 2,729 finished consultant episodes (FCE) and 2,580 admissions for hereditary factor VIII deficiency (ICD-10 code D66) which resulted in 3,165 FCE bed days and 2,096 day cases.[18]

Recommended Treatment Options

There is no treatment option recommended by NICE for prophylaxis of haemophilia A with or without inhibitors. NHS England has a clinical commissioning policy for emicizumab as a further prophylactic treatment option in people with haemophilia A with inhibitors and in people with severe haemophilia A without inhibitors.[19] National Health Service (NHS) recommends preventative treatment for haemophilia A with regular injections of octocog alfa, an engineered version of clotting factor VIII. Injections every 48 hours are often recommended.[20]

Clinical Trial Information

Trial	**FRONTIER 4**; NCT05685238, EudraCT-2022-502215-10; Study of Mim8 in Participants with Haemophilia A with or without inhibitors. Open-label, Long-term Safety and Efficacy **Phase III** - Recruiting **Locations:** 16 EU countries, UK, USA, and other countries **Primary completion date:** April 2028
Trial Design	Non-randomised, parallel assignment, open label
Population	N=425 (planned); Participants with Haemophilia A with or without inhibitors aged 1 year and older
Intervention(s)	Mim8 administered SC once every week, every two weeks, or once monthly for 26 weeks in part 1 of the trial.
Comparator(s)	No comparator
Outcome(s)	Primary outcome measure: - Number of treatment emergent adverse events [Time frame: from visit 1 (week 0) until end of study (up to 283 weeks)]. Measured as count of events.

	See trial record for full list of outcomes
Results (efficacy)	-
Results (safety)	-

Trial	**FRONTIER3;** NCT05306418, EudraCT -2020-003467-26**;** Safety, Efficacy and Exposure of Subcutaneously Administered NNC0365-3769 (Mim8) Prophylaxis in Children with Haemophilia A With or Without FVIII Inhibitors **Phase III -** Recruiting **Locations:** 6 EU countries, UK, USA, Canada, and other countries **Primary completion date:** April 2025
Trial Design	Single group assignment, open label
Population	N=70 (planned); Children with Haemophilia A with or without FVIII inhibitors aged 1 to 11 years
Intervention(s)	Mim8, administered SC once-weekly or once-monthly
Comparator(s)	No comparator
Outcome(s)	Primary outcome measure: - Number of treatment emergent adverse events [Time frame: From treatment initiation to follow up visit (week 0 to week 72)]. See trial record for full list of outcomes
Results (efficacy)	-
Results (safety)	-

Trial	**FRONTIER2;** NCT05053139, EudraCT- 2020-001048-24; A Multinational, Open-label, Randomised, Controlled Study to Investigate Efficacy and Safety of NNC0365-3769 (Mim8) in Adults and Adolescents With Haemophilia A With or Without Inhibitors **Phase III -** Recruiting **Locations:** 16 EU countries, UK, USA, Canada, and other countries **Primary completion date:** May 2024
Trial Design	Randomised, parallel-assignment, open label
Population	N=267 (planned); Subjects with Haemophilia A with or without inhibitors aged 12 years and older
Intervention(s)	Mim8, administered SC once-weekly or once-monthly
Comparator(s)	No prophylaxis (on-demand treatment with their standard of care products)
Outcome(s)	Primary outcome measure:

	- Number of treated bleeds [Time frame: No prophylaxis treatment (Arms 1, 2a and 2b): From randomisation (week 0) to end of main (week 26)] - Number of treated bleeds [Time frame: Prophylaxis treatment (Arms 3 and 4): 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)] See trial record for full list of outcomes
Results (efficacy)	-
Results (safety)	-

Trial	**FRONTIER1;** NCT04204408, EudraCT-2019-000465-20; Safety, Tolerability, Pharmacokinetics and Pharmacodynamics of Single and Multiple Subcutaneous Doses of NNC0365-3769 (Mim8) in Healthy Subjects and in Subjects With Haemophilia A With or Without Factor VIII Inhibitors **Phase II -** Active, not recruiting **Locations:** 6 EU countries, UK, USA, and other countries **Primary completion date:** February 2025
Trial Design	Randomised, parallel assignment, open label for phase 2 part, placebo-controlled
Population	N=275 (actual); Male subjects with congenital haemophilia A with FVIII activity below 1% based on medical records, or considered to be generally healthy, aged 12 years and older
Intervention(s)	Mim8 administered SC once-weekly or once-monthly
Comparator(s)	Matched placebo
Outcome(s)	Primary outcome measures: - Part 1: Number of treatment emergent adverse events [Time frame: From time of dosing (Day 1) to Week 16] - Part 2: Number of treatment emergent adverse events [Time frame: From time of first dosing (Day 1) to Week 12] - Part 2, extension: Number of treatment emergent adverse events [Time frame: From Week 12 up to Week 176 (16 weeks after last dose)] See trial record for full list of outcomes
Results (efficacy)	During the 12-week observation period, 15 treated bleeds were reported in 8 patients, of which 13 bleeds (9 traumatic) were observed in 6 patients from the lowest dose cohort. The 2 bleeds in patients from cohorts 2 and 3 were traumatic, thus neither treated joint nor spontaneous bleeds were observed beyond cohort 1.[21]
Results (safety)	Mim8 was well tolerated following both single and multiple dosing, and no thromboembolic events or related serious adverse events were reported. No occurrences of anti-Mim8 antibodies were reported. The increases in AUC and Cmax with increasing dose were consistent with dose-proportionality.[21]

Estimated Cost

The cost of Mim8 is not yet known.

Relevant Guidance

NICE Guidance

- NICE technology appraisal in development. Concizumab for preventing bleeding episodes in haemophilia A or haemophilia B [ID5009] (GID-TA10972). Expected date of issue to be confirmed.
- NICE technology appraisal in development. Efanesoctocog alfa for treating and preventing bleeding episodes in haemophilia A [ID6170] (GID-TA11106). Expected date of publication: June 2024.

NHS England (Policy/Commissioning) Guidance

- NHS England. Clinical Commissioning Policy: Emicizumab as prophylaxis in people with severe congenital haemophilia A without factor VIII inhibitors (all ages). 170134P. August 2019.
- NHS England. Clinical Commissioning Policy: Emicizumab as prophylaxis in people with congenital haemophilia A with factor VIII inhibitors (all ages). 170067/P. July 2018.
- NHS England. 2013/14 NHS Standard Contract for Haemophilia (all ages). B05/S/a. 2013.

Other Guidance

- NHSGGC Paediatrics for Health Professionals. Haemophilia protocol. November 2020.[22]
- World Federation of haemophilia. WFH Guidelines for the Management of haemophilia, 3rd edition. August 2020.[23]
- A British Society for Haematology Guideline. Guidelines on the use of prophylactic factor replacement for children and adults with Haemophilia A and B. May 2020.[24]
- A United Kingdom Haemophilia Centre Doctors' Organization (UKHCDO) guideline. Recombinant factor VIII products and inhibitor development in previously untreated patients with severe haemophilia A: Combined analysis of three studies. March 2019.[25]

Additional Information

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NB: This briefing presents independent research funded by the National Institute for Health and Care Research (NIHR). The views expressed are those of the author and not necessarily those of the NHS, the NIHR or the Department of Health.