SUMMARY

Overview of the Mim8 FRONTIER clinical development program

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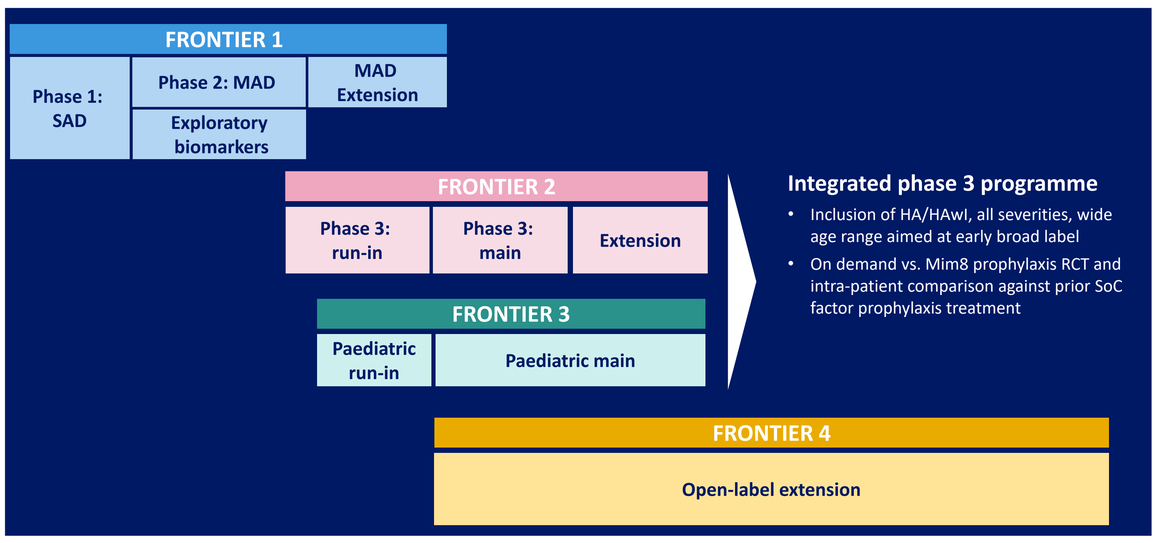
Figure 1 Mim8 clinical development program



HA, Haemophilia A; HAwI, HA with inhibitors; MAD, multiple ascending dose; RCT, randomized clinical trial; SAD, single ascending dose; SoC, standard of care.

Table 1 Key inclusion criteria and recruiting status for the FRONTIER studies

	FRONTIER 1: Phase 1/2	FRONTIER 2: Phase 3	FRONTIER 3: pediatric Phase 3
Key inclusion criteria	**SAD** • Healthy male, aged 18–45 years **MAD** • Male, aged 12–64 years, diagnosed with congenital haemophilia A with or without inhibitors with FVIII activity <1%	• Male/female with diagnosis of congenital haemophilia A with/without inhibitors aged ≥12 years • Participants prescribed treatment with FVIII, or by-passing agents during 26 weeks prior to screening • Participants without prophylactic treatment before enrolment must have ≥5 treated bleeds in the previous 26 weeks • Participants on prophylactic factor treatment with mild or moderate haemophilia must have ≥1 treated bleed in the previous 26 weeks prior to screening • Participants receiving emicizumab prophylaxis must be willing to discontinue and join run-in	• Male/female with diagnosis of congenital haemophilia A, aged between 1–11 years • For previously treated patients: • FVIII concentrate or bypassing agent must have been prescribed in the last 26 weeks, prior to screening • If endogenous FVIII activity ≥1%, patients must have ≥1 treated bleed in the last 26 weeks • For previously untreated patients: • Diagnosis of severe haemophilia A
Recruitment status	Recruitment completed, trial ongoing	Recruiting	Recruiting

FVIII, factor VIII; MAD, multiple ascending dose; SAD, single ascending dose.

Mim8 is a novel, next-generation factor VIIIa mimetic bispecific antibody in development for treatment of people with haemophilia A with or without inhibitors[1]

BACKGROUND

- Mim8 is a novel, bispecific antibody that mimics the function of activated factor VIII (FVIII)
- It is currently in clinical development as a small-volume, subcutaneously administered treatment for people with haemophilia A (PwHA) with and without inhibitors, designed as a weekly to monthly prophylactic treatment[1]
- Here, we provide an overview of the FRONTIER clinical trial program

METHODS

- FRONTIER is a comprehensive clinical trial program designed to expedite development of a new therapeutic option for PwHA. The program evaluates the use of Mim8 in PwHA regardless of severity or presence of inhibitors (**Figure 1; Table 1**)
- All participants from FRONTIER 1–3 will be invited to continue in a long-term, open-label extension study (FRONTIER 4) to collect further safety and efficacy data

STUDY DESIGN

FRONTIER 1

- FRONTIER 1 (EudraCT:2019-000465-20; NCT04204408) is a two-part, global phase 1/2 dose escalation study with a primary objective of investigating Mim8 safety and tolerability in both healthy subjects and PwHA with/without inhibitors
- 101 participants were enrolled, and this study will be used for dose-setting in subsequent FRONTIER clinical studies
- The study start date was January 10, 2020, and the estimated end date is Q2 2023

Part 1: phase 1 single ascending dose (SAD; placebo-controlled double-blind within cohorts)

- 48 healthy volunteers were subcutaneously injected with a single dose of Mim8 or placebo in escalating dose cohorts and observed over 16 weeks

Part 2: phase 2 multiple ascending dose (MAD; open-label)

- 43 participants with severe HA/HAwI received either weekly or monthly doses of subcutaneous Mim8 in escalating dose cohorts. Participants of cohorts 3 and 4 were randomized to weekly or monthly dosing, targeting the same Mim8 average plasma exposure

Exploratory biomarker

- An additional cohort of 10 PwHA, with or without inhibitors, on emicizumab prophylaxis aged ≥12 years were included for exploratory assessment of laboratory biomarkers

Table 2 Primary, secondary endpoints for FRONTIER 1

	Part 1 (SAD)	Part 2 (MAD)
Primary endpoints	• Number of treatment emergent adverse events	
Secondary endpoints	• Number of injection site reactions • Relative change in: D-dimer, prothrombin fragments, fibrinogen, platelets	
	• Change in activated partial thromboplastin time • After a single dose: C_{max}, T_{max}, AUC_{0-inf}, $t_{1/2}$	• Occurrence of anti-Mim8 antibodies • Mean of maximum thrombin generation (weekly/monthly) • After multiple doses: C_{max}, T_{max}, AUC_T

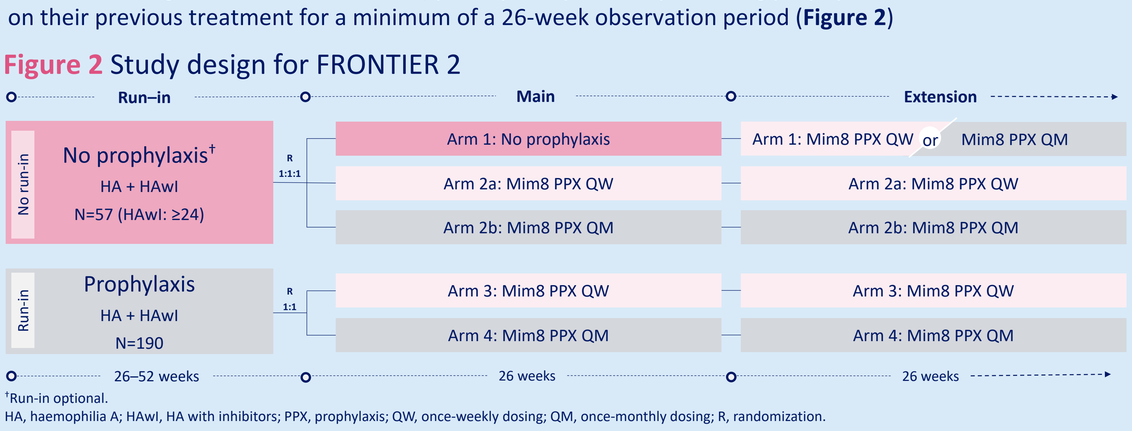
AUC_{0-inf}, area under the Mim8 concentration-time curve between time 0 to infinity; AUC_T, area under the Mim8 concentration-time curve in the dosing interval; C_{max}, maximum concentration to maximum concentration of Mim8; MAD, multiple ascending dose; SAD, single ascending dose; $t_{1/2}$, the terminal half-life of Mim8; T_{max}, maximum time to maximum concentration of Mim8.

STUDY DESIGN

FRONTIER 2

- FRONTIER 2 (EudraCT:2020-001048-24; NCT05053139) is a global phase 3 study in PwHA, with/without inhibitors, with the primary objective of demonstrating the haemostatic effect of Mim8 dosed once weekly or once monthly as bleeding prophylaxis
- This study will investigate Mim8 in comparison to haemophilia A factor treatments
- The study start date was December 2, 2021, and is estimated to end in 2025
- ~250 PwHA will be recruited and receive subcutaneous injections of Mim8 once a week or once a month. Participants will have 13–17 clinic visits
- Before receiving their first dose of Mim8, participants previously receiving prophylactic treatment will remain on their previous treatment for a minimum of a 26-week observation period (**Figure 2**)

Figure 2 Study design for FRONTIER 2



†Run-in optional.
HA, haemophilia A; HAwI, HA with inhibitors; PPX, prophylaxis; QW, once-weekly dosing; QM, once-monthly dosing; R, randomization.

Primary endpoints

- Number of treated bleeds

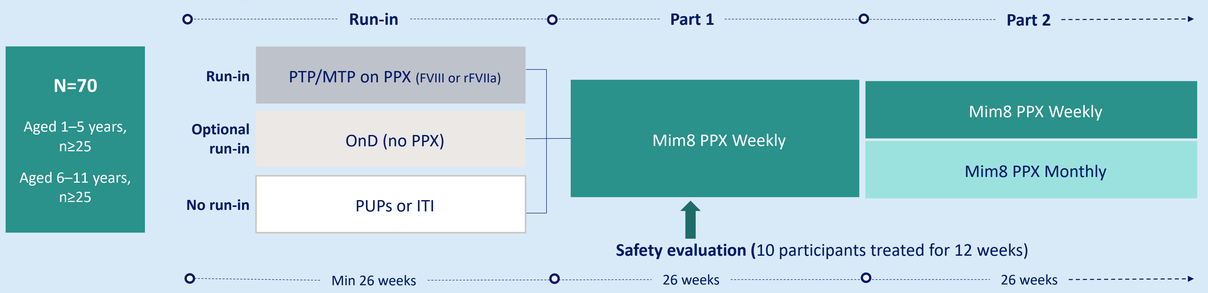
Other key assessments

- Number of injection site reactions
- Occurrence of anti-Mim8 antibodies
- Mim8 plasma concentration
- Patient-reported outcomes: joint pain, physical functioning, treatment burden

FRONTIER 3

- FRONTIER 3 (EudraCT:2020-003467-26; NCT05306418) is a global phase 3 study with the primary objective of investigating the safety of Mim8 in young PwHA (aged 1–11 years) with/without inhibitors (**Figure 3**). The study aims to recruit 70 children
- Depending on their current treatment, participants may join an observational period of ≥26 weeks documenting their current prophylactic treatment, before starting on weekly Mim8 for 26 weeks. After that participants can choose between monthly and weekly dosing regimen for a further 26 weeks (**Figure 3**)
- Study start date was April 4, 2022, and the estimated end date is 2025

Figure 3 Study design for FRONTIER 3



FVIIa, factor VIIa; FVIII, factor VIII; ITI, immune tolerance induction; MTP, minimally treated patient; OnD, on-demand; PPX, prophylaxis; PTP, previously treated patients; PUP, previously untreated patients

Primary endpoints

- Number of treatment emergent adverse events

Other key assessments

- Number of treated bleeds
- Number of injection site reactions
- Occurrence of anti-Mim8 antibodies
- Mim8 plasma concentration
- Patient-reported outcomes: physical functioning, treatment burden

CONCLUSIONS

- The FRONTIER program encompasses three clinical studies and an open-label extension study and aims to investigate Mim8 across a broad patient population. The rapid clinical development of Mim8 could soon provide a novel alternative to current haemophilia A treatments.

REFERENCES

1. Østergaard et al. *Blood.* 2021;138:1258–1268

ACKNOWLEDGEMENTS & DISCLOSURES

All authors are employees of Novo Nordisk A/S, Bagsværd, Denmark
Medical writing and editorial support was provided by Haniya Javaid, William Stainsby, MSci, and Michelle Seddon, all of Paragon (Knutsford, UK), and was funded by Novo Nordisk