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ORIGINAL ARTICLE

Mim8, a novel factor VIIIa mimetic bispecific antibody, shows favorable safety and pharmacokinetics in healthy adults

Paula Persson[1] | Anne-Beth Amstrup[1] | Hans Veit Coester[2] | Irina Matytsina[1] | Selcuk Bas[3]

[1]Novo Nordisk A/S, Søborg, Denmark

[2]Profil Institut für Stoffwechselforschung GmbH, Neuss, Germany

[3]Charité Research Organization, Campus Charité Mitte, Berlin, Germany

Correspondence
Paula Persson, Novo Nordisk A/S, Vandtårnsvej 114, DK-2860 Søborg, Denmark.
Email: papn@novonordisk.com

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Abstract

Background: Mim8 (denecimig) is a novel activated coagulation factor VIII-mimetic bispecific antibody that assembles with activated coagulation FIX and FX on the platelet membrane surface.

Objectives: The FRONTIER1 (NCT04204408, NN7769-4513) single ascending dose and the 4882 pharmacokinetic (PK) studies (NCT05127473, NN7769-4882) examined the safety, tolerability, PK, and pharmacodynamics (PD) of Mim8 in healthy adult males.

Methods: The FRONTIER1 single ascending dose study consisted of 6 cohorts, each with 6 participants who received a single subcutaneous (s.c.) dose of Mim8 and 2 participants who received a placebo. The 4882 PK study had 11 arms, each with 6 participants who received a single s.c. dose of Mim8. The primary endpoint for both studies was treatment-emergent adverse events. Other safety assessments included relative changes in D-dimer, prothrombin fragments 1 and 2, fibrinogen, and platelets. The PK and PD were assessed using Mim8 plasma concentration and activated partial thromboplastin clotting time and thrombin generation, respectively.

Results: Mim8 was well tolerated, and there were no severe treatment-emergent adverse events. The PK properties of Mim8 in both studies were consistent with dose-proportionality. The terminal half-life of Mim8 after a single dose was approximately 1 month, and maximum plasma concentration was reached after 10 days.

Conclusion: The PK and PD profiles suggest that Mim8 is suitable as a long-acting FVIIIa-mimetic bispecific antibody for hemophilia A prophylaxis.

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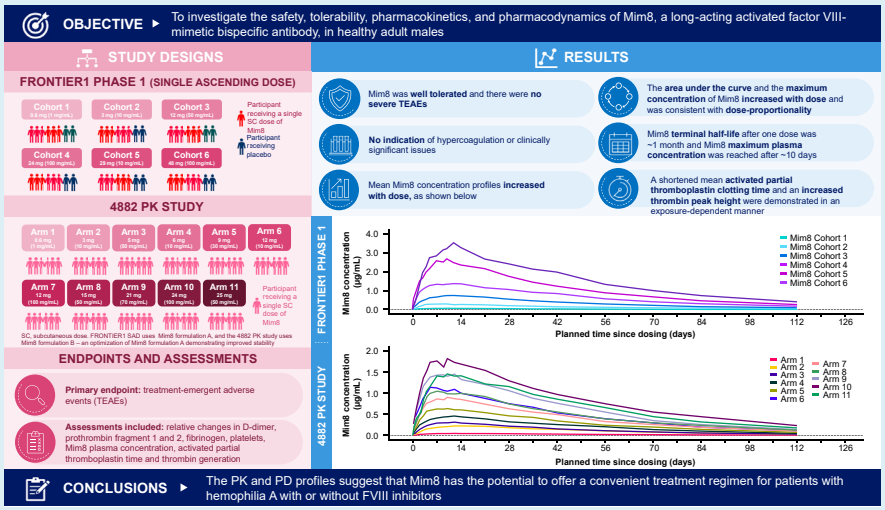

KEYWORDS
factor VIII, hemophilia A, pharmacokinetics, safety, thrombin

Essentials

- Mim8 is a novel drug under development for patients with hemophilia A.
- We report the safety, tolerability, pharmacokinetics, and pharmacodynamics of Mim8.
- Mim8 was well tolerated, and there were no severe adverse effects from treatment.
- Pharmacokinetic and pharmacodynamic profiles suggest Mim8 is suitable as a long-acting drug for hemophilia A prophylaxis.

1 | INTRODUCTION

Hemophilia A is a recessive X-linked congenital bleeding disorder caused by mutations in the *F8* gene encoding coagulation factor VIII (FVIII) on the long arm of the X chromosome [1]. Patients with hemophilia A have a reduced production of FVIII, or they produce defective FVIII molecules [1,2]. Patients with hemophilia A require lifelong FVIII replacement to control or prevent bleeding, often involving multiple, frequent injections of intravenous plasma-derived or recombinant FVIII products. The burden of 3-4 weekly infusions may lead to variable adherence and poorer outcomes [3]. Some patients also develop FVIII inhibitors, which makes FVIII replacement therapy less effective [4]. Consequently, suboptimal hemophilia A management leads to a myriad of complications, such as recurrent joint bleeding, hemophilic arthropathy, and reduced quality of life [5].

Activated coagulation FVIII (FVIIIa) mimetics were developed to reduce the burden of frequent injections, provide an alternative route to intravenous administration (subcutaneous [s.c.]), and overcome the current shortfalls in managing patients with hemophilia A with or without FVIII inhibitors [6,7]. Emicizumab (Genentech, Inc) is the first marketed s.c. FVIIIa-mimetic bispecific antibody (biAb) used as prophylaxis in patients with hemophilia A [8].

Mim8 (denecimig) is a novel FVIIIa-mimetic biAb with an improved potency that binds to activated coagulation FIX (FIXa) and FX, thereby enhancing the catalytic activity of FIXa for the conversion of FX on the surface of activated platelets [6,9]. Mim8 mainly differs from emicizumab due to its monovalent anti-FIXa arm, which better stimulates FIXa's proteolytic activity to activate FX [6]. In hemophilia A mice, Mim8 normalized thrombin generation (TG) and clot formation at potencies up to 18 times higher than an emicizumab sequence-identical analog [9]. Similar findings were reported in hemophilia A plasma and whole blood, which suggests Mim8 could evoke the desired hemostatic response at lower concentrations than other hemophilia A prophylactic agents.

Previous studies in cynomolgus monkeys showed that s.c. administration of up to 3 mg/kg/week of Mim8 (several fold greater than expected clinical exposure) for 26 weeks resulted in relevant pharmacodynamic (PD) effects, which were observed in TG and activated partial thromboplastin clotting time (aPTT) with no signs of thrombi or excessive coagulation activation [6]. Based on nonclinical findings, Mim8 is anticipated to provide convenient and effective prophylaxis in patients with hemophilia A with or without FVIII inhibitors.

Here, we report the safety, tolerability, pharmacokinetics (PK), and PD of Mim8 from 2 phase 1 clinical studies, NN7769-4513/NCT04204408 (FRONTIER1, single ascending dose [SAD]) and NN7769-4882/NCT05127473 (4882 PK study), conducted in healthy adult males. FRONTIER1 SAD was the first human dose (FHD) study with Mim8. In both studies, the participants received a single s.c. dose of Mim8. FRONTIER1 also includes a phase 2 (multiple ascending

doses) element in participants with hemophilia A; however, here, we focused on the SAD part of the study.

2 | METHODS

2.1 | Participants

Healthy male participants were recruited to the FRONTIER1 SAD (NN7769-4513, NCT04204408) and 4882 PK study (NN7769-4882, NCT05127473) using the following criteria: a body mass index (BMI) of 18.5 to 29.9 kg/m^2 (both inclusive); body weight from 60.0 to 100.0 kg (both inclusive); and being considered healthy based on medical history, physical examination, vital signs, clinical laboratory tests, and electrocardiogram results during the screening visit as judged by the investigator [10,11]. The minimum age to participate in both studies was 18 years; however, the maximum ages were 45 and 55 years for the FRONTIER1 SAD and 4882 PK study, respectively. FRONTIER1 SAD followed the recommended participant age span for FHD studies of 18 to 45 years. For the 4882 PK study, which started after FRONTIER1 SAD, a higher upper age limit of 55 years was implemented to facilitate recruitment. Participants with a FVIII activity ≥150% during their screening visit, high risk of thrombosis determined by known history of personal or a first-degree relative with unprovoked deep venous thrombosis, an established diagnosis or clinical signs of arterial or venous thromboembolic disease, and aberrant coagulation markers were excluded [10,11]. Females were excluded from both studies for safety reasons, as nonclinical reproductive toxicology studies have not yet been conducted. All participants provided written informed consent before taking part in both studies, and the studies were conducted after approval from the corresponding authority and ethics committees. Neither of the study was preregistered, and research plans were not shared publicly before the studies were conducted.

2.2 | Study design

FRONTIER1 SAD was a single-center, placebo-controlled, double-blind, randomized, FHD, dose-escalation study conducted from January 2020 to January 2022. The 4882 PK study was a bi-center, parallel-group, double-blind, randomized study conducted from November 2021 to May 2022. In the FRONTIER1 SAD and 4882 PK studies, study products were packed open-label and delivered directly to unblinded pharmacy staff, who were responsible for assembling participant doses. All participants were assigned a unique number in ascending or descending order, and randomization was handled by qualified blinded site staff using a blinded randomization list. Investigators remained blinded to each participant's assigned product throughout the study. Both studies investigated the safety, tolerability, PK, and PD of a single s.c. abdominal injection of Mim8, which was produced from a Chinese hamster ovary cell line using recombinant DNA technology. However, 2 Mim8 drug product strengths (10 and 100 mg/mL) at different concentrations and 2 different formulations were used. The participants in FRONTIER1 SAD received Mim8 formulation A, while those in the 4882 PK study received Mim8 formulation B. Mim8 formulation B is an optimization of Mim8 formulation A to improve stability and will be used for future clinical development.

Table 1 shows the dose concentration of Mim8 administered in each FRONTIER1 SAD cohort. All participants were screened for up to 28 days before receiving a single fixed s.c. dose of Mim8 at 6 dose levels: 0.6 mg (cohort 1), 3 mg (cohort 2), 12 mg (cohort 3), 24 mg (cohort 4), 29 mg (cohort 5), and 48 mg (cohort 6). The decision to ascend to the next dose level was taken by a trial safety group based on interim safety, PK, and PD data. Each cohort included 8 participants: 6 were randomized to receive a single s.c. dose of Mim8, and 2 were randomized to receive a placebo. Sentinel dosing was applied in each cohort whereby 1 participant on Mim8 and 1 on placebo were dosed simultaneously before others in the cohort were dosed. All participants were monitored in-house at the site until 10 days after dosing, followed by an observation period over 16 weeks. In the 4882 PK study, participants received a single fixed s.c. dose of Mim8 at 0.6 mg (arm 1), 3 mg (arm 2), 5 mg (arm 3), 6 mg (arm 4), 9 mg (arm 5), 12 mg (arm 6), 12 mg (arm 7), 15 mg (arm 8), 21 mg (arm 9), 24 mg (arm 10), and 25 mg (arm 11). Dose concentrations for each arm are listed in Table 2. For participants in arms 6 and 7, who received the same fixed dose, the administered dose concentrations were 10 mg/mL and 100 mg/mL, respectively. Each of the 11 arms included 6 participants who were all randomized to receive a single s.c. dose of Mim8. All participants were monitored in-house at the site until 3 days after dosing, followed by an observation period over 16 weeks. In FRONTIER1 SAD and the 4882 PK study, Mim8 was administered subcutaneously in the abdomen using a 30G (13 mm) needle and a 29G (8 mm) needle, respectively.

2.3 | Outcome measures

All the outcomes and safety measures were monitored from baseline (before dosing) to 112 days after dosing. The primary endpoint for the FRONTIER1 SAD and 4882 PK study was the number of treatment-emergent adverse events (TEAEs), which were monitored and classified as serious or nonserious and as mild, moderate, or severe by the investigator.

2.4 | Safety

Both studies monitored the number of injection site reactions, relative changes in D-dimer, prothrombin fragments 1 and 2, fibrinogen, and platelets as safety assessments [10,11].

2.5 | Pharmacokinetics

In both studies, the PK analysis was based on Mim8 plasma concentration, and all PK endpoints were derived using noncompartmental

TABLE 1 Participant demographics for the FRONTIER1 single ascending dose study.

		Cohort 1	Cohort 2	Cohort 3	Cohort 4	Cohort 5	Cohort 6	All active	Placebo	Total
Dose, mg		**0.6**	**3**	**12**	**24**	**29**	**48**			
Dose concentration, mg/mL		**1**	**10**	**50**	**100**	**10**	**100**			
No. of participants		6	6	6	6	6	6	36	12	48
Age at baseline (y)	Mean (min; max)	32.7 (22; 44)	30.7 (24; 35)	35.3 (25; 41)	28.8 (19; 40)	32.5 (22; 42)	28.0 (23; 38)	31.3 (19; 44)	27.5 (19; 39)	30.4 (19; 44)
Race	Asian	0	0	1	0	0	0	1	0	1
	White	6	6	5	6	5	6	34	12	46
	Other	0	0	0	0	1	0	1	0	1
Weight at baseline (kg)	Mean (min; max)	81.3 (71.6; 94.1)	83.5 (68.5; 98.0)	75.6 (67.0; 94.0)	87.6 (71.5; 97.7)	80.7 (70.0; 92.9)	76.7 (63.7; 97.8)	80.9 (63.7; 98.0)	81.2 (68.7; 92.0)	81.0 (63.7; 98.0)
BMI at baseline (kg/m^2)	Mean (min; max)	24.1 (21.6; 26.6)	25.2 (21.6; 28.0)	24.5 (22.4; 30.0)	26.4 (21.1; 30.2)	24.9 (19.2; 28.4)	24.0 (19.9; 29.2)	24.8 (19.2; 30.2)	25.3 (21.0; 28.8)	24.9 (19.2; 30.2)

BMI, body mass index.

TABLE 2 Participant demographics for the 4882 pharmacokinetic study.

		Arm 1	Arm 2	Arm 3	Arm 4	Arm 5	Arm 6	Arm 7	Arm 8	Arm 9	Arm 10	Arm 11	Total
Dose, mg		**0.6**	**3.0**	**5.0**	**6.0**	**9.0**	**12.0**	**12.0**	**15.0**	**21.0**	**24.0**	**25.0**	
Dose concentration, mg/mL		**1**	**10**	**50**	**10**	**30**	**10**	**100**	**50**	**70**	**100**	**50**	
No. of participants		6	6	6	6	6	6	6	6	6	6	6	66
Age at baseline (y)	Mean (min; max)	38.0 (20; 52)	36.3 (25; 42)	39.3 (25; 54)	37.7 (22; 47)	36.0 (25; 48)	37.2 (20; 55)	34.8 (25; 53)	35.0 (24; 42)	32.7 (25; 49)	38.8 (26; 53)	37.5 (24; 54)	36.7 (20; 55)
Race (%)	Asian	0	0	0	0	0	0	1 (16.7)	0	0	0	0	1 (1.5)
	Black or African-American	0	0	0	0	0	0	1 (16.7)	0	0	0	0	1 (1.5)
	White	6 (100)	6 (100)	6 (100)	6 (100)	6 (100)	6 (100)	4 (66.7)	6 (100)	6 (100)	6 (100)	6 (100)	64 (97.0)
Weight at baseline (kg)	Mean (min; max)	78.6 (66; 89)	83.1 (75; 93)	83.5 (69; 96)	83.4 (66; 94)	82.8 (65; 99)	75.7 (63; 92)	78.4 (67; 91)	80.3 (66; 93)	78.4 (62; 96)	78.1 (65; 93)	84.3 (68; 94)	80.6 (62; 99)
BMI at baseline in kg/m^2	Mean (min; max)	24.0 (21.0; 26.0)	25.3 (22.0; 29.0)	25.4 (22.0; 30.0)	25.3 (22.0; 27.0)	25.2 (22.0; 30.0)	23.3 (19.0; 28.0)	23.1 (22.0; 25.0)	24.3 (20.0; 27.0)	24.4 (21.0; 28.0)	25.6 (23.0; 29.0)	26.3 (22.0; 29.0)	24.8 (19.0; 30.0)

BMI, body mass index.

methods. The actual sampling time with respect to time since dosing was used for the derivations. Mim8 plasma concentrations were measured using a validated Meso Scale Discovery electrochemiluminescence immunoassay (Meso Scale Diagnostics).

2.6 | Pharmacodynamics

The PD of Mim8 was investigated using aPTT and TG. The aPTT was analyzed by a validated 1-stage clotting assay using Siemens Pathromtin SL and BCS XP System (Siemens Healthcare Diagnostics Products GmbH). Samples were analyzed for TG after neutralization of endogenous FVIII by the addition of anti-sheep anti-FVIII polyclonal antibodies. In addition, in FRONTIER1 SAD, predose FVIII-neutralized plasma samples were spiked in parallel with increasing amounts of Mim8 and emicizumab. The TG test used FIXa as a reaction trigger and phospholipids to amplify the effect. The triggering reagent was prepared by the laboratory spiking MP-reagent with 50 mU/mL human FXIa, and the final assay concentration of FXIa was 8 U/L. The concentration of phospholipids was 4 μM. The peak height of TG in plasma was measured by the calibrated automated thrombogram method using the Thrombinoscope System (Thrombinoscope BV) consisting of the Thermo Fisher Scientific Fluoroskan Ascent fluorescence photometer and the Thrombinoscope software. The baseline/predose thrombin peak height values (360-468 nM) from FRONTIER1 SAD were used as the normal range and reference control values.

2.7 | Statistical analysis

Descriptive analyses were used to present the demographic data in the FRONTIER1 SAD and 4882 PK studies. The maximum concentration of Mim8 (C_{max}), the area under the Mim8 concentration-time curve from time 0 to infinity ($AUC_{0\text{-}inf}$), the time to maximum concentration of Mim8 (t_{max}), and the terminal half-life of Mim8 ($t_{1/2}$) were assessed using R (The R Foundation) and SAS (SAS Institute Inc) [10,11]. A linear trapezoidal method was used to calculate $AUC_{0\text{-}inf}$. FRONTIER1 SAD analyzed dose-linearity using analysis of covariance with log(PK parameter) as a response, log(dose) as a covariate, and drug product strength as a factor. The PK 4882 study used analysis of covariance with log(PK parameter) as a response and log(dose/bodyweight) and log(dose concentration) as covariates at a 95% CI. In both studies, C_{max} and $AUC_{0\text{-}inf}$ were used as the PK response parameters. The distribution of outcomes was assessed using SD.

2.8 | Data sharing statement

Novo Nordisk's policy on data sharing may be found at https://www.novonordisk-trials.com/for-researchers/how-to-access-clinical-trial-datasets.html

3 | RESULTS

3.1 | Baseline characteristics

A total of 48 and 66 healthy adult males were enrolled and randomized in the FRONTIER1 SAD and 4882 PK studies, respectively. In FRONTIER1 SAD, participant ages ranged from 19 to 44 years, while those in the 4882 PK study were from 20 to 55 years. The mean BMI also varied, ranging from 24.0 to 26.4 in FRONTIER1 SAD and 23.1 to 26.3 in the 4882 PK study. Participants in both studies were predominantly white males: FRONTIER1 SAD (n = 46) and the 4882 PK study (n = 64). The participant demographics, including age, race, weight, and BMI, are summarized in Table 1 (FRONTIER1 SAD) and Table 2 (4882 PK study).

One participant withdrew from cohort 1 (0.6 mg), cohort 2 (3 mg), and cohort 6 (48 mg) in FRONTIER1 SAD due to occupation reasons, unwillingness to participate due to personal reasons, and 1 participant was lost to follow-up, respectively. In the 4882 PK study, 1 participant withdrew from arm 1, 58 days after dosing based on a physician's decision due to noncompliance issues, and the participant attended the end-of-study visit 116 days after dosing.

3.2 | Safety

From baseline to 112 days after dosing, Mim8 was well tolerated in both studies. In FRONTIER1 SAD, 55 TEAEs were reported by 24 of 36 (67%) participants who received Mim8 compared with 24 TEAEs in 11 of 12 (92%) participants who received a placebo across all 6 cohorts. Most TEAEs (21 events [27%]) were classified under the system organ class of gastrointestinal disorders. Other events included infections and infestations (20 events [25%]), and nervous system disorders (14 events [18%]). All events were mild or moderate in severity and resolved before the end of the study. There were no trends in the frequency, type, or severity of TEAEs across all cohorts (Table 3).

In the 4882 PK study, 98 TEAEs occurring in 44 of 66 (67%) participants were reported from baseline to 112 days after dosing. In this study, most events were disorders of the nervous, respiratory, musculoskeletal, and connective tissue systems and infections and infestations. The most reported TEAEs included COVID-19 infection (16 participants [31.0%]) and headache (12 participants [24.2%]). All TEAEs were of mild or moderate severity, and there were no trends in their frequency, type, or severity across all dose groups (Table 4). One participant in arm 6 (12 mg) reported a meniscus injury that was deemed unlikely related to Mim8.

The FRONTIER1 SAD and 4882 PK studies each reported one mild injection site reaction (hematoma) with a diameter of 5 mm and 20 mm, respectively. No severe TEAEs indicating thromboembolic events were reported or led to withdrawal from either study. Furthermore, there were no anti-Mim8 antibodies detected nor any serious adverse reactions that were deemed related to the investigational medicinal product in either study.

TABLE 3 Treatment-emergent adverse events for the FRONTIER1 single ascending dose study.

Dose, mg		Cohort 1 0.6 mg	Cohort 2 3 mg	Cohort 3 12 mg	Cohort 4 24 mg	Cohort 5 29 mg	Cohort 6 48 mg	All active	Placebo
Dose concentration, mg/mL		**1**	**10**	**50**	**100**	**10**	**100**		
		***N* (%)** **E [R]**	***N* (%)** **E [R]**	***N* (%)** **E [R]**	***N* (%)** **E [R]**	***N* (%)** **E [R]**	***N* (%)** **E [R]**	***N* (%)** **E [R]**	***N* (%)** **E [R]**
No. of participants		6	6	6	6	6	6	36	12
All adverse events		3 (50.0) 8 [4.86]	5 (83.3) 9 [5.44]	3 (50.0) 7 [3.79]	5 (83.3) 11 [5.93]	3 (50.0) 6 [3.20]	5 (83.3) 14 [8.01]	24 (66.7) 55 [5.18]	11 (91.7) 24 [6.47]
Serious adverse events		0	0	0	0	0	0	0	0
Adverse events by severity	Mild	3 (50.0) 8 [4.86]	3 (50.0) 3 [1.81]	2 (33.3) 5 [2.71]	5 (83.3) 8 [4.31]	3 (50.0) 5 [2.67]	4 (66.7) 10 [5.72]	20 (55.6) 39 [3.67]	11 (91.7) 17 [4.59]
	Moderate	0	2 (33.3) 6 [3.63]	2 (33.3) 2 [1.08]	2 (33.3) 3 [1.62]	1 (16.7) 1 [0.53]	3 (50.0) 4 [2.29]	10 (27.8) 16 [1.51]	3 (25.0) 7 [1.89]
	Severe	0	0	0	0	0	0	0	0
Related[a]		1 (16.7) 1 [0.61]	0	1 (16.7) 1 [0.54]	0	3 (50.0) 3 [1.60]	2 (33.3) 5 [2.86]	7 (19.4) 10 [0.94]	2(16.7) 3 [0.81]
Injection site reactions[b]		0	1 (2.8) 1 [0.09]	0	0	0	0	1 (2.1) 1 [0.07]	0

%, Percentage of participants with treatment-emergent adverse events; E, No. of treatment-emergent adverse events; *N*, number of participants with a treatment-emergent adverse event; R, number of treatment-emergent adverse events per participant year of exposure (E/total time in study).

[a]Possibly related to the investigational medicinal product as assessed by the investigator.

[b]Hematoma discovered on the sixth day after dosing and resolved on the ninth day after dosing, considered unrelated to the investigational medicinal product.

TABLE 4 Treatment-emergent adverse events for the 4882 pharmacokinetic study.

		Arm 1	Arm 2	Arm 3	Arm 4	Arm 5	Arm 6	Arm 7	Arm 8	Arm 9	Arm 10	Arm 11
Dose, mg/mL		**0.6**	**3.0**	**5.0**	**6.0**	**9.0**	**12.0**	**12.0**	**15.0**	**21.0**	**24.0**	**25.0**
Dose concentration, mg/mL		**1**	**10**	**50**	**10**	**30**	**10**	**100**	**50**	**70**	**100**	**50**
		***N* (%)** **E [R]**	***N* (%)** **E [R]**	***N* (%)** **E [R]**	***N* (%)** **E [R]**	***N* (%)** **E [R]**	***N* (%)** **E [R]**	***N* (%)** **E [R]**	***N* (%)** **E [R]**	***N* (%)** **E [R]**	***N* (%)** **E [R]**	***N* (%)** **E [R]**
All adverse events		4 (66.7) 6 [3.39]	2 (33.3) 2 [1.06]	5 (83.3) 13 [7.03]	5 (83.3) 12 [6.40]	6 (100.0) 18 [9.70]	5 (83.3) 7 [3.72]	5 (83.3) 12 [6.50]	3 (50.0) 9 [4.87]	2 (33.3) 3 [1.65]	2 (33.3) 5 [2.66]	5 (83.3) 11 [5.99]
Serious adverse events		0	0	0	0	0	1 (16.7) 1 [0.53]	0	0	0	0	0
Adverse events by severity	Mild	2 (33.3) 3 [1.69]	2 (33.3) 2 [1.06]	5 (83.3) 8 [4.33]	5 (83.3) 10 [5.33]	6 (100.0) 12 [6.46]	5 (83.3) 6 [3.19]	5 (83.3) 9 [4.88]	2 (33.3) 8 [4.33]	2 (33.3) 3 [1.65]	1 (16.7) 3 [1.59]	5 (83.3) 10 [5.44]
	Moderate	3 (50.0) 3 [1.69]	0	3 (50.0) 5 [2.71]	1 (16.7) 2 [1.07]	3 (50.0) 6 [3.23]	1 (16.7) 1 [0.53]	2 (33.3) 3 [1.63]	1 (16.7) 1 [0.54]	0	2 (33.3) 2 [1.06]	1 (16.7) 1 [0.54]
	Severe	0	0	0	0	0	0	0	0	0	0	0
Adverse event by relationship	Probably or possibly related	1 (16.7) 2 [1.13]	1 (16.7) 1 [0.53]	1 (16.7) 3 [1.62]	3 (50.0) 5 [2.67]	3 (50.0) 4 [2.15]	2 (33.3) 2 [1.06]	4 (66.7) 7 [3.79]	1 (16.7) 4 [2.16]	1 (16.7) 2 [1.10]	1 (16.7) 1 [0.53]	2 (33.3) 2 [1.09]
	Unlikely related	4 (66.7) 4 [2.26]	1 (16.7) 1 [0.53]	5 (83.3) 10 [5.41]	4 (66.7) 7 [3.73]	6 (100.0) 14 [7.54]	4 (66.7) 5 [2.65]	4 (66.7) 5 [2.71]	3 (50.0) 5 [2.71]	1 (16.7) 1 [0.55]	1 (16.7) 4 [2.13]	4 (66.7) 9 [4.90]

%, Percentage of participants with treatment-emergent adverse events; E, number of treatment-emergent adverse events; *N*, number of participants with a treatment-emergent adverse event; R, number of treatment-emergent adverse events per participant year of exposure (E/total time in study).

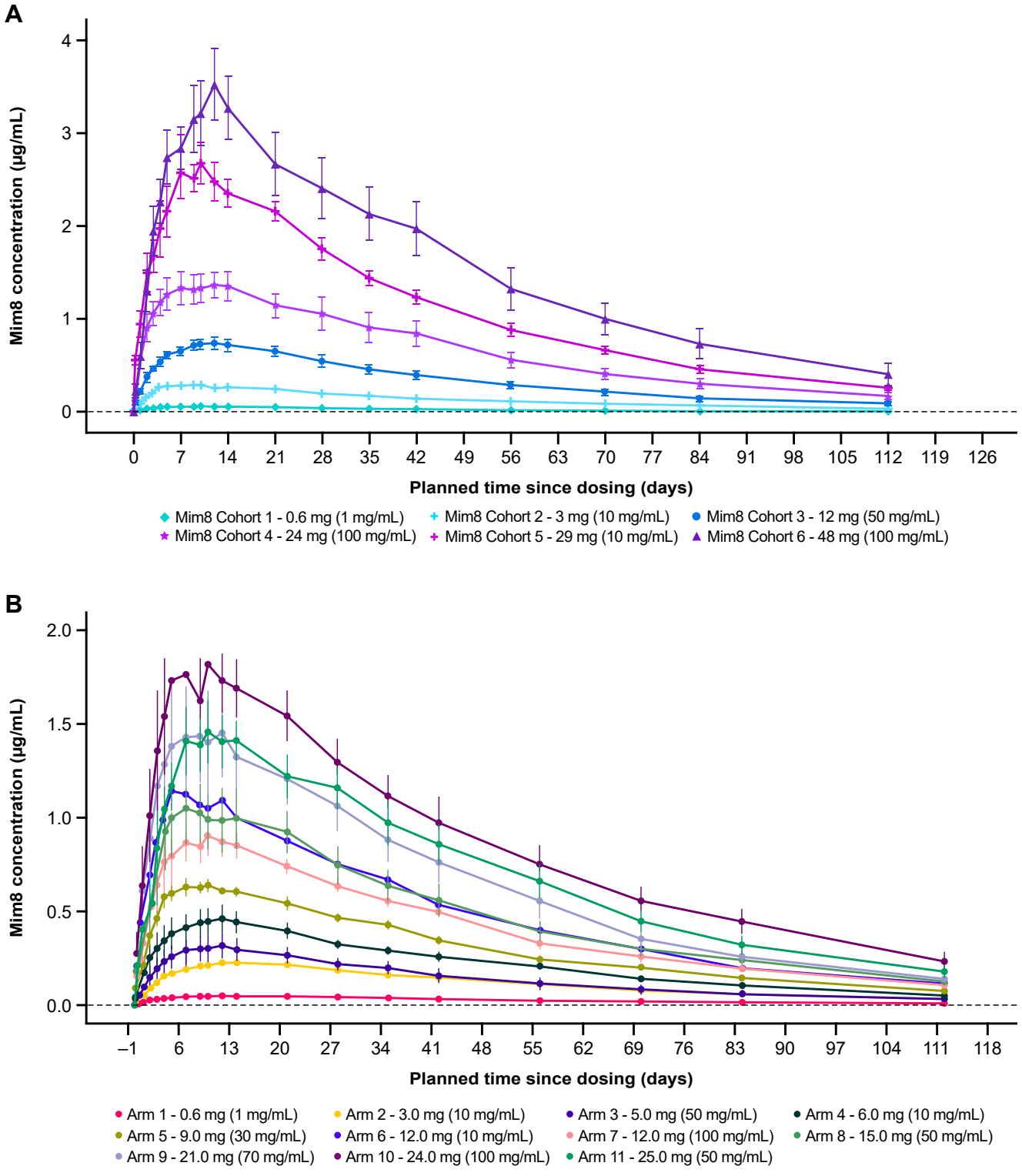

FIGURE Mean profiles of Mim8 plasma concentration (linear scale) - full analysis set. (A) FRONTIER1 SAD. (B) 4882 pharmacokinetic study. Mean ± standard error of the mean. Dotted horizontal line is a reference for lower limit of quantification.

Participants in the FRONTIER1 SAD (Supplementary Figure S1A) and 4882 PK studies (Supplementary Figure S1B) showed no clinically significant changes in D-dimer after Mim8 dosing. Five participants in the 4882 PK study had consistently high D-dimer levels pre- and postdosing with Mim8, but this was not associated with a similar increase in prothrombin fragments 1 and 2. In both the FRONTIER1 SAD (Supplementary Figure S2A) and 4882 PK studies (Supplementary Figure S2B), there was no clear association between administered Mim8 dose and prothrombin fragments 1 and 2. One participant in FRONTIER1 SAD (cohort 6; 48 mg) had abnormal solitary high prothrombin fragment 1 and 2 values that returned to normal ranges within the observation period.

TABLE 5 Pharmacokinetic parameters for the FRONTIER1 single ascending dose study.

		Cohort 1	Cohort 2	Cohort 3	Cohort 4	Cohort 5	Cohort 6	All active
Dose, mg		**0.6**	**3**	**12**	**24**	**29**	**48**	
Dose concentration, mg/mL		**1**	**10**	**50**	**100**	**10**	**100**	
No. of participants		6	6	6	6	6	6	36
C_{max} (μg/mL)	Geometric mean (CV%)	0.06 (21)	0.31 (21)	0.76 (19)	1.40 (24)	2.76 (19)	3.47 (23)	0.80 (242)
	Min; max	0.05; 0.08	0.26; 0.43	0.59; 0.97	1.10; 2.04	2.16; 3.33	2.80; 4.71	0.05; 4.71
$AUC_{0\text{-}inf}$ (ug*d/mL)	Geometric mean (CV%)	3.0 (14)	17.2 (27)	40.7 (28)	77.9 (33)	134.0 (15)	185.5 (35)	42.28 (245)
	Min; max	2.5; 3.7	13.0; 22.9	29.0; 60.1	54.1; 123.9	98.4; 144.9	137.6; 269.7	2.5; 269.7
$t_{1/2}$ (d)	Geometric mean (CV%)	26.8 (12)	32.8 (10)	30.6 (14)	31.8 (14)	30.2 (9)	30.8 (20)	30.5 (14)
	Min; max	23.6; 30.4	29.9; 37.8	26.7; 38.7	25.4; 39.2	26.6; 34.5	25.0; 40.3	23.6; 40.3
t_{max} (d)	Median	10.00	7.00	11.99	8.50	8.99	12.03	10.00
	Min; max	7.0; 14.0	5.0; 14.0	10.0; 14.0	4.0; 14.0	7.0; 10.0	9.9; 13.9	4.0; 14.0

$AUC_{0\text{-}inf}$, area under the Mim8 concentration-time curve from time 0 to infinity; C_{max}, maximum concentration of Mim8; CV%, coefficient of variation in %, $t_{1/2}$, terminal half-life of Mim8; t_{max}, time to maximum concentration of Mim8.

3.3 | Pharmacokinetics

The PK properties of Mim8 in both studies were consistent with dose-proportionality. Mean Mim8 concentration profiles increased with dose, as illustrated in Figure A, B. The $t_{1/2}$ was within the range of 25.9-35.1 days, and the t_{max} was approximately 10 days (7.5-13.8 days).

The $AUC_{0\text{-}inf}$ (Supplementary Figure S3) and C_{max} (Supplementary Figure S4) increased with increasing Mim8 dose, which was consistent with dose-proportionality within each dose concentration. The relative bioavailability decreased linearly as dose concentration increased. A summary of the PK parameters in both studies can be found in Table 5 (FRONTIER1 SAD) and Table 6 (4882 PK study).

3.4 | Pharmacodynamics

Both studies demonstrated a shortened mean aPTT in an exposure-dependent manner, and values returned toward baseline level during the observation period (Supplementary Figure S5A, B). Thrombin peak height increased in a dose-dependent manner (Supplementary Figure S6A, B). In predose FVIII-neutralized plasma samples spiked with Mim8 or emicizumab, Mim8 achieved similar peak thrombin and a slightly higher maximum effect with 15-fold lower plasma concentrations compared with emicizumab, and the *in vitro* profile for Mim8 was in agreement with *ex vivo* data (Supplementary Figure S6C).

4 | DISCUSSION

The FRONTIER1 SAD and 4882 PK studies evaluated the safety, tolerability, PK, and PD of Mim8 formulations A and B, respectively, in healthy adult males. The 4882 PK study, which used formulation B, showed comparable safety, tolerability, PK, and PD profiles with formulation A. The results in both studies demonstrated that a single s.c. dose of Mim8 0.6-48 mg (FRONTIER1 SAD) and 0.6-25 mg (4882 PK study) was well tolerated, and no safety concerns were reported in either study. The PK and PD profiles support nonclinical findings, demonstrating Mim8 as a long-acting FVIIIa-mimetic biAb for hemophilia A prophylaxis.

Nonclinical findings reporting safe Mim8 use at doses several folds greater than expected therapeutic levels were supported in the FRONTIER1 SAD and 4882 PK study [6]. In these 2 studies, all TEAEs were of mild or moderate severity and did not lead to withdrawal from either study. There were no trends based on the type, rate, or severity across all treatment groups, suggesting no relationship between the administered dose and the adverse events. Most TEAEs were resolved before the end of the studies. The findings did not show any safety concerns in adult males within the tested dose ranges.

Despite the procoagulant effects of Mim8 observed in nonclinical studies at high and multiple doses, both the FRONTIER1 SAD and 4882 PK studies did not report any cases of excessive coagulation. Coagulation-related laboratory parameters were monitored up to 112 days after dosing, and there were no clinically significant changes. The observations were consistent with previous nonclinical findings with Mim8 suggesting no safety concerns with excessive coagulation at even higher doses than those in both studies [6,9].

The $t_{1/2}$ of Mim8 was approximately 1 month, which potentially offers patients a convenient treatment option with reduced injection burden. In this way, Mim8 may allow patients with hemophilia A to receive bleeding prophylaxis either weekly, biweekly, or once monthly.

In the FRONTIER1 SAD and 4882 PK studies, the maximum plasma concentration of Mim8 was reached after approximately 10 days. This is comparable with emicizumab, with a t_{max} ranging from 7 to 14.1 days [12]. Mim8 plasma concentrations increased in a dose-proportional manner, suggesting that plasma concentrations can be accurately predicted using doses administered in a range of Mim8

TABLE 6 Pharmacokinetic parameters for the 4882 pharmacokinetic study.

		Arm 1	Arm 2	Arm 3	Arm 4	Arm 5	Arm 6	Arm 7	Arm 8	Arm 9	Arm 10	Arm 11	Total
Dose, mg		**0.6**	**3.0**	**5.0**	**6.0**	**9.0**	**12.0**	**12.0**	**15.0**	**21.0**	**24.0**	**25.0**	
Dose concentration, mg/mL		**1**	**10**	**50**	**10**	**30**	**10**	**100**	**50**	**70**	**100**	**50**	
No. of participants		6	6	6	6	6	6	6	6	6	6	6	66
C_{max} (μg/mL)	Geometric mean (CV%)	0.05 (23)	0.24 (9)	0.30 (48)	0.45 (34)	0.68 (11)	1.25 (13)	0.95 (29)	1.09 (36)	1.49 (46)	1.98 (30)	1.48 (24)	0.63 (74)
	Min; max	0.03; 0.06	0.21; 0.26	0.16; 0.56	0.34; 0.76	0.58; 0.77	1.03; 1.38	0.66; 1.34	0.56; 1.65	1.01; 3.05	1.29; 3.05	1.13; 2.15	0.03; 3.05
$AUC_{0\text{-}inf}$ (day*ug/mL)	Geometric mean (CV%)	3.22 (23)	14.33 (20)	14.94 (50)	26.19 (23)	37.33 (10)	60.20 (7)	51.17 (13)	56.20 (38)	72.89 (37)	105.08 (29)	84.52 (26)	35.49 (70)
	Min; max	2.68; 4.37	10.78; 18.66	5.66; 28.69	20.61; 37.42	31.13; 40.82	56.01; 65.64	41.5; 60.52	29.52; 93.03	48.57; 115.52	74.94; 163.40	59.33; 123.23	2.68; 163.4
$t_{1/2,}$ (d)	Geometric mean (CV%)	35.07(25)	32.72 (25)	25.90 (35)	31.59 (13)	31.78 (5)	31.15 (10)	31.74 (28)	31.17 (16)	27.23 (19)	33.57 (15)	31.02 (13)	31.02 (20)
	Min; max	25.13; 48.36	25.66; 47.38	10.52[a]; 37.46	27.77; 39.84	29.82; 34.32	27.00; 37.11	22.8; 44.24	25.19; 39.55	22.55; 35.72	23.90; 39.20	23.68; 35.32	10.52; 48.36
t_{max} (d)	Median	12.61	12.51	10.99	11.95	9.47	7.98	12.00	11.53	8.10	8.12	12.11	10.05
	Min; max	9.09; 20.11	9.10; 21.18	7.11; 21.12	5.06; 14.09	4.08; 21.10	5.02; 12.01	4.95; 20.92	4.96; 21.11	5.05; 13.14	4.98; 14.09	6.97; 21.05	4.08; 21.18

$AUC_{0\text{-}inf}$ and $t_{1/2}$ were not calculated for the subject in arm 1 who withdrew since only 2 observations in the tail were observed.

$AUC_{0\text{-}inf}$, area under the Mim8 concentration-time curve from time 0 to infinity; C_{max}, maximum concentration of Mim8; CV%, coefficient of variation in %; LLOQ, lower limit of quantification. NA, not applicable; $t_{1/2}$, terminal half-life of Mim8; t_{max}, time to the maximum concentration of Mim8.

[a]A participant had pharmacokinetic values below the LLOQ at visits 16, 17, 18, and 19, which affected the minimum half-life. No antidrug antibodies were detected, and the participant had no abnormal laboratory safety or coagulation parameter values nor any concomitant medication registered.

concentrations. The relative bioavailability of Mim8 decreased linearly as dose concentration increased. Similar observations were reported in other monoclonal antibody studies [13].

Thrombin peak height reflected the hemostatic potential of Mim8. In the FRONTIER1 SAD and 4882 PK study, thrombin peak height was increased in a dose-dependent manner and returned toward baseline levels at the end of both studies, confirming the procoagulant effect of Mim8.

Unlike FVIII, Mim8 does not require an activation step; hence, the hemostatic effect of Mim8 was expected to be overestimated in the aPTT assay. Within the tested doses, Mim8 shortened aPTT without causing any laboratory changes indicating hypercoagulation or clinically significant issues in the participants. Hence, the shortened aPTT was not deemed as an abnormality or indication of an elevated risk of thromboembolic events and other related TEAEs.

5 | CONCLUSION

Both studies demonstrated that a single s.c. dose of Mim8 from 0.6 to 48 mg was well tolerated, and the $t_{1/2}$ of Mim8 was approximately 30 days, which supports weekly to monthly dosing. Generally, the safety laboratory findings from FRONTIER1 SAD and the 4882 PK study are comparable to those reported in emicizumab phase 1 studies. In predose FVIII-neutralized plasma samples spiked with Mim8 or emicizumab, a 15-fold lower concentration of Mim8 showed similar peak thrombin levels compared with emicizumab, and the *in vitro* profile for Mim8 was in agreement with *ex vivo* data. Mim8 formulations A and B were similar with regard to safety, tolerability, PK, and PD. In conclusion, both studies suggest that Mim8 has the potential to offer a more convenient treatment regimen than FVIII replacement for patients with hemophilia A with or without FVIII inhibitors.

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AUTHOR CONTRIBUTIONS

All authors substantially contributed to the study conception and design, acquisition of data, drafting of the article or revising it critically for important intellectual content, gave final approval of the version to be published, and agreed to be accountable for all aspects of the work.

RELATIONSHIP DISCLOSURE

P.P., I.M., and A.B.A. are employees of Novo Nordisk. All other authors did not have competing interests to disclose.

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SUPPLEMENTARY MATERIAL

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