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ORIGINAL ARTICLE

FRONTIER1: a partially randomized phase 2 study assessing the safety, pharmacokinetics, and pharmacodynamics of Mim8, a factor VIIIa mimetic

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Abstract

Background: Mim8 (denecimig) is a factor VIII (FVIII) mimetic bispecific antibody in development for the treatment of hemophilia. Data from the phase 1 part of FRONTIER1 (EudraCT: 2019-000465-20, NCT04204408, and NN7769-4513) suggested that Mim8 was well tolerated in healthy participants and exhibited pharmacokinetic (PK) properties consistent with dose proportionality.

Objectives: The partially randomized, phase 2, multiple ascending dose (MAD) part of FRONTIER1 aimed to evaluate the safety, PK, pharmacodynamics (PD), and exploratory efficacy of Mim8 in participants with hemophilia A with or without FVIII inhibitors.

Methods: The MAD part of FRONTIER1 consisted of 42 participants, assigned to 5 cohorts, with participants in cohorts 3 and 4 randomized 1:1 to dosing weekly or every 4 weeks, respectively. Four of the 42 participants (9.5%) had FVIII inhibitors prior to study enrolment. The primary endpoint was treatment-emergent adverse events (TEAEs). PK and PD were evaluated by Mim8 plasma concentration and thrombin generation, respectively. Exploratory efficacy was assessed via the number of treated bleeds. Safety and PD parameters were also evaluated from an exploratory cohort treated with emicizumab.

Results: Mim8 was well tolerated, with 1 serious TEAE (anxiety-related chest pain) deemed unrelated to Mim8. There was no dose dependency on the number, causality, type, or severity of TEAEs. PK/PD properties supported weekly to monthly dosing approaches, and few participants experienced treated bleeds beyond the lowest dose cohort (1 in cohorts 2 and 3, and 3 in cohort 5).

Conclusion: These data support the continued clinical development of Mim8, and FRONTIER1 has proceeded onto an extension phase.

KEYWORDS
clinical trial, factor VIII, hemophilia A, pharmacokinetics, safety

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1 | INTRODUCTION

Hemophilia A (HA) is an X-linked congenital bleeding disorder. Patients with severe or moderate phenotypes of the disease require regular prophylactic factor VIII (FVIII) replacement or nonfactor therapy such as emicizumab to prevent recurrent spontaneous bleeds, with the latter proving effective in patients with HA with and without FVIII inhibitors [1–3]. Nonfactor therapies have become increasingly popular, with the potential to increase adherence and improve outcomes of patients by simplifying treatment regimens with less invasive and reduced frequency dosing. Additionally, nonfactor therapies enable treatment of patients with inhibitors and do not elicit inhibitor development [4].

Mim8 (denecimig) is a fully human bispecific IgG4 antibody that mimics the function of activated FVIII (FVIIIa) by bridging activated factor IX (FIXa) and factor X (FX), enhancing the proteolytic activity of FIXa and enabling effective activation of FX [5]. The modes of action of Mim8 and emicizumab are similar, but there are differences in their respective anti-FIXa and anti-FX arms that affect their FVIIIa-like function [6]. An *in vitro* study using HA-like blood demonstrated that a 13-fold lower concentration of Mim8 showed similar peak thrombin levels in comparison with a sequence identical analog of emicizumab. This conclusion was supported by more effective amelioration of bleeds observed *in vivo* in a mouse model [5]. Mim8 also has been shown to reduce bleeding in cynomolgus monkey HA animal models [7], and a 26-week safety assessment in cynomolgus monkeys reported no adverse events at doses of up to 3 mg/kg/wk (equivalent to an exposure of 106 μg/mL and several-fold greater than the expected range of clinical exposure) [8].

FRONTIER1 is a phase 1/2 study that investigated the safety, tolerability, pharmacokinetics (PK), and pharmacodynamics (PD) of single ascending doses of Mim8 in healthy participants and multiple ascending doses of Mim8 in patients with HA with or without FVIII inhibitors.

Data from the phase 1, single ascending dose part of the study supported further clinical development of Mim8. The study suggested that Mim8 was well tolerated, with no thrombotic events, anti-Mim8 antibodies, or treatment-related serious adverse events reported. Furthermore, increases in area under the curve from time 0 to infinity ($AUC_{0\text{-}inf}$) and the maximum concentration of Mim8 in plasma (C_{max}) were consistent with dose proportionality [9].

Here, we report data from the phase 2 multiple ascending dose (MAD) part of FRONTIER1. In addition, we also report PD and laboratory safety data gathered from an exploratory cohort consisting of patients with HA treated with commercially available emicizumab.

2 | METHODS

2.1 | Study conduct

The MAD part of FRONTIER1 (EudraCT: 2019-000465-20, NCT04204408, and NN7769-4513) is an ongoing, multinational, partially randomized, open-label study in participants with severe HA with or without FVIII inhibitors. The study was initiated on January 10, 2020, with an estimated study completion date of February 24, 2025.

The study was conducted in accordance with the Declaration of Helsinki; the International Conference on Harmonization Good Clinical Practice Guideline; and the US Food and Drug Administration 21 Code of Federal Regulations Parts 50, 56, and 312. The study was approved according to local regulations by appropriate health authorities and by an independent ethics committee/institutional review board, and written informed consent was taken before any study-related procedure.

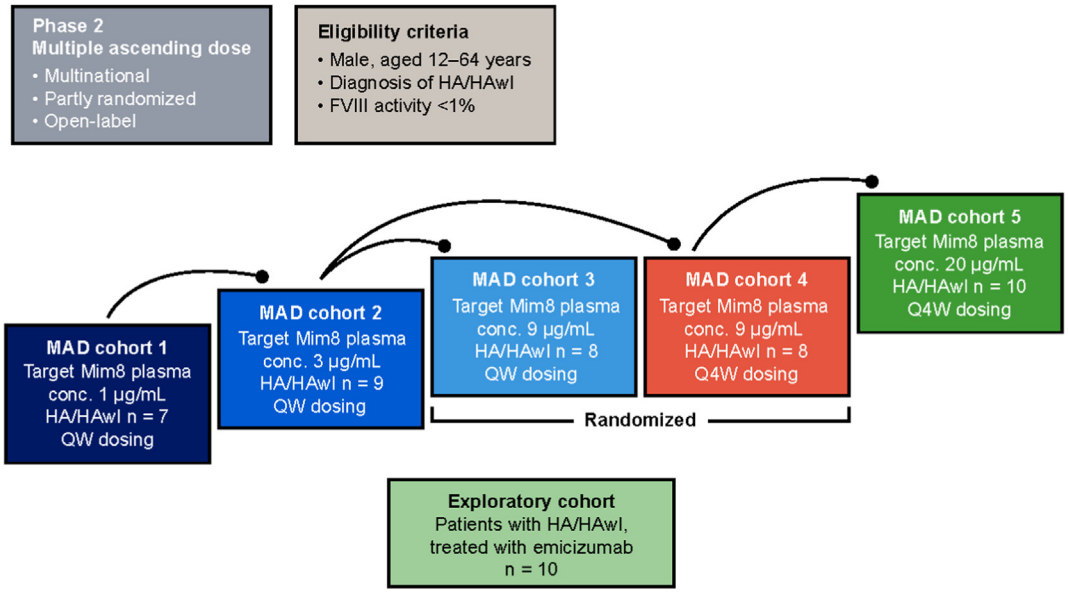

FIGURE 1 Study design. conc, concentration; FVIII, factor VIII; HA, hemophilia A; HAwI, HA with FVIII inhibitors; MAD, multiple ascending dose; QW, once weekly; Q4W, once every 4 weeks.

TABLE 1 Demographics and baseline characteristics.

Characteristic	Cohort 1	Cohort 2	Cohort 3	Cohort 4	Cohort 5	Total
Number of participants, *n*	8	9	8	8	10	43
Enrolled, *n* (%)	8 (100)	9 (100)	8 (100)	8 (100)	10 (100)	43 (100)
Full and safety analysis set, *n* (%)	7 (87.5)	9 (100)	8 (100)	8 (100)	10 (100)	42 (97.7)
Exposed to IMP, *n* (%)	7 (87.5)	9 (100)	8 (100)	8 (100)	10 (100)	42 (97.7)
Inhibitor status, *n* (%)						
Negative	6 (85.7)	8 (88.9)	7 (87.5)	7 (87.5)	10 (100)	38 (90.5)
Positive	1 (14.3)	1 (11.1)	1 (12.5)	1 (12.5)		4 (9.5)
Weight band, *n* (%)						
30-59.9 kg	1 (14.3)	1 (11.1)	1 (12.5)		3 (30.0)	6 (14.3)
≥60 kg	6 (85.7)	8 (88.9)	7 (87.5)	8 (100.0)	7 (70.0)	36 (85.7)
Weight, kg (SD)	76.3 (15.6)	77.6 (12.8)	68.9 (11.4)	78.1 (9.8)	75.1 (15.2)	75.2 (13.0)
Age, years (SD)	30.3 (10.1)	35.8 (17.0)	32.8 (11.4)	32.3 (15.3)	36.7 (13.2)	33.8 (13.3)

IMP, investigational medicinal product; *n*, number of participants.

2.2 | Study design

The MAD part of FRONTIER1 planned enrolment of 40 participants into 5 ascending dose cohorts. Four cohorts (MAD cohorts 1, 2, 3, and 5) received once weekly (QW) doses of Mim8, and 1 cohort (MAD cohort 4) received treatment every 4 weeks (Q4W). Mim8 was administered subcutaneously and was dosed according to the weight range (see below). Participants in cohorts 1, 2, 3, and 5 received a loading dose on days 1 and 8, followed by 10 weekly maintenance doses from day 15 onward. In MAD cohort 4, participants received a loading dose on day 1 only, followed by maintenance doses every 4 weeks. The loading doses were determined via modeling studies.

Participants were dosed according to their weight range (<60 kg/≥60 kg) and received Mim8 loading doses of 2.7 mg/4.9 mg (cohort 1),

TABLE 2 Treatment-emergent adverse events.

	Cohort 1			Cohort 2			Cohort 3			Cohort 4			Cohort 5			Total		
Safety profile overview	***N***	**(%)**	***E***	***N***	**(%)**	***E***	***N***	**(%)**	***E***	***N***	**(%)**	***E***	***N***	**(%)**	***E***	***N***	**(%)**	***E***
Number of participants	7			9			8			8			10			42		
Exposure time (years)	1.48			2.02			1.84			1.79			2.31			9.45		
Adverse events	1	(14.3)	1	7	(77.8)	12	5	(62.5)	10	5	(62.5)	8	5	(50.0)	10	23	(54.8)	41
Serious adverse events							1	(12.5)	1							1	(2.4)	1
Adverse events related to IMP																		
Probable/possible				4	(44.4)	6	1	(12.5)	1	1	(12.5)	1	3	(30.0)	4	9	(21.4)	12
Unlikely	1	(14.3)	1	6	(66.7)	6	4	(50.0)	9	4	(50.0)	7	4	(40.0)	6	19	(45.2)	29
Severity																		
Severe				1	(11.1)	1										1	(2.4)	1
Moderate				1	(11.1)	1	1	(12.5)	1				1	(10.0)	2	3	(7.1)	4
Mild	1	(14.3)	1	7	(77.8)	10	5	(62.5)	9	5	(62.5)	8	4	(40.0)	8	22	(52.4)	36
Outcome																		
Not recovered				1	(11.1)	1				1	(12.5)	1	1	(10.0)	1	3	(7.1)	3
Recovering				1	(11.1)	1							1	(10.0)	1	2	(4.8)	2
Recovered	1	(14.3)	1	7	(77.8)	10	5	(62.5)	10	4	(50.0)	7	5	(50.0)	8	22	(52.4)	36

E, events; IMP, investigational medicinal product; *N*, number of participants.

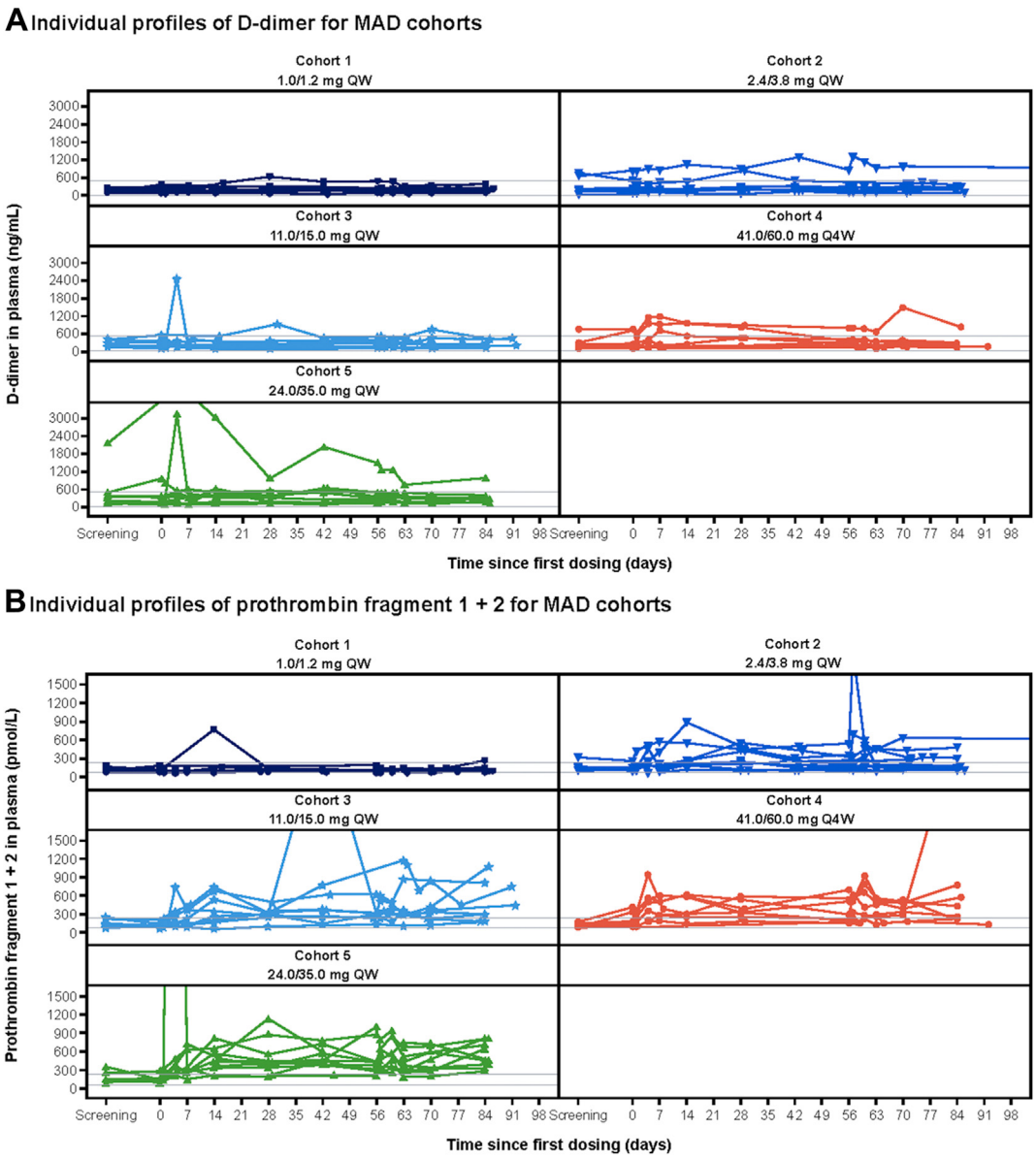

FIGURE 2 Mean profiles of D-dimer and prothrombin fragment for MAD cohorts. (A) Individual profiles of D-dimer for MAD cohorts. Grey horizontal lines indicate reference ranges. D-dimer levels outside the displayed range in cohort 5 were 3628 ng/mL, 4622 ng/mL, 4373 ng/mL, and 3793 ng/mL at days 0, 1, 4, and 7, respectively. MAD, multiple ascending dose; Q4W, once every 4 weeks; QW, once weekly. (B) Individual profiles of prothrombin fragment 1 + 2 for MAD cohorts. Grey horizontal lines indicate reference ranges. The prothrombin fragment 1 + 2 level outside the displayed range in cohort 2 was 1991 pmol/L at day 57. This participant discontinued treatment and had follow-up 119 days after last dose. The prothrombin fragment 1 + 2 level outside the displayed range in cohort 3 was 3410 pmol/L at day 42. The prothrombin fragment 1 + 2 level outside the displayed range in cohort 4 was 3346 pmol/L at day 84. The prothrombin fragment 1 + 2 level outside the displayed range in cohort 5 was 24000 pmol/L at day 4. MAD, multiple ascending dose; QW, once weekly; Q4W, once every 4 weeks.

15 mg/31 mg (cohort 2), 38 mg/65 mg (cohort 3), 90 mg/160 mg (cohort 4), or 83 mg/150 mg (cohort 5) and Mim8 maintenance doses of 1 mg QW/1.2 mg QW (cohort 1), 2.4 mg QW/3.8 mg QW (cohort 2), 11 mg QW/15 mg QW (cohort 3), 41 mg Q4W/60 mg Q4W (cohort 4), or 24 mg QW/35 mg QW (cohort 5). Enrolment into cohorts 3 and 4 was randomized 1:1, with dosing targeting the same plasma concentration of Mim8 with different dosing intervals. A summary of the study design can be seen in Figure 1. Sentinel dosing was applied at all dose levels, with 1 participant dosed in advance to ensure that unexpected adverse events were not experienced by all the participants of a particular cohort. Additionally, the administration of prophylactic FVIII products or bypassing agents was prohibited from 48 hours before the start of treatment with Mim8. Data cut-off occurred when all participants had completed the main part of the study (January 03, 2022).

In the exploratory cohort, blood samples to generate data on laboratory biomarkers were collected from male participants with severe HA, with or without FVIII inhibitors, who were prescribed

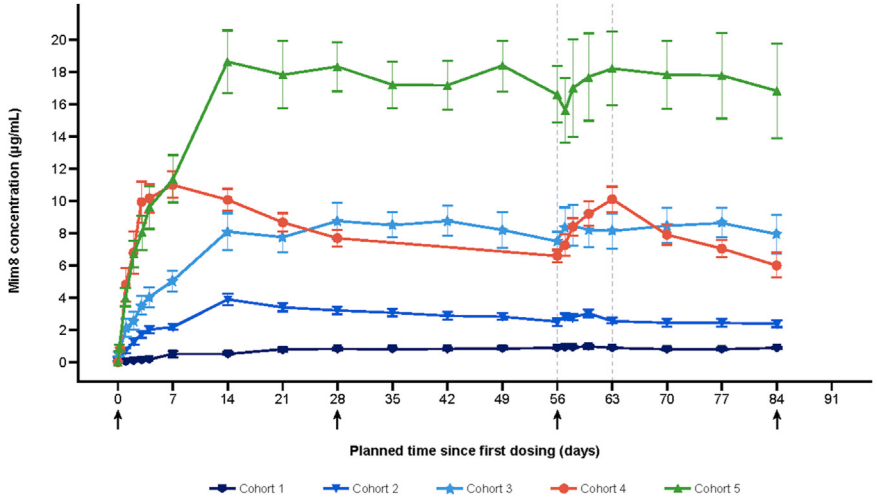

FIGURE 3 Mean profiles of Mim8 concentration. Mean ± SEM. Cohorts 1, 2, 3, and 5 were dosed weekly, while cohort 4 was dosed every 4 weeks. Dosing days for cohort 4 are indicated by an arrow on the respective days. Mim8 concentrations displayed are trough values, except those that are part of PK profiling. Vertical dashed lines indicate the steady-state PK session days 57 to 64 weekly cohorts, or days 57 to 84 for cohort 4. PK, pharmacokinetic; SEM, standard error of the mean.

emicizumab. All dosing frequencies within the emicizumab label were acceptable. The goal was to screen ~10 participants and have 6 participants complete the study in the exploratory cohort. Data cut-off for this cohort also occurred when all participants had completed the study (December 03, 2021).

2.3 | Participant eligibility

All participants in this study were required to be of the male sex, aged 12-64 years (both inclusive), with a body weight of ≥30 kg, and to have congenital HA with FVIII activity of <1%. Participants treated on-demand had to have experienced at least 5 bleeds in the 24 weeks before screening. Participants in the exploratory cohort were required to either undergo or be planning to undergo prescribed treatment with emicizumab.

The following exclusion criteria were defined for all cohorts: known congenital or acquired coagulation disorders other than HA, increased risk of thrombosis (as evaluated by the investigator), any clinical signs or established diagnosis of venous or arterial thromboembolic disease (except previous catheter-associated thrombosis, for which antithrombotic treatment is not currently ongoing), advanced atherosclerotic disease, any autoimmune disease that may increase the risk of thrombosis, and any ongoing or planned immune tolerance induction therapy. In addition to the general exclusion criteria, candidates for the MAD cohorts were deemed ineligible in the event of receiving emicizumab (or any drug product with a similar mode of action) within 5 half-lives before investigational medicinal product (IMP) administration.

2.4 | Study endpoints

The primary endpoint of this study was the number of treatment-emergent adverse events (TEAEs), from the time of dosing to week 12.

2.4.1 | Safety

Secondary safety endpoints included the number of injection site reactions, the occurrence of anti-Mim8 antibodies, and the change in safety biomarkers such as D-dimer and prothrombin fragment 1 + 2 levels from baseline (day 1) to week 12. In addition, the changes in factor IX (FIX) and FX antigen levels were assessed as exploratory endpoints.

2.4.2 | Pharmacokinetics

The PK analysis of Mim8 in this study measured the C_{max} and the area under the curve, from time 0 to the end of the dosing interval ($AUC_{0\text{-}tau}$), using blood samples obtained from day 57 to day 64 for cohorts 1

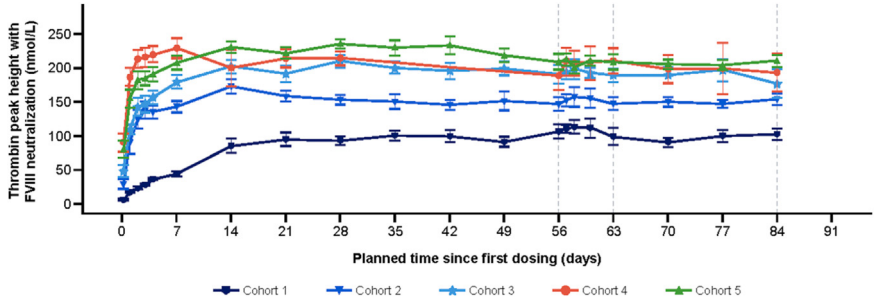

FIGURE 4 Mean profiles of thrombin peak height with FVIII neutralization. Mean ± SEM. Day 1 predose data are not included in the plot due to limited amount of data. Vertical lines indicate PK session 2. The range of peak thrombin height obtained with healthy plasma using the same assay was 360 to 468 nmol/L. FVIII, factor VIII; PK, pharmacokinetic.

to 3 and 5, and from day 57 to day 85 for cohort 4. In addition, the average concentration (C_{avg}) of Mim8 at steady state was derived from the PK profile for all cohorts.

2.4.3 | Pharmacodynamics

Thrombin peak height was measured via an activated factor XI (FXIa)–triggered thrombin generation assay in plasma, both with and without the addition of anti-FVIII antibodies (FVIII neutralization). Anti-FVIII antibodies were added to plasma samples to standardize the assays by neutralizing any possible residual FVIII activity resulting from treatment of breakthrough bleeds.

2.4.4 | Exploratory efficacy

This study documented the number of treated bleeding episodes during the first 12 weeks of treatment.

2.4.5 | Exploratory cohort

Parameters investigated as part of the exploratory safety analysis of the emicizumab cohort included levels of D-dimer, prothrombin fragment 1 + 2, FIX, and FX antigen. In addition to these exploratory safety endpoints, the mean of peak thrombin generation from baseline to week 12 was calculated as an exploratory PD endpoint.

2.5 | Assay methodology

Safety biomarker levels were assessed via standard assays. Anti-Mim8 antibodies were measured using a validated bridging electrochemiluminescence immunoassay with an assay sensitivity of 37 ng/mL antibody. Prior to analysis, the antibody samples were precipitated using polyethylene glycol and the immune complexes were dissociated with acid to overcome drug interference before transfer to a mesoscale plate. Sulfotag labeled Mim8 was then added to the plate, with the aim of specifically detecting anti-Mim8 antibodies. All samples were analyzed in a tiered approach, with a separate screening step and a confirmation step. The assay cut points were calculated based on the variation in signal of 50 healthy donors tested 6 times and a false positive rate of 5% for the screening assay, and 1% for the confirmatory assay. Samples with a result equal to or above the cut point were re-examined to confirm that antibodies were specific to Mim8 and samples below the cut point were reported as antibody-negative.

The FXIa–triggered thrombin generation assay was performed according to the calibrated automated thrombin generation method [10] using platelet-poor plasma triggered with 8 mU/mL FXIa supplemented with 4-μM phospholipid vesicles (MP reagent; Diagnostica Stago).

2.6 | Statistical analysis

An ANCOVA model was used to evaluate dose linearity for C_{max} for the QW-dosing MAD cohorts. The model used log-transformed parameters, with the log-transformed dose divided by the baseline body weight as a covariate. This was repeated using the log-transformed dose as a covariate. For $AUC_{0\text{-}tau}$, the same analyses were repeated for QW and Q4W dosing MAD cohorts.

2.7 | 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#.

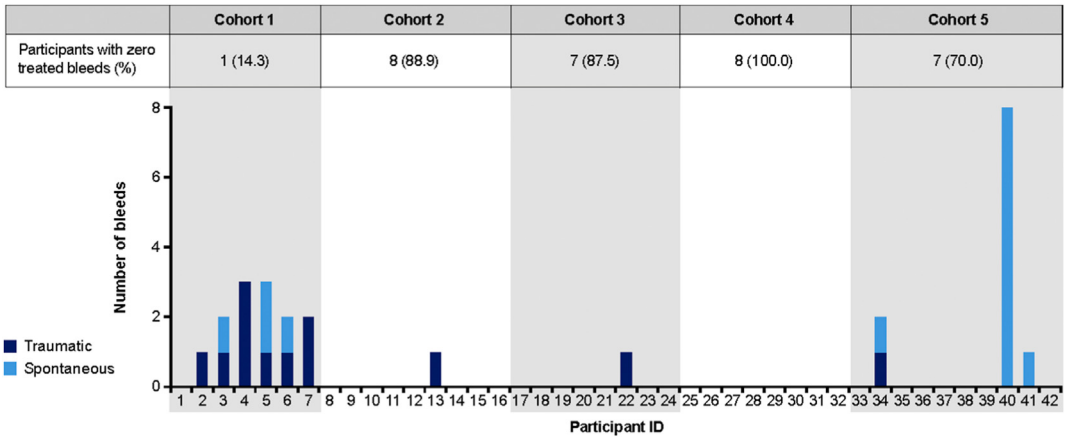

FIGURE 5 Treated bleeds. ID, identification.

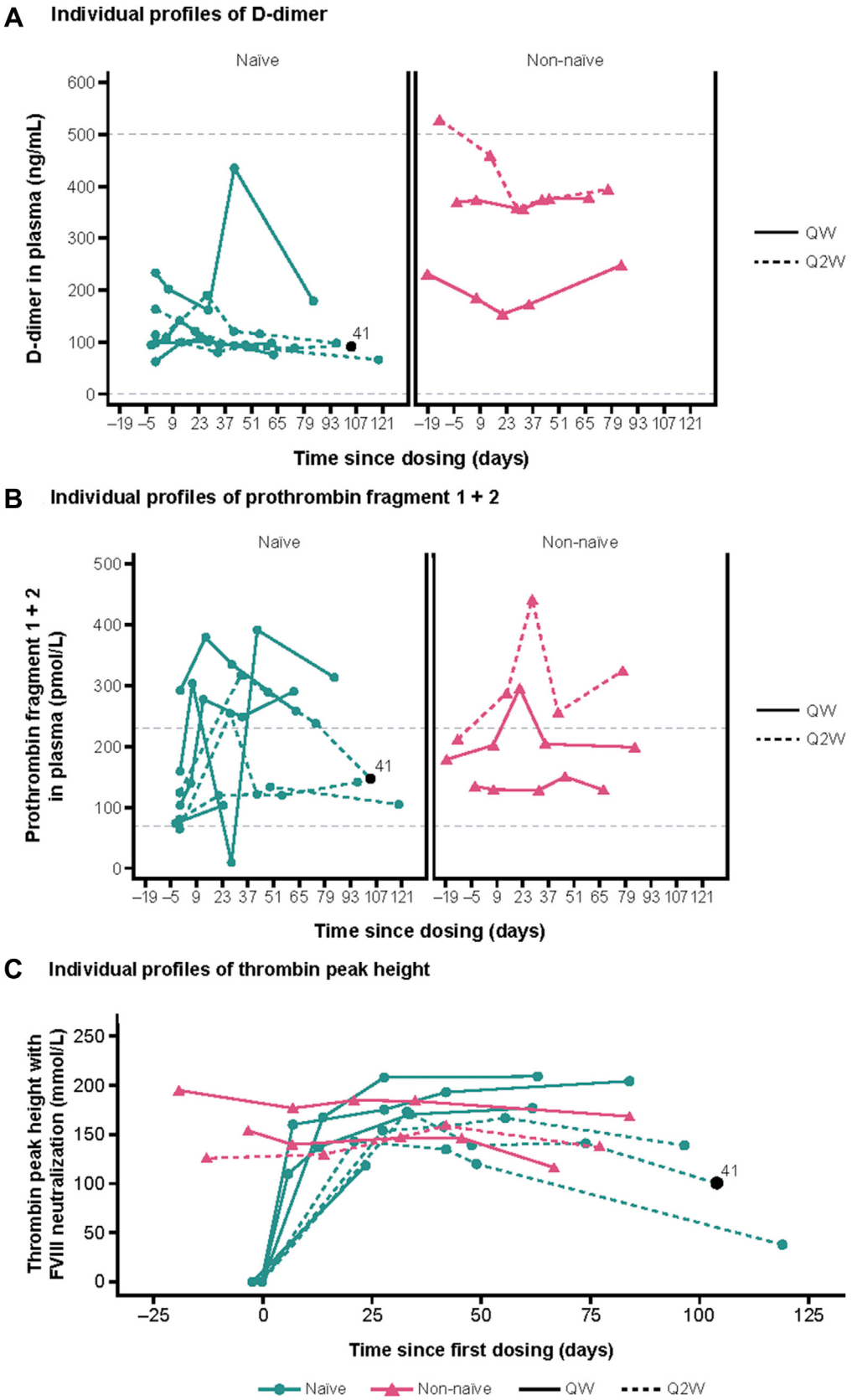

FIGURE 6 Exploratory cohort: individual profiles of D-dimer, prothrombin fragment 1 + 2, and thrombin peak height in patients treated with emicizumab. (A) Individual profiles of D-dimer. The different line patterns mark planned dosing frequency. Planned maintenance dose ranges from 1.5 to 1.6 mg/kg for QW and from 2.8 to 3.1 mg/kg for Q2W. Black circle indicates the number of days between the analysis day and last dose day. Numbers are only shown if doses are taken outside the planned dosing frequency. (B) Individual profiles of prothrombin

3 | RESULTS

3.1 | Study participants

Forty-three participants in total were enrolled in the 5 MAD cohorts (cohort 1, *n* = 8; cohort 2, *n* = 9; cohort 3, *n* = 8; cohort 4, *n* = 8; cohort 5, *n* = 10; Table 1 and Supplementary Figure S1). One participant who enrolled in cohort 1 was withdrawn from the study on day 8 due to a protocol deviation. This participant's PK profile showed no evidence of Mim8 exposure, so the participant was excluded from the safety and full analysis sets. Four of the 42 participants (9.5%) had FVIII inhibitors at the start of the study.

The mean age of the participants was 33.8 years (SD = 13.3 years), with 6 adolescent participants (12-17 years of age; 6/42 [14%]). Most participants (36/42 [85.7%]) were in the ≥60-kg weight band. A total of 418 Mim8 injections were administered, and the total exposure time to Mim8 was 9.5 years.

In the exploratory cohort, 10 participants were screened, exposed to emicizumab, and included in the safety and full analysis set. Of these, 7 were administered emicizumab for the first time, with the remaining 3 established on prior emicizumab prophylaxis. One participant in the emicizumab naïve group was lost to follow-up.

3.2 | Mim8 multiple ascending dose cohorts

3.2.1 | Safety

Twenty-three of 42 participants (54.8%) reported a total of 41 TEAEs (Table 2). There was no dose dependency in the number, causality, type, or severity of TEAEs. Nine of 42 participants (21.4%) experienced 12 TEAEs that were deemed to be probably or possibly related to the IMP; none of these events were severe. No thrombotic events (including thrombotic microangiopathy [TMA]) were reported. In total, 1 participant (2.4%) experienced 1 serious TEAE. This participant (in cohort 3) had a concomitant medical history of anxiety and experienced moderate, noncardiac chest pain, resulting in hospitalization. After a chest computed tomography scan, an echocardiogram, and an electrocardiogram, there were no signs of cardiac ischemia, thromboembolic events, or bleeding. The chest pain was assessed by the investigator to be anxiety-related and considered unlikely to be related to the IMP.

One non-FVIII inhibitor participant, with no history of allergy or hypersensitivity, in cohort 2 experienced a severe hypersensitivity reaction that was considered probably related to the IMP and resulted in study withdrawal. The reaction occurred on the same day as the fourth dose (22 days after the initial dose) of Mim8 and consisted of generalized itching, exanthema, and papules. Mim8 was permanently discontinued ~7 weeks after event onset, and all symptoms gradually improved following treatment discontinuation. The participant tested negative for anti-Mim8 antibodies following both event onset and treatment discontinuation; total IgE levels were elevated around the time of the reaction.

Injection site reactions occurred with 4 of 418 (<1%) total injections in 4 of 42 participants (9.5%). Of these, 3 participants experienced local reactions such as erythema, hematoma, and induration, and 1 participant experienced pain. All reactions were mild, all participants recovered, no events led to treatment discontinuation, and there was no apparent relationship between injection site reactions and Mim8 dosage. Furthermore, no anti-Mim8 antibodies were detected.

Safety biomarkers indicated no signs of excessive coagulation activation. There were no dose-dependent changes in D-dimer levels from baseline to week 12 (Figure 2A), and although there was an indication of an initial increase in D-dimer levels in cohort 4, D-dimer levels returned to the normal range within the 12-week treatment period. D-dimer levels in all MAD cohorts were mainly within the normal range and stable over time, with single outliers observed across the treatment period. Steady-state median prothrombin fragment 1 + 2 levels increased in a dose-dependent manner (cohort 1: 93 pmol/L; cohort 2: 159 pmol/L; cohort 3: 372 pmol/L; cohort 4: 346 pmol/L; cohort 5: 456 pmol/L). Individual profiles in most patients stabilized after steady-state concentrations had been reached; however, single outliers were observed across cohorts and, in some participants, exceeded the upper limit of the normal range. Prothrombin fragment 1 + 2 levels reached a plateau by MAD cohort 3 (Figure 2B). There were no dose-dependent changes in FIX or FX antigen levels from baseline to week 12 in MAD cohorts 1 to 4 (Supplementary Table S1). However, there was an initial increase of FIX and FX antigen levels observed for some participants in MAD cohort 5; these levels returned to baseline by week 12. It should be noted that no patients received concomitant activated prothrombin complex concentrates (aPCCs).

3.2.2 | Pharmacokinetics

Steady-state Mim8 $AUC_{0\text{-}tau}$ and C_{max} increased with dose, consistent with dose proportionality (Figure 3). Steady-state values of Mim8 C_{avg} were comparable between the randomized cohorts 3 (QW dosing) and 4 (Q4W dosing), and individual Mim8 concentrations were within the

fragment 1 + 2. The different line patterns mark planned dosing frequency. Planned maintenance dose ranges from 1.5 to 1.6 mg/kg for QW and from 2.8 to 3.1 mg/kg for Q2W. Black circle indicates the number of days between analysis day and last dose day. Numbers are only shown if doses are taken outside the planned dosing frequency. (C) Individual profiles of thrombin peak height with FVIII neutralization. Predose measurements below LLoQ values are set to 0. The different line patterns mark planned dosing frequency. Planned maintenance dose ranges from 1.5 to 1.6 mg/kg for QW and from 2.8 to 3.1 mg/kg for Q2W. Black circle indicates the number of days between analysis day and last dose day. Numbers are only shown if doses are taken outside of the planned dosing frequency. The range of peak thrombin height obtained with healthy plasma using the same assay was 360 to 468 nmol/L. FVIII, factor VIII; LLoQ, lower limit of quantification; QW, once weekly; Q2W, once every 2 weeks.

expected range for each cohort. Mim8 concentrations for participants with and without FVIII inhibitors were comparable.

3.2.3 | Pharmacodynamics

From day 57 to day 64, mean thrombin peak height (with FVIII neutralization) increased with Mim8 dose (when Mim8 was dosed QW), approaching saturation by the dose level administered to cohort 3 (Figure 4). At steady-state concentrations, peak thrombin levels for cohorts 3 (QW) and 4 (Q4W) were comparable.

3.2.4 | Exploratory efficacy

A total of 26 treated bleeding episodes, of which 14 were spontaneous and 12 were traumatic, occurred in 11 participants in MAD cohorts 1 to 5. There were no treated bleeding episodes in the 4 participants with HA with inhibitors. There were 13 treated bleeding episodes in 6 of 7 participants in MAD cohort 1, 1 treated bleeding episode each in cohorts 2 and 3, and 11 treated bleeding episodes in 3 of the 10 participants in cohort 5. No spontaneous bleeds were reported in cohorts 2 to 4 (Figure 5). The 11 treated bleeds (10 spontaneous, 1 traumatic) in cohort 5 included 8 spontaneous joint bleeds (left knee [3], left shoulder [4], and right ankle [1]) in a single participant. The spontaneous joint bleeds in the 2 other participants in cohort 5 occurred within 2 weeks after enrolment into the study. All bleeds occurred in patients without inhibitors and were treated with FVIII products.

3.3 | Exploratory cohort

3.3.1 | Safety

Safety endpoints (D-dimer, prothrombin fragment 1 + 2, FIX antigen, and FX antigen levels) were measured at week 12 in the exploratory cohort treated with emicizumab. There were no signs of excessive coagulation activation, although prothrombin fragment 1 + 2 increased to levels above the upper limit of the normal range in some participants treated with emicizumab (Figure 6). Four nonserious adverse events (3 events of headache and 1 event of hypertension) were reported by 2 participants. No thrombotic events (including thrombotic microangiopathy) were reported.

3.3.2 | Pharmacodynamics

Thrombin peak height (with FVIII neutralization) increased in participants naïve to emicizumab after starting treatment, and mean (SD) values for thrombin peak height from baseline to week 12 were within the same range in participants naïve to emicizumab treatment (149.74 [31.48] nmol/L) and in those previously treated with emicizumab (153.56 [24.55] nmol/L; Figure 6C).

4 | DISCUSSION

FRONTIER1 is the first clinical study conducted with Mim8, a bispecific FVIIIa mimetic antibody in development for treating patients with HA, with or without FVIII inhibitors. No safety concerns were identified with Mim8, and PK and PD properties were found to be dose-dependent. Furthermore, the comparability between PK and PD data provides support for both weekly and monthly dosing approaches. Mim8 was well tolerated, with 1 serious TEAE deemed unrelated to the IMP and 1 hypersensitivity reaction considered related to Mim8 that resulted in discontinuation of the IMP.

As may be expected of the lowest dose cohort, cohort 1 consisted of the highest proportion of patients who experienced treated bleeds. However, exploratory efficacy data suggest a potential clinical benefit of Mim8, with few participants experiencing treated bleeds beyond cohort 1. Patients in cohorts 3 and 4 were randomized to receive either weekly or monthly doses of Mim8, and demonstrated comparable efficacy data, possibly indicating that either dosing interval can provide beneficial prophylaxis treatment. Although 10 spontaneous bleeding events were treated in cohort 5, 8 of those bleeds occurred in a single participant. In the 12 months before study entry, this participant reported 58 bleeds despite prophylactic FVIII treatment administered once every 3 days. Notably, the 2 spontaneous bleeding events in the 2 other participants in cohort 5 occurred within 2 weeks after enrolment into the study, before steady-state Mim8 levels were achieved. The time from Mim8 dosage to the onset of bleeds reported in this study was distributed over the entire dosing interval. Together with the PK/PD data, this finding suggests that bleed protection remains relatively stable during treatment with Mim8.

The exploratory cohort provided PD and safety biomarker data that were useful as a benchmark for Mim8 against emicizumab. *Ex vivo* thrombin peak height data from the MAD and exploratory cohorts suggested that a ~15-fold lower concentration of Mim8, compared with emicizumab, were needed to achieve the same thrombin peak height (Supplementary Figure 2). This is similar to previous estimations in nonclinical studies [5]. The range of thrombin peak height values for participants receiving emicizumab was comparable with that for participants in MAD cohort 2, which targeted a Mim8 exposure of 3 μg/mL. Similarly, the relative change in prothrombin fragment 1 + 2 levels was comparable between participants naïve to emicizumab treatment and participants in MAD cohort 2 receiving Mim8.

No injection site reactions were reported in the exploratory cohort, but injection site reactions have been reported to be one of the most common side effects of emicizumab, occurring in 15% to 31% of participants treated with emicizumab in phase 3 trials [11–13]. In this phase 2 study, <10% of participants who received Mim8 experienced injection site reactions, corresponding to <1% of total

injections. Phase 3 studies are needed to further investigate the incidence of injection site reactions and pain in patients with HA treated with Mim8.

Some limitations need consideration when interpreting this study. First, although the exploratory cohort provided insightful benchmark data, it is not appropriate to directly compare this cohort to the MAD cohorts due to the relatively small sample sizes. Second, it is not known whether or not variably elevated levels of D-dimer or prothrombin fragment 1 + 2 predict safety or efficacy. Additional clinical and laboratory data from the extension phase of this study, as well as future phase 3 trials, will be needed to address these questions. Furthermore, due to the small sample size, lack of randomization, and short observation period, this study does not enable the evaluation of treatment efficacy in a robust manner.

5 | CONCLUSION

The results from the phase 2, MAD part of FRONTIER1 support further clinical development of Mim8. The data suggest that Mim8 is tolerable, has a favorable safety profile, and supports weekly to monthly dosing approaches. Exploratory efficacy data provide encouraging data suggesting the ability of Mim8 to provide prophylaxis against bleeds in patients with HA. Two phase 3 studies are currently underway to evaluate the efficacy and safety of Mim8, FRONTIER2 (NCT05053139; EudraCT:2020-001048-24), a global study in patients with HA with or without inhibitors, to demonstrate the hemostatic effect of Mim8 dosed once weekly and once monthly as bleeding prophylaxis, and FRONTIER3 (NCT05306418; EudraCT:2020-003467-26), a global study investigating the safety of Mim8 in young patients with HA (aged 1-11 years) with or without inhibitors.

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AUTHOR CONTRIBUTIONS

All authors made substantial contributions to the conception and design of the study and acquisition of data, took part in drafting of the article or revision of 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.

DECLARATION OF COMPETING INTERESTS

S.R.L. has consulted for Argenx, Novo Nordisk, and Takeda. P.C. has served on advisory boards for ApcinteX, Bayer, Boehringer Ingelheim, CSL Behring, Chugai, Freeline, Novo Nordisk, Pfizer, Roche, Sanofi, Spark, Sobi, and Takeda, and has received research funding from Bayer, CSL Behring, Freeline, Novo Nordisk, Pfizer, Sobi, and Takeda. F.L.J. has served as a speaker or on advisory boards for Amgen, Bayer, CSL Behring, Novartis, Novo Nordisk, Pfizer, Roche, Rovi, Sobi, and Takeda, and has received research funding from Sobi. J.M. has received research grants from BioMarin, Novartis, Novo Nordisk, Pfizer, Roche, Sanofi, Spark, and UniQure; served as a consultant for BioMarin, Novo Nordisk, Roche, Sanofi, Spark, and Takeda; and served on a speaker's bureau for the International Society on Thrombosis and Haemostasis, Novo Nordisk, Pfizer, Roche, Sanofi, Takeda, and World Federation of Hemophilia. I.M. and A.L.N. are employed at Novo Nordisk and own stocks in the company. J.W. has received research funding and honorarium from AlfaSigma, Alnylam, Amgen, AstraZeneca, Bayer AG, CSL Behring, Novartis, Novo Nordisk, Octapharma, Pfizer, Roche, Sanofi, Siemens, Sobi, Swixx BioPharma, and Takeda. L.G. has no competing interests to disclose.

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