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ORIGINAL ARTICLE

Safety and effectiveness of recombinant factor XIII-A_2 in congenital factor XIII deficiency: Real-world evidence

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Abstract

Background: Regular factor XIII (FXIII) prophylaxis is standard treatment for congenital FXIII A-subunit deficiency (FXIII-A CD). Recombinant factor XIII-A_2 (rFXIII-A_2) was extensively evaluated in the mentor trials.

Objective: To assess real-world safety and treatment effectiveness of rFXIII-A_2 prophylaxis from the mentor 6 trial.

Patients/Methods: mentor 6 was a noninterventional, postauthorization safety study investigating rFXIII-A_2 prophylaxis in FXIII-A CD. rFXIII-A_2 treatment was observed for 2 to 6 years per patient. The primary end point was documentation of adverse drug reactions (including anti-FXIII antibody development). Secondary end points were serious adverse events (SAEs), medical events of special interest (MESIs), and annualized bleeding rate (ABR).

Results: Among 30 patients (mean age, 25.5 years), there were 44 adverse events (AEs) (30 mild, 13 moderate, 1 severe). Eleven AEs were possibly/probably related to rFXIII-A_2. Of four MESIs, two were unlikely related to rFXIII-A_2 (accidental overdose, deep vein thrombosis), and two were possibly/probably related (nonneutralizing anti-FXIII antibody, decreased therapeutic response). All 10 SAEs were unlikely related to rFXIII-A_2. Over a follow-up of 75.4 patient-years, there were six treatment-requiring bleeds (all trauma-related with no spontaneous bleeds), giving a treatment-requiring

ABR of 0.066; five bleeds were treated successfully with rFXIII-A_2. Eight of nine minor surgeries performed during rFXIII-A_2 prophylaxis reported successful hemostatic outcomes (one missing evaluation).

Conclusions: These data confirm that rFXIII-A_2 prophylaxis is well tolerated as long-term care. There were no spontaneous bleeds, ABR was low, and rFXIII-A_2 successfully treated bleeds in patients receiving rFXIII-A_2 prophylaxis.

KEYWORDS
factor XIII, long-term care, recombinant factor XIII-A_2, safety, treatment effectiveness

Essentials

- Recombinant factor XIII-A_2 (rFXIII-A_2) is approved for prophylaxis in congenital FXIII-A deficiency.
- mentor 6 assessed real-world safety and effectiveness of once-monthly prophylaxis with rFXIII-A_2.
- Prophylaxis with rFXIII-A_2 was well tolerated, and no safety concerns were identified.
- Prophylaxis was effective, with an annualized bleeding rate of 0.066 and no spontaneous bleeds.

1 | INTRODUCTION

Congenital factor XIII deficiency (FXIII-A CD) is a very rare, autosomal recessive bleeding disorder[1,2] usually caused by deficiency of the FXIII A-subunit (FXIII-A).[3-5] With 1513 reported cases worldwide,[6] the prevalence of diagnosed FXIII-CD is approximately 1 case per 5 million, although the expected prevalence is estimated to be 1 in 1 to 2 million.[7-9] The difference between the expected prevalence and the number of identified cases worldwide is likely due to early death of patients along with lack of diagnosis and/or reporting. Patients with severe FXIII-A CD (most diagnosed cases of FXIII-CD are severe, as mild FXIII-A CD is usually asymptomatic) typically experience a lifelong bleeding tendency that manifests from early infancy with umbilical stump bleeding and a very high predisposition to central nervous system bleeding. After the first month of life, such patients experience soft tissue bleeds, muscle hematomas, bleeding after injury and surgery, life-threatening central nervous system bleeding, and, in women, recurrent miscarriage and postnatal bleeding.[1,5,10] A subgroup of patients experience delayed wound healing.[5]

Due to the risk of severe bleeding symptoms in FXIII-A CD and given the long half-life of FXIII, long-term care with regular FXIII prophylaxis is recommended as standard treatment from the time of diagnosis.[1,3,11] Historically, the only sources of FXIII were plasma-derived products (cryoprecipitate or plasma-derived FXIII concentrates [pd-FXIII]).[2,12,13] Recombinant factor XIII-A_2 (rFXIII-A_2; NovoThirteen/Tretten; Novo Nordisk, Bagsværd, Denmark) is the only rFXIII product currently available[9] and, as a highly purified product manufactured in *Saccharomyces cerevisiae*, contains no human or other mammalian-derived products.[4] It also has a long half-life of 13.6 days.[9,13]

Approval of rFXIII-A_2 was based on its evaluation in the extensive mentor clinical trial program, in which 82 patients were monitored closely for a total of 240.6 patient-years. The mentor prophylaxis trials (mentor 1, mentor 2, mentor 5) showed that monthly rFXIII-A_2 prophylaxis has an excellent safety profile and provides a low bleeding rate in adults and children with FXIII-A CD.[3,9,14] Additionally, rFXIII-A_2 provided effective hemostasis during minor surgeries in adults (mentor 2) and demonstrated favorable pharmacokinetic characteristics in patients of all ages (mentor 1, 2, and 4).[9,13,15,16]

This article presents results from mentor 6, a noninterventional postauthorization safety study designed to investigate the safety and effectiveness of rFXIII-A_2 prophylaxis when used as long-term care in the "real-world" setting in patients with FXIII-A CD. The emphasis of mentor 6 was on specific adverse drug reactions (anti-FXIII antibodies, allergic reactions, embolic and thrombotic events, lack of therapeutic effect) and treatment effectiveness.

2 | METHODS

2.1 | Study design

mentor 6 was a prospective, single-arm, multicenter, multinational, noninterventional postauthorization safety study of patients with FXIII-A CD on long-term care with rFXIII-A_2 prophylaxis. Designed to observe the use of rFXIII-A_2 in normal clinical practice for a minimum of 2 years (unless prematurely withdrawn), mentor 6 had a duration of 6 years (May 17, 2013, to June 26, 2019). The study was conducted in seven countries with 17 active sites, with the aim of observing all patients exposed to rFXIII-A_2 in the European Union and additional patients from selected non-EU countries including Canada and the United States. A minimum of 30 patients were anticipated to be enrolled; this was judged by the sponsor and the European Medicines Agency to facilitate an adequate expansion to

the safety experience of rFXIII-A_2 prophylaxis, considering the rarity of the disease.

To test for anti-FXIII antibodies, blood samples were drawn at visit 1 and at any subsequent visit as part of routine clinical care or in cases of lack of therapeutic effect. Such testing was performed only in those countries that allowed blood sampling for anti-FXIII antibody assessment within noninterventional studies. The method used for detecting anti-FXIII antibodies has been previously described.[3]

Prior to study initiation, the protocol, amendments, patient information/informed consent form, and enrollment procedures were reviewed and approved by an independent ethics committee/institutional review board. The study was conducted in accordance with the Declaration of Helsinki[17] and the Guidelines for Good Pharmacoepidemiology Practices[18] and is registered at www.clinicaltrials.gov (ID: NCT01862367).

2.2 | Study subjects

2.2.1 | Mentor 6

Patients with severe FXIII-A CD who were either on prophylaxis or who wanted to begin prophylaxis were eligible. Patients with severe disease were identified by investigators based on patients' medical records, which included (if known) details of the patient's underlying genetic mutation. Special populations such as children, the elderly, pregnant and lactating women, and patients with renal insufficiency were also able to participate. Key exclusion criteria were mental incapacity and unwillingness, or language barriers that precluded adequate understanding or cooperation.

2.3 | Study end points

2.3.1 | Adverse drug reactions

The primary end point was adverse drug reactions related to rFXIII-A_2 during the study period. The adverse drug reactions of specific interest were anti-FXIII antibodies, allergic reactions, embolic and thrombotic events, and lack of therapeutic effect.

2.3.2 | Safety

Secondary safety end points were serious adverse events (SAEs) and medical events of special interest (MESIs). Adverse events were defined as mild (no or transient symptoms; no interference with the patient's daily activities), moderate (marked symptoms; moderate interference with the patient's daily activities), or severe (considerable interference with the patient's daily activities; unacceptable). MESIs were defined as one of the following: anti-FXIII antibodies, allergic reactions, embolic or thrombotic events, lack of therapeutic effect, medication errors and near medication errors, and suspected transmission of an infectious agent via the study product.

2.3.3 | Treatment effectiveness

Secondary treatment effectiveness end points comprised annualized bleeding rate (ABR) during the study period and treatment with rFXIII-A_2 for uses other than prophylaxis in patients with FXIII-A CD (eg, treatment of bleeds, surgeries, and use during pregnancy).

2.3.4 | Trough levels

As this was an observational study, there was no systematic evaluation of FXIII trough values. Instead, blood samples for evaluating FXIII trough levels were drawn periodically at clinic visits, at the physician's discretion. Blood samples were most often analyzed for trough levels at a local laboratory using different FXIII activity assays. Consequently, FXIII activity was reported in different units.

Of the 30 patients enrolled, 27 had at least one central laboratory measurement of plasma FXIII activity in a predose sample. To make an appropriate comparison between trough values in mentor 6 and previous mentor trials, blood samples drawn at 28 $\pm$ 2 days after the previous dose and analyzed with the Berichrom assay at the central laboratory were included in the analyses.

2.4 | Data collection

Clinical history was collected at baseline, and prospective follow-up data on any clinical event (bleeding, pregnancy, surgery), treatment, adverse events (AEs), and complications were collected throughout the study duration (6 years).

Data from patients' medical records, diaries, and laboratory sampling (performed according to clinical practice) were recorded in case report forms (CRFs), and information related to treatment and bleeds was captured in patient diaries by either the patient or the parent/caregiver. In case a patient was unable to enter a treatment in the diary, or was hospitalized, bleeding information was reported in the patient record and subsequently in the CRF by the investigator.

2.5 | Data analysis

All patients were exposed to rFXIII-A_2 and were included in the full analysis set. For the primary end point, specific adverse drug reactions of interest were summarized by the number of reactions and the number and percentage of patients experiencing the reaction. Descriptive statistics were also summarized for secondary end

points, and all participating patients were included in the analyses. The total treatment duration per patient was used to calculate ABR. ABR values from previous mentor trials (mentor 1,[3] mentor 2,[9] mentor 5,[14]) were plotted as a forest plot to provide a pictorial comparison between these trials and the mentor 6 study.

3 | RESULTS

3.1 | Patients

Thirty patients were enrolled from seven countries (the United States [n = 13], Italy [n = 5], Denmark [n = 4], Spain [n = 3], Canada [n = 3], Hungary [n = 1], and the United Kingdom [n = 1]). Patients were categorized as children (aged <18 years [n = 13], including six children aged ≤6 years at baseline), adults (aged 18-65 years [n = 15]), or elderly (aged >65 years [n = 2]). Patient disposition, baseline demographics, and rFXIII-A_2 consumption are summarized in Table 1. The mean (standard deviation [SD]) age in the overall population was 25.5 (18.8) years. Most patients (22 [73.3%]) were White and there were slightly more males than females (17 vs 13). There were no patients with renal insufficiency and no pregnant or lactating women.

Before entry into mentor 6, 29 of the 30 patients were on prophylaxis and one was receiving on-demand treatment. Of the 29 on prophylaxis before entering mentor 6, 25 were on prophylaxis with rFXIII-A_2, including 13 patients who had participated in one of the previous mentor trials. Of the other 4 patients on prophylaxis before entering mentor 6, 3 were receiving a pd-FXIII concentrate prophylactically; for the remaining patient, the product type was not specified. Within the 24 months before entry into mentor 6, patients on prophylaxis had a mean of 0.17 and 1.00 treatment-requiring and non–treatment-requiring bleeds, respectively.

The earlier mentor studies were interventional and recommended a rFXIII-A_2 dose of 35 IU kg^{-1} every 4 weeks. This recommendation was based on studies that showed that, with this dose, virtually all patients would have trough FXIII levels >10% and would therefore be well protected from bleeding. For this study, the same dose was generally continued, although some investigators may have chosen to use different doses. The mean (SD) rFXIII-A_2 dose given for prophylaxis in mentor 6 was 37.2 (12.16) IU kg^{-1}, the median (interquartile range) dosing interval was 29 (28-35) days, and the mean (SD) dose to treat a bleed was 41.0 (7.24) IU kg^{-1}. Of 880 rFXIII-A_2 prophylaxis doses administered during mentor 6, 448 (50.9%) were given in a hospital and 432 (49.1%) were given at home.

For most (20/30) patients, mutation information was available (Table 2). Some of the genotyping had been done through the previous mentor trials in which patients had participated. Of the 20 patients with genotyping data available, 12 (60%) were heterozygous for FXIII deficiency, and 8 (40%) were homozygous. Of the 14 patients with substitution mutations, 9 had missense mutations, 1 had a splice site mutation, 1 had a nonsense mutation, and 2 patients had one missense and one nonsense mutation. For the remaining patient with a substitution mutation, no further genotyping data were available. Similarly, for the 6 patients with nonsubstitution mutations (namely, splice site mutations and/or deletions), no further genotyping data were available.

Five patients withdrew from the study. One was withdrawn by the investigator due to noncompliance with study procedures (incomplete diary entries [withdrawn after 67 days]), 1 was transferred to another hemophilia treatment center (after 436 days), and 3 withdrew for personal reasons (after 175, 400, and 455 days, respectively).

3.2 | Safety

The total time (sum of patient-years) in the study was 75.4 patient-years. Overall, 44 AEs were reported (Table 3); there were 16 AEs in children aged <18 years and 28 AEs in adults aged ≥18 (for analysis of AEs, the 2 elderly patients aged >65 years are included in the "Adult" patient category). Thirty of the reported AEs were mild, 13 were moderate, and 1 was severe. Eleven AEs were possibly/probably related to rFXIII-A_2.

3.3 | Medical events of special interest

Four patients experienced a MESI (defined in section 2.3.2) (Table 4). All MESIs were mild in severity, and all four patients recovered. In two cases, the MESI was unlikely related to treatment with rFXIII-A_2, while in the other two it was possibly/probably related.

The first patient was a female (aged 6 years at baseline) who had a positive test for nonneutralizing antibody. She had been receiving rFXIII-A_2 prophylaxis for 3.5 years (2.5 years in clinical trials [as part of the mentor 4 and mentor 5 trials] and 1 year on marketed product) before enrolling in mentor 6; at baseline, she tested positive for low-titer, nonneutralizing anti-FXIII antibody. One month later she showed the same. However, all tests for neutralizing antibody were negative and FXIII activity was as expected (ranging from 0.126 to 0.513 IU mL^{-1}). There was no loss of treatment effectiveness, the antibody disappeared after 2 months, and the patient (who had a deletion variant mutation) continued in the study without a change in treatment. This MESI was described as mild in severity. No known infections or preceding vaccinations were associated with development of this transient nonneutralizing antibody.

The second patient was a female (aged 6 years at baseline) who experienced a suspected decreased therapeutic response. She reported 41 non–treatment-requiring bleeds (primarily nosebleeds) over 31 months, prompting her physician to report a mild adverse event (MESI) of suspected lack of therapeutic effect. The patient's FXIII activity levels were >0.4 IU mL^{-1} at the time of reporting nose bleeds. She tested negative for anti-rFXIII antibodies. Three nosebleeds

TABLE 1 Patient disposition and baseline demographics

	Children (<18 years)	Adults (18–65 years)	Elderly (>65 years)	Total
Number of patients	13	15	2	30
Age at enrollment, y				
Mean (SD)	9.2 (4.9)	33.9 (11.9)	67.5 (0.7)	25.5 (18.8)
Min-max	2-17	19-62	67-68	2-68
Race, n (%)				
White	8 (61.5)	12 (80.0)	2 (100.0)	22 (73.3)
Black/African American	2 (15.4)	2 (13.3)	0 (0)	4 (13.3)
Other[a]	3 (23.1)	0 (0)	0 (0)	3 (10.0)
NA[b]	0 (0)	1 (6.7)	0 (0)	1 (3.3)
Sex, n (%)				
Male	5 (38.5)	10 (66.7)	2 (100.0)	17 (56.7)
Female	8 (61.5)	5 (33.3)	0 (0)	13 (43.3)
Completed the study, n (%)[c]	12 (92.3)	12 (80.0)	1 (50.0)	25 (83.3)
Underwent minor surgery	3 (23.1)	3 (20.0)	0 (0)	6 (20.0)
Average prophylaxis dose (IU kg^{-1})[d]				
N	420	364	53	837
Mean (SD)	43.7 (12.57)	31.3 (7.71)	26.9 (0.84)	37.2 (12.16)
Median (range)	38.9 (30.3-89.7)	31.2 (18.2-50.7)	26.7 (26.0-28.7)	35.7 (18.2-89.7)
Dosing interval, days				
Mean (SD)	32.8 (16.05)	33.3 (18.68)	28.0 (2.30)	32.7 (16.87)
Median (IQR)	29 (28-35)	29 (28-33)	28 (28-29)	29 (28-35)
Average dose of rFXIII-A_2 to treat a bleed (IU kg^{-1})[e]				
N	4	1	0	5
Mean (SD)	42.2 (7.73)	36.0 (–)	0 (–)	41.0 (7.24)
Median (range)	39.6 (36.3-53.3)	36.0 (36.0-36.0)	…	37.6 (36.0–53.3)

Abbreviations: IQR, interquartile range; N/n, number of patients; NA, not available; rFXIII-A_2, recombinant factor XIII-A_2; SD, standard deviation.

[a]Race was reported as "Other" for three patients; the race of two patients was White, while the race of one patient was unknown.

[b]Race was reported as "not available" for a Spanish patient aged 19 years.

[c]The criterion for completing the study was a minimum of 2 years' participation or 24 exposure days (whichever came first), unless the patient had dropped out.

[d]N, number of doses.

[e]N, number of bleeds.

were treated with aminocaproic acid and compression of the nose. The patient recovered and continued on the study. Nosebleeds are a common symptom in many children, including those without bleeding disorders; in most cases, such bleeds occur due to local (intranasal) causes. In this case, the patient's nosebleeds were believed to be unrelated to her FXIII deficiency.

An adolescent male aged 14 years at baseline had an accidental overdose (63.3 IU kg^{-1}) whereby a whole vial of rFXIII-A_2—rather than half a vial—was administered by accident. This MESI was judged by the investigator to be a medication error, mild in severity, and unlikely related to treatment. The patient experienced no clinical consequences from this accidental overdose and continued in the study for another 2 years and 4 months.

The fourth patient was a male (43 years old at baseline) who, 4 days after being diagnosed with influenza, experienced a distal deep vein thrombosis (DVT) in the cephalic vein of the right arm after the administration of rFXIII-A_2. The development of DVT was attributed to a combination of systemic inflammation due to influenza, local tissue irritation, and endothelial activation caused by ongoing peripheral vein catheter phlebitis. The DVT was mild in severity and unlikely related to rFXIII-A_2; FXIII activity recorded 7 days after development of the DVT was 0.39 IU mL^{-1} as measured by a local laboratory. For the DVT, the patient was

TABLE 2 Available genotyping data for patients in mentor 6

Patient	Zygosity	Mutation type(s)	Submutation type(s)
1	Heterozygous	Substitution	Missense mutation/ nonsense mutation
2	Heterozygous	Substitution, deletions	Missense mutations
3	Heterozygous	Substitution, deletions	Missense mutations
4	Homozygous	Substitution	Splice site mutation
5	Homozygous	Substitution	Missense mutations
6	Heterozygous	Splice site mutation, deletions	NA
7	Heterozygous	Deletions	NA
8	Heterozygous	Splice site mutation, deletions	NA
9	Heterozygous	Substitution	NA
10	Homozygous	Substitution	Missense mutations
11	Homozygous	Substitution	Nonsense mutations
12	Homozygous	Substitution	Missense mutations
13	Heterozygous	Substitution, deletions	Missense mutations
14	Heterozygous	Splice site mutation, deletions	NA
15	Homozygous	Substitution	Missense mutations
16	Homozygous	Deletions	NA
17	Heterozygous	Substitution	Missense mutations
18	Heterozygous	Substitution	Missense mutations
19	Heterozygous	Substitution	Missense mutation/ nonsense mutation
20	Homozygous	Splice site mutation	NA

Abbreviations: NA, not available; the study was not designed to capture detailed gene mutations.

TABLE 3 Safety summary

	Children (<18 years)	Adults (≥18 years)[a]	Total
Number of patients	13	17	30
Patient years in study	37.00	38.36	75.36
All AEs, N	16	28	44
Serious AEs, N	2	8	10
AEs by severity, N			
Mild	12	18	30
Moderate	4	9	13
Severe	0	1	1
AEs by relationship, N			
Probably or possibly related	3	8	11
Unlikely related	13	20	33
MESIs	3	1	4

Abbreviations: AEs, adverse events; MESI, medical event of special interest (MESI is an event that, in the evaluation of safety, has a special focus or is collected to meet regulatory reporting requirements); N, number of AEs.

[a]For analysis of AEs, the two elderly patients aged >65 years were included in the "Adult" patient category.

anticoagulated with heparin for 5 days, and additionally received concomitant antibiotics, Tamiflu, morphine, salbutamol, and a steroid nasal spray. The patient recovered and was discharged 10 days later.

3.4 | Serious adverse events

There were 10 SAEs in seven patients, all of which were considered unlikely to be related to rFXIII-A_2. All patients recovered (Table 4).

3.5 | AEs related to rFXIII-A_2

Eleven AEs in seven patients were considered possibly or probably related to rFXIII-A_2 (Table 4). This included one patient (32-year-old woman; patient 7, Table 4) who had three episodes of chest discomfort. She had a previous medical history of tightness of chest. All three events resolved; the patient completed the study and then began treatment with pd-FXIII. She also experienced a SAE of ovarian rupture, which was unlikely related to rFXIII-A_2.

The superficial thrombophlebitis reported in patient 11 (Table 4) was not considered to be a thrombotic event.

3.6 | Treatment effectiveness

3.6.1 | Bleeding frequency

The overall ABR for treatment-requiring bleeds (requiring treatment with a FXIII-containing product) was 0.066 (Table 5). There were six treatment-requiring bleeds in five patients; all six bleeds were traumatic,

TABLE 4 MESIs, SAEs, and AEs related to rFXIII-A_2

Pt	Age,[a] y	Sex	Event	MESI or SAE	rFXIII-A_2-related-AE	Severity	Relationship to rFXIII-A_2	Outcome
1	3	Female	Sialadenitis	SAE		Moderate	Unlikely	Recovered
2	6	Female	Positive test for non-neutralizing antibody	MESI	X	Mild	Probable	Recovered
3	6	Female	Decreased therapeutic response[b]	MESI	X	Mild	Possible	Recovered
			Pain in extremity	AE	X	Mild	Possible	Recovered
4	12	Female	Posttraumatic headache	SAE		Moderate	Unlikely	Recovered
5	14	Male	Accidental overdose[c]	MESI		Mild	Unlikely	Recovered
6	21	Male	Hemarthrosis	SAE		Moderate	Unlikely	Recovered
7	32	Female	Ovarian rupture	SAE		Moderate	Unlikely	Recovered
			Chest discomfort	AE	X	Mild	Possible	Recovered
			Chest discomfort	AE	X	Mild	Possible	Recovered
			Chest discomfort	AE	X	Moderate	Probable	Recovered
8	33	Male	Sepsis	SAE		Moderate	Unlikely	Recovered
			Sepsis	SAE		Severe	Unlikely	Recovered
9	43	Male	DVT[d]	MESI and SAE		Mild	Unlikely	Recovered
			Dizziness	SAE		Mild	Unlikely	Recovered
			Dizziness	AE	X	Mild	Possible	Recovered
			Influenza	SAE		Moderate	Unlikely	Recovered
10	62	Male	Headache	AE	X	Mild	Possible	Recovered
11	67	Male	Arthralgia	SAE		Moderate	Unlikely	Recovered
			Superficial thrombophlebitis[e]		X	Moderate	Possible	Recovered
12	68	Male	Dizziness	AE	X	Mild	Possible	Recovered
			Fatigue	AE	X	Mild	Possible	Recovered

Abbreviations: AE, adverse event; DVT, deep vein thrombosis; MESI, medical event of special interest (MESI is an event which, in the evaluation of safety, has a special focus or is collected to meet regulatory reporting requirements); rFXIII-A_2, recombinant factor XIII-A_2; SAE, serious adverse event.

[a]Age at baseline.

[b]Assessed by the investigator as suspected lack of therapeutic response.

[c]Assessed by the investigator as a medication error due to rFXIII-A_2 overdose. Medication errors and near medication errors included administration of wrong drug, wrong route of administration, administration of a high dose with the intention to cause harm or an accidental overdose, and any errors in the reconstitution.

[d]Assessed by the investigator as caused by a peripheral vein catheter.

[e]Per the protocol, superficial thrombophlebitis is not considered to be a thromboembolic event.

and no spontaneous treatment-requiring bleeds were reported (Table 6). Bleeds were equally distributed across sexes and age groups.

Four of the six traumatic treatment-requiring bleeds were treated with rFXIII-A_2 at home; two bleeds were treated in a hospital (one with rFXIII-A_2 and another with Fibrogammin). The hemostatic response for all bleeds treated with rFXIII-A_2 was excellent or good. Ten patients experienced 59 non–treatment-requiring bleeds, 41 of which occurred in the 6-year-old female mentioned in section 3.3 (patient 3, Table 4).

3.6.2 | Surgery

There were no major surgeries. Nine minor surgeries were conducted in six patients (Table 7). The hemostatic outcome was successful in eight surgeries; for one surgery, evaluation of hemostatic outcome was missing.

3.6.3 | Trough levels

There were 11 patients with 40 predose (trough) FXIII measurements taken within 28 ± 2 days after the previous dose, and which were assessed at the central laboratory (Table 8). The median (interquartile range [IQR]) trough level at 28 ± 2 days was 0.15 (0.12–0.18) IU mL^{-1}. The geometric mean was 0.159 IU mL^{-1}.

3.7 | Overall ABR summary

An analysis of ABR from mentor 1,[3] mentor 2,[9] mentor 5,[14] and mentor 6 is shown in Figure 1; all ABRs were very low, and there were only two spontaneous bleeds reported during all the mentor trials.

4 | DISCUSSION

Data from this real-world mentor 6 study confirm that rFXIII-A_2 is well tolerated when used as long-term care. No safety concerns were observed; specifically, there were no neutralizing antibodies against FXIII (ie, no inhibitors), no allergic reactions, and no significant thromboembolic events related to rFXIII. Most patients did not experience any AEs or SAEs (23/30 [76.7%]) related to rFXIII-A_2, and there were no withdrawals or deaths due to AEs. This favorable safety profile is in line with that observed in previous mentor trials, which represent the largest clinical development program to date in patients with FXIII-A CD (including mentor 6, 103 patients have been followed for 325 patient-years with 4134 exposures).[3,9,13-16]

Effectiveness of rFXIII-A_2 is supported by mentor 6. Notably, the lack of spontaneous bleeds is remarkable for a rare, severe bleeding disorder in a real-world setting and demonstrates that prophylaxis with rFXIII-A_2 provides excellent hemostatic coverage. The ABR for treatment-requiring bleeds was very low (0.066) and similar to that seen in the mentor clinical trial program (Figure 1).[9] The hemostatic response to rFXIII-A_2 for all treated bleeds was excellent or good. A total of seven bleeds have been successfully treated with rFXIII-A_2 to date; this includes Five bleeds in mentor 6, plus one from mentor 2[9] and another reported by Árokszállási et al.[19] All eight minor surgeries conducted under rFXIII-A_2 prophylaxis for which an evaluation of treatment effectiveness was available showed an excellent or good hemostatic response (Table 7, one evaluation was missing).

TABLE 5 Bleeding frequency

	Total N = 30
No. of bleeds[a]	6
No. of patients with bleeds	5
Range of bleeds per patient	0–2
Total observation period (patient years)	75.3
ABR (95% CI [by Poisson analysis[b]])	0.066 (0.029-0.150)
Cause of bleed, n (%)	
Spontaneous	0 (0)
Traumatic	6 (100)
Hemostatic response	
Excellent	4
Good	2
None	0

Abbreviations: ABR, annualized bleeding rate; CI, confidence interval; MESI, medical event of special interest; n, number of bleeds; N, number of patients.

[a]Treatment-requiring bleeds only (defined as bleeds requiring treatment with any FXIII-containing product). There were also 59 non–treatment-requiring bleeds in 10 patients. Of these 59 bleeds, 41 (most of which were nosebleeds) occurred in a 6-year-old female patient with a reported MESI of "decreased therapeutic response."

[b]A Poisson model with overdispersion was applied. A 95% CI was estimated if the number of bleeds was >1; otherwise, only the Poisson estimate was provided assuming no overdispersion.

4.1 | Study limitations

Some limitations associated with mentor 6 should be noted. First, due to the rarity of FXIII-CD and the very limited available data regarding rare AEs, it was not possible to perform a systematic sample size calculation. The study had a relatively small sample size, also attributable to the rarity of the disease. Only two elderly patients aged >65 years were included; this was mainly due to the fact that patients born with this condition 65 years ago would not have been likely to survive to this age.

TABLE 6 Treatment-requiring bleeds

Pt	Age at baseline, y	Sex	Type of bleed	Cause of bleed	Treatment	Dose[a] (IU kg^{-1})	Days since last prophylaxis	Hemostatic response
1	2	Male	Traumatic	Fell on to abdomen and developed hematoma to penile shaft	rFXIII-A_2	42	18	Excellent
2	12	Female	Traumatic	Distortion of the ankle	rFXIII-A_2	36	16	Excellent
			Traumatic	Fell directly on the knee	rFXIII-A_2	38	23	Excellent
3	13	Female	Traumatic	Slipped on ice face first[b]	rFXIII-A_2	53	7	Excellent
4	21	Male	Traumatic	Trauma of the left knee	rFXIII-A_2	36	10	Good
5	68	Male	Traumatic	Fell and hit leg	Fibrogammin	13	36	Good

Abbreviation: rFXIII-A_2, recombinant factor XIII-A_2.

[a]Patient 1 weighed from 14 to 17.4 kg during the study and was dosed with a total of 666.4 IU throughout, that is, 47.6-38.3 IU kg^{-1}. Therefore, to treat the bleed, he received an extra dose of his normal rFXIII-A_2 prophylactic dose. Patient 3 received two-thirds of a vial (1666 IU) each month from the outset; however, after 6 months in the study, she changed to receive a whole vial (2500 IU) despite a weight of ≈46 kg. She also received a whole vial for the treatment of the traumatic bleeding.

[b]No loss of consciousness, vomiting, headache, or dizziness.

TABLE 7 Minor surgeries performed under rFXIII-A_2 prophylaxis

Patient	Age at baseline, y	Sex	Surgery description	Days since last prophylaxis	Treated with		Outcome[b]
					Presurgery	Postsurgery[a]	
1	2	Male	Revision of circumcision	0 days	...	...	Excellent
2	13	Female	Dental extractions, cavity filling	0 days	Tranexamic acid	Tranexamic acid	Good
3	14	Male	Surgical extraction of four wisdom teeth	0 days	Tranexamic acid	...	Good
4	19	Female	Dental extraction	1 day	...	...	Excellent
			Dental extraction	1 day	...	...	Excellent
5	33	Female	Operative hysteroscopy, polypectomy, dilation, and curettage	12 days	rFXIII-A_2	...	Good
			Dilation/curettage, intrauterine device	15 days	rFXIII-A_2	...	Good
6	43	Male	Gastroscopy with biopsy	1 day	Tranexamic acid	Tranexamic acid	...
			Root canal	3 days	...	...	Excellent

Abbreviation: rFXIII-A_2, recombinant factor XIII-A_2.

[a]Postsurgery is defined as the time period from 1 to 10 days after surgery.

[b]Hemostatic response after surgery.

TABLE 8 FXIII trough measurements

Parameter	
Number of patients with trough values measured within 28 ± 2 days after last dose	11
Number of trough values	40
Geometric mean (coefficient of variation), IU mL^{-1}	0.159 (40.60)
Median (IQR), IU mL^{-1}	0.15 (0.12-0.18)
Minimum-maximum, IU mL^{-1}	0.05-0.32

Abbreviations: IQR, interquartile range; SD, standard deviation.

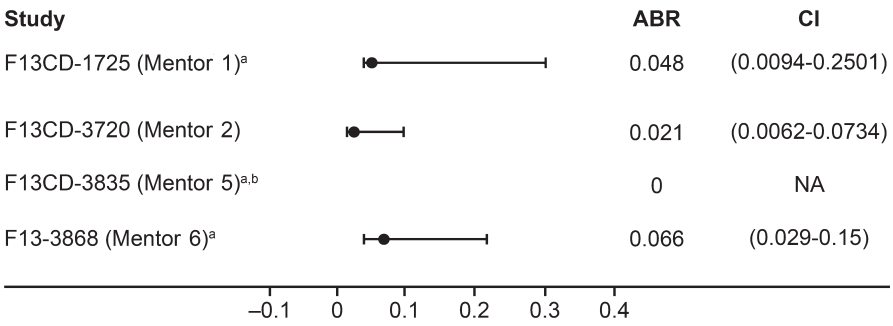

FIGURE 1 Overall ABR summary from all mentor clinical trials. [a]No spontaneous bleeds. [b]No treatment-requiring bleeds were reported. The planned Poisson analysis was not possible with a count of zero bleeds. Data are presented in a forest plot with estimated ABR and corresponding CI as whiskers, as derived in the respective clinical trial reports of mentor 1,[3] mentor 2,[9] mentor 5.[14] Abbreviations: ABR, annualized bleeding rate; CI, confidence interval; NA, not available

As blood samples for the assessment of trough levels were drawn at the discretion of the investigator, trough values could be subject to bias, particularly for those patients with few trough measurements.

Finally, as no patient in the study underwent major surgery or a pregnancy, there remains a lack of information on the use of rFXIII-A_2 in these settings.

5 | CONCLUSION

Real-world data from mentor 6 confirm that rFXIII-A_2 prophylaxis is well tolerated when used as long-term care, with no safety concerns identified throughout the study period. In addition to excellent safety, rFXIII-A_2 prophylaxis resulted in a very low rate of treatment-requiring bleeds, and there were no spontaneous bleeds during the study. Results from this postauthorization safety study also confirm that rFXIII-A_2 can be used for the treatment of bleeds in patients with FXIII-A CD.

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RELATIONSHIP DISCLOSURE

LHP received honoraria and speaker fees from Novo Nordisk, and reimbursements for attending symposia/congresses from Baxter, Bayer Health Care, Novo Nordisk, Octapharma, Pfizer, and SOBI. BAK received research grant support from Novo Nordisk for a project unrelated to this study. GC has been a speaker at satellite symposia during scientific meetings for Roche, Sobi, Novo Nordisk, Werfen, and Kedrion, and has been a member of the steering committee for Uniqure. He has also received institutional research funding from CSL Behring, Pfizer, and Sobi; served on the advisory boards of Ablynx, Alexion, Bayer, Baxalta/Shire, CSL Behring, Novo Nordisk, Pfizer, Roche, Sanofi, Sobi, and Uniqure; and has acted as a consultant for Roche. ACM received honoraria and speaker fees from Bayer, CSL Behring, Novo Nordisk, Pfizer, Roche, Shire, and SOBI. He also received reimbursements for attending symposia/congresses from Bayer, CSL Behring, Novo Nordisk, Pfizer, Roche, Shire, and SOBI. MM has no conflicts to disclose. DN has no conflicts to declare. SD is an employee of Novo Nordisk. MLG is a former employee of Novo Nordisk. MC received research support from Bayer, Bioverativ/Sanofi, CSL Behring, Novo Nordisk, Octapharma, Pfizer, and Shire/Takeda. He has also received honoraria for speaking/participating in advisory boards from Bayer, Bioverativ/Sanofi, Biotest, CSL Behring, Grifols, LFB, Novo Nordisk, Octapharma, Pfizer, Roche, and Shire/Takeda.

AUTHOR CONTRIBUTIONS

LHP, BAK, GC, ACM, DN, and MC were the clinical investigators during mentor 6; MM was the clinical investigator during PRO-RBDD; SD and MLG were involved in the conduct of the study, in interpretation of study results, and the statistical analysis of the data. All authors directed the data analysis and the development of the manuscript and approved the final version of the manuscript.

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