Recombinant FXIII (rFXIII-A_2) Prophylaxis Prevents Bleeding and Allows for Surgery in Patients with Congenital FXIII A-Subunit Deficiency

Manuel Carcao[1] Carmen Altisent[2] Giancarlo Castaman[3] Katsuyuki Fukutake[4] Bryce A. Kerlin[5] Craig Kessler[6] Riitta Lassila[7] Diane Nugent[8] Johannes Oldenburg[9] May-Lill Garly[10] Anders Rosholm[11] Aida Inbal[12]

[1] Division of Haematology/Oncology and Child Health Evaluative Sciences, Research Institute, Hospital for Sick Children, University of Toronto, Toronto, Canada
[2] Haemophilia Unit, Vall d'Hebron University Hospital, Barcelona, Spain
[3] Department of Oncology, Careggi University Hospital, Center for Bleeding Disorders and Coagulation, Firenze, Italy
[4] Department of Laboratory Medicine, Tokyo Medical University, Tokyo, Japan
[5] Ohio State University College of Medicine, Nationwide Children's Hospital, Columbus, Ohio, United States
[6] Georgetown University Medical Center, Washington, DC, United States
[7] Coagulation Disorders Unit, Hematology and Comprehensive Cancer Center, University of Helsinki, Helsinki University Hospital, Helsinki, Finland
[8] Center for Inherited Blood Disorders and UC Irvine Medical School, Children's Hospital of Orange County, Orange, California, United States
[9] Institute for Experimental Haematology and Transfusion Medicine, University Clinic Bonn, Bonn, Germany
[10] Medical & Science, Biopharm, Global Development, Novo Nordisk A/S, Søborg, Denmark
[11] Biostatistics, Biopharm, Global Development, Novo Nordisk A/S, Søborg, Denmark
[12] Sackler Faculty of Medicine, Tel Aviv University, Tel Aviv, Israel

Address for correspondence Manuel Carcao, MD, Division of Haematology/Oncology, Hospital for Sick Children, Room 9416, 555 University Avenue, Toronto, Ontario, Canada M5G 1X8 (e-mail: manuel.carcao@sickkids.ca).

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Abstract

Recombinant factor XIII-A_2 (rFXIII-A_2) was developed for prophylaxis and treatment of bleeds in patients with congenital FXIII A-subunit deficiency. mentor™2 (NCT00978380), a multinational, open-label, single-arm, multiple-dosing extension to the pivotal mentor™1 trial, assessed long-term safety and efficacy of rFXIII-A_2 prophylaxis in eligible patients (patients with severe [$<$0.05 IU/mL] congenital FXIII subunit A deficiency) aged $\geq$6 years. Patients received 35 IU/kg rFXIII-A_2 (exact dosing) every 28 $\pm$ 2 days for $\geq$52 weeks. Primary endpoint was safety (adverse events including immunogenicity); secondary endpoints were rate of bleeds requiring FXIII treatment, haemostatic response after one 35 IU/kg rFXIII-A_2 dose for breakthrough bleeds and withdrawals due to lack of rFXIII-A_2 efficacy. Steady-state pharmacokinetic variables were also summarized. Elective surgery was permitted during the treatment period. Sixty patients were exposed to rFXIII-A_2; their median age was 26.0 years (range: 7.0–77.0). rFXIII-A_2 was well tolerated without any safety concerns. No non-neutralizing or neutralizing antibodies (inhibitors) against FXIII were detected. Mean annualized bleeding rate (ABR) was 0.043/patient-year. Mean spontaneous ABR was 0.011/patient-year. No patients withdrew due to lack of efficacy. Geometric mean FXIII trough level was 0.17 IU/mL. Geometric terminal half-life was 13.7 days. rFXIII-A_2 prophylaxis provided sufficient haemostatic coverage for 12 minor surgeries without the need for additional FXIII therapy; eight procedures were performed within 7 days of the patient's last scheduled rFXIII-A_2 dose, and four were performed 10 to 21 days after the last dose.

Keywords

- recombinant FXIII-A_2
- safety
- congenital FXIII deficiency
- prophylaxis
- surgery

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Introduction

Factor XIII (FXIII) is the terminal enzyme in the blood coagulation cascade and essential for cross-linking fibrin molecules to form an effective and stable blood clot. In plasma, FXIII circulates as an inactive heterotetramer composed of two catalytic FXIII A-subunits and two carrier FXIII B-subunits (FXIII-A_2B_2).[1,2] A deficiency or dysfunction of either the A or B subunit can result in FXIII deficiency. Congenital FXIII deficiency is a rare and serious autosomal recessive coagulation disorder with a high risk of life-threatening bleeding complications.[3] The prevalence of congenital FXIII deficiency is estimated to be approximately 1 in 1 to 2 million people worldwide.[4,5] Its incidence is much higher in certain parts of the world where consanguinity is common; this is particularly the case in Iran, which has the highest reported rate of FXIII deficiency.[6] Patients with congenital FXIII deficiency experience major spontaneous bleeding episodes (e.g. intracranial, intramuscular and gastrointestinal tract bleeds) more frequently than patients with most other rare bleeding disorders[4] and are at a high risk of intraoperative and delayed postoperative bleeds.[3,7,8]

The most common form of congenital FXIII deficiency is A-subunit deficiency, which is more severe and accounts for 95% of all severe deficiency, while B-subunit deficiency is very rare.[9] Patients with congenital FXIII deficiency require FXIII replacement to treat bleeds and, even more importantly, to prevent them (prophylaxis). The long half-life of FXIII, combined with the high risk of life-threatening bleeds associated with FXIII deficiency, makes prophylaxis an attractive and efficacious treatment option. Thus, prophylaxis is strongly recommended for all patients with severe FXIII deficiency.

Until recently, only plasma-derived sources of FXIII have been available (fresh frozen plasma [FFP], cryoprecipitate and plasma-derived FXIII [pdFXIII] concentrate). Such products carry a risk of pathogen transmission[10] and do not contain very concentrated forms of FXIII, such that large volumes need to be administered; pdFXIII concentrate contains approximately 62.5 U of FXIII/mL.

Recombinant FXIII (rFXIII-A_2, Novo Thirteen®; Tretten®, Novo Nordisk, Bagsværd, Denmark) is the only rFXIII product available; it contains a 13-fold higher concentration of FXIII (833 IU/mL) compared with pdFXIII.[11] rFXIII contains only the FXIII-A_2 subunit, offering a treatment option to prevent bleeds in patients with the much more common and more severe form of congenital FXIII deficiency—subunit-A deficiency.[12,13] rFXIII-A_2 is a highly purified product manufactured in *Saccharomyces cerevisiae*; no human or other mammalian blood or tissue products are used during its manufacture;[14,15] thus, FXIII-A_2 does not carry a risk of contamination with infectious agents, including viruses or prions.[16]

The efficacy and safety of rFXIII-A_2 in patients with this rare bleeding disorder have been demonstrated in a large-scale clinical trial programme (mentor™). In the pivotal mentor™1 trial with patients aged ≥6 years, prophylaxis with 35 IU/kg rFXIII-A_2 dosed every 4 weeks provided a good safety profile and resulted in a very low mean annualized bleeding rate (ABR) of only 0.138 bleeds/patient-year.[17] Similarly, the paediatric mentor™5 showed excellent efficacy and safety of prophylaxis with 35 IU/kg rFXIII-A_2 dosed every 4 weeks in patients aged <6 years.[18] Previous reports have shown similar pharmacokinetics (PK) in young children to that of older children and adults.[19,20] In the mentor™ programme to date, no patients treated with rFXIII-A_2 have developed FXIII-neutralizing antibodies (i.e., FXIII inhibitors).[21]

The mentor™2 extension trial is the largest clinical trial performed to date in patients with congenital FXIII deficiency. Here, we report the long-term safety and efficacy results for rFXIII-A_2 replacement therapy dosed every 4 weeks for bleed prevention and for treatment of breakthrough bleeds in children, adolescents and adults with congenital FXIII A-subunit deficiency. As mentor™2 permitted elective surgeries, we also report data on minor surgical procedures conducted in patients receiving rFXIII-A_2 prophylaxis during the trial.

Methods

As the mentor™2 trial is an extension of the pivotal mentor™1 trial, the methods have been reported previously,[17,22] but will be briefly described here.

Trial Conduct

Prior to the start of the trial, written informed consent was obtained from each patient. In addition, the protocol, consent form and patient information sheet were reviewed and approved according to local regulations by appropriate health authorities and independent ethics committees/institutional review boards. The trial was conducted in accordance with the U.S. Food and Drug Administration Code of Federal Regulations,[23] the International Conference on Harmonisation Good Clinical Practice Guidelines,[24] applicable regulatory requirements and the Declaration of Helsinki.[25]

Patients

Eligible patients were aged ≥6 years, weighed ≥20 kg and had a diagnosis of congenital FXIII A-subunit deficiency (FXIII A subunit level of <0.05 IU/mL with genetic confirmation demonstrating homozygosity or compound heterozygosity for FXIII A-subunit deficiency mutation[s]). Key exclusion criteria were any known congenital or acquired coagulation disorder, other than congenital FXIII deficiency; a known history of thromboembolic events; known inhibitors to FXIII; and any medical, social or psychosocial factors expected to impact compliance or safety.

Trial Design

The mentor™2 trial (►**Fig. 1**) was a multicentre, multinational, open-label, single-arm, multiple-dosing, non-randomized safety extension to the pivotal mentor™1 trial.[17] Important protocol amendments to mentor™2 included the addition of new patients who did not enrol from mentor™1 and the option to treat breakthrough bleeds with rFXIII-A_2 (introduced in 2012). Inclusion of re-enrolled patients was also allowed. The per-protocol prophylaxis dose of rFXIII-A_2 was 35 IU/kg (exact dosing given; achieving this required wastage of product when

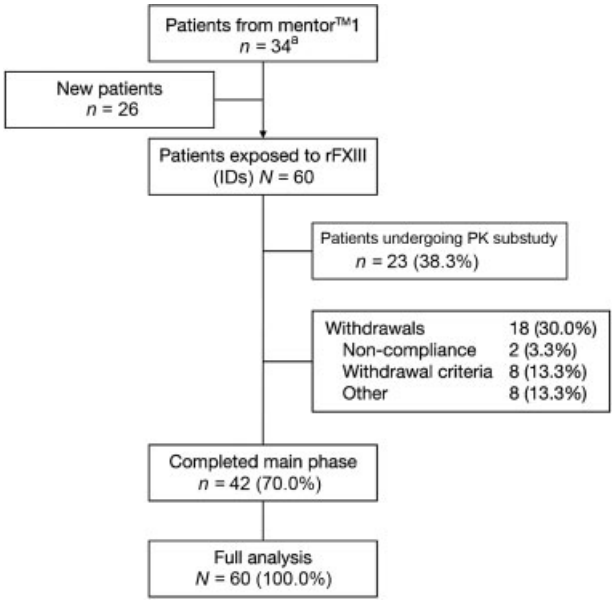

Fig. 1 Patient disposition. ID, identification; *N*, number of patients; PK, pharmacokinetics. Note: A total of 60 patients were enrolled and exposed in the trial, but three were later withdrawn and subsequently re-enrolled with new patient identifications, giving rise to a total of $N = 63$ patient identifications. [a]From the mentor™1 trial, there were 34 patients enrolled into mentor™2.

calculated amount was less than full vial of 2,500 U/vial), given intravenously every 28 ± 2 days for a minimum of 52 weeks. Patients who experienced breakthrough bleeds and required additional FXIII treatment were to be treated according to local standard practice, with the option for treatment with rFXIII-A_2 (a single 35 IU/kg dose was to be used, if possible).

Elective surgery was permitted during the treatment period. For any surgical procedure, if investigators judged that additional FXIII substitution was required, then pdFXIII was to be administered according to local practice. After any administration of pdFXIII to cover surgery, patients would continue with the original rFXIII-A_2 replacement schedule (i.e., dosing every 4 weeks), with the next dose administered 28 ± 2 days after the last scheduled dose.

Objectives and Endpoints

The primary objective was to assess the long-term safety (including any antibody development against rFXIII-A_2—if any) of replacement therapy every 4 weeks with rFXIII-A_2 when used for the prevention of bleeding episodes and for the treatment of breakthrough bleeds in patients with congenital FXIII A-subunit deficiency. Important endpoints comprised the assessment of all adverse events (AEs; both serious and non-serious, including any AEs of special interest, such as antibody development against rFXIII-A_2, medication errors or thromboembolic events). Additional secondary safety endpoints comprised any abnormalities in laboratory variables, vital signs and body measurements. Other secondary objectives were to evaluate the efficacy and summarize the steady-state PK profile of replacement therapy every 4 weeks with rFXIII-A_2. Laboratory sampling and medical assessments were performed every 12 weeks throughout the treatment period.

Efficacy assessments, performed by the patient or caregiver in consultation with the investigator, were based on a 4-point scale ("Excellent", "Good/Effective", "Moderate/Partly Effective" and "Poor"). Haemostatic outcome was only collected for bleeding episodes treated with rFXIII-A_2. The number of patients withdrawn due to lack of treatment efficacy was also recorded.

The Berichrom® FXIII chromogenic activity assay (Siemens Healthcare, Erlangen, Germany) was used to measure FXIII activity.[17,22] A subgroup of patients participated in steady-state PK assessments in which blood samples were collected at pre-dose, 1 and 2 hours and at 3, 7, 14, 21 and 28 days post-dose. Only patients who had already received a minimum of 10 doses of rFXIII-A_2 participated in the PK assessment. PK methods are explained in more detail in Kerlin et al.[22]

For patients undergoing elective surgery, the following assessments were made during the perioperative period: type and severity (major/minor) of surgery, timing of the surgery in relation to the last rFXIII-A_2 dose, haemoglobin levels pre- and post-surgery, dose regimen of pdFXIII, additional haemostatic drugs used, the amount of blood and blood products transfused and AEs. Minor surgery was defined as any invasive operative procedure in which only skin, mucous membranes or superficial connective tissue was manipulated. All AEs, concomitant medication and bleeds were monitored up to 4 weeks after the date of surgery.

Antibody Assays

An anti-rFXIII antibody enzyme-linked immunosorbent assay (ELISA) and an in vitro neutralizing antibody assay were used for immune response screening, confirmation and antibody characterization.[17]

Statistical Analysis

The sample size for this study was estimated to cover the patients migrating from mentor™1 and augmented by 10 to 20 additional patients who had not originally participated in mentor™1.

Sixty unique patients enrolled into mentor™2. All patients were included in the full analysis set and all safety endpoints were summarized using descriptive statistics. As in mentor™1,[17] ABR was based on the number of bleeding episodes requiring FXIII treatment and was evaluated by a Poisson regression model with baseline age as a covariate and total observation time as an offset. The number of bleeds requiring treatment with a FXIII-containing product, haemostatic response to FXIII-A_2 treatment and number of patients withdrawn due to lack of treatment efficacy were tabulated. PK variables were calculated based on non-compartmental methods without prior baseline adjustments, as described by Kerlin et al.[22]

Results

Patients

Sixty patients (16 children aged 7 to <18 years and 44 adults aged 18–77 years) from 34 centres in 12 countries (Austria, Canada, Finland, France, Germany, Israel, Italy, Japan, Spain,

Table 1 Baseline characteristics

	Total
Patients (*N*)[a]	60
Age, median (range), y	26.0 (7.0–77.0)
Adults (≥18 y of age); adolescents/children (6 to <18 y of age)	44:16
Sex (female:male)	22:38
Weight, mean (SD), kg	67.7 (19.9)
Body mass index, mean (SD), kg/m^2	24.3 (5.3)
Race, *N* (%)	
Caucasian	34 (56.7)
Asian	9 (15.0)
Black or African American	6 (10.0)
American Indian or Alaskan Native	1 (1.7)
Other	6 (10.0)
Unknown	4 (6.7)

Abbreviations: *N*, number of patients; SD, standard deviation.
[a]Includes three patients who withdrew from the trial and were subsequently re-enrolled with new patient IDs.

Table 2 Summary of adverse events (AEs)

Summary	Number of patients[a]/ events
All AEs	56 (93.3%); 920
AEs by severity	
Severe	12 (20%); 16
Moderate	26 (43.3%); 119
Mild	54 (90%); 785
AEs by relationship to rFXIII-A_2 treatment	
Probably or possibly related	6 (10%); 7
Unlikely related	56 (93.3%); 890
Missing	6 (10%); 23
AEs leading to withdrawal	0

Abbreviations: rFXIII-A_2, recombinant factor XIII-A_2; %, percentage of patients with AEs.
Note: Non-serious AEs that were symptoms of other AEs were not included.
[a]When summarizing AEs, the three re-enrolled patients were assigned their initial patient IDs to avoid double counting.

Switzerland, UK and United States) were enrolled and exposed to rFXIII-A_2 between 21 September 2009 and 20 October 2015. Thirty-four patients were enrolled from the mentor™1 trial and an additional 26 newly enrolled patients were included (►**Fig. 1**). The median age of patients at enrolment was 26.0 years (range: 7.0–77.0 years; ►**Table 1**); 16 (26.7%) patients were younger than 18 years. The majority of patients were male ($n = 38$; 63.3%) and most were Caucasians ($n = 34$; 56.7%).

Eighteen patients (30.0%) withdrew from the trial (►**Fig. 1**). Three withdrew because they became pregnant and five because they failed to comply with the trial treatment or protocol; thus, these eight patients met the protocol-mandated withdrawal criteria. Two patients were withdrawn due to non-compliance as they were out of the country for 7 weeks. An additional eight patients withdrew due to "other" reasons: patient/family withdrew consent without specifying a reason ($n = 5$); patient elected to stop study treatment and receive commercially available rFXIII-A_2 ($n = 1$); patient undertook a yearlong trip, so could not remain in the study ($n = 1$); and patient wished to be treated with commercially available pdFXIII ($n = 1$). Of the 18 patients who withdrew, three later re-enrolled onto the mentor™2 trial and were given new patient IDs (reasons for initial withdrawal of these patients were patient wishes, pregnancy and compliance issues).

Safety

Patients were exposed to a total of 2,410 rFXIII-A_2 doses, corresponding to 186.5 patient-years of cumulative exposure (an average of 3.1 [range: 0.15–5.37] years per patient). rFXIII-A_2 prophylaxis once every 4 weeks was well tolerated. There were 920 treatment-emergent AEs reported in 56 (93.3%) patients (►**Table 2**); headache and nasopharyngitis were the most common AEs. The vast majority of AEs (904/920; 98.3%) were mild or moderate in severity, while 16/920 (1.7%) were severe. Of the 920 AEs, 19 (occurring in 12 patients) were considered serious, based on seriousness criteria. All 19 serious AEs (SAE) were evaluated as unlikely to be related to rFXIII-A_2 treatment (►**Table 3**); all of these patients with SAEs continued FXIII-A_2 treatment at the same dose. Seven AEs in six patients were evaluated as being possibly/probably related to rFXIII-A_2 (►**Table 3**); however, all six patients recovered. There were 12 AEs of special interest in eight patients, 10 of which were small deviations from the correct dose, ranging from 28.2 to 37.6 IU/kg (►**Table 3**). One event of overdose (~2.3 times the planned dose) was evaluated by the investigator as mild and did not have any clinical consequences. All AEs of special interest were considered mild and the patients recovered. None of these medication errors were judged to have had an impact on the results of the trial.

No anti-rFXIII antibodies (neutralizing or non-neutralizing) were detected in the mentor™2 trial. There were no thromboembolic events, fatal AEs or AEs leading to withdrawal (►**Table 2**) and no anaphylactic or allergic reactions to rFXIII-A_2.

Efficacy

No patients were withdrawn due to lack of rFXIII-A_2 efficacy.

During the trial, the rate of FXIII treatment requiring bleeds was low: eight bleeds in seven patients. Six bleeds were trauma induced and two were spontaneous (►**Table 4**). The spontaneous bleeds were epistaxis (picked nose) in an 8-year-old patient, and a muscular bleed (after considerable physical work) in a 25-year-old patient. There was one intracranial bleeding episode that was the result of a head injury in a severe car accident, occurring 4 days after the patient's last prophylactic dose of rFXIII-A_2. The intracranial bleed was considered unrelated to rFXIII-A_2 treatment by the

Table 3 Details of serious adverse events (SAEs), possible/probable treatment-related adverse events (AEs) and medical events of special interest

Type of AE	*N*	Description	Days since last dose
SAE			
Falls or accidents	10	• Five SAE related to motor vehicle accidents in two patients (female, aged 23; male, aged 29)	• 12 (female, aged 23) and 4 (male, aged 29)
		• Two SAE due to fall/chest injury in one patient (female, aged 48)	• 7 and 23, respectively
		• Two SAE related to a head injury in one patient (female, aged 8[a])	• 8 and 25, respectively
		• One SAE related to a laceration to the head in one patient (male, aged 12)	• 24
Left inguinal hernia	1	Hernia surgical repair under rFXIII-A_2 prophylaxis (male, aged 50)	• 33
Sigmoid diverticulitis	1	Female, aged 57	• 24
Worsening of bilateral chronic otitis media	1	Male, aged 55	• 11
Ectopic pregnancy	1	Led to termination of pregnancy at gestation week 7 (female, aged 25)	• 28
Cerebral ischaemia	1	Secondary to accidental, work-related carbon monoxide poisoning (male, aged 60; history of diabetes mellitus)	• 8
Headache	1	Admitted to hospital due to headaches (female, aged 8[a])	• 25
Suicide attempt	1	Overdose with aspirin and ibuprofen (female, aged 14)	• 20
Atrial septal defect and persistent ductal arteriosus	2	277 days (8 months) after a woman (aged 24) withdrew from trial due to pregnancy her newborn was born with defects	• 277
Possible/probable rFXIII-A_2 treatment-related AE			
Incorrect dose	1	Accidentally dosed 3.0 mL instead of 3.2 mL (male, aged 15)	• 28
Overdose	1	Approximately 2.3 times overdose (80.03 IU/kg instead of 35 IU/kg), no adverse clinical effect (male, aged 8[b])	• 29
Limb injury	1	Bleeding under toenail due to trauma (male, aged 22)	• 28
Arthralgia	1	Left knee pain (male, aged 8[b])	• 22
Leukopenia	1	Asymptomatic leukopenia (female, aged 15)	• 28
Alanine aminotransferase increased	1	Two of 42 tests with elevated values of 52 and 61 U/L (male, aged 26; reference range 6–43 U/L)	• 28
Blood alkaline phosphatase increased	1	Male, aged 63, with chronic hepatitis and a liver cyst (elevated values between 126–154 U/L; reference range 35–125 U/L)	• 28
AEs of special interest			
Incorrect dose	10	Small deviations from the correct dose (seven patients)	–
Overdose	1	Approximately 2.3 times overdose (80 IU/kg instead of 35 IU/kg), no adverse clinical effect (male, aged 8[b])	• 29
Product preparation error	1	Reconstitution with saline (not sterile water; female, aged 14)	• 32

Abbreviations: *N*, number of AEs; rFXIII-A_2, recombinant factor XIII-A_2.
[a]Two different AEs in the same patient.
[b]There were two different AEs in this patient ("arthralgia" and "overdose"); the AE "overdose" was considered a possible/probable rFXIII-A_2treatment-related AE and also an AE of special interest. Patient age refers to age at baseline of the mentor™2 trial.

investigator. No internal organ bleeds or severe gastrointestinal bleeds occurred. The majority of patients (four of seven) who had a FXIII treatment requiring bleed were younger than 18 years (►**Table 5**). Three bleeds occurred within the first 14 days post-rFXIII-A_2 infusion when FXIII levels were predicted to be greater than 0.3 IU/mL in most patients,[22] while five occurred between days 17 and 24 post-rFXIII-A_2 infusion. As such, the mean ABR for patients on study (treated with 35 IU/kg rFXIII-A_2 every 4 weeks) was 0.043 (0.032 and 0.011 for traumatic and spontaneous bleeds/patient-year, respectively; ►**Table 4**). This mean ABR implies only one bleed per 23 patient-years, while the mean spontaneous bleed ABR of 0.011 bleeds/patient-year implies one spontaneous bleed per 91 patient-years.

Table 4 Bleeding episodes requiring treatment with FXIII

	Total
Number of patients	60
Number of patients with bleeds	7
All bleeds	
Number of bleeds	8
Mean ABR[a]	0.043
Spontaneous bleeds	
Number of bleeds	2
Mean ABR[a]	0.011
Traumatic bleeds	
Number of bleeds	6
Mean ABR[a]	0.032

Abbreviations: ABR, annualized bleeding rate; FXIII, factor XIII.
[a]Calculated as the number of bleeds divided by the total patient-years (Poisson estimate).

One traumatic bleed was successfully treated with rFXIII-A_2: the patient suffered a trauma-induced muscular bleed 24 days after the last rFXIII-A_2 dose (►**Table 5**) and a single rFXIII-A_2 dose of 35 IU/kg was administered. The haemostatic response was rated as excellent. No additional FXIII-containing products were necessary to treat the bleed.

Pharmacokinetic Analysis

Steady-state PK data with rFXIII-A_2 have been previously reported.[22] In the current mentor™2 trial, evaluation of all available pre-dose samples from all 60 patients revealed a geometric mean FXIII trough level of 0.17 IU/mL (coefficient of variation: 0.37). In addition, the geometric mean terminal half-life of rFXIII-A_2 was 13.6 (range: 10.1–24.6) days, in line with previously reported PK results for rFXIII-A_2.[22] FXIII trough levels below 0.10 IU/mL were detected sporadically throughout the trial: among a total of 2,245 trough level measurements, only 65 (2.9%) were less than 0.10 IU/mL. In all patients, individual mean FXIII trough levels were greater than 0.10 IU/mL.

Surgery

Twelve minor surgical procedures were performed in nine patients: post-traumatic surgical repair in one patient, and 11 other minor (mostly dental) procedures in eight patients (►**Table 6**). Median (range) patient age at the time of surgery was 31 (19–59) years. Eight of the 12 procedures were performed within 7 days of the patient's last scheduled rFXIII-A_2 dose, and four were performed 10 to 21 days after the last dose. No additional substitution with pdFXIII or rFXIII-A_2 was given for any procedure. Concomitant antifibrinolytics were used in four procedures (tooth extractions [$n = 3$] and colonoscopy [$n = 1$]). In three patients, haemoglobin levels were available before (9.9, 11.8 and 15.8 g/dL, respectively) and immediately after surgery (10.3, 11.6 and 16.5 g/dL, respectively), demonstrating that haemoglobin did not decline in association with surgery. The longest period between a rFXIII-A_2 dose and minor surgery was 3 weeks; based on PK modelling, it was estimated that the patient would have had a FXIII activity level of 0.19 IU/mL (►**Table 6**). There were no reports of unexpected blood loss, requirements for transfusion with blood or blood products and no surgical complications related to FXIII deficiency or treatment for any of these 12 procedures.

Discussion

This paper presents the long-term safety and efficacy results from the mentor™2 extension trial—the largest dataset of any clinical trial in FXIII deficiency involving 186.5 patient-years' worth of data. This is also the first report on minor surgical procedures conducted in patients receiving rFXIII-A_2 prophylaxis.

Table 5 Details of bleeding episodes requiring treatment with FXIII, arranged in ascending age of patients at time of bleed

Age[a]	Gender	Bleed type	Days since last dose	Description	Treatment
8[b]	Female	Traumatic	7	Bruising on arm/soft tissue	pdFXIII
8[b]	Female	Spontaneous	19	Spontaneous epistaxis (possibly after picking her nose)	pdFXIII
10	Male	Traumatic	17	Injury (bruises) to left knee while playing soccer	pdFXIII
12	Male	Traumatic	24	Forehead laceration due to fall on a staircase	pdFXIII
16	Male	Traumatic	24	Haematoma and swelling of right forearm after a fall	rFXIII-A_2
23	Female	Traumatic	12	Bruises to hip, lumbar spine, sternum and head after motor vehicle accident	pdFXIII
25	Male	Spontaneous	20	Muscular bleed in left shoulder after "massive physical work"	pdFXIII
29	Male	Traumatic	4	Subarachnoid subdural and extradural haemorrhage after motor vehicle accident	Cryoprecipitate

Abbreviations: FXIII, factor XIII; pdFXIII, plasma-derived FXIII.
[a]Age at baseline of the mentor™2 trial.
[b]The same patient.

Table 6 Minor surgical procedures undertaken during mentor™2

Age[a]	Gender	Surgical procedure	Days since last rFXIII-A_2 dose	Geometric mean FXIII activity level (IU/mL)
44	Female	Extraction of tooth 18 and tooth root 17	0	0.83
59	Female	Extraction of two teeth	0	0.83
57[c]	Male	Ulnar nerve carpal tunnel syndrome repair	1	0.65[b]
29	Female	Colonoscopy	1	0.65[b]
25	Male	Circumcision revision	1	0.65[b]
33[d]	Female	Tooth extraction	2	0.62[b]
31	Male	Upper left molar extraction	4	0.54[b]
24[e]	Female	Extraction of right upper wisdom tooth	7	0.43
19	Male	Suture of traumatic cut to left forearm	10	0.34[b]
31[d]	Female	Wisdom tooth extraction	11	0.32[b]
25[e]	Female	Extraction of left upper wisdom tooth	17	0.23[b]
58[c]	Male	Removal of polyp from right internal ear and partial removal of polyp from left internal ear	21	0.19

Abbreviations: FXIII, factor XIII; rFXIII-A_2, recombinant factor XIII-A_2.
[a]Age at the time of surgery.
[b]Log-linear interpolated values based on the geometric mean FXIII activity published previously,[22] which assumes an exponential decay between two measurements.
[c,d,e]The same patients.

Safety

Inhibitor (neutralizing antibody) development is the most serious threat associated with the treatment of FXIII deficiency. This has been reported in several patients treated with pdFXIII-containing products.[26] In the current mentor™2 trial as well as in the entire mentor™ trial programme, no patients have developed inhibitors and in the entire mentor™ trial programme only five individuals, all younger than 18 years, have developed transient, non-neutralizing antibodies to rFXIII-A_2 [reviewed in Carcao et al[21]]. These antibodies have been shown to have no inhibitory activity and the individuals did not experience any AEs or bleeding as a result of or in association with these antibodies.[11] It should be noted that no additional patients developed non-neutralizing antibodies in this current mentor™2 trial.

Efficacy

In the mentor™2 trial, rFXIII-A_2 prophylaxis (35 IU/kg every 28 $\pm$ 2 days) resulted in high FXIII trough levels in all patients and consequently excellent haemostatic coverage. This was evident in the absence of spontaneous intracranial, internal organ or severe gastrointestinal bleeds during the mentor™2 trial encompassing 186.5 patient-years. Furthermore, there were only two spontaneous bleeds over the 6-year trial duration. It should be noted that on this prophylactic regimen (35 IU/mL every 28 $\pm$ 2 days), patients would be expected to have FXIII levels in the range of normal (>0.5 IU/mL) for 1 week following an infusion; after this, their FXIII levels would be expected to be in the mild deficiency range (>0.3–0.5 IU/mL) for another week before falling into the moderate deficiency range (0.05–0.3 IU/mL). At no time would any patient experience a FXIII level in the severe (<0.05 IU/mL) deficiency range.

No patients withdrew due to lack of efficacy of rFXIII-A_2 treatment. The spontaneous ABR reported in mentor™2 is comparable to that reported for the marketed pdFXIII product.[27,28]

The treatment of breakthrough bleeds with rFXIII-A_2 was first introduced in 2012 as a protocol amendment during the mentor™2 trial. Given the rarity of bleeds in the mentor™2 trial, only one bleed was treated with rFXIII-A_2; the haemostatic outcome was excellent. Similarly, a recent case study also reported the rapid and successful treatment of a bleed (major intramuscular bleed) with 35 IU/kg rFXIII-A_2 in a patient who was not on the mentor™2 trial.[29] Further case reports would provide valuable information on the effectiveness of rFXIII-A_2 for the treatment of breakthrough bleeds.

Surgery

To date, the only published data on surgery in FXIII deficiency derive from a report of six patients receiving pdFXIII to cover major or minor procedures.[7] As elective surgery was permitted during mentor™2, this trial provided the first data on minor surgical procedures performed in patients receiving rFXIII-A_2 prophylaxis. All 12 minor procedures (1 post-traumatic surgical repair and 11 other procedures) were performed within 1 to 21 days of the last scheduled rFXIII-A_2 dose and additional FXIII substitution was not administered for any of these procedures. In a few of these, anti-fibrinolytic therapy was also given. These findings suggest that prophylaxis with 35 IU/kg rFXIII-A_2 every 4 weeks provides sufficient haemostatic coverage for the perioperative management of minor surgical procedures in patients with congenital FXIII deficiency, without the need for

additional FXIII treatment. While additional FXIII treatment was not deemed necessary by the investigators for surgeries in this study, all FXIII treatment options should still be considered on an individual patient basis.

Of the worldwide number of known patients diagnosed with congenital FXIII deficiency, 4.5% participated in the mentor™2 trial.[30] Despite that, a potential limitation was the low number of children/adolescents ($n = 16$) participating in the mentor™2 trial; however, the current mentor™2 results support those from the mentor™5 trial, which showed efficacy and safety in six paediatric patients aged 1 to 4 years, in which rFXIII-A_2 prophylaxis was well tolerated and provided appropriate haemostatic coverage; the ABR was 0.[18]

In conclusion, results from the multicentre, multinational mentor™2 extension trial showed that rFXIII-A_2 prophylaxis every 4 weeks is well tolerated without identified safety issues; bleeding rates are very low during prophylaxis among patients of all ages with congenital FXIII A-subunit deficiency. None of the patients receiving rFXIII-A_2 as part of the mentor™2 study developed either non-neutralizing or neutralizing antibodies, or experienced spontaneous intracranial haemorrhages, severe bleeds, thromboembolic events, anaphylactic or allergic reactions, exposure to pathogen transmission or any significant changes in haematology or clinical chemistry. In addition, while limited to 12 procedures in nine patients, initial data from mentor™2 for minor surgeries performed in patients receiving rFXIII-A_2 prophylaxis are favourable, and add to the very limited body of evidence currently available on surgery in FXIII-deficient patients.[21]

What is known about this topic?

- Congenital FXIII A-subunit deficiency is a rare, autosomal recessive coagulation disorder with a high risk of life-threatening bleeding.
- Prophylaxis is the preferred treatment option for patients with FXIII A-subunit deficiency.
- rFXIII-A_2 is the only recombinant FXIII A_2-subunit product available to prevent bleeds in patients with congenital FXIII A-subunit deficiency.

What does this paper add?

- The mentor™2 trial represents the largest clinical trial dataset in congenital FXIII A-subunit deficiency, involving 60 unique patients with the disorder.
- rFXIII-A_2 35 IU/kg was given once every 4 weeks (for a total of 186.5 cumulative patient-years) and was well tolerated without hypersensitivity reactions, thromboembolic events or anti-FXIII antibody development.
- rFXIII-A_2 provided excellent long-term haemostatic efficacy with a geometric mean FXIII trough of 0.17 IU/mL, with patients demonstrating a spontaneous ABR that corresponded to one bleed per 91 patient-years. rFXIII-A_2 prophylaxis allowed for effective haemostasis in 12 minor surgical procedures in nine patients without the need for additional FXIII treatment. This is the first report on the effectiveness of rFXIII-A_2 in the surgical setting.

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Author Contributions
M.-L. Garly and A. Rosholm: representing Novo Nordisk A/S study concept and protocol. A. Rosholm: statistical analyses. M. Carcao, C. Altisent, G. Castaman, K. Fukutake, B. Kerlin, C. Kessler, R. Lassila, D. Nugent, J. Oldenburg and A. Inbal: data acquisition. M. Carcao, C. Altisent, G. Castaman, K. Fukutake, B. Kerlin, C. Kessler, R. Lassila, D. Nugent, J. Oldenburg, M.-L. Garly, A. Rosholm and A. Inbal: analysis and interpretation of data. M. Carcao: manuscript drafting. M. Carcao, C. Altisent, G. Castaman, K. Fukutake, B. Kerlin, C. Kessler, R. Lassila, D. Nugent, J. Oldenburg, M.-L. Garly, A. Rosholm and A. Inbal: critical revision and final draft of manuscript.

Conflicts of Interest
M. Carcao has received research funding from Baxalta (now a part of Shire), Bayer HealthCare, Biogen, Novo Nordisk and Pfizer; additionally, he has received honoraria for advisory board participation and for speaking from Baxalta (now a part of Shire), Bayer HealthCare, Biogen, Biotest, CSL Behring, Novo Nordisk, Octapharma and Pfizer. C. Altisent has received honoraria or consultation fees from Baxalta (now a part of Shire), Bayer HealthCare, CSL Behring, Grifols, NovoNordisk, Octapharma, Pfizer and Sobi. G. Castaman has received honoraria for advisory board participation and for speaking from Baxalta (now a part of Shire), Bayer HealthCare, Biogen, CSL Behring, Novo Nordisk, Pfizer and Sobi, and has received research support from CSL Behring and Pfizer. K. Fukutake has received research grants from Baxalta (now a part of Shire), Bayer HealthCare, Biogen, CSL Behring, Japan Blood Products Organization, Kaketsuken, Novo Nordisk, Ortho Clinical Diagnostics and Pfizer, as well as honoraria and personal fees for participating in educational events, advisory board and publications from Abbott, Baxalta (now a part of Shire), Bayer HealthCare, Biogen, CSL Behring, Fujirebio Inc., Kaketsuken, LSI Medience, Novo Nordisk, Pfizer, Roche Diagnostics, Sekisui Medical, Siemens, SRL Inc. and Torii Pharmaceuticals outside the submitted work. B. Kerlin has served as an advisory board member for Bayer Healthcare US and Baxalta (now part of Shire), and has received research support from Novo Nordisk A/S and the CSL Behring foundation. C. Kessler has received grants from Baxalta (now a part of Shire), Bayer HealthCare, Biogen, Novo Nordisk, Octapharma, Pfizer and Roche. In addition, he has received honoraria and personal fees for participating in educational events and advisory boards from Baxalta (now a part of Shire), Bayer Healthcare, Biogen, CSL Behring, Grifols, Novo Nordisk, Octapharma, Pfizer and Roche. R. Lassila has received honoraria for advisory board participation from Baxalta (now a part of Shire), CSL Behring, Novo Nordisk, Octapharma and Pfizer. D. Nugent has no conflicts of interest to declare. J. Oldenburg has

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