Efficacy and safety of a new human fibrinogen concentrate in patients with congenital fibrinogen deficiency: an interim analysis of a Phase III trial

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BACKGROUND: Fibrinogen concentrate is the preferred choice for fibrinogen replacement in congenital fibrinogen deficiency. This study investigated hemostatic efficacy of a new plasma-derived, double virus-inactivated (using two dedicated virus inactivation/elimination steps) human fibrinogen concentrate for on-demand treatment of bleeding episodes (BEs) and surgical prophylaxis.

STUDY DESIGN AND METHODS: In this planned interim analysis of a prospective, multinational Phase III study (NCT02267226), 13 patients with afibrinogenemia (≥12 years) received fibrinogen concentrate (FIBRYGA, Octapharma AG). Hemostatic efficacy was assessed by investigators and an independent data monitoring and endpoint adjudication committee (IDMEAC) using objective four-point criteria and by thromboelastometry maximum clot firmness (MCF).

RESULTS: Fibrinogen concentrate was used on-demand to treat 23 BEs in 11 patients, with 21 (91.3%) requiring a single infusion only. Treatment success was 95.7% (90% confidence interval [CI], 0.81-1.00; assessment missing for one BE) by investigators and 100% (90% CI, 0.88-1.00) by IDMEAC. Mean MCF increased significantly from 0.0 to 6.5 mm (95% CI, 5.65-7.40; $p < 0.0001$) at 1 hour postinfusion of a median (range) dose of 58.8 (33.9-101.7) mg/kg per BE. Four patients received fibrinogen concentrate as surgical prophylaxis, with intraoperative and postoperative treatment success rated 100% (90% CI, 0.50-1.00) by investigators and IDMEAC (median [range] dose per surgery 93.5 [34.1-225.4] mg/kg). No additional hemostatic interventions were required. No deaths, thromboses, or seroconversions were reported.

CONCLUSION: These data showed that the new fibrinogen concentrate was efficacious for on-demand treatment of acute bleeding and surgical prophylaxis in congenital afibrinogenemia patients.

ABBREVIATIONS: AE(s) = adverse event(s); BE(s) = bleeding episode(s); FAS = full analysis set; IDMEAC = independent data monitoring and endpoint adjudication committee; IVR = in vivo recovery; MCF = maximum clot firmness.

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Fibrinogen is the most abundant clotting factor in the human circulation. It plays a pivotal role in hemostasis by promoting clot formation, stabilization, and platelet (PLT) aggregation.[1] Fibrinogen is converted to insoluble fibrin monomers in a polymerization reaction catalyzed by the serine protease thrombin. The resultant fibrin monomers form a stable, cross-linked lattice with PLTs that impedes, and ultimately stops, blood loss.

Physiologic levels of fibrinogen are typically in the range 150 to 450 mg/dL.[2] In a number of inherited disorders, however, quantitative defects in circulating fibrinogen mean that levels are reduced (hypofibrinogenemia; 50 to <150 mg/dL)[3] or completely absent (afibrinogenemia). The quality of circulating fibrinogen may also be affected (dysfibrinogenemia). Afibrinogenemia, the rarest fibrinogen deficiency, has an estimated prevalence of one in 1 million[4,5] and is often diagnosed in the newborn period. It is associated with a variable bleeding tendency that may be life-threatening and is the result of spontaneous or trauma-related bleeds,[3] most frequently affecting the umbilical cord, skin, gastrointestinal and genitourinary tracts, and muscles/joints.[4,6-8] Bleeding in patients with hypofibrinogenemia follows a similar clinical presentation but is generally milder and may be asymptomatic prior to a bleeding episode (BE), typically the result of trauma or surgery.[3,4]

Treatment of patients with congenital fibrinogen deficiency centers on supplementation of endogenous fibrinogen levels. Although infusion with fresh-frozen plasma (FFP) or cryoprecipitate remain options for fibrinogen replacement and are used in some countries,[9,10] their use is limited by variable fibrinogen content, large infusion volumes, or risk of pathogen transmission.[11,12] Instead, fibrinogen supplementation with human fibrinogen concentrate is now considered the treatment of choice for patients with congenital fibrinogen deficiency.[13-15] Compared with cryoprecipitate (and FFP), human fibrinogen concentrate is of greater purity, does not require blood group matching, can be prepared and administered more quickly, and enables more accurate and standardized dosing.[11,16]

For patients with congenital fibrinogen deficiency, the primary therapeutic goal of fibrinogen supplementation is to achieve plasma fibrinogen levels of approximately 100 mg/dL for a minor BE or minor surgery and 150 mg/dL for a major BE or major surgery, as described by Peyvandi and colleagues.[17] To this end, fibrinogen concentrate is used as supplementation for on-demand treatment of acute BEs and for surgical prophylaxis.[18,19]

A new plasma-derived human fibrinogen concentrate has been developed that, unlike alternative concentrates currently licensed for use, is prepared using two dedicated virus inactivation/elimination steps (solvent/detergent and nanofiltration). In a recent Phase II study addressing pharmacokinetics, surrogate efficacy, and safety of this new human fibrinogen concentrate, we reported larger area under the concentration–time curve and slower clearance for the new fibrinogen concentrate relative to active control (a different fibrinogen concentrate) in patients with afibrinogenemia.[20] Both fibrinogen concentrates were comparable in other pharmacokinetic parameters, ability to restore clot strength (maximum clot firmness [MCF]), and safety and tolerability.[20]

Here, we now report the results of a planned interim analysis of the follow-up, ongoing, multinational, open-label Phase III efficacy and safety study in patients with congenital fibrinogen deficiency. For the first time in this rare disease setting, we use objective efficacy criteria as a robust method to determine the hemostatic efficacy of the new fibrinogen concentrate for on-demand treatment of acute BEs and for prophylaxis before surgery.

MATERIALS AND METHODS

Study design

FORMA-02 (NCT02267226) is an ongoing multinational, multicenter, prospective, open-label, uncontrolled, Phase III efficacy and safety study in patients with congenital fibrinogen deficiency. The study began in October 2014 and is being conducted across 13 centers in nine countries (Bulgaria, India, Iran, Lebanon, Russia, Saudi Arabia, Turkey, United Kingdom, United States) with a target enrollment of 24 patients. This planned interim analysis included 13 patients with afibrinogenemia.

All patients received fibrinogen concentrate (FIBRYGA, Octapharma AG) to treat an acute BE or as surgical prophylaxis. Recommended intravenous (IV) injection of fibrinogen concentrate was individually dosed to achieve a target plasma fibrinogen level of 100 mg/dL (accepted lower limit, 80 mg/dL) for minor bleeding or minor surgery and 150 mg/dL (accepted lower limit, 130 mg/dL) for major bleeding or major surgery. Patients therefore received one or more infusions of fibrinogen concentrate for each BE or surgery. After the first and each subsequent infusion, patients were monitored over a treatment observation period. During this period, the recommendation for additional infusions was determined by measuring plasma fibrinogen levels daily and also within 1 hour after each additional infusion. The treatment observation period for each patient was defined according to the severity of the event, lasting at least 3 days for minor bleeding or minor surgery and at least 7 days for major bleeding or major surgery. The actual treatment duration was determined by the investigator based on their judgment of the patient's condition. All bleeding patients were followed for a 30-day safety observation period.

Fibrinogen concentrate was given as an IV bolus injection at a maximum speed of 5 mL/min. Study medication was packed and labeled according to local regulations in vials containing 1 g of lyophilized fibrinogen concentrate powder, reconstituted with 50 mL of water for injection. A single batch of fibrinogen concentrate was used throughout the study.

The study was conducted in accordance with Good Clinical Practice (CPMP/ICH/135/95), the Declaration of Helsinki and national law, and under a US Investigational New Drug (IND) application (IND number 014777). In accordance with local requirements, the study protocol received written approval from the country regulatory authorities, independent ethics committees, and institutional review boards. All patients gave written informed consent.

Study population and inclusion and exclusion criteria

Patients at least 12 years old with a documented diagnosis of congenital fibrinogen deficiency—manifesting as afibrinogenemia or severe hypofibrinogenemia—or with plasma fibrinogen activity of less than 50 mg/dL (or levels below the detection limit of the local assay) were included in the study if they were expected to require on-demand treatment for an acute BE (spontaneous or after trauma) or for surgical prophylaxis before planned elective surgery. Primary exclusion criteria were a life expectancy of less than 6 months, diagnosis with a bleeding disorder other than congenital fibrinogen deficiency (including dysfibrinogenemia), prophylactic treatment with a fibrinogen concentrate, or treatment with any fibrinogen concentrate or other fibrinogen-containing blood product within 2 weeks before the start of treatment for the BE or surgery. Patients were also excluded if they had been treated with any coagulation-active drug within 1 week before treatment for the BE or surgery or had a history of hypersensitivity to the study medication or human plasma proteins.

Objectives

The objectives of the study were to demonstrate the efficacy of fibrinogen concentrate for on-demand treatment of acute BEs and prevention of intra- and postoperative bleeding. We also aimed to evaluate the association between clinical assessment of hemostatic efficacy and the surrogate efficacy endpoint of plasma MCF and to investigate the peak target plasma fibrinogen levels during treatment and the safety of fibrinogen concentrate.

Hemostatic efficacy

Clinical assessment

Hemostatic efficacy of fibrinogen concentrate for on-demand treatment and surgical prophylaxis was conducted using separate objective four-point rating criteria. These criteria are based on key events related to bleeding, including cessation of bleeding, use of other hemostatic interventions, and hemoglobin (Hb) level. The use and success of such criteria have been reported for the clinical investigation of other congenital bleeding disorders.[21,22] All clinical efficacy assessments were also adjudicated by an independent data monitoring and endpoint adjudication committee (IDMEAC). Below we provide a detailed summary of each of the criteria sets (the complete, verbatim rating criteria as used in the clinic setting are provided in Table S1, available as supporting information in the online version of this paper).

For on-demand treatment of BE, hemostatic efficacy was assessed by the treating physician: excellent (immediate and complete cessation of bleeding in the absence of other hemostatic intervention or <10% decrease in Hb compared to before infusion), good (eventual complete cessation of bleeding or <20% decrease in Hb), moderate (incomplete cessation of bleeding and additional hemostatic intervention required or 20%-25% decrease in Hb), and none (no cessation of bleeding and alternative hemostatic intervention required or >25% decrease in Hb).

For surgical prophylaxis, intraoperative efficacy was assessed by the surgeon at the end of surgery, evaluating intraoperative blood loss (excluding due to unexpected complications) relative to the same type of procedure performed in an age- and sex-matched patient with normal hemostasis: excellent (blood loss was lower than or equal to the average expected), good (blood loss was higher than average expected but lower or equal to the maximal expected), moderate (blood loss was higher than maximal expected but hemostasis was controlled), and none (hemostasis was uncontrolled requiring a change in clotting factor replacement regimen).

Postoperative efficacy was assessed by the hematologist, evaluating postoperative blood loss not due to complications of surgery and the use of fibrinogen concentrate: excellent (no bleeding or oozing and all bleeding was controlled with fibrinogen concentrate as anticipated), good (no bleeding or oozing, and control of bleeding required increased dosing with fibrinogen concentrate or additional infusions not originally anticipated), moderate (some bleeding and oozing and control of bleeding required increased dosing with fibrinogen concentrate or additional infusions not originally anticipated), and none (extensive uncontrolled bleeding and oozing and control of bleeding required use of an alternate fibrinogen concentrate).

Clot strength: MCF

As a surrogate measure of hemostatic efficacy, MCF in plasma was quantified using thromboelastometry (ROTEM, Tem International GmbH). In each case, MCF was determined before (≤30 min) the first infusion and at 1 hour after the end of the first and last infusions. Changes

in MCF relative to before infusion were also calculated. Assays were performed using frozen citrated plasma samples and the exTEM activator and were performed by a central laboratory responsible for clot strength measurements as well as fibrinogen measurements in plasma and inhibitor testing (Lund University, Malmö University Hospital). As previously described, the fibrinogen content (and resultant fibrin network) primarily define the MCF when measured in plasma samples.[19]

Assessment of recovery and fibrinogen levels

For the first and last infusions to treat each BE, incremental in vivo recovery (IVR) was calculated as the maximum increase in plasma fibrinogen activity at 1 and 3 hours after infusion compared with preinfusion levels. For all other infusions to treat BEs, IVR was assessed at 1 hour postinfusion. For surgical prophylaxis, IVR was calculated for the loading dose of the first surgical infusion. Plasma fibrinogen levels (mg/dL) were measured by the Clauss method in the central laboratory (Malmö University Hospital) before the first fibrinogen concentrate infusion for each BE. Thereafter, levels were measured daily, including before and within 1 hour after each additional fibrinogen concentrate infusion if required.

Safety

Safety was assessed by monitoring vital signs (systolic and diastolic blood pressure, pulse rate, respiratory rate, body temperature), physical examinations, and routine clinical laboratory assessments (including coagulation variables) at predefined points throughout the study. Adverse events (AEs), including thromboembolic complications and signs of allergic or hypersensitivity reactions, were recorded. Immunogenicity was evaluated before infusion and on Days 14 and 30 postinfusion, and thrombogenicity was assessed by measuring plasma levels of prothrombin fragments 1 (F1) and 2 (F2) and D-dimer at a central laboratory (Synlab Pharma Institute).

Statistical analysis

This planned interim analysis was performed after 11 patients had been treated for at least one acute BE (data cutoff March 2016). The primary focus of the analysis is the full analysis set (FAS)-bleeding population, defined according to the intention-to-treat principle and comprising 11 patients who received at least one infusion of study medication and presented with an acute BE (n = 23 BEs in total). The surgical prophylaxis population comprises four patients (four surgeries; two patients had both surgery and BE), and the total safety population is 13 patients.

This planned interim analysis was descriptive and focused on overall clinical assessment of hemostatic efficacy for all BEs. Based on the hemostatic efficacy four-point rating scales described, "treatment success" for a BE or surgical prophylaxis was defined as a rating of excellent or good (vs. moderate and none). Success rate was the proportion of patients with treatment success. The null hypothesis was that the proportion of patients with treatment success (denoted p) was lower than or equal to 0.7 (H_o: $p \leq 0.7$), versus the alternative hypothesis that the proportion was greater than 0.7 (H_A: $p > 0.7$). This was tested by comparing the lower limit of the two-sided confidence interval (CI) for p versus the predefined threshold of 0.7.

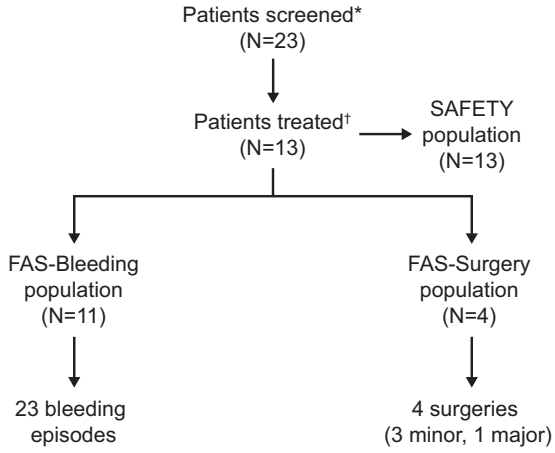

Fig. 1. Patient disposition. *"Patients screened" were screened and gave consent. †"Patients treated" received fibrinogen concentrate for the treatment of BEs or surgical prophylaxis and were included in this interim analysis. Two patients had both surgery and BE.

RESULTS

Patient characteristics

At the time of this planned interim analysis, 23 patients had been screened for the study, of which 13 had been treated with fibrinogen concentrate and were included in the analysis reported here (Fig. 1). All patients had afibrinogenemia (plasma fibrinogen activity < 30 mg/dL at screening) and were older than 12 years of age. The median (range) age of the patients was 30.0 (13-53) years. Two patients were between 12 and 18 years. Of the 13 patients, seven (53.8%) were male and nine (69.2%) were of white race (Table 1). Data presented are for the FAS-bleeding population (n = 11), unless otherwise indicated.

Hemostatic efficacy for on-demand treatment of all BEs

We assessed the hemostatic efficacy of fibrinogen concentrate treatment in 11 patients who experienced 23 BEs (16 spontaneous, seven due to trauma), all of which were minor. For 21 of the 23 (91.3%) BEs, a single infusion of fibrinogen concentrate was required to treat the BE; the remaining two BEs were each treated with two infusions depending on the local fibrinogen levels and the discretion of the investigator. The median (range) dose of fibrinogen concentrate administered per BE and per infusion

was 58.8 (33.9-101.7) and 57.5 (33.9-71.4) mg/kg, respectively (Table 2).

Treatment success for the 23 BEs was 95.7% (90% CI, 0.81-1.00) based on investigator rating using the four-point scale (19 excellent, three good; for one BE, the rating was missing due to the patient suffering an accident [a fall] shortly after the BE treatment and consequently requiring surgery for a patella injury; due to the missing BE rating this assessment was assigned as a "failure"; Table 3). The success of treatment for the two pediatric (≤18 years) patients was rated excellent by the investigators. The lower limit of the success rate was higher than the 0.7 threshold, fulfilling the preestablished statistical criterion for confirming the efficacy of fibrinogen concentrate. Treatment success according to IDMEAC review was 100% (90% CI, 0.88-1.00), with treatment of all 23 BEs, in adults (n = 21) and pediatric (n = 2) patients alike, rated as excellent. The independent IDMEAC ratings were mostly in line with the investigators' ratings and, as per protocol, were considered the final assessment. No additional hemostatic interventions, such as blood transfusions or other blood products, were required in any patients. The hemostatic efficacy of fibrinogen concentrate for treating the 23 BEs was also demonstrated by a significant increase in mean MCF from 0.0 mm at baseline to 6.5 mm (95% CI, 5.65-7.40; $p < 0.0001$) at 1 hour after the first fibrinogen concentrate infusion (Fig. 2).

TABLE 1. Demographic and clinical characteristics*

Variable	Mean (±SD) or number (%)	Median (range)
Age at informed consent (years)	30.7 (±13.0)	30.0 (13.0-53.0)
Height (cm)	164.8 (±12.2)	167.0 (149.0-190.0)
Weight (kg)	70.9 (±16.8)	72.0 (34.0-99.0)
BMI (kg/m^2)	26.0 (±5.6)	25.8 (14.3-39.6)
Sex		
Male	7 (53.8)	
Female	6 (46.2)	
Race		
Caucasian	10 (76.9)	
Asian	3 (23.1)	
Congenital fibrinogen deficiency		
Afibrinogenemia	13 (100)	
Hypofibrinogenemia	0 (0)	

*Safety population, n = 13.
BMI = body mass index.

Hemostatic efficacy for surgical prophylaxis of bleeding

We assessed the efficacy of fibrinogen concentrate as prophylaxis before surgery in four patients (two of these patients also had a BE in the study). Each of these four patients underwent a single surgical procedure: three were minor (left knee radioisotope synovectomy, dental extraction of one tooth, circumcision), and one was major (right eye enucleation with socket reconstruction). A loading dose (median [range], 70.0 [65.8-102.6] mg/kg) before surgery was administered in three cases; in the remaining case, fibrinogen concentrate had been administered shortly before surgery to treat a separate BE and the investigator therefore deemed it unnecessary to administer a loading dose. The median (range) total dose per surgery was 93.5 (34.1-225.4) mg/kg with a median dose per infusion of 26.0 mg/kg, including preoperative loading dose and infusions given after the end of surgery as needed depending on the local fibrinogen levels and the discretion of the investigator. No maintenance doses during

TABLE 2. Fibrinogen concentrate dosages for the treatment of all BEs and administered for surgeries*

Variable	Mean (±SD)	Median (range)
All BEs (FAS-bleeding population)		
Number of exposure-days/infusions	1.1 (±0.29)	1 (1-2)
Fibrinogen concentrate dose per BE		
mg	4652 (±1027)	5,000 (2,000-6,000)
mg/kg	61.2 (±11.5)	58.8 (33.9-101.7)
Fibrinogen concentrate dose per infusion		
mg	4280 (±1100)	5,000 (2,000-6,000)
mg/kg	56.3 (±11.0)	57.5 (33.9-71.4)
Surgeries (FAS-surgery population)†		
Total dose per surgery		
mg	8435 (±6417)	6,620 (3,000-17,500)
mg/kg‡	111.6 (±83.9)	93.5 (34.1-225.4)
Preoperative loading dose (mg/kg)§	79.5 (±20.1)	70.0 (65.8-102.6)
Infusions after end of surgery (mg/kg)§	20.8 (±7.9)	20.5 (12.8-34.1)
Total dose per infusion/exposure-day		
mg	2595 (±2112)	2,000 (1,000-8,000)
mg/kg	34.3 (±27.8)	26.0 (12.8-102.6)

* For BEs, n = 23 BEs in 11 patients; for surgeries, n = 4 surgeries in four patients.
† Unless otherwise stated, data are based on a total of n = 13 infusions.
‡ No maintenance doses during surgery were required in any patient.
§ n = 3 infusions for preoperative loading dose, and n = 10 for infusions after the end of surgery.

TABLE 3. Hemostatic efficacy of a new fibrinogen concentrate for treatment of BEs (FAS-bleeding population)*

	Investigator		IDMEAC	
Efficacy rating	Number (%)	90% CI§	Number (%)	90% CI§
Four-point efficacy scale				
Excellent	19 (82.6)		23 (100)†	
Good	3 (13.0)†		0	
Moderate	0		0	
None	0		0	
Missing	1 (4.4)			
Two-point efficacy scale‡				
Success	22 (95.7)‖	0.81, 1.00	23 (100)	0.88, 1.00
Failure	1 (4.3%)‖		0	

* n = 23 BEs in 11 patients.
† For one patient experiencing one BE, hemostatic efficacy was rated good by the investigator and excellent by the IDMEAC despite underdosing with new fibrinogen concentrate, with resulting maximum plasma fibrinogen levels of not more than 90% of the 100 mg/dL target. Analyses that added this BE to the per-protocol data set showed no impact on overall hemostatic efficacy (21/22 [95.5%] BEs rated as treatment success by investigator and 22/22 [100%] BEs rated as treatment success by IDMEAC).
‡ Efficacy rating of excellent or good indicated success and efficacy rating of moderate or none indicated failure.
§ 90% CI for the success rate was calculated according to Blyth-Still-Casella interval for the proportion of patients with successful hemostatic efficacy using a predefined threshold of 0.7.
‖ For the purpose of success rate calculation, the missing assessment was considered a failure.

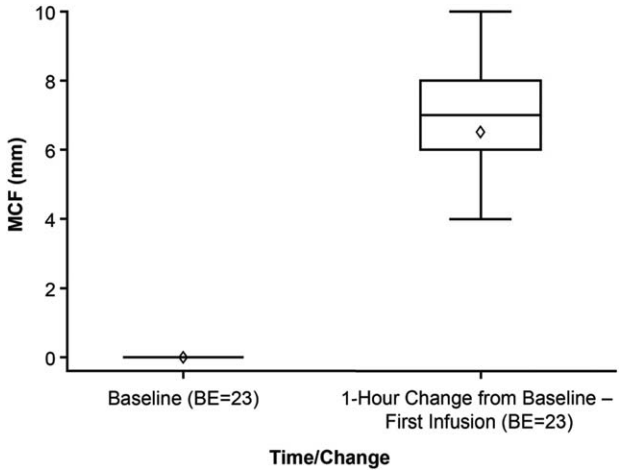

Fig. 2. Maximum clot firmness at baseline and 1 hour after the first fibrinogen concentrate infusion for all BEs (FAS-bleeding population). n = 23 BEs in 11 patients. Boxplots show the median (horizontal line), mean (diamond), upper and lower quartiles (box ends), and minimum and maximum values at 1.5× interquartile range (whiskers).

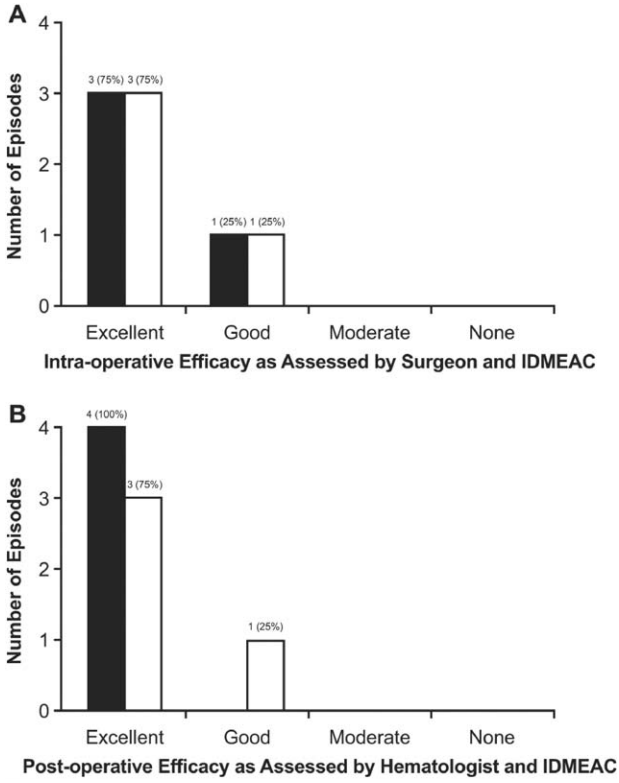

Fig. 3. Intraoperative (A) and postoperative (B) hemostatic efficacy of fibrinogen concentrate in surgical prophylaxis (FAS-surgery population). n = 4 surgeries in four patients. Efficacy rating of excellent or good indicated success, and efficacy rating of moderate or none indicated failure. Ratings of good were all related to the one major surgery performed (right eye enucleation with socket reconstruction). (A) ■, surgeon; □, IDMEAC. (B) ■, hematologist; □, IDMEAC.

surgery were required in any patient. One minor surgery required one postoperative infusion, another minor surgery required two postoperative infusions, and the major surgery required seven postoperative infusions. Further details of fibrinogen concentrate dosages administered for surgeries are provided in Table 2.

The intraoperative and postoperative efficacy of fibrinogen concentrate was demonstrated with treatment success rates of 100% (90% CI, 0.5-1.0) in each case, as determined by the surgeon or hematologist and independently by the IDMEAC using the four-point hemostatic efficacy rating scales (Fig. 3). For all three minor surgeries,

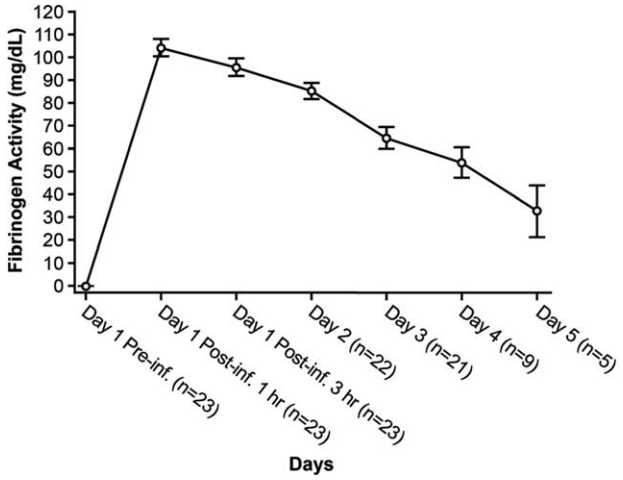

Fig. 4. Fibrinogen plasma levels after the first fibrinogen concentrate infusion for all BEs (FAS-bleeding population). n = 23 BEs in 11 patients. Time points on the x-axis represent days on which fibrinogen activity was tested (by the central laboratory). Circles indicate mean values and horizontal bars the upper and lower SE values. n = number of observations; post-inf = postinfusion; pre-inf = preinfusion; SE = standard error of the mean.

intra- and postoperative efficacy was rated as excellent, and for the one major surgery was rated as good. No cases required additional hemostatic interventions.

Response to fibrinogen concentrate

Assessment of incremental IVR was conducted for the first infusion of fibrinogen concentrate used for the treatment of BEs. The mean ± SD IVR for the 23 BEs in 11 patients was 1.84 ± 0.41 mg/dL/(mg/kg). A slightly lower IVR of 1.42 ± 0.38 mg/dL/(mg/kg) was observed for the loading dose prior to surgery (FAS-surgery population; n = 3 surgeries in three patients as one patient received fibrinogen concentrate for bleeding immediately before surgery and no IVR could therefore be calculated).

Mean plasma fibrinogen levels after the 23 BEs in the 11 patients increased from preinfusion levels after fibrinogen concentrate administration (Fig. 4). The largest mean increase was observed at 1 hour (104.5 ± 18.3 mg/dL, mean ± SD), with a similar level observed at 3 hours (95.9 ± 18.9 mg/dL, mean ± SD). The minimum observation period prescribed in the protocol was 3 days for a minor BE, so there were fewer recorded data points available beyond this time point. Only two patients had maximum plasma fibrinogen levels of not more than 90% of the 100 mg/dL target for minor BEs (43 mg/dL [due to underdosing] and 87 mg/dL). For surgical prophylaxis, the three patients who underwent minor surgery achieved plasma fibrinogen levels approaching or exceeding the target level of 100 mg/dL and above the accepted lower limit of 80 mg/dL, with levels measured at the end of surgery of 89, 98, and 139 mg/dL. The single patient who underwent major surgery had a plasma fibrinogen level of 220 mg/dL at the end of surgery, indicating that the 150 mg/dL target was achieved. Additional doses were recommended if the fibrinogen levels fell below the targets described in the protocol and were based on the clinical judgment of the treating physician and the status of the patient.

TABLE 4. Summary of AEs (safety population)*

	Number of AEs†
AE	16
Patients with AE, n (%)	7 (53.8)
Severity of AE	
Mild	13
Moderate	1
Severe	2‡
Relatedness to treatment (probably or possibly related)	1§
AE leading to discontinuation	0
Death	0

* n = 38 infusions in 13 patients. Unless otherwise indicated, numbers are the number of AEs.
† AEs include TEAEs, occurring between the start of the first fibrinogen concentrate infusion and the end of each 30-day observation and follow-up period, and non-TEAEs, AEs occurring outside of the follow-up period.
‡ Patella fracture and ligament rupture of the left knee in one patient due to a fall.
§ Mild skin reaction (itchiness and redness).
TEAE = treatment-emergent AE.

Safety

Safety data were available for all 13 patients treated with fibrinogen concentrate, either as on-demand therapy for an acute BE or for surgical prophylaxis. No deaths or thrombotic events were reported and no patients developed fibrinogen antibodies during the study (two patients with a history of on-demand treatment with cryoprecipitate were positive for fibrinogen antibodies before the first infusion of fibrinogen concentrate but this was not seen to impact on the observed efficacy and IVR of fibrinogen concentrate treatment).

In total, 16 AEs in seven patients (53.8%) were reported (Table 4). Of these, the majority (13/16, 81.3%) were mild and included AEs such as asthenia and vomiting. Only a single AE (mild skin reaction) was deemed possibly related to fibrinogen concentrate administration and this resolved upon treatment with diphenhydramine and steroids. One moderate and two severe AEs were reported, none of which were related to treatment. The moderate AE was an arthropod sting. The two severe SAEs (patella fracture and ligament rupture in the left knee), which occurred in one patient, were due to a fall. These two severe AEs were the only serious AEs to occur in the study.

DISCUSSION

Human fibrinogen concentrate is now considered the first-line treatment option for patients with congenital fibrinogen deficiency. This was a planned interim analysis of the first, ongoing, prospective, multinational, Phase III efficacy and safety study of a new double virus-inactivated/eliminated human fibrinogen concentrate in a cohort of adult and pediatric patients in the ultrarare setting of congenital afibrinogenemia.

Fibrinogen replacement using this new fibrinogen concentrate was 100% successful in the treatment of all acute BEs and for prophylaxis before planned surgery, as confirmed by an independent adjudication committee. Significant increases in plasma MCF as a surrogate measure of hemostatic efficacy were also observed, supporting the clinical efficacy of this new fibrinogen concentrate in the control of bleeding. Importantly, no cases required the use of additional hemostatic interventions such as blood transfusions or other blood products and treatment with fibrinogen concentrate showed a good safety profile.

The hemostatic efficacy we observed, for both on-demand and surgical prophylaxis, mirrors efficacy data from a previous study investigating treatment with a commercially available fibrinogen concentrate in congenital fibrinogen deficiency. In a retrospective study, Kreuz and coworkers[18] examined 12 patients with afibrinogenemia, hypofibrinogenemia, and/or dysfibrinogenemia and, using a three-point subjective rating scale, reported very good clinical efficacy for the treatment of on-demand BEs (n = 26) and most surgical procedures (n = 11). Assessment of comparability with our own data has its challenges, however, since the criteria used by Kreuz and coworkers[18] to assess efficacy to treat a BE or surgery were not reported. The peak postinfusion fibrinogen levels reported in that study (median [range], 145 [48-215] mg/dL) were slightly higher than we observed; however, this may be related to the higher doses used in their study.[18] Thus, the interim data presented herein are consistent with previous data and support use of the new fibrinogen concentrate for on-demand treatment and as prophylaxis before surgery.

In this first Phase III study performed in afibrinogenemia patients to date, and as described for this interim analysis, we assessed clinical efficacy of fibrinogen concentrate for on-demand treatment and surgical prophylaxis using objective four-point criteria, the first time such criteria have been used in the congenital fibrinogen deficiency setting. Subjective efficacy criteria have been widely used to assess clinical efficacy in fibrinogen deficiency and other inherited coagulopathies,[18,23-25] but evaluation of such data is complicated by the use of subjective, nonstandardized definitions of treatment outcome.[21] Moreover, differences between subjective and more robust objective efficacy criteria for evaluating clinical efficacy have been reported.[21,26] Supported by the successful use of objective criteria in the clinical investigation of other congenital bleeding disorders,[21,22] we therefore developed objective four-point criteria sets as a more robust method to determine the hemostatic efficacy of this new fibrinogen concentrate. Furthermore, all clinical efficacy assessments were adjudicated by an independent committee—it is noteworthy that treatment success was 100% for all cases by this adjudication process.

We also assessed hemostatic efficacy using plasma MCF as a surrogate. In on-demand treatment for acute BEs, and with a starting plasma MCF of 0.0 mm, we observed a significant increase in plasma MCF (6.5 mm). This corroborates the robust clinical outcome data obtained using the objective clinical assessment criteria. Therefore, in conjunction with determination of plasma MCF as a surrogate measure of efficacy with fibrinogen supplementation,[27] the hemostatic efficacy reported here appears to reflect clinical experience.

The new fibrinogen concentrate demonstrated a good safety and tolerability profile, consistent with data reported for other fibrinogen concentrates used for on-demand and prophylaxis treatment.[18,19,28] There were no deaths, thrombotic events, or seroconversions. AEs occurred in seven patients and were mostly mild. A single case of mild skin reaction was deemed possibly related to fibrinogen concentrate, but resolved with treatment. Safety data from this interim analysis, which are in line with those of the Phase II study,[20] indicate that the new fibrinogen concentrate is well tolerated after infusions in both adult and pediatric patients.

The small number of patients included in this interim analysis is a limitation. This reflects the difficulty of recruiting large numbers of patients in a very rare disease setting. All 13 patients assessed had afibrinogenemia, the rarest form of deficiency, affecting approximately one in 1 million people.[4] With a target enrollment of 24 patients when completed, this ongoing Phase III efficacy study will be the largest prospective study of its kind in congenital fibrinogen deficiency.

In conclusion, interim data from the first Phase III study indicate that the new fibrinogen concentrate was successful in the treatment of acute BEs and for surgical prophylaxis in patients aged at least 12 years with congenital fibrinogen deficiency, with 100% efficacy as assessed by IDMEAC. Additional hemostatic interventions were not required for any patient. Fibrinogen concentrate was also shown to increase clot firmness, consistent with hemostatic efficacy. Moreover, fibrinogen concentrate achieved bleeding control with only a single infusion in more than 90% of patients, showed 100% intraoperative and postoperative treatment success as rated by investigators and IDMEAC and was well tolerated. These encouraging clinical efficacy data confirm and extend our previous data describing the favorable pharmacokinetic profile of

this fibrinogen concentrate. Complete data for this first Phase III study are awaited and will support the further clinical investigation of this new human fibrinogen concentrate in patients with congenital fibrinogen deficiency.

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CONFLICT OF INTEREST

BS, CS, and SK are employees of Octapharma. FP has received personal fees from Octapharma, Freeline, Kedrion Biopharma, LFB, Ablynx, Bayer, Grifols, Novo Nordisk, Sobi, and F. Hoffmann-La Roche. KK has received investigator fees from Octapharma. NZ has received research support from Octapharma, Baxalta, CSL Behring, and Generium, and personal fees from Octapharma, Baxalta, CSL Behring, Generium, Sobi, Novo Nordisk, and F. Hoffmann-La Roche. AA, BM, CDK, CR, GdA, MK, and TL have disclosed no conflicts of interest.

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SUPPORTING INFORMATION

Additional Supporting Information may be found in the online version of this article.

Table S1. Objective four-point criteria sets used for the clinical assessment of hemostatic efficacy for on-demand treatment of bleeding episodes and surgical prophylaxis (intra-operative efficacy and post-operative efficacy).