2 Synopsis

Name of Sponsor: CSL Behring GmbH	Individual Study Table Referring to Part of the Dossier Volume: Page:	*(for National Authority Use Only)*
Name of finished product: Recombinant fusion protein linking coagulation factor IX with albumin (rIX-FP)		
Name of active ingredient: Recombinant fusion protein linking coagulation factor IX with albumin		

Study title:

A Phase 3 Open-label, Multicenter, Pharmacokinetics, Safety, and Efficacy Study of a Recombinant Fusion Protein Linking Coagulation Factor IX with Albumin (rIX-FP) in Previously Treated Children with Hemophilia B

Study number: CSL654_3002

Coordinating Investigator:

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Publication (reference): None

Study period: 16 January 2013 (first subject in) to 05 October 2014 (last subject out)	**Phase of development:** 3

Objectives:

Primary objectives:

To evaluate the pharmacokinetics (PK) of a single dose of rIX-FP and to evaluate the safety of rIX-FP with respect to the development of inhibitors to factor IX (FIX) in patients with severe hemophilia B (FIX activity of ≤2%).

Secondary objectives:

To evaluate the safety of rIX-FP based on adverse events (AEs) and the development of antibodies to rIX-FP; to evaluate the clinical response to rIX-FP for the prevention of bleeding episodes; to evaluate the clinical response to rIX-FP in the treatment of bleeding episodes.

Methodology:

This was a prospective, open-label study in subjects <12 years of age to evaluate the efficacy, PK, and

safety of rIX-FP, which is being developed for the prophylaxis and treatment (control and prevention) of bleeding episodes in subjects with congenital FIX deficiency (hemophilia B).

The main study design consisted of a screening period, a PK period, and an active treatment period of weekly prophylaxis therapy with rIX-FP for all subjects. If a subject required a minor, nonemergency surgical procedure during the study, the subject could be treated with rIX-FP for surgical prophylaxis. Subjects were to be withdrawn from the study if a major or emergency surgical procedure was required.

PK analyses were performed. The PK of 50 IU/kg of rIX-FP was evaluated at the beginning of the study in all subjects. The PK of 50 IU/kg of the previous FIX product was evaluated at limited time points at the beginning of the study in a subset of subjects who had no historical PK data of their previous FIX product.

Efficacy and safety assessments were performed at the study site on a monthly basis.

Number of subjects:

A total of 29 subjects provided informed consent and were screened for study participation. Of these, 27 subjects were enrolled and treated with rIX-FP (12 subjects <6 years of age and 15 subjects 6 to <12 years of age).

Diagnosis and main criteria for inclusion:

Male subjects, <12 years of age and with body weight ≥10 kg, with documented severe hemophilia B (FIX activity of ≤2%), who had no prior history of FIX inhibitor formation, and who were currently receiving FIX replacement therapy and had received FIX products ≥150 exposure days (EDs) (6 to <12 years of age) or ≥50 EDs (<6 years of age) were eligible for inclusion in the study.

Investigational product, dose, and mode of administration:

The study product, rIX-FP, was supplied as lyophilized powder in single-use vials for reconstitution and administered as a bolus intravenous (IV) injection. The dose was based on the subject's most current body weight prior to administration and the actual FIX potency (units) as indicated on the vial label.

The recommended doses for prophylaxis treatment were selected based on group PK data and treatment experience from Phase 1 (CSL654_2001) and Phase 1/2 (CSL654_2004) studies. The desired FIX activity level for the treatment of a bleeding episode was based on the recommendation of the World Federation of Hemophilia (WFH), with a minimum dose of 35 IU/kg. The appropriate dose and dosing regimen of rIX-FP for both prophylaxis and on-demand treatment of bleeding episodes were prescribed by the Investigator.

Prophylaxis dosing for all subjects:

Subjects were initially treated with a weekly prophylaxis dose of 35 to 50 IU/kg rIX-FP, which could be adjusted up to a maximum dose of 75 IU/kg, based on the subject's PK data from this study as well as the PK data from the previous rIX-FP study (CSL654_2001), the subject's previous prophylaxis dose with another FIX product, the treatment dose/efficacy data from previous rIX-FP studies (CSL654_2004 and CSL654_3001), the subject's bleeding phenotype, and the subject's physical activity level.

If a subject experienced at least 1 spontaneous breakthrough hemorrhage due to an inadequate treatment dose, the dose of rIX-FP could be increased by an increment of 5 to 15 IU/kg, up to a maximum dose of 75 IU/kg of rIX-FP with a target of maintaining the trough FIX activity level above 3% to 5% (ie, 3 to 5 IU/dL) between doses, while maintaining a treatment interval of 7 days. The prophylaxis treatment dose could also be adjusted to a lower weekly dose due to an unnecessarily high

trough FIX activity level.

On-demand dosing for all subjects:

On-demand treatment in this study refers specifically to treatment of bleeding episodes as needed while subjects were receiving prophylaxis treatment. For the on-demand treatment of a bleeding episode, the subject's PK data from this study, the subject's previous treatment dose with another FIX product, the treatment dose/efficacy data from previous rIX-FP studies (CSL654_2004 and CSL654_3001), and the type, location, and severity of the bleeding episode were utilized for calculating/selecting the treatment doses, with an initial dose of 35 to 50 IU/kg, that could be adjusted up to a maximum of 75 IU/kg.

The study center was to be contacted if hemostasis was not achieved after the first rIX-FP administration. If a bleeding episode required a maintenance dose of rIX-FP (to maintain the FIX activity level after achieving hemostasis for multiple days as recommended by the WFH), the FIX activity level was to be tested prior to the second rIX-FP administration, if feasible, and administered at least 24 hours after the first treatment dose. After hemostasis was achieved, a lower maintenance dose(s) of rIX-FP could be prescribed at the discretion of the Investigator.

Subjects were to maintain the prophylaxis treatment schedule, if possible, while receiving on-demand treatment for a bleeding episode.

Surgical dosing:

If a subject required a minor, nonemergency surgical procedure during the study, the subject could receive rIX-FP for surgical prophylaxis as recommended by the WFH for surgery. During the preoperative treatment period (approximately 1 to 3 hours prior to the start of the scheduled surgery), the subject received a single bolus dose of rIX-FP in order to increase the FIX activity levels to 60% to 80%. During the intraoperative treatment period, additional bolus doses of rIX-FP could be administered, if needed, based on the individual subject's possible variation in recovery and/or clearance, or FIX activity levels. Blood samples for the determination of FIX activity levels were collected prior to and 30 minutes following administration of additional doses of rIX-FP. During the postoperative period, defined as starting at wound closure, additional dosing of rIX-FP could be prescribed at the Investigator's discretion at 3- to 7-day treatment intervals to maintain a required trough FIX activity level as recommended by the WFH.

Duration of treatment:

The main study design consisted of a <1-month screening period and up to a 14-day PK period, followed by an active treatment period of about 11 months. Thus, the duration of the study for an individual subject was expected to be approximately 12 months. A subject could continue in the study if a Phase 3 extension study was not yet enrolling at the time of the subject's planned End-of-study visit.

Reference therapy, dose, and mode of administration:

Not applicable

Criteria for evaluation:

Primary endpoints:

The primary PK endpoint of the study was the PK of a single dose of 50 IU/kg rIX-FP and the subject's previous FIX, derived from the FIX activity level in plasma, and including the following PK parameters: incremental recovery (IR), half-life ($t_{1/2}$), area under the concentration-time curve (AUC) from time point zero to the last sample with quantifiable drug concentration (AUC_{last}), and clearance.

The primary safety endpoint of the study was the number of subjects with FIX inhibitors.

Secondary endpoints:

The secondary safety endpoints of the study included the frequency of related AEs to rIX-FP over the course of the study and the number of subjects who developed antibodies against rIX-FP.

The secondary efficacy endpoints included the consumption of rIX-FP (expressed as number of infusions and IU/kg per month and per year, as well as IU/kg per event), and the proportion of bleeding episodes that required 1, 2, or >2 infusions of rIX-FP to achieve hemostasis.

Other endpoints:

Other endpoints included the Investigator's overall clinical assessment of hemostatic efficacy for treatment of bleeding episodes based on a 4-point ordinal scale, the Investigator's overall clinical assessment of hemostatic efficacy for surgical prophylaxis based on a 4-point ordinal scale (if applicable), annualized bleeding rate (ABR) during the routine prophylaxis treatment period, and quality of life assessed by subjects and their parents/caregivers.

Statistical methods:

PK analysis:

The PK population (subjects who received at least 1 dose of rIX-FP for PK assessment and for whom a sufficient number of analyzable PK samples were obtained to permit the evaluation of the PK profile of rIX-FP) was used to assess the PK of rIX-FP and FIX from a previous FIX product.

For both baseline-corrected and -uncorrected PK parameters, descriptive statistics (n, mean, standard deviation [SD], median, minimum, maximum, and percent coefficient of variation [%CV]) were presented by treatment (rIX-FP and previous FIX product), and age (<6 and 6 to <12 years of age). For mean activity and antigen levels (if available), descriptive statistics were presented for both baseline-corrected and -uncorrected parameters by nominal time points, by treatment, and by age groups. For time to reach maximum concentration (t_{max}), only n, median, minimum, and maximum were presented.

Mean (SD) and individual activity and antigen (when sufficient samples were available) profiles were plotted over time. Individual FIX PK profiles from PK dosing were presented.

Efficacy analysis:

Efficacy summaries and analyses were performed on the Efficacy population (all subjects who participated in the efficacy portion of the study and received at least 1 dose of rIX-FP; main analysis population), and the Per-Protocol (PP) population (all subjects in the Efficacy population who completed the study without any major protocol deviations and who incurred no protocol deviations that pertained to the assessment of treatment efficacy). Unless otherwise indicated, the main analysis was based on the Efficacy population, with results from the PP population providing supportive information. If a subject did not treat a bleed per the protocol, the PP analysis might have excluded the bleed in question, rather than all of the subject's data. For efficacy analyses of bleeds requiring treatment, bleeds treated >4 hours after the start of the bleed and bleeds treated with another product in addition to rIX-FP were excluded from the analyses of the PP population.

The consumption of rIX-FP during routine prophylaxis was summarized using descriptive statistics by age category. The first rIX-FP dose (IU/kg) given per bleeding episode (ie, for on-demand treatment) was also summarized.

The proportion of bleeding episodes requiring 1, 2, or >2 infusions of rIX-FP to achieve hemostasis was tabulated by severity of bleed, location, type, and overall for all bleeds by age category. Treatment was considered successful if hemostasis was achieved with 1 or 2 infusions. The 95% confidence interval (CI) for the rate of success in treating bleeding events was presented.

The ABRs during routine prophylaxis treatment were summarized for spontaneous, joint, and total bleeds overall and by age category. The Investigator's overall clinical assessment of hemostatic efficacy for the treatment of bleeding episodes was tabulated by severity of bleed (minor/moderate bleeds and major bleeds) overall and by age category. The time between the most recent prophylaxis infusion and a spontaneous bleeding episode was also summarized.

Bleeding episodes were summarized by the type of event, location, and severity of bleed. The first dose of rIX-FB used to treat a bleed and the times from the start of bleeding to treatment were also summarized.

For surgical prophylaxis, the Investigator's/surgeon's overall clinical assessment of hemostatic efficacy of surgical prophylaxis, based on a 4-point ordinal scale, was tabulated. The change in hemoglobin level between baseline and lowest intra- and post-operation was summarized descriptively.

Quality of life, social history, and physical activity analyses:

Study subjects who were at least 4 years of age and the parent/caregivers of all study subjects were asked to answer Quality of Life (QoL) questionnaires (Haemo-QoL for subjects ≥4 years of age and Hemo-Sat for parents/caregivers) at the beginning of the study as baseline and at ≥50 EDs/End-of-study visits. The item responses and total score of the Haemo-QoL were summarized by study visit. The total transformed scale score and changes from baseline were summarized descriptively. Results from the Hemo-Sat and responses to the questions on social history and physical activity level were summarized by study visit.

Safety analysis:

Safety analyses were performed on the Safety population (all subjects who received at least 1 dose [or partial dose] of rIX-FP during the study). For estimating the incidence of inhibitor formation to rIX-FP, the numerator included all subjects with inhibitors regardless of EDs to rIX-FP and the denominator included subjects with at least 50 EDs plus subjects with <50 EDs but with inhibitors. A 2-sided 95% CI for the incidence of inhibitor formation was calculated. The SAS FREQ procedure was applied to produce the Clopper-Pearson CI. The inhibitor incidence and 95% CI were also presented for the Safety population. In this presentation, the numerator included all subjects with inhibitors and the denominator included all subjects in the Safety population.

The number and percentage of subjects who experienced at least 1 AE and the number of events were summarized by system organ class (SOC) and preferred term (PT). The descriptive analysis of AEs included the summary of all AEs and serious AE (SAEs) recorded during the study (included those that were not treatment-emergent and those with a date of onset during the surgical period). In addition, treatment emergent AEs (TEAEs) were summarized. Additional TEAE summaries included AEs by maximum relationship, AEs by maximum severity, SAEs, non-serious AEs, and AEs leading to withdrawal. TEAEs occurring during or within 72 hours of the infusion of rIX-FP were also summarized.

Laboratory parameters, local tolerability, antibodies against rIX-FP or Chinese hamster ovary (CHO) host cell proteins, and vital sign results were summarized. The number and proportion of subjects with treatment-emergent abnormal laboratory values or potentially clinically significant vital sign values were tabulated.

Results:

Subject demographics:

All subjects were male and <12 years of age. The majority of subjects were White (26/27 subjects, 96.3%) and non-Hispanic (25/27 subjects, 92.6%). Subjects had an overall mean (SD) age of

5.9 (2.93) years (range, 1 to 10 years). A total of 12 subjects were <6 years of age and 15 subjects were 6 to <12 years of age. Subjects <6 years of age had a mean (SD) age of 3.2 (1.70) years (range, 1 to 5 years) and mean (SD) body mass index (BMI) of 15.61 (1.727) kg/m^2 (range, 13.6 to 19.1 kg/m^2). Subjects 6 to <12 years of age had a mean (SD) age of 8.1 (1.41) years (range, 6 to 10 years) and mean (SD) BMI of 17.64 (3.766) kg/m^2 (range, 12.7 to 26.9 kg/m^2).

Details on exposure are provided below under Safety Results.

PK results:

Overall, 50 IU/kg rIX-FP demonstrated an improved PK profile over previously used FIX products (plasma-derived FIX and recombinant FIX). When compared to 50 IU/kg previous FIX product, 50 IU/kg rIX-FP demonstrated approximately 40% higher IR, an approximately 5-fold longer $t_{1/2}$, an approximately 5- to 6-fold larger AUC, and an 80% reduction in plasma clearance. The PK parameters in subjects <6 years of age were generally comparable to those in subjects 6 to <12 years of age, although mean clearance appeared to be slightly higher in subjects <6 years of age compared with subjects 6 to <12 years of age; this difference was smaller than differences observed with previous FIX product.

Summary of Mean (%CV) FIX PK Parameters by Age Group After Administration of rIX-FP and Previous FIX (PK Population)

PK parameter (Unit)	rIX-FP 50 IU/kg			Previous FIX 50 IU/kg		
	0 to <6 years (N=12)	6 to <12years (N=15)	Total (N=27)	0 to <6 years (N=8)	6 to <12 years (N=9)	Total (N=17)
IR (IU/dL)/(IU/kg)	0.951 (21.5)	1.06 (22.6)	1.01 (22.5)	0.676 (20.7)	0.793 (29.3)	0.738 (26.8)
C_{max} (IU/dL)	48.3 (19.0)	52.9 (23.2)	50.9 (21.8)	34.0 (21.4)	39.3 (30.2)	36.8 (27.3)
$AUC_{0-\infty}$ (IU*h/dL)	4583 (33.2)	5123 (31.4)	4894 (32.0)	886 (70.1)	890 (21.3)	888 (46.9)
AUC_{last} (IU*h/dL)	3891 (32.2)	4369 (26.6)	4157 (29.0)	677 (46.8)	752 (19.5)	719 (32.1)
$t_{½}$ (h)	89.6 (12.5)	92.8 (20.5)	91.4 (17.5)	19.9 (40.3)	17.7 (25.6)	18.6 (33.0)
CL[a] (mL/h/kg)	1.184 (27.8)	1.059 (28.5)	1.112 (28.2)	7.158 (39.0)	5.812 (23.7)	6.401 (33.5)

Abbreviations: AUC = area under the concentration-time curve; CL = clearance; C_{max} = maximum concentration; %CV = percent coefficient of variation; FIX = factor IX; IR = incremental recovery; PK = pharmacokinetic; rIX-FP = recombinant fusion protein linking coagulation factor IX with albumin; $t_{1/2}$ = half-life.

Note: All values are baseline-uncorrected, with the exception of IR and C_{max}, which are presented as baseline-corrected.

[a] Clearance is normalized for body weight.

In subjects <6 years of age and subjects 6 to <12 years of age, respectively, at 7 days after 50 IU/kg rIX-FP administration, mean (SD) FIX activities were 8.35 (3.882) and 9.51 (3.335) IU/dL; at 10 days postdose, mean FIX activities were 5.33 (2.661) and 6.41 (2.986) IU/dL; and at 14 days postdose, mean FIX activities were 2.45 (0.941) and 3.23 (1.450) IU/dL. The PK profile of rIX-FP, and the mean FIX activity level of 2.81 (1.227) IU/dL at 14 days after 50 IU/kg rIX-FP administration, suggest that a prolonged routine prophylaxis treatment interval of up to 14 days is a viable option for subjects <12 years of age.

Efficacy results

The routine weekly prophylaxis regimen with rIX-FP was effective in the prevention of bleeding episodes. The median (Q1, Q3) ABR (total bleeding episodes) and annualized spontaneous bleeding

rate (AsBR) during prophylaxis treatment in the Efficacy population were 3.12 (0.91, 5.91) and 0.00 (0.00, 0.91) bleeding episodes/subject/year, respectively. The ABRs and AsBRs in the 2 age groups were comparable. Further, the ABRs and AsBRs of the 3 subjects in the study who received previous FIX as on-demand treatment prior to study entry were markedly reduced in the study when compared with the number of total and spontaneous bleeding episodes these subjects reported in the last 12 months prior to study entry. The target joints (defined as 3 or more spontaneous bleeds into a single joint within a consecutive 6-months period) reported in 3 subjects prior to study entry were resolved during the study. All subjects maintained a weekly routine prophylaxis regimen throughout the study (the mean [SD] number of prophylaxis infusions per month was 4.31 [0.114] in the Efficacy population). The mean weekly prophylaxis dose in this study (47 IU/kg) was considerably lower than the weekly consumption for routine prophylaxis prior to study entry (107 IU/kg).

A total of 103 of 106 bleeding episodes that required treatment in the Efficacy population were treated successfully with 1 or 2 infusions (probability of success of 97.2% [95% CI: 92.0% to 99.0%]; 88.7% of bleeding episodes were treated with 1 infusion). Successful treatment with 1 or 2 infusions was reported for all bleeding episodes in subjects <6 years of age and for 58 of 61 bleeding episodes (probability of success of 95.1% [95% CI: 86.7% to 98.3%]) in subjects 6 to <12 years of age. Treatment was effective for the vast majority of minor/moderate bleeding episodes (75.0% rated excellent; 21.2% rated good), and for both of the major bleeding episodes (100%) according to the Investigator's assessment. The mean first dose of rIX-FP used to treat a bleeding episode was 48 (11.1) IU/kg overall in the Efficacy population, 49 (13.1) IU/kg in subjects <6 years of age, and 47 (9.4) IU/kg in subjects 6 to <12 years of age.

Hemostatic efficacy for surgical prophylaxis (2 surgeries in 2 subjects) was rated as excellent or good at wound closure (0 hours) and/or 7 days following surgery. No hemostatic interventions or transfusion support were required, and no estimated actual intraoperative blood loss was recorded. Acceptable FIX levels were achieved before and after surgery.

Quality of life results

The transformed scale score of the hemophilia age group-specific QoL questionnaire (the Haemo-QoL) was lower (lower transformed scale scores indicate better quality of life) at the End-of-study visit compared with Screening in children between 8 and 12 years of age and was similar at Screening and at the End-of-study visit in children between 4 and 7 years of age. Nevertheless, there were improvements in scoring for physical health, feeling more positive when dealing with the disease, and participation in sports and school in both age groups.

Safety results

The overall mean (SD) time on study was 13.1 (2.54) months, with a range of 9 to 18 months. Mean (SD [range]) time on study was 11.4 (1.31 [9 to 14]) months for subjects <6 years of age and 14.4 (2.54 [11 to 18]) months for subjects 6 to <12 years of age. The overall mean (SD) exposure in EDs was 61.9 (12.63) EDs (range, 42 to 94 EDs) with a lower number of EDs observed in subjects <6 years of age than subjects 6 to <12 years of age (55.3 [8.88] EDs [range, 42 to 78 EDs] versus 67.3 [12.87] EDs [range, 51 to 94 EDs]), due to subjects 6 to <12 years of age having a longer time on study. A total of 25/27 (92.6%) subjects had ≥50 EDs (10/12 [83.3%] subjects <6 years of age and 15/15 [100.0%] subjects 6 to <12 years of age).

Safety and tolerability data demonstrate that IV infusion of rIX-FP had a favorable safety profile and was well tolerated when administered in pediatric subjects. No inhibitors to rIX-FP and no antibodies to rIX-FP or CHO host cell proteins were detected in any subject. All TEAEs were considered by the Investigator to be not related to rIX-FP. Nearly all of the TEAEs were mild or moderate in intensity. There were no TEAEs leading to study drug withdrawal. Four subjects had 6 serious TEAEs. There

were no deaths. There were no thromboembolic TEAEs and no hypersensitivity TEAEs. There were no notable findings relating to clinical laboratory or vital sign parameters.

Conclusions:

rIX-FP had a favorable safety and tolerability profile in the pediatric population (<12 years of age), with no inhibitors to rIX-FP detected during the study. The routine weekly prophylaxis regimen with rIX-FP was effective in the prevention of bleeding episodes. The PK profile of rIX-FP in the pediatric population (<12 years of age) suggests that a prolonged routine prophylaxis treatment interval of up to 14 days is a viable option for this population. The longer dosing interval for rIX-FP gives physicians and caregivers more options to consider when weighing the risks and benefits of inserting a central venous access catheter for dosing FIX replacement therapy. The prolonged $t_{1/2}$, enhanced exposure, and reduced clearance of rIX-FP suggest that patients with severe or moderate hemophilia B may be able to convert to a bleeding phenotype of mild hemophilia B on a routine weekly prophylaxis regimen. Low AsBRs, effective treatment of bleeding episodes, clinical improvement of target joints, and improved Haemo-QoL scores observed in the study suggest that weekly routine prophylaxis with rIX-FP may provide a new and safe alternative for the prevention and treatment of bleeding episodes in patients with hemophilia B.

Date of the report: 15 January 2015