CLINICAL STUDY PROTOCOL

A Phase 3b Open-label, Multicenter, Safety and Efficacy Extension Study of a Recombinant Coagulation Factor IX Albumin Fusion Protein (rIX-FP) in Subjects with Hemophilia B

Study Number:	CSL654_3003
Study Product:	Recombinant fusion protein linking coagulation factor IX with albumin (rIX-FP)
Development Phase:	3b
Sponsor:	CSL Behring GmbH (CSL) Emil-von-Behring-Strasse 76 35041 Marburg Germany
Protocol Version:	Amendment 6, FINAL
EudraCT Number:	2012-005489-37
IND Number:	CCI
Protocol Date:	03 February 2020
Compliance:	This study will be conducted in accordance with standards of Good Clinical Practice (as defined by the International Conference on Harmonisation), ethical principles that have their origin in the Declaration of Helsinki and all applicable national and local regulations.

LIST OF PERSONNEL AND ORGANIZATIONS RESPONSIBLE FOR CONDUCT OF THE STUDY

A list of personnel and organizations responsible for the conduct of the study will be supplied to study sites as part of the Investigator's Study File. This list will be updated by CSL (or delegate) and provided to the study sites as needed.

SIGNATURE ON BEHALF OF SPONSOR

Study Title: A Phase 3b Open-label, Multicenter, Safety and Efficacy Extension Study of a Recombinant Coagulation Factor IX Albumin Fusion Protein (rIX-FP) in Subjects with Hemophilia B.

Protocol Number: CSL654_3003

I have read the protocol amendment 6 titled "A Phase 3b Open-label, Multicenter, Safety and Efficacy Extension Study of a Recombinant Coagulation Factor IX Albumin Fusion Protein (rIX-FP) in Subjects with Hemophilia B" and confirm that, to the best of my knowledge, the protocol accurately describes the design and conduct of the study.

PPD

PPD

PPD

PPD, CRD H&T TA, Global Clinical Development Hematology & Thrombosis
Clinical Development

Date
(DD MMM YYYY)

SIGNATURE OF INVESTIGATOR

Study Title: A Phase 3b Open-label, Multicenter, Safety and Efficacy Extension Study of a Recombinant Coagulation Factor IX Albumin Fusion Protein (rIX-FP) in Subjects with Hemophilia B.

Protocol Number: CSL654_3003

I have read the protocol amendment 6 titled "A Phase 3b Open-label, Multicenter, Safety and Efficacy Extension Study of a Recombinant Coagulation Factor IX Albumin Fusion Protein (rIX-FP) in Subjects with Hemophilia B".

By signing this protocol, I agree to conduct the clinical study, after approval by an Institutional Review Board or Independent Ethics Committee (as appropriate), in accordance with the protocol, the principles of the Declaration of Helsinki (2008), the standards of Good Clinical Practice (as defined by the International Conference on Harmonisation) and applicable regulatory requirements.

Changes to the protocol will only be implemented after written approval is received from CSL Behring GmbH (CSL) and the Institutional Review Board or Independent Ethics Committee (as appropriate), with the exception of medical emergencies.

I will ensure that study staff fully understand and follow the protocol.

Name of investigator Affiliation of investigator	Date (DD MMM YYYY)

REVISION HISTORY

Date	Version	Summary of Changes
14 May 2013	FINAL (Original)	Not applicable
17 September 2013	Amendment 1	1. Addition of a third group of subjects (Arm 3) to the study design. Arm 3 comprises subjects who have not previously completed a CSL-sponsored rIX-FP lead-in study and who are scheduled to have a major non-emergency surgery within 8 weeks from the start of the initial pharmacokinetic rIX-FP (100 IU/kg) evaluation period. 2. Change in the sample size from 85 to 95. 3. CCI [redacted] 4. Minor corrections and clarifications, including word modifications and administrative changes.
17 February 2014	Amendment 2 (France Only)	1. To add a restriction excluding additional new surgical subjects in France from enrolling in Arm 3. 2. To exclude French subjects enrolled from the lead-in studies from the 21-day prophylaxis regimen. 3. To clarify treatment of a subject if an inhibitor to Factor IX (FIX) is confirmed.
03 June 2014	Amendment 3	• Per agreement with The Paediatric Committee (PDCO) / European Medicines Agency, study in previously untreated patients (PUPs) is added into this study. 1. To add PUPs with severe hemophilia B (FIX activity ≤2%) who have never been treated with FIX clotting factor products (except previous exposure to blood components) as study Arm 4. 2. Change in the sample size from 95 to 115, to include at least 20 PUPs. 3. Independent Data Monitoring Committee is being utilized to provide an independent evaluation of the study.
14 October 2015	Amendment 4	Addition of substudy to assess the pharmacokinetics and safety following subcutaneous administration of rIX-FP in hemophilia B subjects. This substudy will comprise subjects who are currently enrolled in the main study protocol CSL654_3003.

Date	Version	Summary of Changes
14 October 2015	Administrative Letter 1	Clarification: Amendment 3 is not in effect in the following countries: Bulgaria, Canada, France, Israel, Malaysia, South Africa. PUPs may not be enrolled into Arm 4 in these countries.
02 December 2016	Amendment 5	1. Main study: Addition of the ABR for total treated bleeding episodes to the comparisons between prophylaxis regimens for subjects from Study CSL654_3001. Addition of multiple testing procedure to control the overall Type I error rate for ABR and AsBR comparisons between prophylaxis regimens. 2. Main study: Update of overall study duration and study participation of Arms 1, 2 and 3 subjects to approximately 5 years, and addition of visits beyond 36 months. 3. Main study and subcutaneous (SC) substudy: Addition of final analyses of the a) previously treated patient (PTP) data when all PTPs have completed the study and b) SC substudy data when all subjects have completed the SC substudy. 4. Main study: Minor corrections and clarifications, including word modifications and administrative changes throughout the document.
		5. SC substudy: Change in SC dosing in Cohort 3 from single to repeated SC dosing (including home treatment). 6. SC substudy: Addition of optional Cohort 4 for repeated SC dosing that will be opened if additional data are needed to inform further clinical development. 7. SC substudy: Addition of details regarding local tolerability assessments. 8. SC substudy: Addition of SC substudy information to the main study protocol where relevant (eg, objectives and endpoints).

Date	Version	Summary of Changes
03 February 2020	Amendment 6	1. Adjustment of number of PUPs from “at least 20” to “at least 13” to reflect PDCO opinion to allow early termination of PUP enrolment. 2. As study has been completed for PTPs, adjustment of number of PTPs in final PTP analysis (N=83). 3. Adjustment of overall number of subjects to reflect 1 and 2. 4. The frequency of the CSL Safety Management Team meetings has been updated from approximately every 6 months to approximately every 3 months, to reflect an internal process change. Note: Although the study has been closed for PTPs, the PTP information has been retained in the study protocol to avoid substantial rework of the document.

PROTOCOL SYNOPSIS

Title	A Phase 3b Open-label, Multicenter, Safety and Efficacy Extension Study of a Recombinant Coagulation Factor IX Albumin Fusion Protein (rIX-FP) in Subjects with Hemophilia B
Study Number	CSL654_3003
Sponsor	CSL Behring GmbH (CSL)
Development Phase	3b
Study Product	Recombinant fusion protein linking coagulation factor IX with albumin (rIX-FP)
Indication	Prophylaxis of bleeding episodes in patients with congenital factor IX deficiency (hemophilia B); control and prevention of bleeding episodes in patients with hemophilia B.
Study Summary	This phase 3b study aims to evaluate the long-term safety and efficacy of rIX-FP for routine prophylaxis and on-demand treatment of bleeding episodes in children and adults with severe hemophilia B (ie, FIX activity of ≤ 2%). The study will include the following study arms: **Arm 1:** subjects who have completed Study CSL654_3001 Arm 1, Study CSL654_3002, or any other CSL-sponsored rIX-FP (CSL654) lead-in study. **Arm 2:** subjects who were enrolled in Study CSL654_3001 Arm 2. **Arm 3** (No subjects in France may enroll in Arm 3): subjects who have not previously completed a CSL-sponsored rIX-FP lead-in study who are scheduled to have a major non-emergency surgery within approximately 8 weeks from receiving the first rIX-FP injection (ie, during the pharmacokinetics [PK] evaluation period). **Arm 4:** previously untreated patients (PUPs) with severe hemophilia B (FIX activity ≤2%) who have never been treated with FIX clotting factor products (except previous exposure to blood components). The study consists of a treatment period of up to approximately 5 years for Arms 1, 2 and 3, and up to approximately 3 years for Arm 4. During the treatment period, subjects will administer rIX-FP as routine prophylaxis, prevention, and on-demand treatment. All subjects in Arm 3 (No subjects in France may enroll in Arm 3) will undergo an initial rIX-FP (100 IU/kg) PK evaluation period and

complete a surgery substudy before having the option to start routine prophylaxis.

All subjects in Arm 4 will undergo an rIX-FP (50 IU/kg) PK evaluation at Day 1 as the first dose if feasible or during the study after at least 7 days washout from the previous rIX-FP dose, when the subject is in non-bleeding state.

Up until the month 6 visit, subjects in Arm 1-3 will administer rIX-FP routine prophylaxis with the following treatment intervals:

Arm 1: rIX-FP administered once every 7, 10, or 14 days.

Arm 2: rIX-FP administered once every 7 days (subjects from study CSL654_3001 Arm 2 with less than 26-weeks experience with weekly prophylaxis).
rIX-FP administered once every 14 days (subjects from study CSL654_3001 Arm 2 with at least 26-weeks experience with weekly prophylaxis).

Arm 3 (No subjects in France may enroll in Arm 3): rIX-FP administered once every 7 days until the month 6 visit.

After the month 6 visit, all subjects (Arms 1, 2, and 3) will administer rIX-FP once every 7, 10, or 14 days for approximately 30 months.

Subjects ≥ 18 years of age (except subjects from France, regardless the age) also have the option to administer rIX-FP once every 21 days. Any subject transferring to a 21-day treatment interval for the first time must have completed at least 6 months of prophylaxis treatment with a 14-day treatment interval and have undergone a PK evaluation with a single rIX-FP injection of 100 IU/kg.

At the end of the study, subjects from the lead-in studies are expected to have accumulated at least 100 rIX-FP exposure days (EDs) during their enrollment in all CSL-sponsored rIX-FP studies.

Arm 4:

Subjects in Arm 4 will administer rIX-FP as weekly prophylaxis and / or on-demand, prevention during the first 12 months, and then on weekly routine prophylaxis until completing 50 EDs. Subjects who complete 50 EDs are permitted to continue weekly routine prophylaxis with rIX-FP until the completion of the study.

Surgical Prophylaxis Substudy

All subjects in Arm 3 (No subjects in France may enroll in Arm 3) should start the surgery substudy within approximately 8 weeks from receiving the first rIX-FP injection (ie, during the PK evaluation period). If a subject in either Arms 1 or 2 requires a major or minor surgical non-emergency procedure during the study, or if a subject in Arm 4 requires a minor surgical procedure during the study, the subject may also be enrolled in the surgery substudy.

Approximately 3 hours before the surgical procedure, the subject will receive a single bolus injection of rIX-FP in order to increase the plasma FIX activity level to 60% to 80%, or higher. At the investigator's discretion, additional bolus injections of rIX-FP may be administered during surgery or during the postoperative period, defined as the start of wound closure, to maintain a required trough FIX activity level.

Subcutaneous (SC) Substudy

Subjects enrolled in this substudy will be sequentially assigned to a cohort (Cohort 1 [single dose of 25 IU/kg], Cohort 2 [single dose of 50 IU/kg], Cohort 3 [15 doses of 25 IU/kg every 3 days], and an optional Cohort 4 [15 doses of ≤ 50 IU/kg every 5 days, with the actual dose in this cohort to be determined by CSL based on the PK results from Cohort 3). In all cohorts, rIX-FP will be administered SC at least 14 days after the previous intravenous (IV) rIX-FP administration.

In Cohorts 1 and 2, blood samples for PK analysis will be collected at selected time points through Day 15 (336 hours). Following collection of the last SC PK sample at the 336 hour time point on Day 15, a single IV dose of 50 IU/kg rIX-FP will be administered and blood samples for PK analysis will be collected at selected time points. Subjects will return in 2 weeks (Day 28) for an end of substudy visit to assess safety. After the end of substudy visit on Day 28, Cohort 1 and 2 subjects will return to their IV rIX-FP prophylaxis regimen in the main study.

In Cohorts 3 and 4, blood samples for PK analysis will be collected at before the first SC dose, before selected SC doses, as well as for a serial PK profile after the first and the final SC doses. Subjects will return 2 weeks after their last SC dose for an end of substudy visit for collection of the final SC PK sample and for safety assessments. After the end of substudy visit, Cohort 3 and 4 subjects will return to their IV rIX-FP prophylaxis regimen in the main study.

Primary Objective(s)	The primary objective of this study is to evaluate the safety of rIX-FP as measured by new cases of inhibitors against FIX in all subjects, including PUPs, with severe hemophilia B. The PK parameter in PUPs will also be collected.
Primary Endpoint(s)	• The total number subjects who develop inhibitors against FIX during the approximately 3-year participation in this study. • PK parameters of incremental recovery (IU/dL per IU/kg) of 50 IU/kg rIX-FP (Arm 4 only)
Secondary Objective(s)	The secondary objectives of the study are: • To evaluate the efficacy of rIX-FP routine prophylaxis when administered at various treatment intervals. • To compare the efficacy of rIX-FP routine prophylaxis between 2 different treatment intervals and versus on-demand treatment. • To further evaluate the safety of rIX-FP. • To evaluate the efficacy of treatment of bleeding episodes in Arm 4 PUPs.
Secondary Endpoint(s)	• Annualized bleeding rate (ABR) for spontaneous treated bleeds and total treated bleeds for each assigned treatment interval (7 days, 10 days, 14 days, and 21 days). • Comparison of the AsBR and ABR between: o 14-day routine prophylactic treatment in this study compared with on-demand only treatment from Study CSL654_3001 Arm 2. o 7-day prophylaxis regimen with the 14-day prophylaxis regimen. o 7-day prophylaxis regimen with the extended prophylaxis regimen (10-day or 14-day). • Consumption of rIX-FP during routine prophylaxis expressed as IU/kg per month per subject. • Incidence of adverse events and related adverse events to rIX-FP over the course of the study. • Hemostatic response to treatment of bleeding episodes with rIX-FP as assessed by the investigator based on a 4-point scale (Arm 4 only).
CCI [redacted]	

	CCI [redacted]
CCI [redacted]	
Study Design	Multicenter, open-label, phase 3b study.
Number of Subjects	This study will enroll approximately 96 male subjects, including all eligible subjects from rIX-FP lead-in studies, approximately 10 subjects requiring major non-emergency surgery and at least 13 PUPs.

	Any subjects requiring non-emergency surgery or any subjects in Arm 4 requiring minor surgery during the course of the study may be enrolled in the surgery substudy. Up to a maximum of 24 subjects will enroll in the SC substudy.
Study Duration	For subjects in Arms 1, 2, and 3, the duration of the study for an individual subject is expected to be approximately 5 years or the time it takes to achieve a total of 100 EDs during the subject's enrollment in any CSL-sponsored rIX-FP studies. For subjects in Arm 4, the duration of the study is expected to be approximately 3 years or the time it takes to achieve a total of 50 EDs. The study may be stopped at a specific study site after all subjects at the site have completed the 5-year study period or ≥ 50 subjects overall have achieved a total of 100 EDs or after regulatory approval and rIX-FP becomes commercially available in the respective country. The duration of the SC substudy for an individual subject is expected to be approximately 30 days in Cohorts 1 and 2, approximately 57 days in Cohort 3, and approximately 85 days in Cohort 4.
Study Population and Main Criteria for Eligibility	***Exclusion Criteria*** Subjects meeting any of the following exclusion criteria must not be enrolled into the study: **All subjects**: • **Arms 1, 2, 3 and 4**: Currently receiving a therapy not permitted during the study, as defined in Section 7.3. • **Arms 1 and 2 only**: Unwilling to participate in the study for a total of 100 EDs. • **Arms 1, 2, 3 and 4**: Any issue that, in the opinion of the investigator, would render the subject unsuitable for participation in the study. ***Inclusion Criteria*** **Arm 1 and Arm 2:** Subjects who completed either Study CSL654_3001, Study CSL654_3002, or any other CSL-sponsored rIX-FP (CSL654) lead-in study. **Arm 3:** The main eligibility criteria for subjects in Arm 3 (However, subjects(s) in France will NOT be eligible to be enrolled into Arm 3 of the study):

Inclusion Criteria

- Scheduled to have a major non-emergency surgery within approximately 8 weeks from the anticipated date of receiving the first rIX-FP injection.
- Not previously completed a CSL-sponsored rIX-FP lead-in study.
- Male, 12 to 70 years of age.
- Documented severe hemophilia B (FIX activity of ≤ 2%), or confirmed at screening by the central laboratory.
- Subjects who have received FIX products (plasma-derived and / or recombinant FIX) for > 150 EDs, confirmed by their treating physician.
- No confirmed history of FIX inhibitor formation at screening by the central laboratory.

Exclusion Criteria

- Known hypersensitivity (ie, allergic reaction or anaphylaxis) to any FIX product or hamster protein.
- Known congenital or acquired coagulation disorder other than congenital FIX deficiency.
- Currently receiving IV immunomodulating agents such as immunoglobulin or chronic systemic corticosteroid treatment.
- Low platelet count, kidney or liver disease.
- Human immunodeficiency virus positive with a CD4 count < 200/mm^3.

Arm 4: The main eligibility criteria for subjects in Arm 4 are:

Inclusion Criteria

- Male, up to 18 years of age.
- Documented severe hemophilia B (FIX activity of ≤ 2%), or confirmed at screening by local or central laboratory.
- Subjects who have never been treated with FIX clotting factor products (except previous exposure to blood components).
- No confirmed history of FIX inhibitor formation.

Exclusion Criteria

- Known congenital or acquired coagulation disorder other than congenital FIX deficiency (except for vitamin K deficiency of the newborn).

	• Known kidney or liver dysfunction or any condition which, in the investigator's opinion, place the subject at unjustifiable risk. **SC Substudy:** The main eligibility criteria for subjects in the SC substudy are: ***Inclusion Criteria*** • Male subjects, at least 18 years of age. • Subjects who are currently enrolled in Study CSL654_3003 with hemophilia B (FIX activity ≤ 2%). • Subjects who have received rIX-FP for ≥ 100 EDs (Cohorts 1 and 2) or for ≥ 50 EDs (Cohorts 3 and 4). • Body weight between 50.0 and 100.0 kg, both inclusive. • Body mass index (BMI) between 18.0 and 29.9 kg/m^2. ***Exclusion Criteria*** • Use of rIX-FP within 14 days before SC administration of rIX-FP. • Experienced a life-threatening bleeding episode or had major surgery during the 3 months prior to substudy entry (Day 1).
Study Product Dose, Dosing Regimen and Administration	Subjects in Arms 3 and 4 will receive their first 2 doses at the study center and be monitored for at least 3 hours. Following WFH's guideline, subjects in Arm 4 must be treated in a clinic or hospital setting under the medical supervision of a physician experienced in the treatment of hemophilia patients and where proper medical care for possible allergic reaction can be provided during the initial 10 to 20 treatments with rIX-FP. ***Prophylaxis Treatment*** <u>Subjects in Arm 1, 2 or 3:</u> Before the month 6 visit, subjects will administer rIX-FP as routine prophylaxis using either a 7-, 10-, or 14-day treatment interval. After the month 6 visit, subjects may remain on their current treatment interval or they may be switched to a 7-, 10-, 14-, or 21-day treatment interval. Subjects in France may not take part in the 21-day treatment regimen. <u>Subjects in Arm 4:</u> Before the month 12 visit, subjects may receive rIX-FP as weekly routine prophylaxis (preferred) or only on-demand treatment when bleeding occurs (may combine prevention doses) at the investigator's discretion. After the month 12 visit, subjects will be on weekly prophylaxis for the remaining duration of the study.

The dose of rIX-FP administered for routine prophylaxis will be based on the subject's previous experience (ie, in a lead-in study) and / or the targeted FIX activity trough level (target FIX activity level > 2%, but optimally between 5% and 15%. The maximum dose of rIX-FP for routine prophylaxis will be 50 IU/kg per injection for subjects using a 7-day treatment interval, 75 IU/kg per injection for subjects using a 10- or 14-day treatment interval, and 100 IU/kg per injection for subjects using a 21-day treatment interval. Subjects in France may not take part in the 21-day treatment regimen. The dose of rIX-FP for a subject using the 7-day treatment interval should not be higher than the dose they used in the lead-in study and / or a trough FIX activity of 20%.

On-demand Treatment

On-demand treatment with rIX-FP will be used for all bleeding episodes requiring treatment. The dose of rIX-FP (35 to 75 IU/kg) will be determined by the investigator, based on the effective on-demand treatment dose used in the lead-in study and / or the subject's PK data (determined in a lead-in study or Study CSL654_3003).

Prevention Before Vigorous Physical Activity or Physical Therapy

During the study, subjects may administer rIX-FP as a preventative treatment before vigorous physical activity or before physical therapy (ie, as a part of rehabilitation after major surgery) that, in the subject's experience, is likely to result in bleeding.

Preventative treatment before vigorous physical activity should not be used more frequently than **once per month**.

Preventative treatment before physical therapy (ie, after major surgery) should not be used more frequently than **once per week** during the first 3 months of either starting the prophylaxis treatment period (subjects in Arm 3, which excludes subjects in France) or returning to routine prophylaxis (subjects in Arms 1 or 2).

The dose of rIX-FP will be 35 to 50 IU/kg, as determined by the investigator and / or based on the subject's previous experience.

Subcutaneous Treatment in the Subcutaneous Substudy

Subjects will be sequentially assigned to a cohort, and receive a single SC dose of rIX-FP (in Cohorts 1 and 2) or repeated SC doses of rIX-FP (in Cohorts 3 and 4). The SC doses of rIX-FP will be administered at up to 4 injection sites, a minimum of 2.5 cm apart, with a volume of up to 4 mL per site. Subcutaneous administration may occur on the

	stomach, thigh or upper arm. The first SC rIX-FP dose should be administered at least 14 days after the previous IV rIX-FP administration (21 days if subject is on a 21-day prophylaxis regimen in the main study). In Cohorts 1 and 2, subjects will be administered a single IV dose of 50 IU/kg rIX-FP at Day 15 (336 hours). After the end of substudy visit, Cohort 3 and 4 subjects will return to their IV rIX-FP prophylaxis regimen in the main study.
Comparator Product, Dose, Dosing Regimen and Administration	Not applicable.
Efficacy Assessments	The efficacy of rIX-FP treatment in the prevention and treatment of bleeding episodes will be assessed based on the following: • Total consumption of rIX-FP (number of EDs and mean IU/kg per year per subject and per bleeding episode) and consumption per routine prophylaxis, prevention before physical activity, and on-demand treatment. • Number of spontaneous and total bleeding episodes and corresponding ABRs per treatment interval. • Investigator's overall clinical assessment of hemostatic efficacy for treatment of major bleeding episodes. • Number of rIX-FP injections required to achieve hemostasis.
Safety Assessments	Safety will be assessed based on the following variables: • Adverse events and serious adverse events. • Local tolerability. • Serum biochemistry and hematology. • Physical examination and vital signs. • Inhibitors against FIX. • Antibodies against rIX-FP and Chinese hamster ovary cell-derived proteins.
Pharmacokinetics	Subjects beginning routine prophylaxis treatment using a treatment interval of 21 days for the first time (age ≥ 18 years, excludes subjects in France) and subjects in Arm 3 (also excluded in France) will undergo a PK evaluation with a single injection of rIX-FP (100 IU/kg). Subjects in Arm 4 may also undergo a PK evaluation at the beginning of the study with a single injection of rIX-FP (50 IU/kg). For this PK evaluation, blood samples will be taken for the measurement of the FIX activity level and incremental recovery.

	In addition, PK evaluation of 50, 75, or 100 IU/kg rIX-FP may also be assessed at the investigator's discretion or CSL's request, in the event of (but not limited to), poor efficacy, suspicion of inhibitor development, or before major surgery. Subjects in France may be discontinued from receiving the study product and participating in any further study procedures if the subject is confirmed to have developed an inhibitor against FIX with a titer > 5 Bethesda units (BU)/mL. The trough FIX activity level will be assessed after each major bleeding episode (if feasible) and at specified visits. See Appendix 2 for PK assessments in the SC substudy.
Pharmacodynamics	Not applicable.
Other Assessments	Other assessments to be made during the study include: • A hemophilia-specific treatment satisfaction questionnaire (Hemo-Sat; CSL654_3002 lead-in study only). • CCI [redacted] • Social and physical activity assessment.
Statistical Analyses	All safety and efficacy data will be summarized using descriptive statistics for continuous data, or frequencies and percentages for categorical data. ***Efficacy Analyses*** AsBRs and ABRs will be derived for each treatment interval assigned to the subject while on routine prophylaxis (7-day, 10-day, 14-day, and 21-day), and will not include the time either during or the first 3 months after the surgery substudy, the time during the SC substudy, and subjects in Arm 4. AsBRs and ABRs will be summarized across subjects using descriptive statistics. A crude rate will also be calculated for each treatment interval along with an exact two-sided 95% confidence interval assuming a Poisson-distributed event rate. A comparison of AsBRs and ABRs will be performed between 14-day routine prophylaxis treatment in this study compared with on-demand only treatment from Study CSL654_3001 Arm 2. A further analysis will be conducted with the subjects from lead-in Study CSL654_3001 to assess whether the 14-day prophylaxis regimen is non-inferior to the 7-day prophylaxis regimen from Study CSL654_3001 (plus data

	obtained from the extension study, if available) based on the mean of AsBR and ABR. The non-inferority analysis will also be conducted for extended regimens (either 14-day or 10-day regimen) and the 7-day prophylaxis regimen. Non-inferiority will be evaluated by comparing the lower bound of a 95% confidence interval for a mean difference with a pre-established margin. Consumption of rIX-FP will be summarized with descriptive statistics according to treatment interval and overall. For subjects from Study CSL654_3002, responses to the treatment satisfaction questionnaire and age group-specific CCI questionnaire (Hemo-Sat and CCI, respectively) will be summarized with descriptive statistics. Data from the surgery substudy will be summarized as case narratives or with descriptive statistics or counts, where appropriate. ***Safety Analyses*** The number and proportion of subjects with positive tests for inhibitors to FIX during the study will be tabulated separately for PTPs (Arm 1, 2 and 3) and PUPs (Arm 4). Inhibitor antibodies against FIX will be categorized as low titer (≥ 0.6 to 5 BU/mL) and high titer (> 5 BU/mL). An exact 95% binomial confidence interval for inhibitor development among subjects treated with rIX-FP will be presented. The number and proportion of subjects with adverse events and serious adverse events, which are study-emergent, will be tabulated. Laboratory, vital signs and physical examination assessments will be summarized. *Pharmacokinetic Analyses* Incremental recovery and FIX activity levels will be summarized using descriptive statistics. See Appendix 2 for the statistical analyses planned in the SC substudy. Further details regarding the statistical analysis will be provided in the Statistical Analysis Plan (SAP).
Interim Analyses	No interim analyses are planned. The following analyses are planned before study closure: 1. The final analysis of the SC substudy data will be conducted once all subjects have completed the SC substudy.

2. The final analysis of PTPs (including surgical data from PTPs) will be conducted when all PTPs have completed the study.

In addition, safety, efficacy and / or PK data and subject characteristics may be reported to regulatory authorities before study closure.

TABLE A - SCHEDULE OF ASSESSMENTS: TREATMENT PERIOD (ARMS 1, 2 AND 3)

Assessments	Day 1 [B] Arm 1 & 2	Month [A] 3 [C]	6 [L]	9 [C]	12	18, 30, 42, 54	24, 36, 48, 60	50 EDs [D]	End of Study
Informed consent	X								
Demographics, lead-in study data	X								
Eligibility assessment	X								
Social and physical activity	X		X		X	X	X		X
Relevant medical history [E]	X								
Physical examination	X				X		X		X
Vital signs	X				X		X		X
Body weight and height [F]	X	X	X	X	X	X	X		
Blood biochemistry and hematology (LL)	X				X				X
Inhibitors against FIX (CL)	X		X		X	X	X	X	X
Ab against rIX-FP & CHO cell proteins (CL) [G]	X				X		X	X	X
Plasma FIX activity (CL)	X[M]		X		X	X	X		
Plasma FIX activity (LL)			X		X				
Retain blood sample [H]									X
Dispense subject eDiary	X								
Review subject eDiary		X	X	X	X	X	X		X
Assess treatment efficacy for a major bleed		X	X	X	X	X	X		X
Review treatment regimen [I]			X		X	X	X		
Hemo-Sat questionnaire [J]					X				
CCI					X				
Retrieve eDiary									X
Adverse events	<----------On an ongoing basis---------->							X	X [K]
Concomitant therapy	<----------On an ongoing basis---------->							X	X

Ab = antibody; CHO = Chinese hamster ovary; CL = central laboratory; ED = exposure day; eDiary = electronic diary; FIX = coagulation factor IX; LL = local laboratory; CCI; rIX-FP = recombinant coagulation factor IX albumin fusion protein.

Notes to the schedule of assessments:

A: Time window: ± 2 weeks. All visits should occur within 2 calendar days before the next scheduled prophylactic administration of rIX-FP. A month is 28 days.

B: Day 1 assessments to be completed only by subjects in Arms 1 or 2. Data that will be transferred from the end of study visit or earlier visit (where relevant) of the lead-in study include demographics, rIX-FP EDs, age cohort in lead-in study, arm in lead-in study, social and physical activity, laboratory assessments (serum biochemistry, hematology), vital signs, physical examination, body height and weight, and antibody assessments (inhibitors against FIX, antibodies against rIX-FP & CHO cell-derived proteins), plasma FIX activity (in subjects from CSL654_3001 study only), adverse events, and concomitant therapy.

C: For subjects from lead-in Study CSL654_3001 Arm 1, the month 3 and month 9 visits may be conducted via telephone, if the investigator deems that there is no safety risk to the subject. For subjects from lead-in Study CSL654_3001 and CSL654_3002, the month 9 visit may be conducted via telephone, if the investigator deems that there is no safety risk to the subject. The month 3 visit may be omitted for subjects in Arm 2 who have attended a follow-up after visit in the previous 3 months to transition from a 7-day rIX-FP treatment interval to a 14-day rIX-FP treatment interval.

D: Visit to occur within a month after a subject has experienced a total of 50 rIX-FP EDs in this extension study. If the 50 EDs visit is to occur within 3 months of a follow-up visit, the scheduled follow-up visit may be omitted by conducting all follow-up assessments, in addition to assessments required for the 50 EDs visit, during the 50 EDs visit.

E: Record genotype and current joint score including scoring system and date of the assessment.

F: Height to be recorded on day 1 and thereafter at annual intervals only (ie, month 12, 24, etc). Height measurements on the month 12, 24, 36, and 48 visits are optional for subjects ≥ 18 years of age. Measurement of body weight may be omitted at month 3 and month 9 if the visit is conducted via telephone.

G: A sample that tests positive for antibodies against rIX-FP will be retested to discriminate between plasma-derived FIX, recombinant FIX and albumin antibodies.

H: Retain samples will be collected for potential serology testing at a later date.

I: Investigator to review treatment efficacy and change treatment regimen (dose and / or treatment interval), if necessary.

J: CCI [redacted]

K: The observation period for adverse event (and serious adverse event) reporting in an individual subject will start at the time of giving written informed consent for participation in the current study and finish with the end of study visit. However, adverse events ongoing at the end of study visit will be followed until resolution or 30 days after the final administration of rIX-FP during this study, whichever is sooner.

L: Arm 2 Subjects should attend an unscheduled visit and complete assessments as specified for the 6-month visit if they are to switch to a 14-day treatment interval before completion of the 6-month period. Under such circumstances, the 3-month visit may be omitted.

M: Sample collected in subjects coming from Study CSL654_3002 after consenting for CSL654_3003.

TABLE B - SCHEDULE OF ASSESSMENTS: PHARMACOKINETIC PERIOD

		50 IU/kg (Arm 4) or 100 IU/kg rIX-FP PK Visit [A]					
Assessments	**Before injection**	**0 hour (injection)**	**30 min**	**72 hours [B] (3 days)**	**168 hours [C] (7 days)**	**336 hours [D] (14 days)**	**504 hours [D] (21 days)**
Time Window	< 12 hours before injection		± 5 min	± 24 hrs	± 24 hrs	± 24 hrs	± 24 hrs
Weight and height	X						
Plasma FIX level (central)	X		X	X	X	X	X
Retain blood sample [E]	X						
Administration of rIX-FP		X					
Dispense subject eDiary [F]		X					
Training of self-administration [F]		X	X	X	X		
Adverse events		<----------On an ongoing basis---------->					
Concomitant therapy		<----------On an ongoing basis---------->					

eDiary = electronic diary; FIX = coagulation factor IX; PK = pharmacokinetic; rIX-FP = recombinant coagulation factor IX albumin fusion protein.

A: 100 IU/kg PK completed only by subjects in Arm 3 (no subjects in France may enroll in Arm 3) or subjects ≥18 years who have completed at least 6 months of treatment and planning to begin routine prophylaxis treatment using a 21-day treatment interval for the first time. Subjects in France may not take part in the 21 day treatment regimen. The PK evaluation should be performed after a washout period of at least either 4 days for a current marketed FIX product (ie, subjects in Arm 3 (no subjects in France may enroll in Arm 3) or 14 days for rIX-FP (subjects currently being treated with rIX-FP). 50 IU/kg PK completed by subjects in Arm 4 (see Table D for assessments prior to rIX-FP injection). The investigator may also choose to complete a PK assessment of 50, 75 or 100 IU/kg (as appropriate) rIX-FP with selected time points before starting surgical prophylaxis with rIX-FP, at the investigator's discretion or CSL's request, or in the event of (but not limited to) poor efficacy or suspicion of inhibitor development. Samples may be tested in the local laboratory in addition to the central laboratory. Subjects in France may be discontinued from receiving the study product and participating in any further study procedures if the subject is confirmed to have developed an inhibitor against FIX with a titer > 5 BU/mL.

B: Optional time point for subjects planning to be switched to a 21-day treatment interval, and Arm 4.

C: Optional time point for Arm 4 subjects.

D: Optional time point for subjects in Arm 3 before major surgery (No subjects in France may enroll in Arm 3). Not done for Arm 4.

E: Retain samples will be collected before the first injection of rIX-FP (subjects in Arm 3 only, excludes subjects in France) for potential serology testing at a later date.

F: Subjects in Arm 3 only (subjects in France may not enroll in Arm 3). Before completion of the PK evaluation period (at a time point determined by the investigator), the eDiary should be dispensed and subjects should be trained on injection technique, dosing regimen, and use of the eDiary.

TABLE C - SCHEDULE OF ASSESSMENTS: SUBJECTS IN ARM 3(NO SUBJECTS IN FRANCE MAY ENROLL IN ARM 3)

	Screening	PK Period	Before surgery	Surgery Substudy	Day 1 [A] Arm 3	Treatment Period
Time window	-1 to -28 days		7 to 56 days after PK injection	Surgery day to 28 ± 7 days after surgery		
Assessments						
Informed consent	X					
Demographics	X					
Eligibility assessment	X					
Social and physical activity	X					
Relevant medical and treatment history [B]	X					
Physical examination	X					
Vital signs	X					
Body weight and height	X				X [C]	
Blood biochemistry and hematology (LL)	X					
Inhibitors against FIX (CL)	X					
Ab against rIX-FP & CHO cell proteins (CL) [D]	X					
Plasma FIX activity (CL and LL)	X					
Begin prophylaxis treatment with rIX-FP					X [E]	
Adverse events	X		X		X	
Prior / concomitant therapy	X		X		X	

Complete Schedule of Assessments: Pharmacokinetic Period (Table B)

Complete Schedule of Assessments: Surgery Substudy – Major Surgery

Complete Schedule of Assessments: Treatment Period (Table A)

Ab = antibody; CHO = Chinese hamster ovary; CL = central laboratory; eDiary = electronic diary; FIX = coagulation factor IX; LL = local laboratory; PK = pharmacokinetics; rIX-FP = recombinant coagulation factor IX albumin fusion protein.

Notes to the schedule of assessments:

A: The Day 1 visit should occur after completion of the surgery substudy and should occur at the same time as the End of Surgery Substudy visit.

B: Record history of hemophilia B including genotype and current joint score (including scoring system and date of the assessment), and treatment history with a marketed FIX.

C: Body weight only.

D: A sample that tests positive for antibodies against rIX-FP will be retested to discriminate between plasma-derived FIX, recombinant FIX and albumin antibodies.

E: Subjects in Arm 3 **(No subjects in France may enroll in Arm 3)** who require physical therapy (ie, rehabilitation after surgery), may administer rIX-FP as preventative treatment (no more than once per week) in addition to the administration of rIX-FP as routine prophylaxis. Preventative treatment before physical therapy is permitted only during the first 3 months of the treatment period.

TABLE D - SCHEDULE OF ASSESSMENTS: SUBJECTS IN ARM 4

Assessments	Screen[B] (up to 28 days)	(PK[A])				Months[I] (±1 week)												Months (±2 week)							50 EDs	EoS[L]
		Prior dose	30±5 mins	Day 3	Day 7	1	2	3	4	5	6	7	8	9	10	11	12	15	18	21	24	27	30	33		
Informed consent	X																									
Demographics	X																									
Eligibility assessment	X																									
Relevant medical history	X																									
Physical examination	X					X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X		X
Vital signs[C]	X					X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X		X
Body weight and height	X	X				X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X		
Biochemistry&hematology[D]	X[E]																X				X					X
Inhibitors against FIX (CL)	X[E]					X	X	X	X	X	X			X			X		X		X		X		X	X
Ab to rIX-FP/CHO (CL)[F]	X[E]										X						X				X				X	X
Plasma FIX activity (CL)[H]		X	X	X	X	X	X	X			X						X				X					X
Plasma FIX activity (LL)	X[J]																									
Retain blood sample[G]		X																								X
Dispense subject eDiary[K]																	X									
Review subject eDiary						<---------- On an ongoing basis during eDiary usage ---------->																				X
Review treatment efficacy						<---------- On an ongoing basis ---------->																				X
Adverse events	<---------- On an ongoing basis ---------->																									
Concomitant therapy	<---------- On an ongoing basis ---------->																									

Ab = antibody; CHO = Chinese hamster ovary; CL = central laboratory; eDiary = electronic diary; FIX = coagulation factor IX; LL = local laboratory; PK = pharmacokinetics; rIX-FP = recombinant coagulation factor IX albumin fusion protein; EoS=End of Study.

Subjects will be treated in the study center or medical facility under medical supervision during the initial 10 to 20 treatment with rIX-FP. The first 2 infusions must be monitored on-site for at least 3 hours.

A: PK can start at Day 1 as the first dose or/and during the study after ≥7 days washout from the previous rIX-FP dose, when the subject is in non-bleeding state. See Table D for PK sampling time points. (Day 1 is the day subject receives his first dose with rIX-FP)
B: Tests that require blood sample for screening period (from ICF day to Day 1 prior to dose) can be divided to multiple days or combined with Day 1 tests. The screening day can be the same day for first dose of rIX-FP (either on-demand, prophylaxis or PK dose).
C: Vital signs include blood pressure, temperature and heart rate.
D: Includes liver and renal function test (Albumin, Alanine Aminotransferase, Aspartate Aminotransferase, Alkaline Phosphatase, Bilirubin, Direct Bilirubin, Protein, Blood Urea Nitrogen or Urea, and Creatinine).
E: Documented biochemistry & hematology results from 6 months prior to screening are acceptable; otherwise, samples may be collected during the screening period or at Day 1. Samples for antibodies/inhibitor must be collected during the screening period or prior to first dose of rIX-FP.
F: A sample that tests positive for antibodies against rIX-FP will be retested to discriminate between pdFIX, rFIX and albumin antibodies.
G: Retain samples will be collected prior to the first dose of rIX-FP for potential serology testing at a later date.
H: Optional samples at Day 3 or Day 7 of PK assessment, or during the month 1, 2 or 3 for FIX activity if feasible.
I: If subjects receive treatment for less than 3 doses per month, they may omit the site visit(s) until they received ~5 doses.
J: FIX activity tested at local Laboratory if no previous FIX data available in medical records.
K: Subject eDiary may be dispensed once caregiver is trained to administer rIX-FP at home, but not prior to receiving a minimum of 10 infusions at the study center or medical facility under medical supervision.
L: End of Study for Arm 4 is the Month 36 visit.

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LIST OF ABBREVIATIONS

Abbreviation	Definition
Ab	Antibody
ABR	Annualized bleeding rate
AsBR	Annualized spontaneous bleeding rate
AE	Adverse event
AESI	Adverse event of special interest
ALP	Alkaline phosphatase
ALT	Alanine aminotransferase
AR	Accumulation ratio
AST	Aspartate aminotransferase
AUC	Area under the concentration-time curve
$AUC_{0\text{-last}}$	Area under the concentration-time curve from zero up to an infinite time
$AUC_{0\text{-inf}}$	Area under the concentration-time curve from zero up to the last measurable time
CCI [redacted]	
BU	Bethesda unit
CHO	Chinese hamster ovary
CL	Central Laboratory
C_{max}	Maximum concentration
CCI [redacted]	
CCI [redacted]	
EBL	Estimated blood loss
eCRF	Electronic case report form
ED	Exposure day
eDiary	Electronic diary
FDA	Food and Drug Administration
FIX	Coagulation factor IX
GCP	Good Clinical Practice
ICF	Informed Consent Form
ICH	International Conference on Harmonisation of Technical Requirements for Registration of Pharmaceuticals for Human Use
IDMC	Independent Data Monitoring Committee
IEC	Independent Ethics Committee
IR	Incremental recovery
IRB	Institutional Review Board
IU	International unit
IV	Intravenous
LL	Local Laboratory
MedDRA	Medical Dictionary for Regulatory Activities

Abbreviation	Definition
PK	Pharmacokinetic
PP	Per-protocol
PT	Preferred term
PTP	Previously Treated Patient
PUP	Previously Untreated Patient
CCI [redacted]	
rIX-FP	Recombinant coagulation factor IX albumin fusion protein
SAE	Serious adverse event
SAP	Statistical analysis plan
SC	Subcutaneous
SD	Standard deviation
SMT	Safety Management Team
SOC	System organ class
SRC	Safety Review Committee
$t_{1/2}$	Terminal half-life
TAT	Thrombin-antithrombin
T_{max}	Time to reach C_{max}
$T_{max, ss}$	Time to reach C_{max} at steady state
V_{ss}	Volume of distribution at steady state
WFH	World Federation of Hemophilia

1. INTRODUCTION

1.1 BACKGROUND

Hemophilia B is an X-linked recessive inherited bleeding disorder resulting from a deficiency of coagulation factor IX (FIX), a coagulation factor central to the process of blood coagulation [Giangrande, 2005]. Signs and symptoms of hemophilia B are variable, depending on the severity of FIX deficiency and the location of bleeding. Most often, bleeding is characterized by spontaneous or trauma-induced hemorrhage into joints, muscles, and soft tissues. Recurrent bleeding in the same location may lead to permanent injury of the joint. Rare but life-threatening bleeding may also occur in the central nervous system, throat, or gastrointestinal tract.

The goal of therapy for hemophilia B is to treat or prevent hemorrhage, thereby reducing disabling joint and tissue damage, and improving CCI [redacted]. Replacement therapy with FIX provides a temporary correction of the factor deficiency and reduces bleeding tendencies. Currently, plasma-derived and recombinant FIX products are used for the prophylactic and on-demand treatment of hemophilia B. However, plasma-derived products are associated with risks related to transmission of infectious viruses such as human immunodeficiency virus, hepatitis B virus, and hepatitis C virus. Both plasma-derived and recombinant FIX products have a short half-life and, therefore, require dosing 2 to 3 times a week in order to achieve a significant reduction of bleeding episodes. In addition, repeat dosing may be required to control bleeding episodes with a relatively short bleeding-free period following administration. The need for frequent intravenous (IV) injections of either plasma-derived or recombinant FIX products carries significant burden for patients and the physicians treating their disorder. Such a regimen in younger children often (but not always), requires the insertion of a venous access device that must be kept extremely clean to avoid infectious complications and prevent the development of clots in the line. The risk and morbidity associated with such devices may prevent some very young children with hemophilia from receiving adequate care.

A FIX product that has a prolonged half-life and better recovery rate may allow patients to achieve adequate hemostasis with fewer injections.

1.2 BACKGROUND INFORMATION ON RECOMBINANT FUSION PROTEIN LINKING COAGULATION FACTOR IX WITH ALBUMIN (rIX-FP)

1.2.1 Overview

Recombinant fusion protein linking coagulation factor IX with albumin (rIX-FP) is a purified recombinant protein, generated by the genetic fusion of recombinant human albumin to the c-terminus of recombinant FIX, with a cleavable linker. The protein comprises 1018 amino acids in a single chain glycopeptide with a molecular weight of approximately 125 kDa. Albumin is an abundant natural carrier molecule that is not involved in immune defense and does not act as an adjuvant for the immune system.

rIX-FP is produced in Chinese hamster ovary (CHO) cells, which have been characterized and shown to be free of known infectious agents. rIX-FP is not derived from human blood and contains no preservatives or added animal or human components. In addition, 3 (2 dedicated) virus inactivation / reduction steps are applied in the manufacturing process (see the Investigator's Brochure for further details).

This phase 3b study of rIX-FP is intended to evaluate long-term data on the safety and efficacy of rIX-FP for routine prophylaxis and on-demand treatment of bleeding episodes in children and adults with severe hemophilia B (ie, FIX activity of ≤ 2%).

1.2.2 Nonclinical Evaluation

Nonclinical studies of rIX-FP have demonstrated an acceptable safety profile, favorable pharmacokinetic (PK) properties and hemostatic efficacy.

Single and repeat dose nonclinical rIX-FP safety studies have been conducted in rats and cynomolgus monkeys. In both species, the IV administration of rIX-FP, either as a single

injection (500 IU/kg) or as a daily injection (up to 500 IU/kg/day) over 28 consecutive days, was well tolerated with no toxicologically significant changes [rats: studies APQ0005, 8244656, and APQ0009 and cynomolgus monkeys: studies APQ0002 and APQ0001]. In both species, the no observed adverse effect level for repeat doses of rIX-FP was 500 IU/kg [studies APQ0009 and APQ0001], representing at least a 5-fold safety margin over the proposed standard clinical dose of rIX-FP. Repeat dosing was associated with the development of antihuman FIX antibodies (rats and cynomolgus monkeys) and antihuman albumin antibodies (rats and 1 cynomolgus monkey).

Studies investigating local tolerance [Study APQ0008] and the thrombogenic potential [Study S22456] of rIX-FP have been conducted in rabbits. There was no local irritation, or treatment-related macroscopic or microscopic pathology findings, irrespective of the route of administration of rIX-FP (ie, IV, intra-arterial and perivenous injection). In addition, there was no thrombogenic activity observed in a rabbit venous stasis model (Wessler test) at any of the rIX-FP doses tested (75, 150, and 500 IU/kg).

Nonclinical studies have shown that rIX-FP has favorable PK properties, which might allow the reduction of dosing frequency in patients with hemophilia B. In a PK study in cynomolgus monkeys, rIX-FP was administered as a single IV injection at doses of 50 or 100 IU/kg body weight [Study APQ0002]. The PK properties of rIX-FP were linear (ie, dose independent) over the dose range tested and were independent of sex. The mean terminal half-life ($t_{1/2}$) was 42.2 hours, which is more than 3 times greater than published data for a recombinant human FIX product ($t_{1/2}$ = ~12.7 h) [McCarthy et al., 2002]. Studies in rats, rabbits, and FIX-deficient mice have also demonstrated that rIX-FP has improved PK parameters (ie, increased recovery, terminal half-life and area under the concentration-time curve [AUC]) compared with published results of a currently marketed recombinant FIX product [Metzner at al., 2009].

The pharmacodynamic activity of rIX-FP has been studied in 2 animal models deficient in FIX (dogs and mice). In the dog model, administration of rIX-FP (100 IU/kg IV) was associated

with a shortening of the activated partial thromboplastin time and whole blood clotting time [Study 040200011]. In FIX deficient mice, the IV administration of rIX-FP (50, 100, and 200 IU/kg) was associated with a significant dose-dependent reduction of total blood loss, time to hemostasis and activated partial thromboplastin time compared with the control (isotonic saline) [Study NBM 04/09].

Further details on the outcomes of nonclinical studies are available in the Investigator's Brochure for rIX-FP.

1.2.3 Previous Clinical Experience

1.2.3.1 Study CSL654_2001: phase 1, open-label, multicenter, dose-escalation, safety and pharmacokinetic study

The primary study objective of Study CSL654_2001 was to assess the safety of the IV administration of rIX-FP in previously treated subjects with hemophilia B [Study CSL654_2001]. Subjects (age: 15 to 58 years) were administered a single injection of rIX-FP at a dose of either 25 IU/kg (9 subjects), 50 IU/kg (14 subjects), or 75 IU/kg (9 subjects). rIX-FP was well tolerated for the duration of the study. Of the 25 unique study subjects, 3 subjects reported a total of 4 adverse events (AEs) that were possibly related to rIX-FP treatment. Two of these AEs (1 subject: a mild headache and feeling hot 50 minutes after injection) resolved in 5 to 10 minutes without treatment. The other 2 AEs (1 subject: mild constipation; 1 subject: erythema at injection site), resolved within the same day without treatment. None of the subjects, including 7 subjects exposed to 2 doses of rIX-FP, had developed inhibitors to FIX, or antibodies to rIX-FP or albumin 4 weeks after the first injection of rIX-FP.

The study also investigated the PK profile of rIX-FP in 22 subjects. At an rIX-FP dose of 50 IU/kg (n = 13), the mean baseline-adjusted incremental recovery (IR) (0 to 30 minutes) was higher for rIX-FP compared with both recombinant FIX (46% higher; n = 8) and plasma-derived FIX (25% higher; n = 4). rIX-FP also exhibited an approximately 5-fold longer

mean baseline-corrected half-life (mean ± standard deviation [SD]: 91.57 ± 20.74 hours), 7-fold larger mean baseline-adjusted AUC and 7-fold slower clearance when compared with the subject's previous FIX product. In addition, rIX-FP maintained a baseline-corrected mean trough level of 7.4% and 2.5% at Day 7 and Day 14, respectively, after administration of 25 IU/kg rIX-FP.

1.2.3.2 Study CSL654-2004: phase 1/2, open-label, multicenter, pharmacokinetic, safety and efficacy study

Study CSL654_2004 evaluated the safety, PK, and efficacy of rIX-FP for both prophylaxis and on-demand treatment of bleeding episodes in subjects with hemophilia B. A total of 17 male subjects were enrolled from hemophilia treatment centers in Israel and Bulgaria; the mean age was 26 years (range 13 to 46 years). The study design consisted of an initial 10 to 14-day PK evaluation period, followed by an approximately 11-month safety and efficacy evaluation period of both prophylaxis and on-demand treatment of bleeding episodes with rIX-FP. Subjects could remain on study and receive rIX-FP treatment until their enrollment in the CSL654_3001 study.

A total of 14/17 (82.4%) subjects reported 46 treatment-emergent AEs, none of which were considered related to rIX-FP by the investigator. All AEs were mild or moderate in severity. There were no serious adverse events (SAEs) reported, and there were no withdrawals due to AEs. No inhibitors to FIX were reported, and there were no clinically significant changes in serum biochemistry, hematology, urinalysis, or vital signs. Before dosing with rIX-FP, 1 subject had positive antibodies to rIX-FP, plasma-derived FIX, and BeneFIX. However, by week 12, this subject tested negative for all antibodies tested (rIX-FP, plasma-derived FIX and BeneFIX®).

All subjects receiving prophylaxis therapy were placed on a weekly (ie, 7-day treatment interval) rIX-FP treatment regimen throughout the study. For each subject, the dose of rIX-FP was initially determined based upon the PK profile of rIX-FP and the subject's bleeding phenotype, but could be adjusted at the investigator's discretion. The mean FIX consumption

was reduced compared with the previous FIX therapy; the mean weekly dose of rIX-FP was 58.6 ± 10.7 IU/kg during the last 12 weeks of the study, compared with a mean weekly dose of their previous product of 87.7 ± 45.8 IU/kg.

In the prophylaxis treatment group, 8/13 (61.5%) subjects reported a total of 47 bleeding episodes that required treatment with rIX-FP. In the on-demand treatment group (n = 4), all subjects (ie, 4 subjects) reported a total of 38 bleeding episodes that required treatment. All bleeding episodes requiring treatment (n = 85) were successfully treated with 1 or 2 doses of rIX-FP. The mean ABR was lower for both spontaneous and total bleeding episodes in the prophylaxis group (mean ± SD: spontaneous ABR = 1.3 ± 1.5; total ABR = 4.4 ± 4.7; n = 13) compared with the on-demand treatment group (mean ± SD: spontaneous ABR = 21.7 ± 4.0; total ABR = 26.8 ± 2.7; n = 4). The annualized rate of traumatic bleeding episodes was similar for the prophylaxis and on-demand treatment groups. In both treatment groups, there were no major bleeding episodes and no maintenance doses of rIX-FP required.

The PK of rIX-FP were evaluated in 13 subjects receiving either prophylactic or on-demand therapy. After a single IV injection of 25 IU/kg rIX-FP, the mean FIX activity level was 3.75% and 2.67% above baseline at Day 7 and Day 14, respectively, and the mean half-life of rIX-FP was 95 hours.

1.2.3.3 Studies CSL654_3001 and CSL654_3002

Studies CSL654_3001 and CSL654_3002 are pivotal studies that evaluate the PK, safety, and efficacy of rIX-FP for the prophylaxis and on-demand treatment of bleeding episodes in subjects with hemophilia B.

Study CSL654_3001, which will enroll approximately 60 subjects (age: 12 to 65 years), will consist of an initial 10- to 14-day PK evaluation period. After this period, subjects will receive either prophylaxis therapy or on-demand treatment with rIX-FP:

- Subjects in Arm 1 (approximately 35 subjects) will receive prophylaxis therapy for a period of approximately 13 months. Initially, subjects will administer rIX-FP (initial

dose: 25 to 50 IU/kg) with a treatment interval of 7 days. After at least 26 weeks of prophylaxis therapy, subjects will either switch to a treatment interval of 10 or 14 days, or continue using a treatment interval of 7 days. The dose of rIX-FP will be adjusted for each subject to target a trough FIX activity of > 1% between doses.

- Subjects in Arm 2 (approximately 21 subjects) will receive on-demand treatment with rIX-FP for approximately 26 weeks and then switch to prophylaxis therapy for the remainder of the study (approximately 30 weeks). During prophylaxis therapy, subjects will administer rIX-FP (initial dose: 35 to 50 IU/kg) with a treatment interval of 7 days. The dose of rIX-FP will be adjusted for each subject to target a trough FIX activity of > 1% between doses.

Study CSL654_3002, which will enroll approximately 24 subjects (age: < 12 years), will consist of an initial 14-day PK evaluation period, and an approximately 11-month (50 exposure days [EDs]) treatment period, during which, subjects will receive prophylaxis therapy with rIX-FP (initial dose: 35 to 50 IU/kg) administered with a treatment interval of 7 days.

Both studies (CSL654_3001 and CSL654_3002) will also evaluate the hemostatic efficacy of rIX-FP for surgical prophylaxis.

Study CSL654_3001 began enrolling subjects in February 2012 and Study CSL654_3002 began enrolling subjects in January 2013.

1.3 STUDY OVERVIEW

This is a prospective, open-label study to evaluate the long term safety and efficacy of rIX-FP, which is being developed for the prophylaxis and treatment of bleeding episodes in subjects with hemophilia B. The study will include, but not limited to, study subjects who were enrolled in either Study CSL654_3001 or CSL654_3002, in addition to the subjects requiring major non-emergency surgery who have not previously completed a CSL-sponsored rIX-FP lead-in study. Previously untreated patients (PUPs), who have never been treated with FIX clotting factor products (except previous exposure to blood components) and

meet the enrollment requirements may also be enrolled after at least 10 subjects (<12 years of age, including a minimum of 5 subjects < 6 years of age) completed 50 EDs and PK investigations are completed (as required in EMA guideline). At the end of this study, subjects from the lead-in studies CSL654_3001 or CSL654_3002 are expected to have accumulated at least 100 rIX-FP EDs during enrollment in all CSL-sponsored rIX-FP studies. During the study, subjects may also participate in the surgical prophylaxis substudy (see Appendix 1) or in the subcutaneous (SC) substudy (see Appendix 2).

This extension study consists of a prophylaxis treatment period (up to approximately 5 years for Arms 1, 2 and 3; up to approximately 3 years for Arm 4) during which subjects will administer rIX-FP as routine prophylaxis. During an initial 6-month period, subjects will receive prophylactic treatment with rIX-FP administered using the following treatment intervals:

- **Arm 1:** Once every 7, 10, or 14 days (subjects who have completed studies CSL654_3001 Arm 1 or CSL654_3002, or any other CSL-sponsored rIX-FP [CSL654] lead-in study).
- **Arm 2:** Once every 7 days (subjects from Study CSL654_3001 Arm 2 with less than 26 weeks of experience with weekly prophylaxis) or once every 14 days (subjects from Study CSL654_3001 Arm 2 with at least 26-weeks experience with weekly prophylaxis).
- **Arm 3:** Once every 7 days (subjects who have not previously completed a CSL-sponsored rIX-FP [CSL654] lead-in study). No subjects in France may enroll in Arm 3.

After this initial 6-month period, all subjects in Arm 1, 2 and 3 will receive prophylactic therapy with rIX-FP administered once every 7, 10, 14, or 21 days for an additional approximately 30 months. Subjects in France may not take part in the 21-day treatment regimen. Subjects transferring to a 21-day treatment interval must be ≥ 18 years of age. Any subject transferring to a 21-day treatment interval for the first time must have completed at least 6 months of prophylactic treatment with a 14-day treatment interval and must undergo an initial PK

evaluation period with a single rIX-FP dose of 100 IU/kg. During the study, a subject may undergo additional rIX-FP PK evaluations at the investigator's discretion or CSL's request.

Subjects in Arm 3 who require major non-emergency surgery will undergo an initial PK evaluation (100 IU/kg rIX-FP) to determine the incremental recovery and FIX activity. These subjects will then complete the surgery substudy (see Appendix 1) after which they may start the prophylaxis treatment period.

If any subject from a lead-in study requires a major or minor surgical non-emergency procedure during the prophylaxis treatment period, the subject may be enrolled in the surgery substudy (see Appendix 1).

Arm 4: During an initial 6-month period, subjects will receive prophylactic treatment with rIX-FP administered using once every 7 days as preferred regimen. Nevertheless, during the first 12 months, subjects may also receive on-demand and / or prevention treatment only.

Subjects in Arm 4 will undergo an rIX-FP (50 IU/kg) PK evaluation at Day 1 as the first dose if feasible or during the study after at least 7 days washout from the previous rIX-FP dose, when the subject is in non-bleeding state.

If any Arm 4 subjects require a minor surgical non-emergency procedure during the study, the subject may be enrolled in the surgery substudy (see Appendix 1).

Subcutaneous Substudy (see Appendix 2)

Subjects enrolled in the SC substudy will be sequentially assigned to a dose cohort (Cohort 1 [single dose of 25 IU/kg], Cohort 2 [single dose of 50 IU/kg], Cohort 3 [15 doses of 25 IU/kg every 3 days], and an optional Cohort 4 [15 doses of ≤ 50 IU/kg every 5 days, with the actual dose in this cohort to be determined by CSL based on the PK results from Cohort 3]).

Subjects will return 2 weeks after their last SC dose for an end of substudy visit to collect the final SC PK sample and assess safety. After the end of substudy visit, Cohort 3 and 4 subjects will return to their IV rIX-FP prophylaxis regimen in the main study.

1.4 POTENTIAL RISKS AND BENEFITS

The use of a replacement FIX product with a longer half-life and better recovery rate than currently available products should enable a longer interval between infusions for patients with hemophilia B. By reducing the burden on patients and physicians treating this disorder, such a product may also result in an improvement in patient compliance. In addition, it may permit primary prophylaxis in some young children without requiring the insertion of a venous access device.

Potential risks associated with rIX-FP are expected to be similar to the currently marketed recombinant FIX products and include the development of antibodies against FIX and development of thromboembolic complications. In addition, there is a risk of development of albumin and CHO cell-derived protein antibodies. The potential risks associated with treatment with rIX-FP are discussed in detail in Section 7.4 of the Investigator's Brochure.

The results from the rIX-FP nonclinical program and the data from previous clinical studies, support the evaluation of an rIX-FP treatment interval of between 7 and 14 days. The safety and efficacy of rIX-FP (100 IU/kg) using a 21-day treatment interval will also be examined in this study. Given that nonclinical studies in rats and cynomolgus monkeys have shown a no observed adverse effect level of 500 IU/kg, there is not expected to be any additional safety concerns regarding the use of rIX-FP at a dose of 100 IU/kg. There is a risk that administration of rIX-FP at a treatment interval of 21 days might be less effective at preventing bleeds than when administered at a treatment interval of 14 days or less. However, the PK evaluation of rIX-FP at a dose of 100 IU/kg will provide information on the trough FIX activity level using this dose of rIX-FP. In addition, prophylaxis treatment using a 21-day treatment interval will only be available to subjects ≥ 18 years of age and who have completed at least 6 months of prophylaxis treatment with a 14-day treatment interval, with subjects in France excluded. If

subjects do not benefit from a treatment interval of 21 days, they will be able to transfer to the 7-, 10-, or 14-day treatment interval at any time, at the discretion of the investigator.

This study will document all key safety factors including immunogenicity, thrombogenicity, hypersensitivity, and other AEs in the intended therapeutic population.

Thus, the associated benefit-risk assessment of the study is acceptable for subjects enrolled in the study.

2. STUDY OBJECTIVES AND ENDPOINTS

2.1 PRIMARY OBJECTIVE AND ENDPOINT

2.1.1 Primary Objective

The primary objective of this study is to evaluate the safety of rIX-FP as measured by new cases of inhibitors against FIX in subjects, including PUPs, with severe hemophilia B. The PK parameters in PUPs will also be collected.

2.1.2 Primary Endpoints

- The total number of subjects who develop inhibitors against FIX during the approximately 3-year participation in this study.
- PK parameter of incremental recovery (IU/dL per IU/kg) of 50 IU/kg rIX-FP (Arm 4 only).

2.2 SECONDARY OBJECTIVES AND ENDPOINTS

2.2.1 Secondary Objectives

The secondary objectives of the study are:

- To evaluate the efficacy of rIX-FP routine prophylaxis when administered at various treatment intervals.
- To compare the efficacy of rIX-FP routine prophylaxis between 2 different treatment intervals and versus on-demand treatment.
- To further evaluate the safety of rIX-FP.
- To evaluate the efficacy of treatment for bleeding episodes in PUPs.

2.2.2 Secondary Endpoints

- Annualized bleed rate (ABR) for spontaneous treated and total treated bleeds for each assigned treatment interval (7 days, 10 days, 14 days, and 21 days).

- Comparison of the annualized spontaneous bleeding rate (AsBR) and ABRbetween:
  - 14-day routine prophylactic treatment in this study compared with on-demand only treatment from Study CSL654_3001 Arm 2.
  - 7-day prophylaxis regimen with the 14-day prophylaxis regimen.
  - 7-day prophylaxis regimen with the extended prophylaxis regimen (10-day or 14-day).
- Consumption of rIX-FP during routine prophylaxis expressed as IU/kg per month per subject.
- Incidence of AEs and related AEs to rIX-FP over the course of the study.
- Hemostatic response to treatment of bleeding episodes with rIX-FP in PUPs as assessed by the investigator based on a 4-point scale (Arm 4 only).

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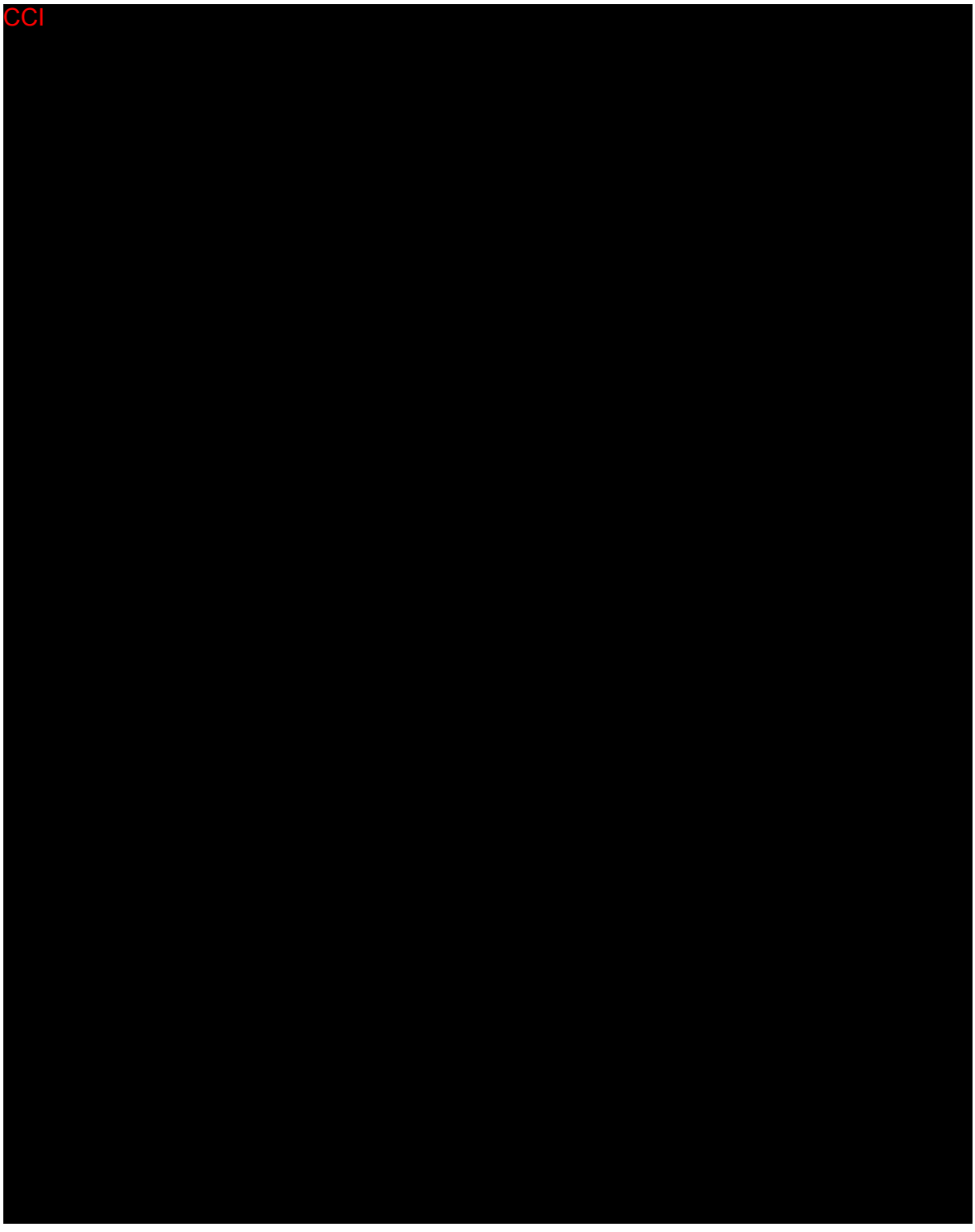
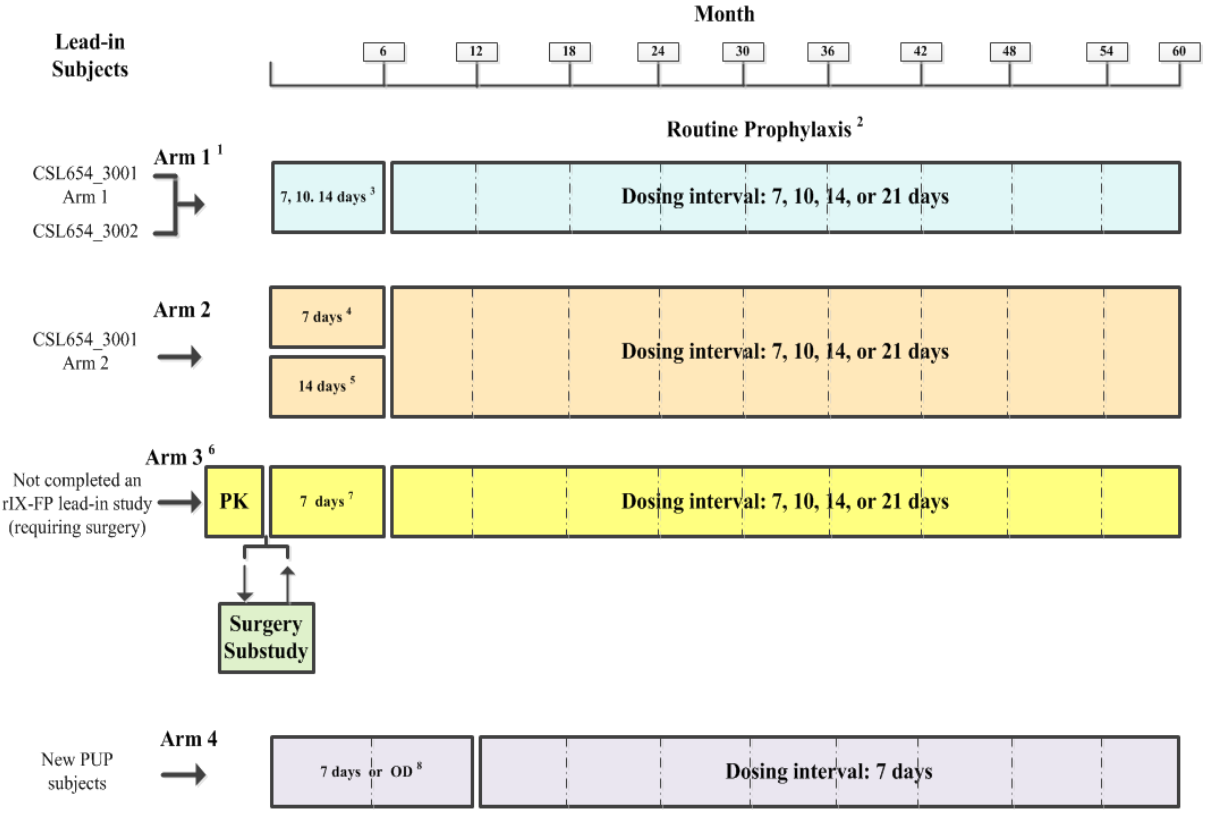


3. STUDY DESIGN

3.1 STUDY DESIGN AND RATIONALE

This is a multicenter, open-label, phase 3b study to investigate the long-term safety and efficacy of rIX-FP for the routine prophylaxis and on-demand treatment of bleeding episodes in subjects with hemophilia B. Subjects will be eligible to enter the study if they have completed studies CSL654_3001 or CSL654_3002, or any other CSL-sponsored rIX-FP (CSL654) study and meet all other eligibility criteria. In addition, subjects who have not previously completed a CSL-sponsored rIX-FP lead-in study may be eligible to enter the study if they require major non-emergency surgery and meet all other eligibility criteria, or if they are PUPs who meet the eligibility criteria.

Figure 1. Study Overview



1. Subjects from studies CSL654_3001 Arm 1, CSL654_3002, and subjects who have completed any other CSL-sponsored rIX-FP study are to participate in Arm 1 of the study.
2. Following the initial 6-month treatment period, all subjects may continue to use the same treatment interval, or change to 7, 10, or 14 days. Subjects ≥ 18 years of age, who have completed at least 6 months of prophylaxis treatment with a 14-day treatment interval, may also change to a 21-day treatment interval (not applicable for France). The treatment interval may be changed at each 6-month follow-up assessment or earlier if deemed medically necessary by the investigator. Subjects must undergo an initial pharmacokinetics evaluation with a single injection of rIX-FP (100 IU/kg) before starting treatment with a 21-day treatment interval for the first time (Subjects in France may not be assigned to a 21-day treatment regimen). Dose of rIX-FP administered for routine prophylaxis regimens is to be based on the subject's previous response to rIX-FP therapy and / or FIX trough activity. During routine prophylaxis therapy, subjects may also administer rIX-FP as on-demand (OD) therapy for bleeding episodes and may enroll in the surgery substudy (see Appendix 1) if they require a major or minor non-emergency surgical procedure.
3. Treatment interval (7, 10, or 14 days) for each subject to be determined by the investigator based on the treatment interval used in the lead-in study and / or investigator and subject preference.
4. All subjects who participated in Arm 2 of the CSL654_3001 lead-in study and who have < 26 weeks experience with a 7-day treatment interval at the start of this extension study are to continue a 7-day treatment interval for the first 6 months of the study or until they have accumulated ≥ 26 weeks experience with a 7-day treatment interval. At the end of this period, subjects in this group will be encouraged to switch to a 14-day treatment interval for a period of at least 6 months.
5. All subjects who participated in Arm 2 of the CSL654_3001 lead-in study and who have ≥ 26 weeks experience with a 7-day treatment interval at the start of this extension study are to start a 14-day treatment interval for the first 6 months of the study.
6. Subjects in Arm 3 (no subjects in France may participate in Arm 3) must undergo an initial rIX-FP pharmacokinetics evaluation before starting the surgery substudy. No subjects from France may enroll in Arm 3.
7. After completion of the surgery substudy, subjects may begin prophylaxis treatment with a 7-day treatment interval. Subjects in Arm 3 who require physical therapy (ie, rehabilitation after surgery), may administer rIX-FP as preventative treatment (no more than once per week) in addition to the administration of rIX-FP as routine prophylaxis. Preventative treatment before physical therapy is permitted only during the first 3 months of the treatment period.
8. Subjects in Arm 4 will administer rIX-FP as weekly prophylaxis and / or on-demand, prevention during the first 12 months, and then on weekly routine prophylaxis until completing 50 EDs. Subjects who complete 50 EDs are permitted to continue weekly routine prophylaxis with rIX-FP until the completion of the study..

3.1.1 Routine Prophylaxis: First 6 Months

Arm 1: Subjects from all lead-in studies (excluding CSL654_3001 Arm 2)

During the first 6 months, subjects in Arm 1 will administer rIX-FP as routine prophylaxis either using the same treatment interval as in the lead-in study or using a different treatment interval of 7, 10, or 14 days, as determined by the investigator. The dose of rIX-FP administered will be based on the subject's previous response to rIX-FP therapy and / or trough FIX activity (see Section 6.2.1) and dose guidelines in Section 3.2.1.4 and Table 1.

Arm 2

Subjects from lead-in Study CSL654_3001 Arm 2 who have ***≥ 26 weeks*** *experience with rIX-FP prophylaxis therapy with a 7-day treatment interval*

During the first 6 months, subjects in this group will administer rIX-FP (75 IU/kg) as routine prophylaxis using a treatment interval of 14 days.

Subjects from lead-in Study CSL654_3001 Arm 2 who have ***< 26 weeks*** *experience with prophylaxis rIX-FP therapy with a 7-day treatment interval*

During the first 6 months, subjects in this group will administer rIX-FP as routine prophylaxis using a treatment interval of 7 days. The dose of rIX-FP administered will be the same as the dose used by the subject for routine prophylaxis in the lead-in study (see Section 6.2.1).

After a subject has accumulated at least 26 weeks experience with prophylaxis rIX-FP therapy (ie, lead-in study and current study combined), they may switch to a 14-day treatment interval or continue using a 7-day treatment interval until completion of the initial 6-month period. Subjects should attend an unscheduled visit and complete assessments as specified for the 6-month visit if they are to switch to a 14-day treatment interval before completion of the 6-month period. Under such circumstances, the 3-month visit may be omitted.

Arm 3 (Does not include any subjects in France)

Upon completion of the surgery substudy, subjects in Arm 3 may begin the prophylaxis treatment period in the main study. During the first 6 months, subjects will administer rIX-FP as prophylaxis using a treatment interval of 7 days. The dose (25 to 50 IU/kg) of rIX-FP administered will be based on the subject's trough FIX activity (see Section 6.2.1). During the first 3 months of the treatment period (ie, after surgery), subjects may also administer rIX-FP, no more than once per week, as a preventative treatment before physical therapy, if needed (see Section 3.2.3).

Arm 4

Subjects in Arm 4 will administer rIX-FP as weekly prophylaxis and / or on-demand, prevention during the first 12 months, and then on weekly routine prophylaxis until completing

50 EDs. Subjects who complete 50 EDs are permitted to continue weekly routine prophylaxis with rIX-FP until the completion of the study. The dose (25-50 IU/kg initially, up to 75 IU/kg) of rIX-FP administered will be based on the subject's clinical response, PK information or FIX trough activity.

3.1.2 Routine Prophylaxis: 6 Months to End of Treatment Period

After completion of the initial 6-month treatment period, subjects from Arms 1, 2 and 3 will administer rIX-FP as routine prophylaxis using a treatment interval of 7, 10, or 14 days for the remainder of the study. Subjects from lead-in Study CSL654_3001 Arm 2, who were using a 7-day treatment interval during the previous 6 months, will switch to a 14-day treatment interval for at least 6 months.

From 6 months onwards, subjects (Arm 1, 2 and 3) may use the same treatment interval or they may change treatment interval in consultation with the investigator at any of the subsequent 6-month follow-up visits (see Section 3.2.1.2). For the first 12 months of the study, subjects in Arm 4 are encouraged, but not required, to be on weekly prophylaxis. The dose of rIX-FP administered will be between 35 and 75 IU/kg (see Section 6.2.1).

Subjects ≥ 18 years of age may also administer rIX-FP as routine prophylaxis using a 21-day treatment interval at a dose of 100 IU/kg. Subjects in France may NOT switch to a routine prophylaxis regimen using a 21-day treatment interval. Subjects < 18 years of age are not permitted to use a treatment interval of 21 days.

Subjects who transfer to a 21-day treatment interval for the first time must have completed at least 6 months of prophylaxis treatment with a 14-day treatment interval and have undergone PK evaluation with 100 IU/kg rIX-FP (see Section 3.1.3).

3.1.3 Pharmacokinetic Evaluation of rIX-FP (100 IU/kg)

Subjects must undergo a PK evaluation with a single injection of rIX-FP (100 IU/kg) if either 1) they are in Arm 3 (excludes subjects in France) or 2) they intend to begin administering rIX-

FP as routine prophylaxis using a 21-day treatment interval for the first time. The PK evaluation should be performed after a washout period of either at least 4 days for a current marketed FIX product (Arm 3) or at least 14 days for rIX-FP. Samples for PK evaluation will be collected before administration of rIX-FP, 30 minutes after the completion of the injection (to evaluate peak FIX activity level and incremental recovery) and at specified time points after injection (see Table B - Schedule of Assessments: Pharmacokinetic Period).

3.1.3.1 Pharmacokinetic Evaluation of rIX-FP as Needed

The investigator may also choose to complete a PK assessment of 50, 75 or 100 IU/kg (as appropriate) rIX-FP with selected time points before starting surgical prophylaxis with rIX-FP (for subjects from lead-in studies), at the investigator's discretion or CSL's request, or in the event of (but not limited to) poor efficacy or suspicion of inhibitor development. Subjects in France may be discontinued from receiving the study product and participating in any further study procedures if the subject is confirmed to have developed an inhibitor against FIX with a titer > 5 BU/mL.

3.1.3.2 Pharmacokinetic Evaluation of rIX-FP for Arm 4

For Arm 4 subjects, a PK assessment of 50 IU/kg rIX-FP with selected time points (Table B - Schedule of Assessments: Pharmacokinetic Period) or incremental recovery is to be done only at the beginning of the study, and also may be done at the investigator's discretion at any time.

3.1.4 On-demand Treatment of Bleeding Episodes

During the study, on-demand treatment with rIX-FP will be used for all bleeding episodes requiring treatment. The dose of rIX-FP will be determined by the investigator, based on the subject's previous experience during the lead-in study or this study, and the dose and / or maintenance dose required to achieve and maintain the FIX activity level recommended by the World Federation of Hemophilia (WFH) (see Section 3.2.2 for further details) or the investigator's local hospital treatment guidelines.

3.1.5 Preventative Treatment Before Vigorous Physical Activity or Physical Therapy

During the study, subjects may also administer rIX-FP as a single injection immediately before vigorous physical activity that, in the subject's experience, is likely to result in bleeding or before physical therapy (ie, rehabilitation after surgery) (see Section 3.2.3). The recommended dose of rIX-FP is between 35 and 50 IU/kg, administered as a single injection.

3.1.6 Surgical Prophylaxis

All subjects in Arm 3 (excludes subjects in France) should start the surgery substudy (Appendix 1) within 8 weeks from receiving the first rIX-FP injection (ie, during the PK evaluation period).

If a subject in either Arms 1 or 2 requires major or minor non-emergency surgery or subject in Arm 4 requires minor surgery during the study, the subject may also be enrolled in the surgery substudy. A major surgery is defined as a surgical procedure that involves anesthesia (general, spinal, epidural, or regional block) or respiratory assistance or one that requires hemostatic support for a period exceeding 5 consecutive days (including but not limited to orthopedic and cardiac surgery) [Srivastava et al., 2013]. However, some common surgeries (such as permanent venous access placement or removal, circumcision and some simple dental procedures) for the subjects in Arm 4 may not be able to be avoided, therefore, they may be permitted in consultation with the CSL medical monitor. Details of the surgery substudy, including study design, visit schedules and study assessments are presented in Appendix 1.

If a subject requires an extremely minor surgical procedure during the study (ie, a procedure that would be expected to require only a maintenance dose of rIX-FP after the procedure), the subject may be administered a single prophylaxis injection of rIX-FP before the surgery, without enrollment into the surgery substudy.

3.1.7 Subcutaneous Substudy

See Appendix 2 for details.

3.2 DOSE AND DOSING REGIMEN

3.2.1 Routine Prophylaxis Treatment

3.2.1.1 rIX-FP Treatment Interval

During the first 6 months of the study, subjects or their caregivers will administer rIX-FP as routine prophylaxis using the following treatment intervals:

- Arm 1: 7, 10, or 14 days.
- Arm 2: 7 or 14 days.
- Arm 3: 7 days. (No subjects in France may participate in Arm 3)
- Arm 4: 7 days (preferred for the first 12 months of the study; required after the first 12 months of the study).

For subjects in Arm 1, the treatment interval will be chosen by the investigator at the beginning of the study based on the subject's previous experience (ie, during the lead-in study) and subject preference.

For subjects in Arm 2, the treatment interval will be based on the duration of their prophylaxis treatment in the lead-in study; a 14-day treatment interval will be assigned to subjects who completed at least 26 weeks of prophylaxis treatment during the lead-in study and a 7-day treatment interval will be assigned to subjects who did not complete at least 26 weeks of prophylaxis treatment during the lead-in study. Subjects in Arm 2 who start on a 7-day treatment interval and complete a total (ie, during the lead-in study and this study) of at least 26 weeks of prophylaxis treatment, should then switch to a 14-day treatment interval for a period of at least 6 months.

Upon completion of the surgery substudy, subjects in Arm 3 (not applicable to France) may begin the prophylaxis treatment period in the main study. During the first 6 months, subjects in this group will administer rIX-FP as routine prophylaxis using a treatment interval of 7 days. The dose (25 to 50 IU/kg) of rIX-FP administered will be based on the subject's trough FIX activity (see Section 6.2.1).

At the end of the initial 6-month period, subjects in Arm 1, 2 and 3 may remain on their current treatment interval or they may be switched to a 7, 10, or 14-day treatment interval. Subjects ≥ 18 years of age may also be switched to a 21-day treatment interval after completing at least 6 months of a 14-day prophylaxis regimen and a 100 IU/kg rIX-FP PK evaluation period (see Section 3.1.3). Subjects in France may NOT switch to a routine prophylaxis regimen using a 21-day treatment interval.

3.2.1.2 Changing the rIX-FP Treatment interval (subjects in Arm 1, 2 and 3)

During each 6 months of the treatment period, the treatment interval *should not* be changed unless deemed necessary by the investigator for the subject's safety (with the exception of subjects from lead-in Study CSL654_3001 Arm 2 who have <26 weeks experience with prophylaxis rIX-FP therapy with a 7-day treatment interval). At the end of each 6-month period (ie, at the 6 month, 12 month, etc follow-up visits) the investigator may choose to change the treatment interval based on their assessment of efficacy / safety, subject treatment compliance, and / or subject preference.

3.2.1.3 Changing the rIX-FP Treatment interval (subjects in Arm 4)

During the first 12-month period, subjects in Arm 4 are encouraged, but not required to be on weekly prophylaxis regimen with rIX-FP. At the end of the initial 12-month period, subjects are required to be on a weekly prophylaxis regimen for rest of the study.

3.2.1.4 rIX-FP Dose

The dose of rIX-FP administered for routine prophylaxis will be based on the subject's previous experience (ie, during a lead-in study) and / or the targeted FIX activity trough level (target FIX activity level > 2%, but optimally, between 5% and 15%). The FIX activity trough level must not be targeted to ≥ 20% without approval from CSL.

The maximum dose of rIX-FP for routine prophylaxis will be 50 IU/kg per injection for subjects using a 7-day treatment interval and 75 IU/kg per injection for subjects using a 10- or 14-day treatment interval (Table 1), unless a higher dose for a given subject is approved by

CSL. The dose of rIX-FP will be 100 IU/kg per injection for subjects using a 21-day treatment interval (Table 1). For all treatment intervals, the total dose of rIX-FP administered for routine prophylaxis over a 28-day period is not to exceed 250 IU/kg, without approval from CSL.

Table 1. Dose Guidelines for Routine Prophylaxis Treatment

	Treatment interval			
	7 Days	**10 Days [1]**	**14 Days**	**21 Days**
Suggested dose (IU/kg)	25 to 50	50 to 75	75	100
Maximum dose (IU/kg)	50 [2]	75	75	100

1. The 10-day treatment interval may be based on a schedule of once every 10 calendar days or 3 times a month (ie, 1st, 11th and 21st day of each month).
2. An rIX-FP dose higher than 50 IU/kg is acceptable if the FIX activity trough level is < 5% at Day 7 and a higher trough level is necessary to prevent spontaneous bleeding.

3.2.2 On-demand Treatment of Bleeding Episodes

On-demand treatment with rIX-FP will be used for all bleeding episodes requiring treatment. If a subject experiences a bleeding episode, rIX-FP should be administered within 4 hours after the start of the bleeding episode. The dose of rIX-FP will be determined by the investigator, based on the effective on-demand treatment dose used in the lead-in study and / or the subject's PK data with a minimum rIX-FP dose of 35 IU/kg and a maximum dose of 75 IU/kg. After hemostasis is achieved, maintenance dose(s) of rIX-FP may be prescribed at the discretion of the investigator.

Subjects receiving on-demand treatment for a bleeding episode should maintain or delay (but not skip) the prophylaxis treatment schedule, at the investigator's discretion. The window between the last treatment for the bleeding episode and the next prophylaxis injection should not be longer than the number of days of the current treatment interval (ie, 7, 10, 14, or 21 days). In addition, any two injections of rIX-FP should be at least 24 hours apart.

3.2.3 Prevention Before Vigorous Physical Activity or Physical Therapy

During the study, subjects may administer rIX-FP as a preventative treatment before vigorous physical activity or before physical therapy (ie, as a part of rehabilitation after major surgery) that, in the subject's experience, is likely to result in bleeding. rIX-FP should be administered as preventative treatment at a dose of 35 to 50 IU/kg, as determined by the investigator based on the subject's previous experience.

Preventative treatment should be administered in addition to routine prophylactic treatment (ie, subjects administering rIX-FP as a preventative treatment should maintain the routine prophylaxis treatment schedule) or may be combined with on-demand regimen (may combine with prevention doses) during the first 12 months in Arm 4 subjects only.

Prevention Before Vigorous Physical Activity

Preventative treatment before vigorous physical activity should not be used more frequently than **once per month**. If more frequent treatment is required (eg, because of participation in regular sporting activities), the treatment interval or dose used for prophylaxis treatment should be adjusted, as appropriate (eg, reduction of the treatment interval from 14 days to 7 days or increase in the rIX-FP dose if the subject is using a 7-day treatment interval).

Prevention Before Physical Therapy

Preventative treatment before physical therapy should not be used more frequently than **once per week** during the first 3 months of either starting the prophylaxis treatment period (subjects in Arm 3) or returning to routine prophylaxis (subjects in Arms 1 or 2). After this 3-month period, preventative treatment should not be used more often than **once per month**.

3.3 PLANNED STUDY DURATION

For subjects in Arms 1, 2, and 3, the duration of the study for an individual subject is expected to be approximately 5 years or the time it takes to achieve a total of 100 EDs during enrollment in any CSL-sponsored rIX-FP studies. For subjects in Arm 4, the duration of the study is expected to be approximately 3 years or the time it takes to achieve a total of 50 EDs.

The overall study duration (ie, first subject's first visit to the last subject's end of study visit) is expected to be approximately 5 years. The study may end after 100 EDs of rIX-FP have been achieved in ≥ 50 subjects overall for rIX-FP (ie, treatment received across all studies). The study may be stopped at a specific study site after all subjects at the site have either completed the 5-year study period, or ≥ 50 subjects overall have achieved a total of 100 EDs, or after regulatory approval and rIX-FP becomes commercially available in the respective country.

3.4 PLANNED NUMBER OF SITES

The study is planned to be conducted at approximately 40 study sites worldwide.

3.5 PLANNED NUMBER OF SUBJECTS

This study will enroll approximately 96 male subjects, including all eligible subjects from CSL-sponsored rIX-FP (CSL654) lead-in studies, approximately 10 subjects who require major non-emergency surgery and at least 13 PUPs.

3.6 STUDY MONITORING PROCEDURES

3.6.1 Independent Data Monitoring Committee

The Independent Data Monitoring Committee (IDMC) is an independent expert advisory group consisting of three medically qualified persons with appropriate expertise in subjects with hemophilia B, in the treatment with FIX replacement therapy and / or evaluation of AEs and laboratory results relevant for detecting any possible safety issues, and one statistician. An IDMC is being utilized to provide an independent evaluation of the study at predefined intervals with regard to the progress of Arm 4 of the study and the safety data, namely for the incidence, frequency, and nature of AEs and bleeding events. Meetings will be held approximately every 6 months, with ad hoc meetings scheduled as needed, including after every newly confirmed inhibitor (≥ 0.6 BU/mL) and / or severe allergic reaction in Arm 4 subjects. The initial meeting will occur after the first 5 PUP subjects have been dosed and

reached the Month 1 FIX inhibitor evaluation, or there is a confirmed inhibitor or severe allergic reaction.

3.6.2 Other Monitoring Committees

3.6.2.1 CSL Safety Management Team

The primary goal of the CSL Safety Management Team (SMT) is to minimize risk to subjects in clinical trials. The SMT supports the Global Clinical Safety and Pharmacovigilance group in the evaluation of safety-related information and makes decisions to accomplish this goal.

Core membership includes representatives from the following groups: Global Clinical Safety and Pharmacovigilance (ie, Clinical Safety Physician, Clinical Safety Scientist), Clinical Development (ie, Clinical Program Director, Medical Monitor, and Clinical Scientist), Clinical Operations and Biostatistics. The SMT is responsible for the identification and evaluation of safety issues, risk management, and risk communication. Meetings will be held approximately every 3 months, with ad hoc meetings scheduled as needed, including after every newly confirmed inhibitor in Arm 4.

3.6.2.2 Safety Review Committee in the Subcutaneous Substudy

See Appendix 2, sections “Study Design and Rationale” and “Study Monitoring Procedures” for details.

4. SELECTION AND WITHDRAWAL OF SUBJECTS

4.1 ELIGIBILITY CRITERIA

The study population will be selected on the basis of the inclusion and exclusion criteria described in the sections below. Subject eligibility should be reviewed and documented by an appropriately medically qualified member of the investigator’s study team before subjects are included in the study.

4.1.1 Inclusion Criteria

Subjects meeting all of the following inclusion criteria may be enrolled into the study (However, subject(s) in France will NOT be eligible to be enrolled into Arm 3 of the study):

- **Arms 1, 2, 3 and 4:** Written informed consent for study participation obtained before undergoing any study-specific procedures.
- **Arms 1 and 2:** Completed a CSL-sponsored rIX-FP (CSL654) study, including studies CSL654_3001 or CSL654_3002.
- **Arms, 1, 2, 3 and 4:** Investigator believes that the subject or subject's parent(s) or legally acceptable representative(s) is willing and able to adhere to all protocol requirements including correct use of the electronic diary (eDiary).

Arm 3 only (No subjects in France may enroll in Arm 3):

- Scheduled to have a major non-emergency surgery within approximately 8 weeks from the anticipated date of receiving the first rIX-FP injection.
- Not previously completed a CSL-sponsored rIX-FP lead-in study.
- Male subjects, 12 to 70 years of age.
- Documented severe hemophilia B (FIX activity of ≤ 2%), or confirmed at screening by the central laboratory.
- Subjects who have received FIX products (plasma-derived and / or recombinant FIX) for > 150 exposure days (EDs), confirmed by their treating physician.
- No confirmed history of FIX inhibitor formation (defined as two consecutive positive tests –requiring a confirmatory test on a second separately drawn blood sample shortly after the previous positive test), no confirmed detectable inhibitors (defined as < 0.6 Bethesda units [BU]/mL) at screening by the central laboratory, and no family history of inhibitor formation against FIX.

Arm 4 only:

- Male, up to 18 years of age.
- Documented severe hemophilia B (FIX activity of ≤ 2%), or confirmed at screening by local or central laboratory.

- Subjects who have never been treated with FIX clotting factor products (except previous exposure to blood components).
- No confirmed history of FIX inhibitor formation.

4.1.2 Exclusion Criteria

Subjects meeting any of the following exclusion criteria must not be enrolled into the study (However, subject(s) in France will NOT be eligible to be enrolled into Arm 3 of the study):

All subjects:

- **Arms 1, 2, 3 and 4:** Currently receiving a therapy not permitted during the study, as defined in Section 7.3.
- **Arms 1 and 2 only**: Unwilling to participate in the study for a total of 100 EDs.
- **Arms 1, 2, 3 and 4**: Any issue that, in the opinion of the investigator, would render the subject unsuitable for participation in the study.

Arm 3 only (No subjects in France may enroll in Arm 3):

- Known hypersensitivity (allergic reaction or anaphylaxis) to any FIX product or hamster protein.
- Known congenital or acquired coagulation disorder other than congenital FIX deficiency.
- Currently receiving IV immunomodulating agents such as immunoglobulin or chronic systemic corticosteroid treatment.
- Platelet count < 100,000/µL at screening.
- Human immunodeficiency virus-positive subjects with a CD4 count < 200/mm^3. A human immunodeficiency virus-positive subject may participate in the study and receive antiviral therapy at the discretion of the investigator.
- Serum aspartate aminotransferase (AST) or serum alanine aminotransferase (ALT) concentration > 5 x ULN at Screening.
- Serum creatinine concentration > 2 x ULN at Screening.
- Evidence of thrombosis, including deep vein thrombosis, stroke, myocardial infarction or arterial embolus within 4 months before the first administration of rIX-FP.

- Use of any investigational medicinal product other than rIX-FP within 4 weeks before the first administration of rIX-FP.

Arm 4 only:

- Known congenital or acquired coagulation disorder other than congenital FIX deficiency (except for vitamin K deficiency of the newborn).
- Known kidney or liver dysfunction or any condition which, in the investigator's opinion, place the subject at unjustifiable risk.
- Use of any investigational medicinal product within 4 weeks before the first administration of rIX-FP.
- If a subject experiences a life-threatening bleeding episode or requires a major surgical procedure before the first administration of rIX-FP.

4.2 SUBJECT WITHDRAWAL

4.2.1 Subject Withdrawal

Subjects may withdraw from the study at any time at their own request, or they may be withdrawn at any time at the discretion of the investigator or CSL for safety, behavioral or administrative reasons (eg, due to an AE, protocol violation, loss to follow-up, subject noncompliance, and study termination).

In accordance with the International Conference on Harmonisation (ICH) principles of Good Clinical Practice (GCP) the investigator always has the option to advise a subject to withdraw from the study if the subject's safety or well-being is compromised by his further participation in the study. Concern for the interests of the subject must always prevail over the interests of the study.

Subjects may be discontinued from receiving the study product and participating in any further study procedures if:

- Subjects in France may be discontinued from receiving the study product and participating in any further study procedures if the subject is confirmed to have

developed an inhibitor against FIX with a titer > 5 BU/mL. Alternatively, at the investigator's discretion, a subject who develops inhibitors to rIX-FP may remain in the study until a better treatment option becomes available to the subject or until the end of study visit, whichever comes first.

- The subject uses a marketed FIX during the study, except when rIX-FP is not available and / or if a marketed FIX is required as rescue medication.
- The subject does not comply with the assigned treatment schedule or is, in the opinion of the investigator and / or CSL, delinquent or delayed in using the eDiary.
- **For subjects in Arm 3 only (not applicable to France**: if a major non-emergency surgical procedure is not performed within approximately 8 weeks of starting the rIX-FP (100 IU/kg) PK evaluation period, CSL may request the subject to be rescreened or withdrawn from the study.
- **For subjects in Arm 4 only:** if a major surgery (except permanent venous access placement or removal, circumcision and some non-complicated unavoidable dental procedures) is required during the study or severe hypersensitivity or inhibitor to FIX (titer > 5 BU/mL) occurred, the subject should be withdrawn from the study.

If a subject is withdrawn from the study or further participation is declined, they will continue to have access to medical care and will be treated as per routine medical practice.

4.2.2 Procedures for Handling Withdrawals

If a subject declines further participation or is withdrawn from the study, attempts will be made to complete and document the end of study assessments. If the subject is withdrawn from the study after receiving rIX-FP, every effort will be made to ensure that the relevant safety assessments are completed. The subject may also be asked by the investigator to complete other study assessments.

If the subject withdraws from the study, and also withdraws consent for disclosure of future information, CSL may retain and continue to use any data collected before such withdrawal of consent.

In the event that a subject withdraws from the study, the investigator should record the reason and date of withdrawal in the electronic case report form (eCRF) and in the subject's medical records.

4.2.3 Replacement Policy

Subjects in Arms 1 or 2 withdrawn from the study will not be replaced. Subjects in Arm 3 withdrawn from the study before completing the surgery substudy may be replaced. Subjects in Arm 4 withdrawn prior to completing 50 EDs may be replaced.

5. STUDY INTERVENTIONS

5.1 DESCRIPTION OF INVESTIGATIONAL PRODUCT

5.1.1 Recombinant fusion protein linking coagulation factor IX with albumin (rIX-FP)

5.1.2 Comparator Product

Not applicable.

5.2 PACKAGING, LABELING, SUPPLY AND STORAGE

5.2.1 Packaging and Labeling

rIX-FP will be packaged and labeled according to current ICH Good Manufacturing Practice and GCP guidelines, and national legal requirements.

5.2.2 Supply and Storage

rIX-FP will be supplied to the study sites. rIX-FP must be stored at the investigator site under temperature-monitored conditions in a secure storage area as specified in the Investigator Manual.

Instructions for the storage and handling of rIX-FP at the subject's home are described in the Investigator Manual.

5.3 ACCOUNTABILITY AND DESTRUCTION

All supplies of rIX-FP must be accounted for throughout the study. Drug inventory and accountability logs / reports, dated and signed by the investigator or delegate (eg, pharmacist), must be retained at the study site as verification of final accountability of rIX-FP. *For Japan sites only, the drug inventory and accountability logs / reports must be dated and signed by the head of the medical institute or the study drug storage manager (if assigned by the head of medical institute)*.

Information on the accountability, return and destruction of rIX-FP is provided in the site's Investigator Manual.

5.4 OTHER INTERVENTION(S)

Not applicable.

5.5 RESCUE THERAPY

A marketed FIX concentrate may only be used as rescue medication for the treatment of a bleeding episode when rIX-FP is not available or in the event that hemostatic control is not achieved after at least 2 injections of rIX-FP.

6. ALLOCATION, DOSING AND ADMINISTRATION

6.1 ALLOCATION TO TREATMENT

6.1.1 Subject Assignment

After providing written informed consent, the subject will be issued with a unique subject identification number. Subjects in Arms 1 or 2 will be issued with the identification number that was assigned in the lead-in study. Subjects in Arms 3 (excludes subjects in France) and 4 will be issued with a new unique identification number. The subject identification number will be used to identify the subject for the duration of the study. Subject identification numbers will not be reassigned or reused.

6.1.2 Randomization Procedures

Not applicable.

6.1.3 Blinding Procedures

Not applicable.

6.2 DOSING AND ADMINISTRATION

The investigator (or delegate) will administer or dispense rIX-FP only to subjects included in this study or their caregivers following the procedures set out in this study protocol. Subjects or their caregivers or qualified study personnel will administer the rIX-FP as a bolus IV injection. For subjects in Arm 4, the rate of administration should be at approximately 200 IU

per minute in young children or determined by the subject's comfort level at investigator's discretion.

In the SC substudy, subjects will be sequentially assigned to a dose cohort, and receive a single SC dose of rIX-FP (25 IU/kg in Cohort 1; 50 IU/kg in Cohort 2) or repeated SC doses of rIX-FP (25 IU/kg every 3 days in Cohort 3; ≤ 50 IU/kg every 5 days in optional Cohort 4, with the actual dose in this cohort to be determined by CSL based on the PK results from Cohort 3). See Appendix 2 for details.

rIX-FP is supplied in single-use vials, which contain nominally CCI [redacted]

The **actual IU**, which is printed on the rIX-FP vial label, will be used for the calculation and documentation of each dose of rIX-FP.

When making the dose calculation, the total actual units (ie, as per the prescribed dose) may be rounded up or down to target full vials (as actual IU), if possible, but the final dose needs to be within 10% of the prescribed dose. The dose of rIX-FP is based on the subject's most current body weight as recorded in the eCRF.

6.2.1 Adjustment of Dose for Prophylaxis and On-demand Treatment

The dose of rIX-FP required for either prophylaxis or on-demand treatment will be based on the subject's previous experience (ie, during Study CSL654_3001 or CSL654_3002) and / or the target FIX activity. The following formula will be used to calculate dose based on FIX activity:

Number of factor IX IU required (IU)	=	Body weight (kg)	X	Desired factor IX increase (% or IU/dL)	X	Reciprocal of observed recovery (IU/kg per IU/dL)

The target trough FIX activity for routine prophylaxis is greater than 2%, but optimally, between 5 and 15% above baseline.

The target FIX activity for on-demand therapy (ie, for treatment of a bleeding episode) is between 40% and 80%.

6.3 TREATMENT COMPLIANCE

Subjects will record the dose, time of the dose and rIX-FP consumption for prophylaxis, prevention and on-demand treatment of bleeding episodes in the eDiary. In addition, subjects will bring all of their used vials (and unused, if requested) of rIX-FP to the study site at every visit. Treatment compliance will be monitored by counting the number of returned vials, the results of which will be recorded in the Drug Accountability Log. rIX-FP use, as reported by the subject in the eDiary, will also be reconciled to the returned vials.

For prophylaxis treatment, a subject will be regarded as compliant with treatment if both criteria below are met:

- Regimen compliance: The subject receives at least 80% of the injections of rIX-FP at the scheduled injection frequency during the study period where dosing is expected to occur within the following target days:
  - For the 7-day treatment interval: injection of rIX-FP occurs between Days 6 and 8 after the previous prophylaxis injection.
  - For the 10-day treatment interval (ie, every 10 days or 3 times per month): injection of rIX-FP occurs between Days 8 and 11 after the previous prophylaxis injection.
  - For the 14-day treatment interval: injection of rIX-FP occurs between Days 13 and 15 after the previous prophylaxis injection.
  - For the 21-day treatment interval (not applicable to subjects in France): injection of rIX-FP occurs between Days 20 and 22 after the previous prophylaxis injection.

- Dose compliance: The subject receives 80% to 120% of the prescribed dose, based on the actual dose, for at least 80% of injections.

7. CONTRAINDICATIONS, PERMITTED THERAPIES AND PROHIBITED THERAPIES

7.1 CONTRAINDICATIONS AND PRECAUTIONS TO FURTHER DOSING

In the event the subject experiences a hypersensitivity reaction, the study treatment must be stopped immediately by discontinuation of the injection. In the event the subject experiences a hypersensitivity reaction or develops an inhibitor to FIX or antibodies to rIX-FP, the CSL medical monitor must be contacted before the administration of additional doses of rIX-FP. Subjects in France may be discontinued from receiving the study product and participating in any further study procedures if the subject is confirmed to have developed an inhibitor against FIX with a titer > 5 BU/mL.

7.2 PERMITTED THERAPIES

The following therapies are PERMITTED during the study, if needed:

- Blood product transfusion (whole blood, erythrocytes [red blood cells], FFP or platelets) and emergency use of FIX concentrate when rIX-FP is not available or in the event that hemostatic control is not achieved after at least 2 injections.
- Heparin use is limited to 200 IU/day, if needed, to maintain patency of IV lines.
- Antifibrinolytic agents.
- Antibiotic and antiviral agents.

Standard thrombosis prophylaxis is permitted, and should be documented in the eCRF.

7.3 PROHIBITED THERAPIES

The following therapies are NOT PERMITTED during the study:

- Elective use of FIX concentrates other than rIX-FP.
- Any investigational product other than rIX-FP.

To be used with caution: with the exception of selective cyclooxygenase-2 inhibitors, non-steroidal anti-inflammatory drugs are known to have an effect on blood clotting. It is therefore

important that the investigator give careful consideration to the use of non-steroidal anti-inflammatory drugs in subjects participating in this study. If possible, alternative medication for pain relief, such as paracetamol / acetaminophen, should be used.

Subjects are not to be enrolled into the study if they receive any prohibited therapy or any therapy in a prohibited dosage that cannot be discontinued or reduced to a permitted dose before enrollment.

If administration of any prohibited therapy becomes necessary during the study, the subject may be withdrawn from further study participation.

7.4 DIETARY AND LIFESTYLE RESTRICTIONS

Not applicable.

7.5 OVERDOSE

Overdose is defined as the accidental or intentional injection of any dose of a product that is considered by the investigator to be excessive. The effects of any potential overdose with rIX-FP have not been studied. Any overdose (ie, a single dose > 100 IU/kg rIX-FP, except when used for surgical prophylaxis or prophylaxis treatment administered every 21 days) should be documented in the eCRF, as described in Section 9.7.1.

8. STUDY PROCEDURES AND VISIT SCHEDULE

8.1 CLINICAL PROCEDURES

The clinical procedures that will be conducted during this study related to the evaluation of population demographics and safety are provided in Table 2. Refer to the Laboratory Manual for detailed instructions on how the assessments should be performed.

Table 2. Clinical Procedures: Demographics and Safety Evaluation

Assessment	Description
Demographics	Date of birth, age, sex, race and ethnicity.
Medical and surgical history (Arm 3 and 4)	Relevant medical history especially regarding the history of hemophilia B including: • Date severe or moderately severe hemophilia B first diagnosed. • Number of bleeding episodes (spontaneous, trauma, surgery-associated, and unknown) during the previous 12 months. • Human immunodeficiency virus status.
Medical history (Arm 4 only)	• Family history of inhibitors against FIX
Treatment history (Arm 3 only)	Treatment history with FIX including: • Date of first prophylaxis treatment. • Product type (pdFIX, rFIX, investigational product). • Drug name. • Modality of treatment (on-demand, routine prophylaxis, post-surgery, prevention prior to activity). • Dose and treatment schedule. • Estimated or documented treatment exposure days
Lead-in study data (Arms 1 and 2 only)	• Total rIX-FP exposure days • Prior therapies including treatment regimen at the end of the lead-in study • Age cohort at start of lead-in study (subjects from CSL654_3002 only) • Study arm in lead-in study (subjects from CSL654_3001 only)
Social and physical activity (Arms 1, 2 and 3 only)	• Subject's living arrangement • Number of days the subject missed from school or work (if relevant) • Number of days the caregiver(s) missed from work due to the need of caring for the subject (if relevant) • Number of important life activities missed due to hemophilia for subject and caregiver (if relevant) • Hospital visits due to hemophilia (not including study-related visits). • Overall activity level and sport(s) activities
Relevant medical history	• Genotype • Current joint score, scoring system and date of the assessment
Physical examination	As per the site's standard procedure
Vital signs	• Body temperature • Height and body weight • Blood pressure (systolic and diastolic) • Heart rate (per minute)

Assessment	Description
Biochemistry	• Albumin • ALP • ALT • AST • Bilirubin • Direct Bilirubin • Protein • Blood Urea Nitrogen or Urea • Creatinine
Hematology	• Hemoglobin • Red blood cell (erythrocyte) count • Hematocrit • White blood cell (leukocyte) count • Platelet count • White blood cell differential (optional)
CCI	• Hemo-Sat questionnaire (subjects from CSL654_3002 only) • CCI
Immunogenicity	Factor IX inhibitors and antibodies specific to rIX-FP and Chinese hamster ovary cell-derived proteins.
Genotype (Arm 4)	If FIX inhibitor is confirmed, genotype of FIX

ALP = alkaline phosphatase; ALT = alanine aminotransferase; AST = aspartate aminotransferase; FIX = coagulation factor IX; pdFIX = plasma-derived factor IX; CCI; rFIX = recombinant FIX; rIX-FP = recombinant fusion protein linking coagulation factor IX with albumin.

The timing and frequency of all clinical procedures are described in the Section 8.9 and Table A - Schedule of Assessments: Treatment Period and Table C - Schedule of Assessments: Subjects in Arm 3 and Table D – Schedule of Assessment: Subjects in Arm 4. See Appendix 2 for details and the Schedules of Assessment for the SC substudy.

Refer to the Laboratory Manual for details about the collection, storage, handling and transportation of biological specimens.

8.2 SUBJECT/CAREGIVER TRAINING AND TREATMENT AT HOME

On Day 1 (Arms 1 and 2) or during the PK evaluation period (Arm 3) or during visits prior to provide eDiary to caregiver (Arm 4), and all follow-up visits, the investigator or delegate will ensure that the subject and / or caregiver has been trained sufficiently to allow for home therapy to occur in the subsequent months of the study (see Appendix 2 for details regarding the SC substudy). At this time, the subject/caregiver will be instructed in the following:

- Correct reconstitution technique for rIX-FP.
- Correct IV access and administration technique.
- Correct drug storage.

- Adverse event reporting.
- Correct completion of eDiary.

For treatment received by the subject at home, the subject / caregiver will report (not limited to) the following information in the eDiary:

- Details of the rIX-FP administration (eg, total actual IU per injection, number of vials used, and start date and time of injection).
- Type of treatment (routine prophylaxis, prevention [before vigorous physical activity or physical therapy], on-demand, post-surgery).

For bleeding episodes:

- Type of bleeding episode (spontaneous, traumatic, unknown, or post-surgery).
- Site of the bleed (ie, joint, muscle, mucosal membrane) and specific location.
- Time of start of symptoms of bleeding.

Local tolerability at the injection site will be assessed throughout the study by the subject. Subjects will record in the eDiary their judgment on the overall perception of the local reactions on a scale of none (0), very slight (1), slight (2), moderate (3) and severe (4) approximately 30 minutes after the end of the rIX-FP infusion.

8.3 CONTROL OF MAJOR BLEEDING EPISODES

Major bleeding episodes are defined as a bleed for which a subject is required to seek treatment at the hemophilia center from the treating physician. A major bleeding episode includes intra-cranial hemorrhage, gastrointestinal, and severe bleeding into a joint or muscle (ie. iliopsoas muscle). All other bleeding episodes will be classified as minor / moderate unless the investigator assessment notes otherwise.

The investigator will record the following in the eCRF:

- Reason for use of rIX-FP and type of the bleeding episode (spontaneous, traumatic, unknown, or post-surgery).
- Time of the start of bleeding.
- Dose of rIX-FP (IU/kg).

- Number of used vials and total actual IU used.
- Date and start time of each injection.
- Local tolerability.
- Concomitant therapy and other hemostatic product usage (if any).
- Rescue FIX concentrate usage (if any).
- Response to rIX-FP treatment using a 4-point scale (Table 3).

Table 3. Efficacy Evaluation for Treatment of Major Bleeding Episodes

Excellent	Hemostasis clinically not significantly different from (eg, achieved hemostasis comparable to that expected for a similar bleed in a non-factor deficient patient) or actual blood loss is not more than 20% higher than the estimated predicted blood loss for the type of injury or problem
Good	Normal or mildly abnormal hemostasis in terms of quantity and / or quality (eg, slight oozing, prolonged time to hemostasis with somewhat increased bleeding compared to a non-factor deficient patient) or estimated actual blood loss is greater than 20% but less than or equal to 30% higher than the estimated predicted blood loss for this type of injury or problem
Moderate	Moderately abnormal hemostasis in terms of quantity and / or quality (eg, moderate hemorrhage that is difficult to control) with estimated blood loss greater than what is defined as Good
Poor / No response	Severely abnormal hemostasis in terms of quantity and / or quality (eg, severe hemorrhage that is difficult to control) and / or additional hemostatic intervention required with other FIX product, cryoprecipitate, or plasma more than expected for the type of injury or problem

8.4 CONTROL OF MINOR AND MODERATE BLEEDING EPISODES (Arm 4 only)

Caregivers of Arm 4 subjects will record information (see Section 8.2) in the eeDiary on the bleeding episode and treatment received by the subject at home after the caregiver has been trained on home infusion. If the subject receives treatment at the site, the investigator will record information on the bleeding episode and treatment in the eCRF.

The caregiver should contact site study staff at approximately 24 hours after the first treatment dose for the bleeding episode to report the response to treatment, including objective signs of bleeding (ie, swelling, tenderness, and / or decreased range of motion in the case of musculoskeletal hemorrhage) and to discuss if additional treatment or maintenance dose will be needed.

The response to rIX-FP treatment will be evaluated via a 4-point scale (Table 4) by the Investigator at each Visit after a review of the treatment record.

Table 4. Efficacy Evaluation for Treatment of Minor and Moderate Bleeding Episodes

Excellent (effective)	No additional infusion required after the first infusion in order to achieve hemostasis, unmistakable/obvious improvement in objective signs of bleeding (ie, swelling, tenderness, and / or decreased range of motion in the case of musculoskeletal hemorrhage) approximately 24 hours after the first FIX infusion.
Good (effective)	Requires a second infusion in order to achieve hemostasis, significant/recognized improvement in signs of bleeding at approximately 24 hours after the first infusion.
Moderate (not effective)	Requires more than two infusions to achieve hemostasis, and slight beneficial effect at approximately 24 hours after the first infusion.
Poor/No response (not effective)	Requires additional hemostatic intervention with other FIX product, or plasma to achieve hemostasis and no improvement at all or condition worsens (ie, signs of bleeding) at approximately 24 hours after the first infusion.

The Investigator rating of hemostatic efficacy will take into account both the number of infusions required to achieve hemostasis (primary factor for PI's assessment) and the objective signs of bleeding approximately 24 hours after the first infusion as reported to the site by the caregiver or observed by site personnel.

8.5 TREATMENT FOR A SURGICAL PROCEDURE

If a non-emergency surgical procedure is necessary, the subject may be enrolled in the surgery substudy. The details of the substudy are described in Appendix 1.

8.6 INHIBITORS AND ANTIBODIES

The presence of antibodies against rIX-FP and CHO cells and inhibitors of FIX will be assessed by the central laboratory. Details regarding sample collection, handling, deep freezing of samples and shipment to the central laboratory are given in the Laboratory Manual in the Investigator Site File.

A tiered approach for immunogenicity testing for antibodies to rIX-FP will be employed during the study:

1. **Screening assay**: The screening assay is a direct-binding ELISA assay, capable of detecting antibodies against rIX-FP in blood samples from subjects.
2. **Confirmation assays**: If the antibody titer is above the cut-off level for the screening assay, the same sample will be tested in a separate direct-binding ELISA assay to confirm the specific antibody signal and to discriminate between plasma-derived FIX, rIX-FP, and albumin antibodies. In the event that all confirmation assays are negative, the screening assay will be considered a false positive result.
3. **Neutralization assay for inhibitors**: The neutralizing capacity of antibodies will be assessed by a FIX potency assay. To quantify anti-FIX neutralizing antibodies, the Bethesda assay with the Nijmegen modification will be used, and the results expressed as Bethesda Units per mL (BU/mL).

In cases where the inhibitor titer is determined to be above the cut-off level (0.6 BU/mL), a second blood sample should be collected and be tested by the central laboratory for confirmation, and additional testing such as PK / incremental recovery tests will be performed. The subject's information will be presented to the SMT and IDMC for its recommendation.

8.7 RETENTION OF SAMPLES

Retention samples of serum will be obtained before the first dose of rIX-FP (subjects in Arms 3 and 4 only) and at the end of study visit for later viral safety testing, if needed and with the subject's consent. Retention samples will be stored by CSL for 5 years.

8.8 CONCOMITANT THERAPIES

For subjects in Arms 3 and 4, all drugs taken by a subject within 30 days before the screening visit and during screening are regarded as prior therapy and must be documented in the eCRF.

All therapies currently being administered to a subject either at the time of or after signing informed consent, and which continue to be administered in addition to rIX-FP during the study, are regarded as concomitant therapies and must be documented as such in the eCRF. Nonpharmacological interventions (eg, physical therapy or a minor surgical procedure performed outside of the surgical substudy) are also regarded as concomitant therapy and must be documented in the eCRF.

8.9 VISIT SCHEDULE

The timing and frequency of the study visits in the main study are described in the Table A - Schedule of Assessments: Treatment Period and the Table C - Schedule of Assessments: Subjects in Arm 3 and Table D – Schedule of Assessment: Subjects in Arm 4.

See Appendix 1 for details on study visits and the Schedule of Assessments in the surgery substudy.

See Appendix 2 for details on study visits and the Schedules of Assessments in the SC substudy.

8.9.1 Screening Visit (Arms 3 and 4 only) or Day 1 Visit (Arms 1 and 2 only)

All subjects **must provide written informed consent** before any study-specific assessments or procedures are performed.

Written informed consent is not required for assessments or procedures performed according to standard of care (eg, for diagnosis or treatment); results from such assessments may be used in the determination of study eligibility. In addition, results from laboratory / clinical assessments (eg, biochemistry, hematology, vital signs, body height and weight, physical

examination) and antibody assessments collected at the end of study visit of the lead-in study will be used as Day 1 values (Arms 1 and 2 only).

If the subject is not eligible for the study, the primary reason for screen failure must be entered in the eCRF.

8.9.1.1 Screening Visit (Arm 3 only)

The following procedures will be performed and documented by the investigator or delegate:

- Demographics.
- Review inclusion and exclusion criteria.
- Social and physical activity.
- Relevant medical and treatment history.
- Physical examination.
- Vital signs.
- Body weight and height.
- Obtain blood samples for biochemistry and hematology.
- Obtain blood samples for:
  - Inhibitors against FIX.
  - Antibodies against rIX-FP.
  - Antibodies against CHO cell-derived proteins.
- Obtain blood sample for measurement of plasma FIX.
- Prior and concomitant therapy.
- Start monitoring of AEs.

8.9.1.2 Screening Visit (Arm 4 only)

The following procedures will be performed and documented by the investigator or delegate:

- Demographics.
- Review inclusion and exclusion criteria.
- Relevant medical history.
- Family history of inhibitor against FIX.

- Physical examination.
- Vital signs.
- Body weight and height.
- Obtain blood samples for biochemistry and hematology, if feasible, unless results within 6 months are available in the subject's medical records.
- Obtain blood sample for measurement of plasma FIX (LL), unless data is available in the subject's medical records.
- Obtain blood samples for:
  - Inhibitors against FIX.
  - Antibodies against rIX-FP.
  - Antibodies against CHO cell-derived proteins.
- Prior and concomitant therapy.
- Start monitoring of AEs.
- If a subject experiences a life-threatening bleeding episode (including bleeding in the central nervous system, gastrointestinal tract, neck/throat, or severe trauma-induced bleeding) or requires a major surgical procedure prior to the first administration of rIX-FP, the subject will not be enrolled into the study and will be counted as a screen failure.

8.9.1.3 Day 1 Visit (Arms 1 and 2 only)

The following information will be transferred from the end of study visit or earlier visit (where relevant) of the lead-in study:

- Information on demographics.
- Lead-in study data (rIX-FP EDs, age cohort in lead-in study [CSL654_3002 study only], arm in lead-in study [CSL654_3001 study only], prior therapies including treatment regimen at the end of the lead-in study).
- Social and physical activity.
- Physical examination.
- Vital signs.
- Body weight and height.

- Results from biochemistry and hematology assessments.
- Results for inhibitors against FIX, antibodies against rIX-FP, antibodies against CHO cell-derived proteins.
- Results for plasma FIX activity (CSL654_3001 subjects only).
- Concomitant therapy.
- Ongoing AEs.

The following procedures will be conducted at the Day 1 visit:

- Review inclusion and exclusion criteria.
- Record relevant medical history (genotype and joint score including scoring system and date of assessment).
- Obtain blood sample for measurement of plasma FIX activity (central laboratory) for subjects from the CSL654_3002 study.
- Start monitoring of AEs.
- Any new concomitant therapy (ie, not reported at the end of study visit of the lead-in study).
- Record the dose regimen (dose and treatment interval) and administration information in the eCRF, if the subject is administered the first injection of rIX-FP during the visit.
- Dispense eDiary.
- If considered necessary, reinstruct subject on injection technique, dosing regimen, and use of eDiary.
- Schedule next visit.

8.9.2 Day 1 Visit (Arms 3 and 4)

8.9.2.1 Day 1 (Arm 3 only, which excludes any subjects from France)

After completion of the surgery substudy, subjects must complete the Day 1 visit if they choose to remain in the study. This Day 1 visit will occur on the same day as the End of Surgery

Substudy visit. At this visit, the following procedures will be performed by the investigator or delegate:

- If necessary, reinstruct subject on injection technique.
- Body weight.
- Assign and instruct subject on dosing regimen.
- Record AEs and concomitant therapies.
- After the Day 1 visit, subjects in Arm 3 should complete the study according to Table A - Schedule of Assessments: Treatment Period.

8.9.2.2 Day 1 visit (Arm 4 only)

The Day 1 visit may occur on the same day as the Screening visit, if all inclusion criteria are met.

The following procedures will be conducted at the Day 1 visit PRIOR to the administration of rIX-FP:

- Review inclusion and exclusion criteria to confirm eligibility for the study.
- Physical examination.
- Vital signs.
- Body weight and height.
- Collect blood samples prior to first dose of rIX-FP (if not collected at Screening):
  - Biochemistry and hematology (LL), unless results within 6 months are available in the subject's medical records.
  - Plasma FIX level (CL).
  - Inhibitors against FIX (CL).
  - Antibodies against rIX-FP and CHO cell-derived proteins (CL).
- Prior and concomitant therapy.
- Administer the first dose of rIX-FP.

The following procedures will be conducted at the Day 1 visit FOLLOWING the administration of rIX-FP:

- Monitor subject for at least 3 hours under medical supervision.

- Record the dose, administration information and reason for the dose in the eCRF.
- If the first dose is for PK assessment, sample for FIX activity will be collected 30 minutes post administration.
- Record AEs and concomitant therapy.

8.9.3 Other Visits during the Treatment Period (Arm 1, 2 and 3)

8.9.3.1 Month 3 Visit and Month 9 Visit

The following procedures will be performed and documented by the investigator or delegate:

- Body weight (omitted if visit conducted via telephone).
- Review subject eDiary.
- Assess treatment efficacy for major bleeding episodes, if applicable.
- Record AEs and concomitant therapies.
- If considered necessary, reinstruct subject on injection technique, dosing regimen, and use of eDiary.
- Schedule next visit.

For subjects from lead-in Study CSL654_3001 Arm 1, the visit at month 3 may be conducted via telephone, if the investigator deems that there is no safety risk to the subject.

For all Arm 2 and 3 subjects, the visit at month 9 may be conducted via telephone, if the investigator deems that there is no safety risk to the subject.

The month 3 visit may be omitted for subjects in Arm 2 who have attended a follow-up after visit in the previous 3 months to transition from a 7-day rIX-FP treatment interval to a 14-day rIX-FP treatment interval.

8.9.3.2 Month 6 Visit

The following procedures will be performed and documented by the investigator or delegate:

- Record social and physical activity.
- Body weight.

- Obtain blood samples for:
  - Inhibitors against FIX.
  - Plasma FIX activity) (central and local laboratory).
- Review subject eDiary.
- Assess treatment efficacy for major bleeding episodes, if applicable.
- Review treatment regimen (ie, dose and / or treatment interval) and modify, if necessary. Record any changes in treatment regimen in the eCRF.
- Record AEs and concomitant therapies.
- If considered necessary, reinstruct subject on injection technique, dosing regimen, and use of eDiary.
- Schedule next visit.

8.9.3.3 Month 12 Visit

The following procedures will be performed by the investigator or delegate:

- Record social and physical activity.
- Physical examination.
- Vital signs.
- Body weight and height (height optional for subjects ≥ 18 years).
- Obtain blood sample for biochemistry and hematology assessments.
- Obtain blood samples for:
  - Inhibitors against FIX.
  - Antibodies against rIX-FP.
  - Antibodies against CHO cell-derived proteins.
- Obtain blood sample for measurement of plasma FIX activity (central and local laboratory).
- Review subject eDiary.
- Assess treatment efficacy for major bleeding episodes, if applicable.
- Review treatment regimen (ie, dose and / or treatment interval) and modify, if necessary. Record any changes in treatment regimen in the eCRF.

- Record AEs and concomitant therapies.
- Parents or the caregiver of subjects to complete Hemo-Sat questionnaire (for subjects who transferred from the CSL654_3002 lead-in study).

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- If considered necessary, reinstruct subject on injection technique, dosing regimen, and use of eDiary.
- Schedule next visit.

8.9.3.4 Months 18, 30, 42, and 54 Visits

The following procedures will be performed by the investigator or delegate:

- Record social and physical activity.
- Body weight.
- Obtain blood samples for inhibitors against FIX.
- Obtain blood sample for measurement of plasma FIX activity (central laboratory).
- Review subject eDiary.
- Assess treatment efficacy for major bleeding episodes, if applicable.
- Review treatment regimen (ie, dose and treatment interval) and modify, if necessary. Record any changes in treatment regimen in the eCRF.
- Record AEs and concomitant therapies.
- If considered necessary, reinstruct subject on injection technique, dosing regimen, and use of eDiary.
- Schedule next visit.

8.9.3.5 Months 24, 36, 48, and 60 Visits

The following procedures will be performed by the investigator or delegate:

- Record social and physical activity.
- Physical examination.
- Vital signs.
- Body weight and height.
- Obtain blood samples for:
  - Inhibitors against FIX.
  - Antibodies against rIX-FP.
  - Antibodies against CHO cell-derived proteins
- Obtain blood sample for measurement of plasma FIX activity (central laboratory).
- Review subject eDiary.
- Assess treatment efficacy for major bleeding episodes, if applicable.
- Review treatment regimen (ie, dose and treatment interval) and modify, if necessary. Record any changes in treatment regimen in the eCRF.
- Record AEs and concomitant therapies.
- If considered necessary, reinstruct subject on injection technique, dosing regimen, and use of eDiary.
- Schedule next study visit.

8.9.4 Other Visits During the Treatment Period (Arm 4 only)

8.9.4.1 First 10 to 20 administrations of rIX-FP

Subjects must be treated in a clinic/hospital setting capable of treating severe allergic reactions during the initial 10 (required minimum) to 20 (at investigator's discretion) infusions. The first two doses must be monitored under medical supervision for at least 3 hours, and the remaining doses are monitored for at least 30 minutes. Some of those visits for administrations of rIX-FP can occur during the scheduled monthly visits after samples for laboratory testing are

collected. The dose, administration information, reason for the dose and assessment of local tolerability must be recorded in the eCRF.

8.9.4.2 Visit at Month 1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 11 and 12

Subjects will visit the study center as outlined in the Schedule of Assessments (Table D), preferably within 2 days prior to the next planned infusion of rIX-FP (or as close to the next rIX-FP infusion as possible) if subject is receiving routine prophylaxis.

The following procedures will be performed at every visit:

- Physical examination.
- Vital signs.
- Weight and height.
- Review concomitant therapy.
- Review AEs since last visit.
- Review the subject eDiary (if applicable) and investigator assessment of efficacy for treated bleeding events.
- If considered necessary, reinstruct subject/caregiver on injection technique, dosing regimen, and use of eDiary.

The following procedures will be performed, in addition to the procedures listed above:

- Blood samples for FIX inhibitors at Months 1, 2, 3, 4, 5, 6, 9 and 12 (CL). In addition, inhibitor testing should be performed at any time if there is any suspicion of inhibitor development.
- Blood samples for antibodies against rIX-FP and CHO cells at Months 6 and 12 (CL).
- Blood samples for local laboratory safety evaluation (hematology and Biochemistry) at Month 12 visit.
- Blood samples for FIX activity level at Months 1, 2, 3, 6 and 12 (CL).

If a subject receives less than 3 doses per month, they may omit the site visit(s) until the first 5 doses have been administered.

In the event a subject misses a study visit, the study personnel should contact the study subject by telephone and collect pertinent study-related information and document accordingly in the medical record. All subject data should be reviewed at the next scheduled visit and recorded in the CRF.

In the event a subject misses any visit at which testing for inhibitor is required, an unscheduled visit should be arranged as soon as possible during the subject's first 20 EDs, otherwise all required laboratory tests can be conducted during the next site visit.

The subject's caregiver may begin administering rIX-FP at home after the subject has received a minimum of 10 treatments of rIX-FP at the site. The investigator or delegate will ensure that the caregiver has been trained sufficiently to allow for home therapy to occur in the subsequent months of the study. The study center personnel will instruct the caregiver on the reconstitution and administration of rIX-FP and correct completion of the eDiary prior to issuing the eDiary as outlined in Section 8.2.

8.9.4.3 Months 15, 18, 21, 24, 27, 30 and 33 Visits

Subjects will visit the study center as outlined in the Schedule of Assessments (Table D), preferably within 24 hours (or as close to the next rIX-FP infusion as possible) prior to the next planned infusion of rIX-FP.

The following procedures will be performed by the investigator or delegate at every visit:

- Physical examination.
- Vital signs.
- Weight and height.
- Review concomitant therapy.
- Review AEs.
- Review the subject eDiary (if applicable) and investigator assessment of efficacy.
- If considered necessary, reinstruct caregiver/subject on injection technique, dosing regimen, and use of eDiary.

The following procedures will be performed, in addition to the procedures listed above at Month 18, 24 and 30 Visit ONLY:

- Obtain blood samples for inhibitor to FIX (CL).

The following procedures will be performed, in addition to the procedures listed above at Month 24 Visit ONLY:

- Obtain blood sample for biochemistry and hematology assessments (LL).
- Blood samples for FIX activity and antibodies against rIX-FP and CHO cells (CL).

8.9.5 Completion of 50 rIX-FP EDs During the Study (all subjects)

The following procedures will be performed by the investigator or delegate:

- Obtain central laboratory blood samples for:
  - Inhibitors against FIX.
  - Antibodies against rIX-FP
  - Antibodies against CHO cell-derived proteins.
- Record AEs and concomitant therapies.

8.9.6 Unscheduled Visits if Inhibitor to FIX is confirmed

The following procedures will be performed:

- Obtain blood sample for genotyping if no test results are available in subject medical records.
- Obtain blood samples for PK assessment if feasible.
- Review concomitant therapy.
- Review AEs.
- Review the eDiary (if applicable) and investigator assessment of efficacy of any treated bleeding episodes.

8.9.7 End of Study (all subjects)

The scheduled end of study participation for an individual subject occurs with completion of the end of study visit, after which, no further study-related procedures will be performed. The end of study visit may be combined with another planned visit if the two visits are less than 2 months apart. The following procedures will be performed by the investigator or delegate at the end of study visit:

- Record social and physical activity (except Arm 4).
- Physical examination.
- Vital signs.
- Obtain blood sample for biochemistry and hematology.
- Obtain blood samples for:
  - Inhibitors against FIX.
  - Antibodies against rIX-FP.
  - Antibodies against CHO cell-derived proteins.
  - FIX activity (Arm 4 only).
- Obtain retain blood sample for serology.
- Review subject eDiary and ensure all data have been submitted.
- Retrieve eDiary.
- Assess treatment efficacy for major bleeding episodes, if applicable.
- Record AEs and concomitant therapies.

8.9.8 Pharmacokinetic Evaluation of 100 IU/kg rIX-FP

Subjects in France will not take part in the PK of 100 IU/kg rIX-FP.

Before a subject either begins administering rIX-FP as routine prophylaxis using a 21-day treatment interval (excludes subjects in France), or begins administering rIX-FP for the first time (Arm 3), they must first undergo a PK evaluation period with a single injection of rIX-FP (100 IU/kg). The PK evaluation should be performed after a washout period of either

at least 4 days for a marketed FIX (subjects in Arm 3) or at least 14 days for rIX-FP (subjects currently being treated with rIX-FP).

The following procedures will be conducted during the PK evaluation period:

- Body weight.
- Obtain blood sample for measurement of plasma FIX activity (central laboratory) before injection of rIX-FP.
- Obtain retain blood sample (Arm 3 only).
- Investigator or delegate to administer a single injection of rIX-FP at a dose of 100 IU/kg rIX-FP.
- Obtain blood samples for measurement of plasma FIX activity at the following time points after injection of rIX-FP:
  - 30 ± 5 minutes.
  - 72 ± 24 hours (ie, 3 ± 1 days) as an optional time point for subjects planning to be switched to 21-day treatment interval.
  - 168 ± 24 hours (ie, 7 ± 1 days).
  - 336 ± 24 hours (ie, 14 ± 1 days). This time point is optional for subjects in Arm 3.
  - 504 ± 24 hours (ie, 21 ± 1 days). This time point is optional for subjects in Arm 3. *Samples are to be taken only if no bleeding occurred before sample collection*.
- Record AEs and concomitant therapies before, during and after injection of rIX-FP.
- If considered necessary, reinstruct subject on injection technique, dosing regimen, and use of eDiary.
- Schedule next study visit.

For subjects in Arm 3 only, before the end of the PK evaluation period, the investigator or delegate should:

- Dispense eDiary.
- Instruct subject on injection technique, dosing regimen, and use of eDiary.

8.9.9 Pharmacokinetic Evaluation of 50 IU/kg rIX-FP (Arm 4)

The subjects in Arm 4 may be first undergoing a PK evaluation as the first dose with a single injection of rIX-FP (50 IU/kg) or during the study.

The following procedures will be conducted PRIOR to rIX-FP administration:

- Body weight and height.
- Obtain blood sample for measurement of plasma FIX activity (central laboratory) before injection of rIX-FP.
- Investigator or delegate to administer a single injection of rIX-FP at a dose of 50 IU/kg rIX-FP.

The following procedures will be conducted FOLLOWING rIX-FP administration:

- Obtain blood samples for measurement of plasma FIX activity at the following time points after injection of rIX-FP:
  - 30 ± 5 minutes.
  - 72 ± 24 hours as an optional time point.
  - 168 ± 24 hours as an optional time point.
- Record AEs and concomitant therapies before, during and after injection of rIX-FP.

8.9.10 Unscheduled Visits

Unscheduled visits, including brief PK assessments, may be arranged at any time point during the study, at the discretion of the investigator or upon request of the subject or CSL.

9. ADVERSE EVENTS

9.1 DEFINITIONS

9.1.1 Adverse Event

As per the ICH guidelines, an AE is any untoward medical occurrence in a patient or clinical investigation subject administered a pharmaceutical product and which does not necessarily

have a causal relationship with this treatment. An AE can, therefore, be any unfavorable and unintended sign (including an abnormal, clinically significant laboratory finding), symptom, or disease temporally associated with the use of a medicinal (investigational) product, whether or not considered related to the medicinal (investigational) product.

The period of observation for AEs extends from the time the subject gives informed consent until the end of study (see Section 9.4 for further details).

Adverse events may include:

- Exacerbation (ie, an increase in the frequency or severity) of a pre-existing condition. Illness present before study entry should be recorded in the medical history section of the eCRF and only be reported as an AE if there is an increase in the frequency or severity of the condition during the study.
- A clinical event occurring after consent but before rIX-FP administration.
- Intercurrent illnesses with an onset after administration of rIX-FP.

Adverse events do not include:

- A bleeding episode that occurs as a result of the subject's unchanged, pre-existing hemophilia condition.
- Events identified at baseline that meet exclusion criteria.
- Medical or surgical procedures (the condition that leads to the procedure may be reported as the AE, as appropriate).
- A trauma itself, however, an injury other than bleeding (eg, bone fracture) resulting from the trauma should be documented as an AE.
- Situations where an untoward medical occurrence has not taken place. For example:
  - Planned hospitalizations due to pre-existing conditions, which have not worsened.
  - Hospitalizations that occur for procedures not due to an AE (eg, cosmetic surgery, elective surgery or social admission).
  - Hospitalizations for a diagnostic procedure where the hospital stay is less than 24 hours in duration or for normal disease management procedures.

- Overdose of rIX-FP or any concomitant therapy **that does not** result in any adverse signs or symptoms.

If a bleeding episode occurs, whether spontaneous or as the result of trauma or injury, ONLY the injury should be recorded as an AE or SAE. The bleeding episode, whether spontaneous or resulting from the injury, should not be recorded as an AE, but as a bleeding episode on the appropriate eCRF page.

For laboratory safety parameters, any instances of absolute values being outside the reference range or changes at any visit after study start that are considered by the investigator as clinically significant must recorded in the eCRF as AEs. In addition, at the investigator's discretion, any changes or trends over time in laboratory parameters can be recorded in the eCRF as AEs if such changes or trends are considered to be clinically relevant, even if the absolute values are within the reference range.

Laboratory findings do not need to be reported as AEs in the following cases:

- Laboratory parameters already beyond the reference range at Day 1 of the lead-in study (subjects in Arms 1 or 2) or at screening (subjects in Arm 3 or Arm 4), unless a further increase/decrease can be considered an exacerbation of a pre-existing condition.
- Abnormal laboratory parameters caused by mechanical or physical influences on the blood sample (eg, in vitro hemolysis) and flagged as such by the laboratory in the laboratory report.
- Abnormal parameters that are obviously biologically implausible (eg, values that are incompatible with life or outside the measuring range).
- An abnormal laboratory value that cannot be confirmed after repeat analysis, preferably in the same laboratory (ie, the previous result could be marked as not valid and should not necessarily be reported as an AE).

9.1.2 Adverse Events of Special Interest

There are several AEs that will be monitored closely as adverse events of special interest (AESIs) to enable an adequate risk-benefit evaluation of rIX-FP versus standard therapy during the study and additional data may be requested for these events. The AESIs will be:

- AEs associated with confirmed (ie, with second blood sample) inhibitor formation.
- Thrombotic and / or embolic events.
- Anaphylaxis.

AESIs should be considered medically significant and are therefore SAEs. The expedited reporting procedures for SAEs are described in detail in Section 9.6.

9.1.3 Serious Adverse Event

An SAE is defined as any untoward medical occurrence that at any dose:

- **Results in death** – The event must be the cause of death for the SAE to meet this serious criterion.
- **Is life-threatening** – The term "life-threatening" refers to an event in which the subject was at risk of death at the time of the event; it does not refer to an event that hypothetically might have caused death if it had been more severe.
- **Requires in-patient hospitalization or prolongation of existing hospitalization** – CSL considers "hospitalization or prolongation of existing hospitalization" for at least 24 hours as the defining criterion for an SAE. Hospital admissions for planned surgery or for normal disease management procedures (eg, for treating major bleeding episodes, diagnostic procedures, admission or procedures that are not considered AEs [see Section 9.1.1]) are not considered as defining criteria for SAEs.
- **Results in persistent or significant disability or incapacity.**
- **Is a congenital anomaly or birth defect.**
- **Is medically significant** – A medically significant event is defined as an event that does not necessarily meet any of the SAE criteria, but which is judged by a physician to potentially jeopardize the subject or require medical or surgical intervention to prevent one of the above outcomes listed as an SAE criterion.

Adverse events that do not fall into the above categories are defined as nonserious AEs.

9.2 SEVERITY OF ADVERSE EVENTS

The severity of each AE (ie, nonserious and SAEs) is to be assessed by the investigator as follows:

Severity	Definition
Mild	A type of AE that is usually transient and may require only minimal treatment or therapeutic intervention. The event does not generally interfere with usual activities of daily living.
Moderate	A type of AE that is usually alleviated with additional specific therapeutic intervention. The event interferes with usual activities of daily living, causing discomfort but poses no significant or permanent risk of harm to the subject.
Severe	A type of AE that interrupts usual activities of daily living, or significantly affects clinical status, or may require intensive therapeutic intervention.

CDISC SDTM Severity Intensity Scale for Adverse Event Terminology

9.3 CAUSALITY OF ADVERSE EVENTS

The causal relationship of an AE to rIX-FP must always be assessed by the investigator. All AEs will be classified as either **related** or **not related** to rIX-FP. If a causality assessment is not provided for an AE (including an SAE) at the time of database lock, that AE will be considered related to rIX-FP.

The degree of certainty with which an AE is attributed to rIX-FP or an alternative cause (eg, natural history of the underlying disease, concomitant therapy) will be determined by how well the event can be understood in terms of:

- Known pharmacology of rIX-FP.
- Clinically and / or pathophysiologically plausible context.
- Reaction of a similar nature previously observed with similar products, or reported in the literature for similar products as being product related (eg, headache, facial flushing, pallor).

- Plausibility supported by the temporal relationship (eg, the event being related by time to administration or termination of treatment with rIX-FP, drug withdrawal or reproduced on rechallenge).

9.4 OBSERVATION PERIOD FOR ADVERSE EVENTS

The observation period for AE (and SAE) reporting in an individual subject will start at the time of giving written informed consent for participation in the current study and finish with the end of study visit.

If the investigator becomes aware of an SAE that has started after the observation period has finished, and the event could in some way be associated with rIX-FP, then this must also be reported to CSL and included in the clinical database (see Section 9.6).

9.5 ADVERSE EVENT REPORTING

9.5.1 Adverse Events

At each clinical evaluation, the investigator (or delegate) will determine whether any AEs have occurred. AEs will be recorded in the AE page of the eCRF. If known, the medical diagnosis of an AE should be recorded in preference to the listing of individual signs and symptoms. The investigator must follow up on the course of an AE until resolution or stabilization. If an AE is ongoing after the end of study visit, the AE will continue to be followed up until resolution, stabilization, or for 30 days after the final administration of rIX-FP during the study, whichever is sooner.

9.5.2 Adverse Events of Special Interest

Any AESI should be reported as an SAE as described in detail in Section 9.6.

9.6 SERIOUS ADVERSE EVENT REPORTING

This study will comply with all applicable regulatory requirements and adhere to the full requirements of ICH Topic E2A (Clinical Safety Data Management: Definitions and Standards for Expedited Reporting).

For SAEs occurring during the study, the investigator or delegate will enter all relevant information in the AE page of the eCRF. An electronic document containing the AE page and other applicable pages of the eCRF must be sent (via facsimile or email) to the sponsor together with a **Notification of Serious Adverse Event at Investigator Site** cover page, which has been signed and dated by the Investigator. If an electronic document is not able to be generated (eg, internet access problem), a handwritten paper SAE report must be completed, which must be signed and dated by the investigator.

All SAEs that occur during the course of the study, whether or not causally related to rIX-FP, must be reported immediately (within 24 hours of the investigator becoming aware of the event) to CSL. ***For Japan sites only, the investigator must also inform the head of the medical institution of the SAE and related information in accordance with the Japanese regulatory requirements and ICH GCP.***

Adverse events occurring in the period between the times the subject gave written informed consent and the first exposure to rIX-FP that meet one or more of the seriousness criteria for AEs must be reported to CSL in the same manner as other SAEs and will be included in the clinical study database.

Any SAE that occurs after the end of study visit that is considered to be causally related to rIX-FP must be **reported immediately (ie, within 24 hours of the investigator becoming aware of the event) to CSL**. ***For Japan sites only, the investigator must also inform the head of the medical institution of the SAE and related information in accordance with the Japanese regulatory requirements and ICH GCP.***

Contact details and guidance for reporting SAEs will be provided to study site before the study starts.

9.6.1 Requirements for Immediate Reporting of Serious Adverse Events

The minimum reporting requirements for immediate reporting of SAEs include:

- Identifiable subject.
- Suspected medicinal product and / or procedure.
- Event term.
- Identifiable reporting source.

In addition, the investigator must:

- Report all SAEs to the relevant Institutional Review Board (IRB) / Independent Ethics Committee (IEC) within the timeframe specified by the IRB / IEC.
- Submit follow-up reports to CSL Clinical Safety and Pharmacovigilance until the SAE has resolved, or, in the case of permanent impairment, until stabilized.
- Ensure that the causality assessment for all SAEs is entered in the eCRF.

If the minimum requirements for reporting are fulfilled, the investigator should not wait to receive additional information to fully document the event before notifying CSL.

When submitting SAE reports and any other related reports (eg, discharge summaries) to CSL, subjects should be identified only by their subject number and study number. The investigator should not include the subject's name, date of birth, or address.

In cases of death, the investigator should supply CSL and the IRB / IEC (as applicable) with any additional information as it becomes available (eg, autopsy reports and detailed medical reports).

The procedure to be followed if an ongoing AE becomes an SAE after the end of the observation period for AEs is described in Section 9.9.

9.7 OTHER SIGNIFICANT EVENT REPORTING

9.7.1 Overdose

Any overdose that is considered by the investigator to be medically significant and resulting in adverse signs and symptoms must be reported as an SAE (see Section 9.6).

9.7.2 Pregnancy and Lactation

The subject must immediately notify the investigator if his female partner becomes pregnant while participating in the study, or up to and including 30 days after the last dose of rIX-FP.

CSL must be notified within 5 days of the investigator becoming aware of the pregnancy. Whenever possible, a pregnancy in a female partner of a male subject exposed to rIX-FP should be followed to term so as to assess any potential occurrence of congenital anomalies or birth defects. Any follow-up information, including premature termination and the status of the mother and child after delivery, should be reported by the investigator to CSL using a Pregnancy Reporting / Outcome Form.

9.8 IRB / IEC REPORTING REQUIREMENTS

The time frame within which an IRB / IEC must be notified of deaths and investigational product-related unexpected SAEs is stipulated by each IRB / IEC. It is the investigator's responsibility to comply with the requirements for IRB / IEC notification. CSL will provide investigators with all details of all SAEs reported to regulatory authorities.

9.9 FOLLOW-UP OF ADVERSE EVENTS

Every effort should be made to follow-up subjects who continue to experience an AE or an SAE on completion of the study until either the AE resolves or there has been a period of 30 days after the final administration of rIX-FP during this study. All follow-up information (and attempted follow-up contacts) should be documented in the subject's medical records. Details of the subject's progress should also be submitted to CSL Global Clinical Safety and Pharmacovigilance.

10. ASSESSMENTS

10.1 SUBJECT CHARACTERISTICS

Subject characteristics to be evaluated will include:

- Demographic data.
- Medical and surgical history.
- Treatment history (rIX-FP or other FIX).

10.2 EFFICACY ASSESSMENTS

The efficacy of rIX-FP treatment in the prevention and treatment of bleeding episodes will be assessed based on the following:

- Total consumption of rIX-FP (number of EDs and mean IU/kg per year per subject and per bleeding episode) and consumption per routine prophylaxis, prevention before physical activity, and on-demand treatment.
- Number of spontaneous and total bleeding episodes and corresponding ABRs per treatment interval.
- Investigator's overall clinical assessment of hemostatic efficacy for treatment of major bleeding episodes.
- Number of rIX-FP injections required to achieve hemostasis.

10.3 SAFETY ASSESSMENTS

Safety will be assessed based on the following variables:

- Inhibitors against FIX.
- AEs and SAEs.
- Local tolerability.
- Serum biochemistry and hematology.
- Physical examination.
- Vital signs.
- Antibodies against rIX-FP.

- Antibodies against CHO cell-derived proteins.

Clinical laboratory tests will be performed at time points as detailed in the Table A - Schedule of Assessments: Treatment Period. More frequent evaluations may be performed, if clinically indicated, at the discretion of the investigator.

10.4 PHARMACOKINETIC AND PHARMACODYNAMICS

10.4.1 Pharmacokinetic Analyses

10.4.1.1 Trough factor IX activity level

During the study, blood samples will be taken for the assessment of trough FIX activity level at each major bleeding episode (if feasible) and the specified visits.

10.4.1.2 Pharmacokinetic Evaluation of rIX-FP

In addition, subjects beginning routine prophylaxis treatment using a treatment interval of 21 days (not applicable for subjects in France) for the first time and subjects in Arm 3, will undergo a PK evaluation with a single injection of rIX-FP (100 IU/kg). For this PK evaluation, blood samples will be taken for the measurement of the FIX activity level at the following time points (required or optional; see Section 8.9.8) after injection.

- 30 ± 5 minutes
- 72 ± 24 hours (ie, 3 ± 1 days)
- 168 ± 24 hours (ie, 7 ± 1 days)
- 336 ± 24 hours (ie, 14 ± 1 days)
- 504 ± 24 hours (ie, 21 ± 1 days) (not applicable for subjects in France)

If during the PK assessment period, a subject experiences a bleeding episode, no further blood samples will be taken as part of PK assessment, regardless of whether the bleeding episode is treated or not. The PK may or may not need to be repeated.

A PK evaluation of 50, 75, or 100 IU/kg rIX-FP (with selected time points) may also be assessed (for Arm 4 subjects 50 IU/kg only), at the investigator's discretion or CSL's request,

in the event of (but not limited to) poor efficacy, suspicion of inhibitor development, or before major surgery.

The incremental recovery and FIX activities will be reported. Additional PK parameters (eg, AUC, $t_{1/2}$) may be calculated, if deemed appropriate.

10.4.2 Pharmacodynamic Analyses

Not applicable.

10.4.3 Pharmacokinetic / Pharmacodynamic Relationships

Not applicable.

10.4.4 Pharmacokinetic Analyses (Subcutaneous Substudy)

See Appendix 2.

10.5 OTHER ASSESSMENTS

Other assessments to be made during the study include:

- A hemophilia-specific treatment satisfaction questionnaire (Hemo-Sat) will be completed by parents or caregivers of subjects from the CSL654_3002 lead-in study.
- CCI
- Social and physical activity.

11. STATISTICS

11.1 SAMPLE SIZE ESTIMATION

The choice of sample size for this study is not based on statistical power considerations. This study will enroll approximately 96 subjects, including all eligible subjects from rIX-FP lead-in

studies and approximately 10 subjects requiring major non-emergency surgery who have not previously received treatment with rIX-FP and at least 13 PUPs. The target is at least 50 subjects completing 100 EDs during enrollment in all CSL-sponsored rIX-FP studies, as per the European Medicines Agency guidelines [EMA, 2009].

11.2 DESCRIPTION OF ANALYSIS DATASETS

11.2.1 Pharmacokinetic Population

The PK population will comprise subjects who have received at least 1 dose of rIX-FP and have blood samples drawn for PK assessment. For the PK parameter assessment of the 100 IU/kg rIX-FP dose, subjects will be excluded from analysis if an insufficient number of analyzable PK samples were obtained to permit the evaluation of at least 1 PK parameter for rIX-FP, excluding samples obtained after receiving a dose of rIX-FP or any other FIX product for the treatment of a bleeding episode during the PK sampling period.

11.2.2 Safety Population

The safety population will consist of all subjects who received at least 1 dose of rIX-FP in this extension study.

11.2.3 Efficacy Population

The efficacy population will consist of all subjects in the safety population who participate in the non-surgical efficacy portion of the study.

11.2.4 Per-protocol Population

The per-protocol (PP) population will include all subjects in the efficacy population who complete the study without any major protocol deviations that would affect the assessment of the efficacy endpoints. In some cases, subjects may be retained in the PP population with partial data up to the point of a major deviation.

11.2.5 Surgical Population

The surgical population, which is a subset of the safety population, will include all subjects who have received at least 1 dose of rIX-FP for a surgical procedure in this study.

11.2.6 Subcutaneous Population

The SC population, which is a subset of the safety population, will include all subjects who have received at least 1 SC dose of rIX-FP in the SC substudy.

11.3 STATISTICAL ANALYSES AND METHODS

All safety and efficacy data will be summarized. Unless otherwise indicated, all summaries and analyses will be based on the experience of subjects in this study only and not on the combined experience in this plus lead-in studies. Continuous data will be summarized using descriptive statistics including means, standard deviations, medians, first and third quartiles, and minimums and maximums. Categorical variables will be summarized with frequencies and percentages.

Unless otherwise indicated, baseline is defined as the Day 1 visit in this study. In general, only available data will be used in summaries and analyses unless otherwise specified in the Statistical Analysis Plan (SAP).

A complete description of the statistical analyses and methods will be provided in an SAP, which will be finalized before the database is locked.

Note: The planned statistical analyses for the SC substudy are detailed in Appendix 2.

11.3.1 Subject Disposition and Characteristics

11.3.1.1 Subject Disposition

The number of subjects who enrolled into this study, who completed the study, who discontinued the study, who completed 100 EDs, and who failed to complete 100 EDs in this

study by reason for discontinuing the rIX-FP or withdrawing from the study, will be presented in summary tables. The reason for discontinuing the rIX-FP or withdrawing a subject from the study will be listed by subject. The number of subjects in each analysis population will be summarized overall.

11.3.1.2 Subject Characteristics

Demographics and baseline subject characteristics at the time of enrollment in this study will be presented in summary tables and data listings. Select information such as medical history at enrollment and treatment regimen at end of study, will also be presented in summary tables to help characterize the subject population in this study. The data source for these additional summaries will be the datasets used to report final results (details on the choice of variables and their source will be provided in the SAP).

11.3.2 Efficacy Analyses

All efficacy summaries and analyses for non-surgical efficacy data will be performed on the efficacy population. Additional analyses may be performed on the PP population. Where noted here or in the SAP, overall summaries may be further broken down by lead-in study (and by Arm in Study CSL654_3001) or new subjects, age group, or geographic region.

Efficacy summaries and analyses of surgical data will be performed on the surgical population.

11.3.2.1 Primary Efficacy Analysis

This study does not have a primary efficacy endpoint since the evaluation of efficacy is not a primary objective.

11.3.2.2 Secondary Efficacy Analyses

The AsBR and ABR will be derived for each treatment interval assigned to the subject (7 days, 10 days, 14 days, and 21 days), and will not include the time either during or the first 3 months after the surgery substudy, the time during the SC substudy, and subjects in Arm 4. Rates will be calculated as the number of applicable bleeding episodes divided by the total duration the

subject was assigned prophylaxis treatment for the given treatment interval. Disjoint periods of observation with the same treatment interval may be combined within a subject for those periods when the subject was treated for at least 3 months to insure stable treatment. Duration of treatment for each period will begin when the subject receives the first dose of the assigned prophylaxis regimen. ABRs will be summarized across subjects using descriptive statistics. A crude rate will also be calculated for each treatment interval along with an exact two-sided 95% confidence interval under the assumption that counts follow a Poisson distribution with common underlying intensity.

AsBR and ABR are considered secondary endpoints in this study. Other types of bleeding episodes (eg, traumatic) will be summarized in a similar manner as these secondary endpoints.

A comparison of AsBR and ABR will be performed between 14-day routine prophylactic treatment in this study compared with on-demand only treatment from Study CSL654_3001 (Arm 2). A Wilcoxon rank sum test will be performed on the matched-pairs at the two-sided 0.05 level to test the hypothesis that the median difference in rates differs from zero. Descriptive statistics will also be provided.

The analysis of AsBR will also be conducted with subjects from both Study CSL654_3001 and the present extension study to assess whether a similar treatment effect exists between the 7-day prophylaxis regimen and the 14-day prophylaxis regimen.

In order to demonstrate that a similar treatment effect also exists for the 14-day prophylaxis regimen and 7-day prophylaxis regimen, the mean AsBR will be compared between the 2 prophylaxis regimens to evaluate non-inferiority. Following the same clinically acceptable difference used in the CSL654_3001 study, a non-inferiority margin of 6 spontaneous bleeds/year has been selected.

The null and alternative hypotheses for the AsBR are as follows:

$H_{0:}\ \mu_{7\text{-day}} - \mu_{14\text{-day}} \leq -6$

$H_{1:}\ \mu_{7\text{-day}} - \mu_{14\text{-day}} > -6$

To establish non-inferiority of the 14-day regimen versus the 7-day regimen for the AsBR, the lower confidence limit of the 95% confidence interval, based on a one-sample (paired) t-distribution, for the difference between the two means (7-day regimen - 14-day regimen) must be greater than -6 spontaneous bleeds/year.

The same analysis will be conducted for the comparison of ABR. The clinical difference of 6 total bleeds/year is selected when switching from 7-day prophylaxis regimen to 14-day prophylaxis regimen. Futhermore, the non-inferority analysis of AsBR and ABR between the extended regimens (14-day or 10-day) and the 7-day regimen will be conducted in a similar manner.

Similar comparisons of ABR and AsBR between treatment regimens will also be conducted for the subgroup of pediatric subjects.

Multiple comparisons and multiplicity: A fixed-sequence multiple testing procedure will be used to control the overall Type I error rate at the two-sided 0.05 level for the secondary efficacy analysis. Specifically, the test between 14-day prophylaxis regimen and On-demand will first be performed at the two-sided 0.05 level of significance. Only if the 14-day regimen is found to be effective, will the 14-day prophylaxis regimen be non-inferior to 7-day prophylaxis regimen at pre-specified margin. Only if 14-day prophylaxis regimen is demonstrated non-inferior to the 7-day regimen, will the extended prophylaxis regimen (10-day or 14-day) be non-inferior to the 7-day regimen.

Consumption of rIX-FP will be summarized with descriptive statistics according to treatment interval and overall. No formal statistical inferences will be performed on these summary measures. Standardized yearly totals will be calculated for each subject by dividing the subject's observed total by total duration (days/365.25 days per year); standardized monthly totals will be calculated by dividing the yearly estimate by 12. Calculation of duration will begin on the date of the first prophylactic injection at the assigned treatment interval. Periods when the subject is not receiving routine prophylaxis (surgery substudy, SC substudy) or

treatment for any bleeding episodes including preventative injections, will not be included in summaries of consumption or in the calculation of ABRs.

Five measures of consumption will be reported: number of injections per subject (per month and per year), IU/kg per subject (per month and per year), and IU/kg per event. One measure is identified as a secondary endpoint in this study: IU/kg per month per subject for routine prophylaxis treatment. All measures will be summarized by treatment modality (continuous prophylaxis, intermittent prophylaxis, on-demand treatment, and total) and by lead-in study. Additionally, IU/kg per subject will be summarized by geographic region. Other related measures may be reported, such as total IUs per subject, as specified in the SAP.

Investigator assessment of hemostatic response to treatment of bleeding episodes in Arm 4 subjects will be summarized using descriptive statistics.

CCI

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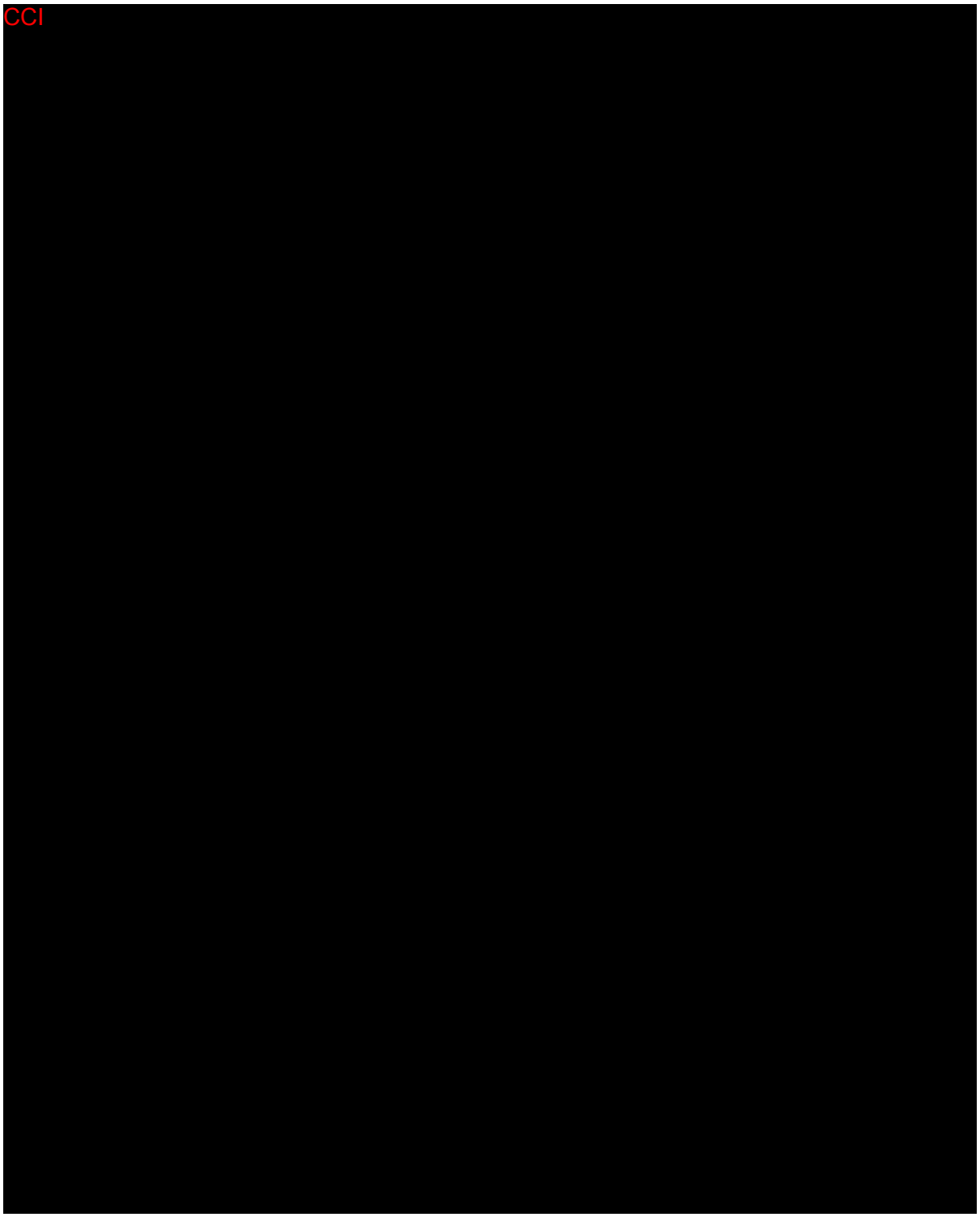

11.3.2.4 Additional Efficacy Information from the Surgery and Subcutaneous Substudies

Surgical data will be summarized as case narratives or with descriptive statistics or counts where appropriate.

The investigator's overall clinical assessment of hemostatic efficacy for surgical prophylaxis, based on the four point ordinal scale (excellent, good, moderate, poor/none), will be presented.

The change in hemoglobin level between baseline and nadir-intra- and post-operation may be presented.

A comparison of the pre-operative predicted surgical blood loss (average and maximum) for a non-hemophilic individual undergoing the same type and extent of surgical procedure and the estimated interoperative blood loss may be presented. Additionally, a comparison of pre-operative predicted transfusion requirements for a non-hemophilic individual undergoing the same type and extent of surgical procedure and the actual transfusion may be presented.

Additional surgical displays will include the type of surgery, the relationship to hemophilia (related / not related), rIX-FP consumption (including dose regimen, IU and IU/kg per dose, and time relationship for each injection during the surgery substudy and per surgery), and complications.

No additional efficacy data will be obtained from the SC substudy.

11.3.3 Safety Analyses

Safety summaries will be performed on the safety population unless otherwise specified. No formal statistical comparisons will be made unless specified.

11.3.3.1 Primary Safety Analysis

The number and proportion of subjects with positive tests for inhibitors to FIX during the study will be tabulated. Subjects must have two tests that are positive to be classified as having an

inhibitor. Inhibitor antibodies against FIX will be categorized as low titer (≥ 0.6 to 5 BU/mL) and high titer (> 5 BU/mL). A two-sided 95% exact Clopper-Pearson binomial confidence interval (one-sided if no events are observed) for inhibitor development among subjects treated with rIX-FP, by PTP and PUP, will be presented.

11.3.3.2 Adverse Events

Adverse events will be recorded from the time when informed consent is granted at the start of this extension study until study completion (or the end of study visit upon early termination). In this study, study-emergent AEs are defined as those with onset on or after Day 1 in this extension study.

Adverse events will be coded using the Medical Dictionary for Regulatory Activities (MedDRA). The number and percentage of subjects who experience AEs will be summarized overall by system organ class (SOC) and preferred term (PT) and will also be summarized based on maximum severity and relationship to rIX-FP.

Descriptive analysis of AEs will include:

- Incidence of study-emergent AEs, AESIs and SAEs grouped by SOC and PT.
- Incidence of study-emergent AEs, grouped by SOC and PT, with reference to the relationship to rIX-FP and maximum severity.
- Incidence of study-emergent AEs leading to withdrawal grouped by SOC and PT.
- Incidence of related AEs to rIX-FP over the course of the study.

Individual listings of all AEs will also be provided.

Serious AEs, deaths, and discontinuations due to AEs will be summarized and supported by individual subject data listings.

A summary of study-emergent AEs by SOC and PT will be provided by treatment interval. Subjects who change the frequency of dosing during the duration of this extension study may be counted more than once in this summary.

11.3.3.3 Local Tolerability

Local tolerability will be assessed via the frequency and severity of reported local reactions including the subject assessment and investigator assessment.

11.3.3.4 Laboratory Safety Parameters

Laboratory results along with the change from baseline will be summarized by parameter and study visit. The change from baseline to the smallest value after first dose of study product, largest value after first dose of study product, and final value will also be summarized. For laboratory parameters with positive or negative results, the number and proportion with positive study-emergent results will be summarized at each visit.

The number and proportion of subjects with study-emergent abnormal laboratory values will be tabulated. Study-emergent abnormal laboratory values are those in which the baseline value is normal and post-baseline value is abnormal. Laboratory values will be converted to the project-defined unit of measurement.

11.3.3.5 Vital Signs

Vital signs results along with the change from baseline will be summarized by parameter and study visit. The number and proportion of subjects with study-emergent potentially clinically significant vital sign values by study visit (blood pressure, heart rate, and body temperature) will be tabulated. Criteria for potentially clinically significant values will be documented in the SAP.

11.3.3.6 Virus Safety

Results from virus safety samples (if tested) will be displayed in a listing.

11.3.3.7 Inhibitors to Factor IX

The number and proportion of subjects with a confirmed FIX inhibitor titer above the cut-off level (≥ 0.6 BU/mL) will be tabulated.

11.3.3.8 Antibodies to rIX-FP and CHO Cell-derived Proteins

The number and percentage of subjects with rIX-FP and CHO cell-derived protein antibody titers above the cut-off level for the respective confirmation assays will be tabulated.

11.3.3.9 Additional Safety Information from the Surgery and Subcutaneous Substudies

Safety assessments and events, including AEs, which occur during the protocol-defined preoperative, intraoperative, or postoperative periods of the surgery substudy and in the SC substudy will be summarized in separate tables.

11.3.4 Pharmacokinetics and Pharmacodynamic Data

11.3.4.1 Pharmacokinetics

In the main study, incremental recovery will be calculated using the PK samples obtained following injection of 100 IU/kg rIX-FP or 50 IU/kg rIX-FP for subjects in Arm 4. Incremental recovery (IU/mL per IU/kg) is defined as FIX activity (IU/mL) obtained 30 minutes following injection, per dose of (IU/kg) injection. Incremental recovery and FIX activity levels will be summarized.

FIX activity levels from central and local laboratories will be summarized with descriptive statistics and listed by subject and assessment. Trough levels, if available, will be summarized by treatment interval.

See Appendix 2 for details on the PK analyses in the SC substudy.

11.3.4.2 Pharmacodynamics

Not applicable.

11.3.5 Other Analyses

Subgroup analyses may be performed, and these will be specified in the SAP.

11.3.6 Interim Analysis

No interim analyses are planned. The following analyses are planned before study closure:

1. The final analysis of the SC substudy data will be conducted when all subjects have completed the SC substudy.

2. The final analysis of PTPs (including surgical data from PTPs) will be conducted when all PTPs have completed the study.

In addition, safety, efficacy and / or PK data and subject characteristics may be reported to regulatory authorities before study closure.

12. QUALITY ASSURANCE

The study may be subject to an audit by CSL, an authorized representative(s) of CSL and / or inspections by an authorized regulatory authority (eg, US Food and Drug Administration [FDA]). Regulatory authorities may request access to all study documentation, including source documents for inspection and copying, in keeping with local regulations. CSL will immediately notify the investigator of an upcoming audit / inspection.

In the event of an audit, all pertinent study-related documentation must be made available to the auditor(s). If an audit or inspection occurs, the investigator at each study site will permit the auditor / inspector direct access to all relevant documents and allocate their time as well as the time of relevant staff to discuss the findings and any relevant issues.

13. REGULATORY AND ETHICS CONSIDERATIONS

13.1 REGULATORY CONSIDERATIONS

CSL or its agents will submit the appropriate documents to the local regulatory agencies and will await approval before study start.

This study will be conducted under a Clinical Trial Application, a Clinical Trial Notification or an FDA Investigational New Drug application, as appropriate and documented in accordance with the applicable regulatory guidelines and requirements.

The procedures set out in this study protocol are designed to ensure that CSL and the investigator abide by the principles of the current ICH GCP guideline on the conduct, evaluation and documentation of this study, as described in ICH Topic E6 (Guideline for GCP). The study will also be carried out according to all applicable international and national regulatory requirements.

13.2 Institutional Review Board / Independent Ethics Committee

The investigator must submit the protocol and informed consent forms (ICFs) for review by an authorized and properly constituted (according to local guidelines) IRB / IEC. Written approval must be received from the IRB / IEC before commencement of the study.

13.3 SUBJECT INFORMATION AND INFORMED CONSENT

The principles of informed consent in the Declaration of Helsinki must be implemented in this clinical study before protocol-specified procedures are carried out. Information should be given in both oral and written form whenever possible and deemed appropriate by the IRB / IEC. Subjects, their relatives (or if necessary, legally acceptable representatives) must be given ample opportunity to inquire about details of the study.

Should there be any amendments to the protocol that would directly affect the subject's participation in the study (eg, a change in any procedure), the ICF must be amended to incorporate this modification. Subject must be informed of the change and they must sign the amended ICF indicating that they re-consent to participate in the study.

13.4 SUBJECT IDENTIFICATION AND CONFIDENTIALITY

All subject names and contact details will be kept confidential. Subjects will be identified throughout documentation and evaluation by the number allotted to them during the study. Each subject will be told that all study findings will be handled in the strictest confidence.

The investigator at the study site will be responsible for retaining sufficient information about each subject (eg, name, address, phone number and identity in the study) so that regulatory agencies or CSL may access this information should the need arise. These records should be retained in a confidential manner as long as legally mandated according to local requirements.

Subject medical records pertaining to the study may be inspected / audited at any time by CSL employees or their duly authorized representatives, a regulatory authority or the IRB / IEC. All records accessed will be strictly confidential. Consent to participate in the study includes consent to these inspections / audits.

13.5 INDEMNITY AND COMPENSATION

It is CSL policy that persons who participate in CSL's clinical studies should be no worse off for their having been involved in the study. These persons include the subjects / volunteers, the investigator, the hospital and the IRB / IEC.

CSL has taken out insurance to cover its obligations under both the Indemnity and the Compensation guidelines for injury to subjects involved in the study.

Other details regarding compensation and the obligations of the investigator / CSL are provided in the Clinical Trial Agreement for the study (see Section 14.1).

14. ADMINISTRATIVE CONSIDERATIONS

14.1 CLINICAL TRIAL AGREEMENT

This study will be conducted under a Clinical Trial Agreement between CSL ("Sponsor") and the institution(s) representing the investigational study site(s) ("Authority"). Financial support

to the investigational site(s) will be detailed in the Clinical Trial Agreement. The Clinical Trial Agreement must be signed before the commencement of the study and will clearly delineate the responsibilities and obligations of investigator and CSL, and will form the contractual basis under which the clinical study will be conducted.

14.2 CLINICAL STUDY REGISTRATION AND RESULTS DISCLOSURE

CSL will provide the relevant study protocol information in public database(s) before or at commencement of the study. CSL may also provide study information for inclusion in national registries according to local regulatory requirements.

Results of this study will be disclosed according to the relevant regulatory requirements. All publications in peer-reviewed medical journals resulting from this study will be listed in the original study protocol registration record.

14.3 IMPLEMENTATION OF THE PROTOCOL / PROTOCOL AMENDMENT(S)

With the exception of medical emergencies, no changes or deviations in the conduct of the signed protocol will be permitted without documented approval of the CSL Medical Monitor and the IRB / IEC. In the event of a medical emergency, the investigator at the study site will institute any medical procedures deemed appropriate. However, all such procedures must be promptly reported to the CSL Medical Monitor and the IRB / IEC.

Modifications to the protocol that may affect subject safety or the way the study is to be conducted will be documented in a protocol amendment, which must be approved by the IRB / IEC.

Administrative changes to the protocol, defined as minor corrections and / or clarifications that have no effect on the way the study is to be conducted, will not require IRB / IEC approval, but will be submitted to the IRB / IEC for their information.

14.4 PROTOCOL DEVIATIONS

All instances where the requirements of the study protocol were not complied with will be tracked. Corresponding subjects may be withdrawn from the study at the discretion of the investigator and / or CSL. Study protocol deviations arise when subjects who have been entered in the study deviate from the IRB / IEC-approved study protocol.

If a major protocol deviation (ie, a deviation that could have a significant effect on the subject's safety, rights, or welfare and / or on the integrity of the study data) occurs, the investigator must notify CSL and the appropriate IRB / IEC as soon as possible or as per local requirements.

14.5 DOCUMENTATION AND RECORD KEEPING

14.5.1 Data Collection

The investigator (or delegate) will maintain individual records for each subject. These records should include dates when a subject visited the study site, records of vital signs, medical history, or physical examinations, administration of rIX-FP or concomitant therapy, any AEs experienced, and other notes as appropriate. These records constitute source data.

An eCRF will be provided by CSL (or delegate) for each subject enrolled into the study. The investigator is responsible for ensuring accurate and proper completion of the eCRF in a timely manner so that it always reflects the latest observations on the subjects enrolled in the study. All entries on the eCRF must be backed up by source data unless there is prior agreement that the eCRF is the source data.

All source data will be kept according to all applicable regulatory requirements. Source data must be completed legibly for each subject enrolled into the study and signed by the investigator (or delegate).

The subject eDiary will be completed by the subject, or caregiver, at home. Data entered into the eDiary constitute electronic source data. At each clinic / telephone visit, the investigator will review the eDiary entries with the subject.

14.5.2 Data Quality Assurance

Data generated throughout the study will be monitored and the eCRFs checked against the subject records for completeness and accuracy. CSL's study monitor (or delegate) will perform this function.

Following completion of eCRF pages and entry of the data into a database, the data will be checked electronically for consistency and plausibility. Queries will be generated for questionable data and clarification sought from the investigator. These data queries must be resolved in a timely manner by the investigator (or delegate).

14.5.3 Record Retention

An investigator study file prepared by CSL (or delegate), containing all applicable documents for use at the study site, will be made available to the investigator before the start of the study. All study documentation and materials maintained in the investigator study file must be kept in conformance with applicable national laws and regulations.

All study documentation and materials maintained in the investigator study file at the study site must be available for inspection by the CSL's study monitor (or delegate) to determine that all required documentation is present and correct.

The study may be audited or inspected by qualified delegates from CSL or a competent regulatory authority.

Following completion of the study, the investigator is responsible for archiving the investigator study file, the subject's records and the source data according to applicable regulatory requirements.

14.6 STUDY AND SITE CLOSURE

CSL reserves the right to prematurely discontinue or suspend the study either at a particular site or at all study sites at any time and for any reason. If such action is taken, the CSL Study

Monitor (or delegate) will discuss this with the investigator (*for Japan sites only: the head of the medical institute*) at each study site at that time and notify them in writing. If the study is suspended or terminated for safety reasons all investigators (*for Japan sites only: the heads of the medical institutes*) and the relevant regulatory agencies will be immediately notified of the action as well as the reason for it. The investigator (*for Japan sites only: the head of the medical institute)* at each study site will advise the IRB / IEC overseeing the study at their site.

14.7 CLINICAL STUDY REPORT

A final clinical study report will be written after the completion of the study. In addition, study reports will be written when a) all subjects have completed the SC substudy and b) when all PTPs have completed the study (see Section 11.3.6). These reports will be integrated into the final clinical study report.

CSL or its agent will write the report in consultation with the investigator or, if applicable, a nominated coordinating investigator (or delegate). It is required by CSL that the coordinating investigator will sign the clinical study report.

Progress reports may be provided to the relevant regulatory bodies in accordance with their requirements.

14.8 USE OF DATA AND PUBLICATIONS

The rights and obligations of investigators and CSL concerning any formal presentation or publication of data collected as a direct or indirect result of this study will be addressed specifically in the Clinical Trial Agreement for the study.

15. REFERENCES

Giangrande P. Hemophilia B: Christmas disease. Expert Opin Pharmacother. 2005;6:1517-24.

Guideline on clinical investigation of recombinant and human plasma-derived factor IX products, 21 July 2011, EMA/CHMP/BPWP/144552/2009.

McCarthy K, Stewart P, Sigman J, et al. Pharmacokinetics of recombinant FIX after intravenous and subcutaneous administration in dogs and cynomolgus monkeys. Thromb Haemost. 2002;87:824-30.

Metzner HJ, et al. Genetic fusion to albumin improves the pharmacokinetic properties of factor IX. Thromb Haemost. 2009;102:634-44.

Srivastava A, Brewer, AK, Mauser-Bunschoten, EP, et al. WFH guidelines: Guidelines for the management of haemophilia. Haemophilia 2013;19:e1-e47.

Study 8244656. Nonclinical study report. rIX-FP and rIX-FP-B: Single dose intravenous (bolus) administration toxicity study in the rat followed by a 5 day treatment-free period. 2011.

Study 040200011. Nonclinical study report. rIX-FP: Single dose pharmacokinetic and pharmacodynamic study by Intravenous (bolus) administration to hemophilia B dogs. 2010.

Study APQ0001. Nonclinical study report. rIX-FP: Toxicity study by intravenous (bolus) administration to cynomolgus monkeys for 4 Weeks. 2010.

Study APQ0002. Nonclinical study report. rIX-FP: Single dose pharmacokinetic study by intravenous (bolus) administration to cynomolgus monkeys. 2010.

Study APQ0005. Nonclinical study report. rIX-FP: Single dose toxicity study by intravenous (bolus) administration to CD rats. 2010.

Study APQ0008. Nonclinical study report rIX-FP: Local tolerance study in the rabbit following intravenous, intra-arterial or perivenous injection. 2010.

Study APQ0009. Nonclinical study report. rIX-FP: Toxicity study by intravenous (bolus) administration to CD rats for 4 weeks followed by a 2 week recovery period. 2010.

Study NBM 04/09. Nonclinical study report. Correction of hemostasis in FIX ko mice following treatment with rIX-FP. 2010.

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Study CSL654_2001. Clinical study report. An open-label, multicenter, dose-escalation safety and pharmacokinetic study of a recombinant coagulation FIX albumin fusion protein (rIX-FP) in subjects with hemophilia B. December 2011.

Study CSL654_2004. Clinical study report. A phase 1/2 open-label, multicenter, safety and efficacy study of a recombinant coagulation factor IX albumin fusion protein (rIX-FP) in subjects with hemophilia B. August 2012.

Study CSL654_3001. Clinical study report. A phase 2/3 open-label, multicenter, safety and efficacy study of a recombinant coagulation factor IX albumin fusion protein (rIX-FP) in subjects with hemophilia B. November 2014.

Study CSL654_3002. Clinical study report. 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. January 2014.

Appendix 1. SURGERY SUBSTUDY

Table of Contents: Surgery Substudy

SCHEDULE OF ASSESSMENTS: SURGERY SUBSTUDY – MAJOR SURGERY

Period	Before Surgery			During Surgery	After Surgery		
Timing		**-3 hours**		**N/A**	**0 hours**	**Every 24 hours up to 72 hours or discharge [A]**	**End of Substudy Day 28 [B]**
Time Window	Up to 28 days before	-6 hours			+6 hours	± 6 hours	± 7 days
Eligibility assessment		X					
Surgery description		X					
Physical examination		X			X	X	X
Vital signs		X		X	X	X	X
Body weight		X					
Hematology [C]		X		X	X	X	X
Plasma FIX activity [D]	X [E]		X [F]	X [G]	X [G]	X [G]	X
FIX inhibitors [H]	X						X
antibodies against rIX-FP [H]	X						X
Planned rIX-FP dose	X						
Blood loss estimate	X				X		
Hemostatic intervention [I]	X			X	X	X	
Administer rIX-FP [J]		X		X [G]	X [G]	X [G]	
Hemostasis assessment [K]					X	X	
Efficacy assessment					X	X	
Adverse events	X	<----------On an ongoing basis---------->					
Concomitant therapy	X	<----------On an ongoing basis---------->					

FIX = coagulation factor IX; N/A = not applicable; rIX-FP = recombinant coagulation factor IX albumin fusion protein.

Notes to the Schedule of Assessments: Surgery Substudy – Major Surgery

A: Assessments to be completed every 24 hours up to 72 hours or up to hospital discharge, whichever occurs first.

B: Assessments to be completed at end of surgery substudy for all subjects (Day 28). This visit is also the Day 1 visit for subjects in Arm 3, if they choose to remain in the main study after surgery.

C: Hematology assessments (local laboratory) include: hemoglobin, hematocrit, platelet count, red blood cell (erythrocyte) count, white blood cell (leukocyte) count, white blood cell differential (optional).

D: Plasma FIX activity will be assessed by both the local laboratory and a central laboratory.

E: Assessment is not required if the FIX recovery rate has been assessed within the previous 28 days or for subjects in Arm 3.

F: Blood samples will be taken between ~30 minutes after the administration of rIX-FP and before major surgery (timing dependent on the time required for the local laboratory to process the sample).

G: If an additional injection of rIX-FP is needed during the perioperative period, a blood sample should be taken before the administration of rIX-FP for the assessment of FIX activity by the local laboratory.

H: To be completed only for subjects in Arms 1 or 2.

I: Planned and actual hemostatic interventions or transfusions other than rIX-FP (eg, whole blood, red blood cells, fresh frozen plasma or platelets).

J: Additional injections of rIX-FP may be needed to maintain the required plasma FIX activity level. Blood samples should be taken and tested for plasma FIX activity before each injection of rIX-FP, if feasible, so that the required dose can be calculated based on the plasma FIX activity.

K: Hemostasis assessment includes: quantitation of postoperative bleeding through surgical drains and the occurrence of late rebleeding episodes; the presence and extent of any surgical wound hematomas and whether they require surgical evacuation.

SCHEDULE OF ASSESSMENTS: SURGERY SUBSTUDY – MINOR SURGERY

Period	Before Surgery			During Surgery	After Surgery		
Timing	**-3 hours**			**N/A**	**0 hours**	**At Discharge**	**End of Substudy**
Time Window	Up to -6 hours				+6 hours	± 6 hours	
Eligibility assessment	X						
Surgery description	X						
Physical examination					X	X	X
Vital signs					X	X	X
Body weight	X						
Plasma FIX activity [A]	X [B]		X [B]	X [C]	X [C]	X [C]	X
Sample for FIX inhibitors							X
Sample for antibodies against rIX-FP							X
Blood loss estimate			X		X		
Hemostatic intervention [D]			X	X			
Planned rIX-FP dose during surgery			X				
Administer rIX-FP		X		X [C]	X [C]	X [C]	
Hemostasis assessment [E]					X	X	
Efficacy assessment					X	X	
Adverse events	X	<----------On an ongoing basis---------->					
Concomitant therapy	X	<----------On an ongoing basis---------->					

FIX = coagulation factor IX; N/A = not applicable; rIX-FP = recombinant coagulation factor IX albumin fusion protein.

Notes to the Schedule of Assessments: Surgery Substudy – Minor Surgery

A: Plasma FIX activity may be assessed by the local laboratory and / or the central laboratory.
B: Blood samples (optional) may be taken before and ~30 minutes after rIX-FP administration to confirm the incremental recovery.
C: Additional injections of rIX-FP may be needed to maintain the required plasma FIX activity level. Blood samples should be taken and tested for plasma FIX activity before each injection of rIX-FP, if feasible, so that the required dose can be calculated based on the plasma FIX activity.
D: Planned and actual hemostatic interventions or transfusions other than rIX-FP (eg, whole blood, red blood cells, fresh frozen plasma or platelets.
E: Hemostasis assessment includes estimated actual intraoperative blood loss, blood loss expected as integral to the procedure and unexpected blood loss due to unforeseen complications.

INTRODUCTION

This substudy of Study CSL654_3003 will examine the efficacy of rIX-FP in patients with hemophilia B who are undergoing non-emergency major or minor surgery. Efficacy will be measured in both the intraoperative and postoperative periods. In addition, safety endpoints, including antibodies against rIX-FP, inhibitors to FIX and other AEs throughout the duration of the study in all study subjects will be monitored.

The substudy will be conducted in compliance with this study protocol, ICH GCP, and the applicable regulatory requirement(s).

STUDY OBJECTIVES AND ENDPOINTS

Primary Objective and Endpoint

Primary Objective

The primary objective of the substudy is to evaluate the efficacy of rIX-FP in the prevention and control of bleeding in patients with severe hemophilia B during surgical procedures.

Primary Endpoint

Investigator's (or surgeon's) overall clinical assessment of hemostatic efficacy for surgical prophylaxis, based on a four point ordinal scale (excellent, good, moderate, poor / none)

Secondary Objective and Endpoints

Secondary Objective

The secondary objective of the study is to evaluate the safety of rIX-FP during the intraoperative and postoperative periods.

Secondary Endpoints

The secondary endpoints of this surgery substudy are:

- The frequency of AEs related to rIX-FP during the intraoperative and postoperative periods.
- The occurrence of FIX inhibitors.
- The occurrence of antibodies against rIX-FP.

- Comparison of predicted and intraoperative estimated blood loss.
- Comparison of predicted and actual transfusion requirements.
- Change in hemoglobin levels between baseline, intraoperatively and postoperatively.

STUDY DESIGN

This is a prospective, open-label substudy to evaluate the efficacy and safety of rIX-FP to prevent bleeding during surgery in patients with congenital FIX deficiency (hemophilia B). The study will consist of intraoperative and postoperative safety and efficacy evaluation periods with rIX-FP. Subjects must meet all of the inclusion criteria of the main study and require non-emergency major or minor surgery. A major surgery is defined as a surgical procedure that involves anesthesia (general, spinal, epidural or regional block), respiratory assistance, or requires hemostatic therapy for periods exceeding 5 consecutive days (including but not limited to orthopedic and cardiac surgery).

Approximately 3 hours before the non-emergency surgical procedure, the subject will receive a single bolus injection of rIX-FP in order to increase the plasma FIX activity level to either 60% to 80%, or higher, as recommended by the WFH for major surgery, or higher if recommended by the guidelines of the local hospital / practice. Additional bolus injections of rIX-FP may be administered during a major surgery, if needed. Blood samples for the determination of FIX levels will be collected before administration of additional doses of rIX-FP, if feasible. During the postoperative period, defined as the start of wound closure, additional bolus injections of rIX-FP may be administered to maintain a required trough FIX activity level as recommended by the WFH, at the investigator's discretion.

Details of the surgical procedure are to be documented as outlined in *Perioperative Prophylaxis for Surgeries*. Efficacy and safety data during and after surgery will be recorded, including time / dose of rIX-FP with documentation of total consumption, investigator's assessments of blood loss and overall efficacy, transfusion requirements and AEs.

Number of Subjects

Any subjects requiring surgery during the course of the main study (CSL654_3003) will be enrolled in the surgery substudy, with a combined target enrollment of at least 5 subjects and 10 major surgeries across the lead-in studies and this study.

Duration

The substudy design includes a 1 to 14 day (or longer, if needed) active treatment period. Subjects will then return to the treatment plan of the main study at Day 28 ± 7 days. The duration of the active treatment period will depend on the type of surgery and local standard.

SELECTION OF SUBSTUDY POPULATION

To be eligible for the substudy, subjects must meet all eligibility criteria of the main study protocol and:

- Must require non-emergency surgery.
- Must provide written informed consent for substudy participation.

ALLOCATION, DOSING AND ADMINISTRATION

Dose and Dosing Rationale

There will be 3 treatment periods in this substudy: preoperative, intraoperative and postoperative. The dose of rIX-FP will be selected based on the subject's PK data obtained during the lead-in study or this (CSL654_3003) study, including incremental recovery and clearance, and the recommendations of the WFH.

The desired FIX increase (% or IU/dL), as recommended by the WFH (see Appendix 3) for the control of bleeding during surgery should be calculated based on an individual subject's PK data using the following formula:

Number of factor IX IU required (IU)	=	Body weight (kg)	X	Desired factor IX increase (% or IU/dL)	X	Reciprocal of observed recovery (IU/kg per IU/dL)

Selection and Timing of Dose for Each Subject in the Substudy

Preoperative treatment

Approximately 3 hours before the start of the scheduled surgery, the subject will be administered 1 bolus injection of rIX-FP. The dose of rIX-FP (50 to 100 IU/kg, or higher) will be selected based on the subject's individual PK parameters, in order to increase the FIX levels to 60% to 80%, or higher.

Intraoperative treatment

The subject may receive intraoperative doses of rIX-FP, depending on the FIX activity levels, type of surgery and local standard of care. FIX activity levels should be measured before major surgery to ensure the trough FIX activity level is maintained at 60% to 80% during major surgical procedures. In the event of the need for repeat dosing during the surgery, the FIX activity level should be measured.

Postoperative treatment

The subject will receive postoperative injections of rIX-FP from 1 to 14 days (or longer, if needed), depending on the FIX activity levels, type of surgery and as recommended by the WFH. FIX activity levels should be measured before repeat dosing. Removal of sutures or drains is best carried out at the time of peak FIX activity level.

CONCOMITANT THERAPY

All drugs currently being taken by a subject after the screening visit, and which continue to be taken during the substudy, are regarded as concomitant therapy and must be documented in the eCRF. Nonpharmacological intervention (eg, physical therapy or a minor surgical procedure performed outside of the surgical substudy) is also regarded as concomitant therapy and must be documented in the eCRF.

The following concomitant therapy is PERMITTED during the study if needed:

- Blood product transfusion (whole blood, erythrocytes [red blood cells], FFP or platelets), documented as planned blood product transfusion before the start of the surgery, if its use is planned.
- Heparin use is limited to 200 U/day, if needed, to maintain patency of IV lines.
- Antifibrinolytic agents.
- Antibiotic and antiviral agents.
- Tranexamic acid or epsilon aminocaproic acid.
- Local hemostatic measures (eg, oxidized cellulose and fibrin glue).
- Standard thrombosis prophylaxis.
- Marketed FIX concentrate may be used ONLY as rescue medication.

As recommend in WFH guidelines, postoperative pain may be managed initially by IV morphine or other narcotic analgesics, followed by an oral opioid. As pain decreases, paracetamol or acetaminophen may be used.

VISIT SCHEDULE

A. Major Surgery

Procedures to be performed before and after major surgery are provided in the Schedule of Assessments: Surgery Substudy – Major Surgery.

The following procedures will be performed **BEFORE** (within 30 minutes preferred, unless otherwise stated) administration of rIX-FP:

- Eligibility assessment.
- Record type of surgery and association (if any) with hemophilia.
- Physical examination.
- Vital signs.
- Body weight.
- Obtain blood sample for hematology (local laboratory).

- Obtain blood samples for measurement of plasma FIX activity before and ~30 minutes after rIX-FP administration to confirm the incremental recovery (up to 28 days before surgery; central and local laboratory).
- Obtain blood samples for:
  - Inhibitors against FIX (up to 28 days before surgery for subjects in Arms 1 or 2; central laboratory).
  - Antibodies against rIX-FP (up to 28 days before surgery for subjects in Arms 1 or 2: central laboratory).
- Review concomitant therapy.
- Review AEs since last visit.
- rIX-FP should be administered approximately 3 to 6 hours before surgery.
- Blood samples for measurement of plasma FIX activity should be collected 30 minutes after administration of rIX-FP and immediately before a major surgery starts. If feasible, the samples should be tested at the local laboratory as well as the central laboratory.

Before surgery, the following estimates must be made by the surgeon or physician performing the procedure:

- Estimate of intraoperative predicted blood loss (PBL) (average and maximum).
- Estimate planned hemostatic intervention (other than rIX-FP).
- Estimate planned transfusion during surgery.
- Estimate planned rIX-FP dose during surgery.
- Estimates must be based on a patient without hemophilia, undergoing the same surgical procedure.

During Surgery

The following information should be recorded during surgery:

- Vital signs.
- Blood samples before injection of rIX-FP for plasma FIX activity level (central and local laboratory).

- Dose of rIX-FP administered (if needed). If the dose of rIX-FP is more than the planned dose, the reason for the discrepancy should be documented, including any unforeseen complications.
- Additional hemostatic interventions and / or transfusions required during surgery (including blood products and other coagulation factor[s]). In the event that the actual additional hemostatic interventions and / or transfusions required are higher than the estimated planned hemostatic interventions (other than rIX-FP) and / or transfusions required, the possible reason(s) should be documented as:
  - Inadequate hemostasis.
  - Incorrect dose or dose regimen of rIX-FP.
  - Expected as integral to the extended procedure.
  - Unexpected or unforeseen complication.
  - Other.
- Obtain blood sample for hematology (local laboratory).

Immediately After (0 hours) Surgery

- Physical examination.
- Vital signs.
- Blood sample for hematology (local laboratory).
- Blood samples before injection of rIX-FP (if needed) for plasma FIX activity level (central and local laboratory).
- Dose of rIX-FP (if needed).
- Additional hemostatic interventions and / or transfusions required (including blood products and other coagulation factor[s]). In the event that the actual additional hemostatic interventions and / or transfusions required are higher than the estimated planned hemostatic interventions (other than rIX-FP) and / or transfusions required, the possible reason(s) should be documented as:
  - Inadequate hemostasis.
  - Incorrect dose or dose regimen of rIX-FP.
  - Expected as integral to the extended procedure.

- Unexpected or unforeseen complication.
- Other.

- Record AEs and concomitant therapies.
- Using clinical judgment, the investigator (in consultation with the surgeon) will evaluate the intraoperative hemostasis of the subject after the end of the surgical procedure according to the efficacy scale (Investigator's Evaluation of Efficacy of Surgical Treatment).
- Intraoperative estimated blood loss (EBL). The estimated EBL will be based on the anesthesiologist's record of EBL during the surgical procedure. If an anesthesiologist was not present during the procedure, EBL will be estimated by the surgeon or physician performing the procedure. In the event that the **actual** intraoperative EBL is higher than the intraoperative PBL, the possible reason(s) should be documented as:
  - Inadequate hemostasis.
  - Incorrect dose or dose regimen of rIX-FP.
  - Blood loss expected as integral to the procedure.
  - Unexpected blood loss due to unforeseen complications.
  - Other.

After Surgery (24 to 72 Hours or up to Discharge)

After surgery, the following procedures should be performed (ie, during hospital / clinical care and discharge):

- Physical exam every 24 hours up to 72 hours postoperation or hospital discharge, whichever is earlier.
- Vital signs every 24 hours up to 72 hours postoperation or hospital discharge, whichever is earlier.
- Blood sample for hematology every 24 hours from 0 hours to 72 hours postoperation or hospital discharge, whichever is earlier.
- Quantitation of postoperative bleeding through surgical drains and the occurrence of late rebleeding episodes up to 72 hours or hospital discharge, whichever is earlier.

- The presence and extent of any surgical wound hematomas and whether they require surgical evacuation.
- Blood samples before injection of rIX-FP (if needed) and 30 minutes after additional doses of rIX-FP are administered (if needed) for plasma FIX activity level (central and local laboratory).
- Dose of rIX-FP (if needed).
- Additional hemostatic interventions and / or transfusions required during surgery (including blood products and other coagulation factor[s]).
- Record AEs and concomitant therapies.
- Investigator evaluation of efficacy every 24 hours, from wound closure (0 hours) to 72 hours, or until hospital discharge or until discontinuation of therapy, whichever is earlier.
- Post-surgery prophylactic injections, with or without additional preventative treatment before physical therapy should be administered from post-surgery to the end of the surgery substudy.
- If a subject does not start / restart prophylaxis, the subject should be withdrawn from the study and the rationale for the decision should be documented in the eCRF. In addition, attempts should be made to complete and document the end of study assessments (main study).

End of Participation in the Surgery Substudy (Day 28)

After surgery and discharge from the hospital or treating clinic, the subject may require rehabilitation or physical therapy, depending on the type of surgery. All injections of rIX-FP administered should be documented in the eDiary or eCRF.

The End of Substudy visit should be conducted at Day 28 after last surgery (in the event that an additional surgery is performed) (see Section C) and routine prophylaxis therapy with rIX-FP should be started (subjects in Arm 3) or restarted (subjects in Arms 1 or 2).

B. Minor Surgery

Procedures to be performed before and after minor surgery are provided in the Schedule of Assessments: Surgery Substudy – Minor Surgery. If, during the surgery, unforeseen circumstances result in the procedure fitting the definition of a major surgical procedure (ie, requires anesthesia, respiratory assistance or hemostatic support for a period exceeding 5 consecutive days), the assessments detailed for major surgery (Section A) should be completed.

Before Surgery

The following procedures will be performed **BEFORE** administration of rIX-FP for surgical prophylaxis:

- Eligibility assessment.
- Record type of surgery and association (if any) with hemophilia.
- Body weight.
- Obtain blood samples (optional) for measurement of plasma FIX activity level (central and / or local laboratory).
- Review concomitant therapy.
- Review AEs since last visit.
- rIX-FP should be administered approximately 3 to 6 hours before surgery.
- Blood samples (optional) for measurement of plasma FIX activity should be collected 30 minutes after administration of rIX-FP and, if feasible, tested at the local laboratory immediately before the surgery. Alternatively, the subject's incremental recovery rate will be used to calculate the dose of rIX-FP without testing the FIX activity level at the local laboratory.

Before surgery, if feasible, the following estimates must be made by the surgeon or physician performing the procedure:

- Estimate of intraoperative predicted blood loss (PBL) (average and maximum).
- Estimate planned hemostatic intervention (other than rIX-FP).
- Estimate planned transfusion during surgery.

- Estimate planned rIX-FP dose during surgery.
- Estimates must be based on a patient without hemophilia, undergoing the same surgical procedure.

During Surgery

The following information should be recorded:

- Blood samples before injection of rIX-FP (if an additional dose is needed and sample collection is feasible) for plasma FIX activity level (central and local laboratory).
- Dose of rIX-FP administered (if needed). If the dose of rIX-FP is more than the planned dose, the reason for the discrepancy should be documented, including any unforeseen complications.
- Additional hemostatic interventions and / or transfusions required during surgery (including blood products and other coagulation factor[s]). In the event that the actual additional hemostatic interventions and / or transfusions required are higher than the estimated planned hemostatic interventions (other than rIX-FP) and / or transfusions required, the possible reason(s) should be documented as:
  - Inadequate hemostasis.
  - Incorrect dose or dose regimen of rIX-FP.
  - Unexpected or unforeseen complication.
  - Other.

Immediately After (0 hours) Surgery

- Physical examination.
- Vital signs.
- Blood samples before injection of rIX-FP (if needed) for plasma FIX activity level (central and local laboratory).
- Dose of rIX-FP (if needed).
- Record AEs and concomitant therapies.
- Using clinical judgment, the investigator (in consultation with the surgeon) will evaluate the intraoperative hemostasis of the subject after the end of the surgical procedure

according to the efficacy scale (Investigator's Evaluation of Efficacy of Surgical Treatment).

- Intraoperative estimated blood loss (EBL). The EBL will be based on the anesthesiologist's record of EBL during the surgical procedure. If an anesthesiologist was not present during the procedure, EBL will be estimated by the surgeon or physician performing the procedure. In the event that the actual intraoperative EBL is higher than the intraoperative PBL, the possible reason(s) should be documented as:
  - Inadequate hemostasis.
  - Incorrect dose or dose regimen of rIX-FP.
  - Blood loss expected as integral to the procedure.
  - Unexpected blood loss due to unforeseen complications.
  - Other.

At Discharge

At discharge, the following procedures should be performed:

- Physical examination.
- Vital signs.
- Blood samples for FIX activity level (central and local laboratory).
- Dose of rIX-FP (if needed).
- Record AEs and concomitant therapies.
- Quantification of postoperative bleeding.
- Investigator evaluation of overall efficacy.
- Prophylaxis rIX-FP therapy should be restarted as soon after the surgical procedure as medically appropriate. If a subject does not restart prophylaxis, the subject should be withdrawn from the study and the rationale for the decision should be documented in the eCRF. In addition, attempts should be made to complete and document the end of study assessments (main study).

C. End of Participation in the Substudy (Major and Minor Surgery)

The end of substudy participation for an individual subject occurs with the end of the postoperative period, which is defined as completion of the final substudy visit and the resumption of the main study protocol. Subjects in Arm 3 may end participation in the study at this visit or start routine prophylaxis treatment in the main study.

The following procedures will be performed at the final substudy visit:

- Physical examination.
- Vital signs.
- Blood samples for hematology (major surgery only).
- Blood samples for antibodies against rIX-FP and FIX inhibitor (central laboratory).
- Blood sample for FIX activity level (central and local laboratory).
- Record AEs and concomitant therapies.

For some minor surgical procedures, the End of Surgery Substudy visit may be combined with hospital discharge.

D. Discontinuation Procedures for the Substudy (Major and Minor Surgery)

The following assessments must be performed at an early termination visit for any subject who has received rIX-FP and discontinues participation in the study (main study and substudy) prematurely:

- Vital signs.
- Physical examination.
- Blood samples for laboratory safety evaluation (hematology and serum chemistry).
- Blood samples for antibodies against rIX-FP, FIX inhibitor and CHO cells (central lab).
- Blood sample for FIX activity level (central and local lab).
- Retain blood sample.
- Record AEs and concomitant therapies.

STUDY VARIABLES AND METHODS OF ASSESSMENT

For an overview of the study variables and measurement times, see the Schedule of Assessments: Surgery Substudy – Major Surgery and the Schedule of Assessments: Surgery Substudy – Minor Surgery.

Subject Characteristics

See Section 10.1 for details.

Efficacy Variables

Overview of Variables

The primary clinical efficacy parameters assessed in the study are study product usage and hemostasis assessments by the Investigator.

Primary efficacy variable:

Investigator's evaluation of efficacy of rIX-FP prophylaxis during surgery.

Secondary efficacy variables*:*

- Comparison of predicted and estimated intraoperative blood loss.
- Comparison of predicted and actual transfusion requirements.
- Change in hemoglobin levels between baseline, intra-operation and post-operation.

Methods of Assessment

Perioperative Prophylaxis for Surgeries

The investigator will document the following:

- Type of surgery.
- Relationship to hemophilia: related/not related.
- Dose of rIX-FP.
- Preoperative predicted blood loss (average and maximum) for a non-hemophilic individual undergoing the same type and extent of surgical procedure.

- Predicted hemostatic intervention other than rIX-FP and transfusion requirements (if any) for a non-hemophilic individual undergoing the same type and extent of surgical procedure.
- Actual use of additional hemostatic interventions other than rIX-FP and transfusion blood products following the start of injection with rIX-FP (including blood products and other coagulation factor[s]).
- The estimated intraoperative blood loss.
- The presence and extent of any surgical wound hematomas noting whether they require surgical evacuation.
- Quantification of postoperative bleeding through surgical drains and the occurrence of late rebleeding episodes.
- Hemoglobin levels at baseline and nadir-intra- and post-operation.

Investigator's Evaluation of Efficacy of Surgical Treatment

Excellent	Hemostasis clinically not significantly different from normal (eg, achieved hemostasis comparable to that expected during similar surgery in a non factor-deficient patient) in the absence of other (unplanned) hemostatic intervention or estimated actual blood loss during surgery is not more than 20% higher than the estimated predicted blood loss for the intended surgery.
Good	Normal or mildly abnormal hemostasis in terms of quantity and / or quality (eg, slight oozing, prolonged time to hemostasis with somewhat increased bleeding compared to a non-factor deficient patient in the absence of other [unplanned] hemostatic intervention) or estimated actual blood loss is greater than 20% but less than or equal to 30% higher than the estimated predicted blood loss for intended surgery.
Moderate	Moderately abnormal hemostasis in terms of quantity and / or quality (eg, moderate hemorrhage that is difficult to control) with estimated blood loss greater than what is defined as Good.
Poor / No Response	Severely abnormal hemostasis in terms of quantity and / or quality (eg, severe hemorrhage that is difficult to control) and / or additional hemostatic intervention required with another factor IX product for complete resolution.

Safety Variables

Overview of Variables

Safety will be assessed on the basis of the following variables:

- AEs including SAEs and AESIs.
- Laboratory safety parameters (blood tests).
- Vital signs.
- Physical examination.
- Antibodies against rIX-FP.
- Inhibitors against FIX.

Methods of Assessment

See Section 10.2 and Section 10.3 for details.

STATISTICS

Determination of Sample Size

The number of subjects in the surgery substudy is not powered for statistical significance.

Analysis Populations

Surgical population

See Section 11.2.5 for details.

Statistical Analyses and Methods

See Section 11.3 for details.

Appendix 2. SUBCUTANEOUS SUBSTUDY

Table of Contents: Subcutaneous Substudy

A. SINGLE-DOSE COHORTS 1 AND 2

SCHEDULE OF ASSESSMENTS FOR COHORTS 1 AND 2: SUBCUTANEOUS ADMINISTRATION SUBSTUDY SCREENING, PK ASSESSMENT AND SAFETY FOLLOW-UP

	Screening	Active Treatment Period											PK & Safety Follow-up	
Substudy Day		**Day 1 [A] (before SC dose)**	**Day 1**	**Day 1 (after SC dose)**	**Day 1**	**Day 2**	**Day 3**	**Day 4**	**Day 6**	**Day 8**	**Day 11**	**Day 15 [B]**	**Day 15**	**Day 28**
Assessment Time Point			**0 h**	**0.5 h**	**3 h**	**24 h**	**48 h**	**72 h**	**120 h**	**168 h**	**240 h**	**336 h**	**0.5 h**	
Assessment Time Window	**1 to -28 d**			**± 10 m**	**± 30 m**	**± 3 h**	**± 6 h**	**± 6 h**	**± 6 h**	**± 6 h**	**± 6 h**	**± 6 h**	**± 10 m**	**± 4 d**
Informed consent	X													
Eligibility assessment	X	X												
Physical examination		X										X		X
Vital signs [C]		X		X								X		X
Plasma FIX activity (CL, optional LL)[D]		X		X	X	X	X	X	X	X	X	X	X	X
Inhibitors against FIX (CL)		X										X		X
Antibodies against rIX-FP and CHO cells (CL)[E]		X										X		X
Activation of coagulation tests (CL)[F]		X		X	X	X								
SC dosing of rIX-FP [G]			X											
IVdosing of rIX-FP IV												X [H]		

	Screening	Active Treatment Period											PK & Safety Follow-up	
Substudy Day		**Day 1 [A] (before SC dose)**	**Day 1**	**Day 1 (after SC dose)**	**Day 1**	**Day 2**	**Day 3**	**Day 4**	**Day 6**	**Day 8**	**Day 11**	**Day 15 [B]**	**Day 15**	**Day 28**
Assessment Time Point			**0 h**	**0.5 h**	**3 h**	**24 h**	**48 h**	**72 h**	**120 h**	**168 h**	**240 h**	**336 h**	**0.5 h**	
Assessment Time Window	**1 to -28 d**			**± 10 m**	**± 30 m**	**± 3 h**	**± 6 h**	**± 6 h**	**± 6 h**	**± 6 h**	**± 6 h**	**± 6 h**	**± 10 m**	**± 4 d**
Adverse events		< ----------On an Ongoing Basis----------												
Concomitant therapies		< ----------On an Ongoing Basis----------												

CHO = Chinese hamster ovary; CL = central laboratory; d = day; FIX = coagulation factor IX; IU = international unit; IV = intravenous; LL = local laboratory; m = minutes; rIX-FP = recombinant coagulation factor IX albumin fusion protein; SC = subcutaneous; TAT = thrombin-antithrombin.

Notes to the Schedule of Assessments for Cohorts 1 and 2:

A: Subjects are considered to be in the main study until Day 1 of the substudy.
B: Day 15 assessments, including administration of IV rIX-FP, may occur earlier if the LL FIX activity is ≤ 2 IU/dL.
C: Vital signs include measurement of body weight. Weight only measured Day 1 (prior to dose), Day 15 and Day 28.
D: Blood PK samples are at predose and at 0.5, 3, 24, 48, 72, 120, 168, 240 and 336 hours after the start of SC administration; at predose and at 0.5 hours post IV administration and at End of Substudy (Day 28). Samples will be tested by the central laboratory; however, the site may request to have additional samples tested by the local laboratory (LL). If LL FIX activity is ≤ 2 IU/dL, at any time point, subsequent time points may be omitted and the IV dose may be administered. If LL FIX activity is > 5 IU/dL at 336 hours, up to 3 additional blood PK samples may be taken every 48 hours (384, 432, and 480 hours) until LL is < 5 IU/dL, and the IV dose delayed until completion of the additional PK sampling at the discretion of the investigator.
E: A sample that tests positive for antibodies against rIX-FP will be retested to discriminate between plasma-derived FIX, recombinant FIX and albumin antibodies.
F: Blood samples for activation of coagulation tests include D-dimer, TAT, and prothrombin F1+2.
G: SC rIX-FP should be administered at least 14 days after the previous IV rIX-FP administration (21 days if subject is on a 21-day prophylaxis regimen).
H: Intravenous administration of rIX-FP will occur after the Day 15 blood draws.

B. REPEATED-DOSE COHORTS 3 AND 4

SUBCUTANEOUS SUBSTUDY - SCHEDULE OF ASSESSMENTS FOR COHORT 3: DOSING AND VISIT SCHEDULE

		Dose 1	Dose 2	Dose 3	Doses 4 to 12; Dose 14	Dose 13	Dose 15	PK & Safety Follow-up [C]	
Substudy Day for Cohort 3 [A]	**Scree-ning**	**Day 1 [B]**	**Days 2 to 4**	**Day 7**	**Days 10 to 34; Day 40**	**Day 37**	**Day 43**	**Days 44, 45, 46, 47, and 53**	**Day 57 (EOS)**
Time Windows	**1 to -28 days**	**See "Cohort 3 Sampling Schedule" for details**				**See "Cohort 3 Sampling Schedule" for details**			
Informed consent	X								
Eligibility assessment	X	X							
Physical examination		X							X
Vital signs		X [D]					X [D]		X [D]
Predose plasma FIX activity (CL)		X		X		X	X		
Postdose plasma FIX activity (CL) [E]		X	X				X	X	X
Inhibitors against FIX (CL)		X [F]							X [F]
Antibodies against rIX-FP and CHO cells (CL)		X [F]							X [F]
Activation of coagulation tests (CL) [E]		X	X				X	X	X
SC dosing of rIX-FP at study site		X [G]	X	X		X	X		
Training for SC home administration				X					
Dispense IMP [H]				X		X			
SC dosing of rIX-FP at home					X				
eDiary review			X	X		X	X	X	X
IMP return/accountability						X	X		

Substudy Day for Cohort 3 [A]	Screening	Dose 1	Dose 2	Dose 3	Doses 4 to 12; Dose 14	Dose 13	Dose 15	PK & Safety Follow-up [C]	
		Day 1 [B]	Days 2 to 4	Day 7	Days 10 to 34; Day 40	Day 37	Day 43	Days 44, 45, 46, 47, and 53	Day 57 (EOS)
Time Windows	**1 to -28 days**	**See "Cohort 3 Sampling Schedule" for details**				**See "Cohort 3 Sampling Schedule" for details**			
Investigator assessment of local tolerability [I]		X	X	X		X	X	X	X
Subject assessment of local tolerability					X [J]				
Adverse events		< ----------On an Ongoing Basis---------- ->							
Concomitant therapies		< ----------On an Ongoing Basis---------- ->							

CHO = Chinese hamster ovary; CL = central laboratory; EOS = end of substudy; FIX = coagulation factor IX; IU = international unit; IV = intravenous; rIX-FP = recombinant coagulation factor IX albumin fusion protein; PK = pharmacokinetics; SC = subcutaneous; TAT = thrombin-antithrombin.

Notes to the Schedule of Assessments for Cohort 3:

A: Dosing schedule in Cohort 3: 25 IU/kg every 3 days. Doses 4 to 12 and Dose 14 are administered by the subject at home.

B: Subjects are considered to be in the main study until Day 1 of the substudy.

C: For subjects who discontinue before SC Dose 15, the site should perform the serial PK assessments after the subject's final SC dose, if possible. If this is not possible, at a minimum an EOS PK sample should be taken.

D: SBP, DBP, heart rate, and body temperature assessed before dose and at 30 min after dose. In addition, body weight and height at Day 1 (before dose), and body weight at the EOS visit (336 hours after final SC dose).

E: See the "Cohort 3 Sampling Schedule" for details on the sampling time points and time windows.

F: Blood samples for inhibitors against FIX and for antibodies against rIX-FP and CHO cells must be taken a) before the first SC dose and b) after the final SC dose but before the subject returns to IV treatment in the main study. See the "Cohort 3 Sampling Schedule" for details.

G: First rIX-FP SC dose should be administered at least 14 days after the previous rIX-FP IV administration in the main study (21 days if subject is on a 21-day prophylaxis regimen).

H: Includes IMP for SC home administration and for on-demand IV treatment of any bleeding episodes that may occur during the SC home administration periods.

I: See the "Cohort 3 Sampling Schedule" for the time points of local tolerability assessment by the investigator.
J: Subjects will record their overall perception of local tolerability in the eDiary at 0.5, 8, and 24 hours after each SC injection at home.

SUBCUTANEOUS SUBSTUDY – COHORT 3 SAMPLING SCHEDULE AND INVESTIGATOR LOCAL TOLERABILITY ASSESSMENTS FOR SC DOSES ADMINISTERED AT STUDY SITE

SC Dose [A]	1					2	3 & 13	15			PK & Safety Follow-up[D]					
Substudy Day [A]	1			2	3	4	7 & 37	43			44	45	46	47	53	57
Time Point	Pre [B]	0.5 h	3 & 8 h	24 h	48 h	72 h [C]	Pre	Pre	0.5 h	3 & 8 h	24 h	48 h	72 h	96 h	240 h	336 h
Time Windows		±10 m	±30 m	±3 h	±24 h	±6 h	±24 h	±24 h	±10 m	±30 m	±3 h	±6 h	±6 h	±6 h	±6 h	±6 h
Plasma FIX activity (CL)	X	X	X	X	X	X[E]	X[E]	X[E]	X	X	X	X	X	X	X	X
Inhibitors against FIX (CL)	X															X
Antibodies against rIX-FP and CHO cells (CL)[F]	X															X
Activation of coagulation tests (CL)[G]	X	X	X	X				X	X	X	X					X
Investigator assessment of local tolerability		X	X	X	X	X[H]	X[H]		X	X	X	X	X	X	X	X

CHO = Chinese hamster ovary; CL = central laboratory; FIX = coagulation factor IX; IU = international unit; IV = intravenous; rIX-FP = recombinant coagulation factor IX albumin fusion protein; PK = pharmacokinetics; SC = subcutaneous; TAT = thrombin-antithrombin.

Notes to the Cohort 3 Sampling Schedule:

A: Doses 4 to 12 and Dose 14 are administered by the subject at home (see "Schedule of Assessments for Cohort 3 – Dosing and Visit Schedule").
B: Pre = predose PK sample
C: The 72-h FIX activity sample represents the predose sample for Dose 2.

D: For subjects who discontinue from the SC substudy before SC Dose 15, the site should perform the serial PK assessments after the subject'sfinal SC dose, if possible. If this is not possible, at a minimum an EOS PK sample should be taken.
E: This plasma FIX activity sample must be taken BEFORE the dose given at these visits.
F: A sample that tests positive for antibodies against rIX-FP will be retested to discriminate between plasma-derived FIX, recombinant FIX and albumin antibodies.
G: Blood samples for activation of coagulation tests include D-dimer, TAT, and prothrombin F1+2.
H: Local tolerability assessment at 30 min after Doses 2, 3, and 13.

SUBCUTANEOUS SUBSTUDY - SCHEDULE OF ASSESSMENTS FOR COHORT 4: DOSING AND VISIT SCHEDULE

		Dose 1	Dose 2	Dose 3	Doses 4 to 12; Dose 14	Dose 13	Dose 15	PK & Safety Follow-up [C]	
Substudy Day for Cohort 4 [A]	**Scree-ning**	**Day 1 [B]**	**Days 2, 3, 4, 6**	**Day 11**	**Days 16 to 56; Day 66**	**Day 61**	**Day 71**	**Days 72, 73, 74, 75, 81**	**Day 85 (EOS)**
Time Windows	**1 to -28 days**	**See "Cohort 4 Sampling Schedule" for details**				**See "Cohort 4 Sampling Schedule" for details**			
Informed consent	X								
Eligibility assessment	X	X							
Physical examination		X							X
Vital signs		X [D]					X [D]		X [D]
Predose plasma FIX activity (CL)		X		X		X	X		
Postdose plasma FIX activity (CL) [E]		X	X				X	X	X
Inhibitors against FIX (CL)		X [F]							X [F]
Antibodies against rIX-FP and CHO cells (CL)		X [F]							X [F]
Activation of coagulation tests (CL) [E]		X	X				X	X	X
SC dosing of rIX-FP at study site		X [G]	X	X		X	X		
Training for SC home administration				X					
Dispense IMP [H]				X		X			
SC dosing of rIX-FP at home					X				
eDiary review			X	X		X	X	X	X
IMP return/accountability						X	X		

		Dose 1	Dose 2	Dose 3	Doses 4 to 12; Dose 14	Dose 13	Dose 15	PK & Safety Follow-up [C]	
Substudy Day for Cohort 4 [A]	**Scree-ning**	**Day 1 [B]**	**Days 2, 3, 4, 6**	**Day 11**	**Days 16 to 56; Day 66**	**Day 61**	**Day 71**	**Days 72, 73, 74, 75, 81**	**Day 85 (EOS)**
Time Windows	**1 to -28 days**	**See "Cohort 4 Sampling Schedule" for details**				**See "Cohort 4 Sampling Schedule" for details**			
Investigator assessment of local tolerability [I]		X	X	X		X	X	X	X
Subject assessment of local tolerability					X [J]				
Adverse events		< ----------On an Ongoing Basis---------- ->							
Concomitant therapies		< ----------On an Ongoing Basis---------- ->							

CHO = Chinese hamster ovary; CL = central laboratory; EOS = end of substudy; FIX = coagulation factor IX; IU = international unit; IV = intravenous; rIX-FP = recombinant coagulation factor IX albumin fusion protein; PK = pharmacokinetics; SC = subcutaneous; TAT = thrombin-antithrombin.

Notes to the Schedule of Assessments for Cohort 4:

A: Dosing schedule in Cohort 4: ≤50 IU/kg every 5 days (Sponsor will determine the actual dose based on PK results from Cohort 3). Doses 4 to 12 and Dose 14 are administered by the subject at home.

B: Subjects are considered to be in the main study until Day 1 of the substudy.

C: For subjects who discontinue before SC Dose 15, the site should perform the serial PK assessments after subject's final SC dose, if possible. If this is not possible, at a minimum an EOS PK sample should be taken.

D: SBP, DBP, heart rate, and body temperature assessed before dose and at 30 min after dose. In addition, body weight and height at Day 1 (before dose), and body weight at the EOS visit (336 hours after final SC dose).

E: See the "Cohort 4 Sampling Schedule" for details on the sampling time points and time windows.

F: Blood samples for inhibitors against FIX and for antibodies against rIX-FP and CHO cells must be taken a) before the first SC dose and b) after the final SC dose but before the subject returns to IV treatment in the main study. See the "Cohort 4 Sampling Schedule" for details.

G: First rIX-FP SC dose should be administered at least 14 days after the previous rIX-FP IV administration in the main study (21 days if subject is on a 21-day prophylaxis regimen).
H: Includes IMP for SC home administration and for on-demand IV treatment of any bleeding episodes that may occur during the SC home administration periods.
I: See the "Cohort 4 Sampling Schedule" for the time points of local tolerability assessment by the investigator.
J: Subjects will record their overall perception of local tolerability in the eDiary at 0.5, 8, and 24 hours after each SC injection at home.

SUBCUTANEOUS SUBSTUDY - COHORT 4 SAMPLING SCHEDULE AND INVESTIGATOR LOCAL TOLERABILITY ASSESSMENTS FOR SC DOSES ADMINISTERED AT STUDY SITE

SC Dose [A]	1						2	3 & 13	15			PK & Safety Follow-up [D]					
Substudy Day [A]	1			2	3	4	6	11 & 61	71			72	73	74	75	81	85
Time Point	Pre [B]	0.5 h	3 & 8 h	24 h	48 h	72 h	120 h [C]	Pre	Pre	0.5 h	3 & 8 h	24 h	48 h	72 h	96 h	240 h	336 h
Time Windows		±10 m	±30 m	±3 h	±6 h	±6 h	±24 h	±24 h	±24 h	±10 m	±30 m	±3 h	±6 h	±6 h	±6 h	±6 h	±6 h
Plasma FIX activity (CL)	X	X	X	X	X	X	X [E]	X [E]	X [E]	X	X	X	X	X	X	X	X
Inhibitors against FIX (CL)	X																X
Antibodies against rIX-FP and CHO cells (CL) [F]	X																X
Activation of coagulation tests (CL) [G]	X	X	X	X					X	X	X	X					X
Investigator assessment of local tolerability		X	X	X	X	X	X [H]	X [H]		X	X	X	X	X	X	X	X

CHO = Chinese hamster ovary; CL = central laboratory; FIX = coagulation factor IX; IU = international unit; IV = intravenous; rIX-FP = recombinant coagulation factor IX albumin fusion protein; PK = pharmacokinetics; SC = subcutaneous; TAT = thrombin-antithrombin.

Notes to the Cohort 4 Sampling Schedule:

A: Doses 4 to 12 and Dose 14 are administered by the subject at home (see "Schedule of Assessments for Cohort 4 – Dosing and Visit Schedule").
B: Pre = predose PK sample
C: The 120-h FIX activity sample represents the predose sample for Dose 2.

D: For subjects who discontinue before SC Dose 15, the site should perform the serial PK assessments after the subject's final SC dose, if possible. If this is not possible, at a minimum an EOS PK sample should be taken.
E: This plasma FIX activity sample must be taken BEFORE the dose given at these visits.
F: A sample that tests positive for antibodies against rIX-FP will be retested to discriminate between plasma-derived FIX, recombinant FIX and albumin antibodies.
G: Blood samples for activation of coagulation tests include D-dimer, TAT, and prothrombin F1+2.
H: Local tolerability assessment at 0.5 h after Doses 2, 3, and 13.

INTRODUCTION

Background

This substudy of CSL654_3003 will evaluate the safety and PK of single and repeated subcutaneous (SC) administration of rIX-FP in adults with severe hemophilia B (ie, FIX activity of ≤ 2%) who are currently enrolled in the main CSL654_3003 study. Safety will be measured by the frequencies of AEs, SAEs, investigator and subject assessments of local tolerability, and the incidence of inhibitors to rIX-FP. Pharmacokinetic endpoints will be measured based on FIX activity.

Nonclinical Evaluation

PK characteristics following SC administration of rIX-FP were assessed in hemophilia B mice, rabbits, pigs and cynomolgus monkeys. SC administration of rIX-FP in all species was systemically and locally well tolerated. Respective bioavailabilities following SC administration were 31% to 50% (hemophilia B mice), 43% to 55% (rabbits), 22% (pigs) and 9.29% to 17% (cynomolgus monkeys). Furthermore, exposure values in hemophilia B mice, rabbits, and cynomolgus monkeys were higher than those of marketed human FIX products (BeneFIX® or Berinin® P).

A single SC dose in hemophilia B mice provided a clear hemostatic effect compared to the control group, with a significant reduction in time to hemostasis and total blood loss. Efficacy of SC rIX-FP treatment was also superior to BeneFIX® administered SC. Additional activated partial thromboplastin time (aPTT) measurement at the end of the study demonstrated a significant reduction of aPTT values versus saline controls as well as BeneFIX® treated mice.

Tolerability of SC injection was investigated in the rabbit. A single SC injection of rIX-FP was tolerated with no observed in-life findings, and minor local findings in histopathology, potentially being volume dose-dependent.

Collectively, the nonclinical data demonstrate that SC administration of rIX-FP to various animal species was tolerated with only minor local findings in rabbits and resulted in adequate bioavailability leading to pharmacodynamically-relevant exposure levels.

Potential Risks and Benefits

Potential risks associated with SC administration of rIX-FP are expected to be similar to the IV route of administration, and include the development of antibodies against FIX (including neutralizing antibodies [inhibitors]) and hypersensitivity reactions. The potential risks associated with treatment with rIX-FP and specifically with SC administration are discussed in detail in Section 7.4 of the Investigator's Brochure.

The use of a FIX replacement product with an extended half-life could be significantly beneficial to those affected by hemophilia B. SC administration of rIX-FP may allow routine prophylaxis treatment for hemophilia B patients without the need for IV injections. This route of administration may be beneficial particularly for those patients who have poor venous access, and may eliminate the need for an indwelling catheter.

The associated benefit-risk assessment of the substudy is acceptable for subjects enrolled in the substudy.

STUDY OBJECTIVES AND ENDPOINTS

CCI [redacted]

CCI [redacted]

STUDY DESIGN

Study Design and Rationale

This is an open-label, multicenter substudy to assess the safety, tolerability, and PK following single and repeated ascending SC doses of rIX-FP in hemophilia B subjects. Subjects will be treated in 1 or more of the 4 planned, sequential dose cohorts. Note: Cohort 4 is optional and will only be opened if the results of Cohorts 1 to 3 reveal that additional data on repeated SC dosing is required to inform the further clinical development. Each cohort will enroll a minimum of 4 and a maximum of 6 subjects.

- Cohort 1: single SC dose of 25 IU/kg rIX-FP.
- Cohort 2: single SC dose of 50 IU/kg rIX-FP.

- Cohort 3: repeated SC doses of 25 IU/kg rIX-FP every 3 days (15 doses).
- Cohort 4: repeated SC doses of ≤ 50 IU/kg rIX-FP every 5 days (15 doses); actual dose to be used in this cohort will be determined by the Sponsor based on PK results from Cohort 3.

Male hemophilia B patients, ≥ 18 years, currently enrolled in CSL654_3003, who have at least 100 EDs (Cohorts 1 and 2) or 50 EDs (Cohorts 3 and 4) to rIX-FP and weigh ≥50 kg to ≤ 100 kg will be eligible for the substudy.

Up to 28 days prior to SC administration of rIX-FP, subjects will be screened to determine eligibility for the substudy. Subjects will be sequentially assigned to a cohort (Cohort 1, 2, 3 or 4). SC administration of rIX-FP will be performed at least 14 days after the previous IV rIX-FP administration (21 days if subject is on a 21-day prophylaxis regimen). Blood samples for PK analysis will be collected at the time points detailed in the Schedule of Assessments for Cohorts 1 and 2).

In Cohorts 1 and 2, following collection of the last SC PK sample, a single IV dose of 50 IU/kg rIX-FP will be administered. If LL FIX activity is > 5 IU/dL at 336 hours, up to 3 additional PK blood samples may be taken every 48 hours (384, 432, and 480 hours) until LL is < 5 IU/dL, and the IV dose delayed until completion of the additional PK sampling at the discretion of the investigator. Following IV administration of rIX-FP, blood samples for PK analysis will be collected at selected time points (see Schedule of Assessments for Cohorts 1 and 2). Subjects will return in 2 weeks (Day 28) for an end of substudy visit to assess safety. After the end of substudy visit on Day 28, subjects will return to their IV rIX-FP regimen in the main study.

After at least 4 subjects in Cohort 1 have reached Day 15, plasma exposure after SC administration (FIX activity levels) and safety, including inhibitor results, will be reviewed by a Safety Review Committee (SRC). If no safety concerns are identified, dosing of Cohort 2 may start.

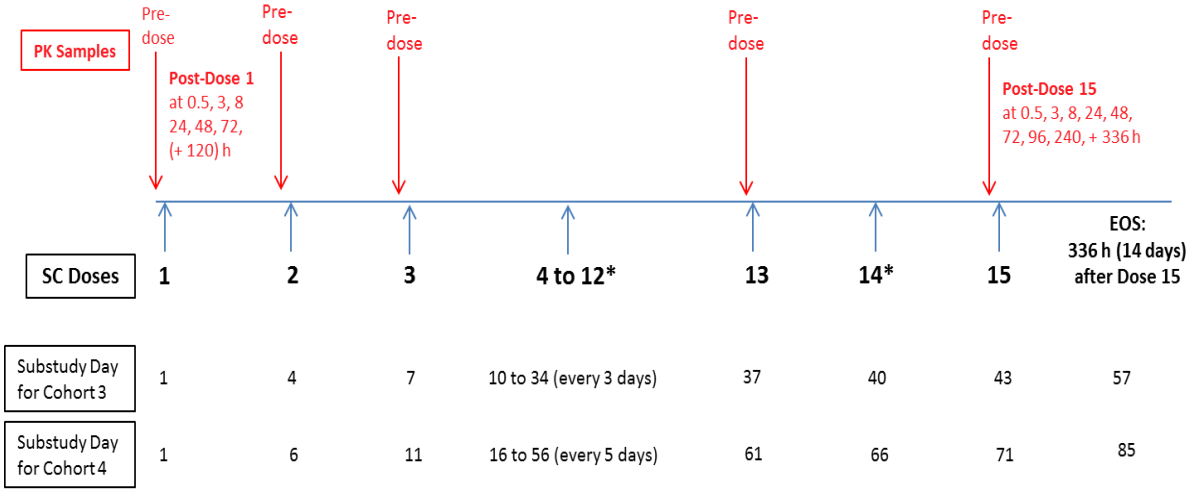
After at least 4 subjects in Cohort 2 have reached Day 15, plasma exposure after SC administration (FIX activity levels) and safety will be reviewed by an SRC. After review of the data, a decision will be made to enroll Cohort 3.

In Cohorts 3 and 4, subjects will be sequentially assigned to SC doses of 25 IU/kg every 3 days (Cohort 3) or to SC doses of ≤ 50 IU/kg every 5 days (Cohort 4), for a total of 15 SC doses in each cohort. rIX-FP will be administered SC at least 14 days after the previous IV rIX-FP administration (21 days for subjects on a 21-day IV regimen in the main study). Blood samples for PK analysis will be collected before the first SC dose, before selected SC doses administered at the study site, and for a serial PK profile after the first and the final SC doses. Doses 4 to 12 and Dose 14 will be administered by subjects/caregivers at home. Subjects will return 14 days after their final SC dose for an end of substudy visit for collection of the final PK sample and for safety assessments. After the end of substudy visit, subjects will return to their IV rIX-FP regimen in the main study.

After at least 4 subjects in Cohort 3 have completed SC treatment, plasma exposure after SC administration (FIX activity levels) and safety will be reviewed by the SRC.

An overview of the SC substudy design for Cohorts 3 and 4 is presented in Figure 2.

Figure 2 Subcutaneous Substudy: Dosing / PK Sampling Scheme and Substudy Visit Days for Cohorts 3 and 4



EOS = end of substudy; PK = pharmacokinetic; SC = subcutaneous.
Notes:
1. The 120-h sample after SC Dose 1 will only be taken in Cohort 4.
2. Doses with an asterisk will be administered by the subject/caregiver at home. All other doses will be given at the study site.

If a subject experiences a bleeding episode during the PK sampling period, the subject should treat the bleed with his standard on-demand IV dose of rIX-FP as prescribed in the main study.

Dose and Dosing Regimen

Each SC dose of rIX-FP will be administered in up to 4 injection sites, with a volume of up to 4 mL per site.

The starting dose will be 25 IU/kg (as a single dose in Cohort 1 and as repeated doses in Cohort 3), with dose escalation in Cohort 2 to 50 IU/kg (single dose) and to ≤ 50 IU/kg (repeated doses) in optional Cohort 4.

Planned Substudy Duration

The maximum total substudy duration of each subject will be approximately 30 days for subjects in Cohorts 1 and 2, approximately 57 days for subjects in Cohort 3, and

approximately 85 days for subjects in Cohort 4. Subjects will then return to the IV treatment plan of the main study.

The overall substudy duration (ie, first subject's Day 1 visit to the last subject's end of substudy visit) is expected to be 18 to 22 months and includes estimated durations for screening, enrollment of the subjects into the substudy, and the final visit.

Planned Number of Subjects

This substudy will enroll approximately 4 to 6 male subjects each in Cohorts 1 to 4 (ie, up to a maximum of 24 subjects). Subjects may enroll in more than 1 cohort.

Study Monitoring Procedures

Adverse events and local tolerability will be monitored for all subjects enrolled in the substudy, and AE reporting will be performed as described in the main protocol. After at least 4 subjects in Cohort 1 have reached Day 15, SC exposure (FIX activity levels) and safety assessments will be reviewed by the SRC. If no safety concerns are identified, dosing of Cohort 2 may start. The same procedure will be followed before a decision is made to enroll subjects in Cohorts 3 and 4.

Enrollment into the substudy and further SC administration of rIX-FP will be halted for review by the SRC and recommendation for continuation if any of the following occurs:

- One subject experiences anaphylaxis that is causally related to SC administration of rIX-FP.
- One subject experiences a serious hypersensitivity event that is causally related to SC administration of rIX-FP.

Cohorts 1 and 2: The SRC will meet after a cohort has data available through Day 15 for 4 subjects and will review safety and SC exposure (FIX activity levels). If no safety concerns are identified, the SRC will make a recommendation to continue to the next cohort.

Cohorts 3 and 4: The SRC will meet after at least 4 subjects from Cohort 3 have completed the SC treatment period; a decision regarding Cohort 4 will be made after this meeting. In addition, there will be an ad-hoc meeting of the SRC if any of the following occurs:

- One subject experiences anaphylaxis that is causally related to SC administration of rIX-FP.
- One subject experiences a serious hypersensitivity event that is causally related to SC administration of rIX-FP.

The substudy will be stopped if 1 subject develops an inhibitor to FIX during the substudy.

SELECTION OF SUBSTUDY POPULATION

Inclusion Criteria

Subjects meeting all of the following inclusion criteria may be enrolled into the substudy:

1. Male subjects, at least 18 years of age.
2. Subjects who are currently enrolled in Study CSL654_3003 with hemophilia B (FIX activity ≤ 2%).
3. Subjects who have received rIX-FP for ≥ 100 EDs (Cohorts 1 and 2) or for ≥ 50 EDs (Cohorts 3 and 4).
4. Body weight between 50.0 and 100.0 kg, both inclusive.
5. Body mass index (BMI) between 18.0 and 29.9 kg/m^2.
6. Written informed consent for substudy participation obtained before undergoing any specific procedures.

Exclusion Criteria

Subjects meeting any of the following exclusion criteria must not be enrolled into the substudy:

1. Use of rIX-FP within 14 days before SC administration of rIX-FP.

2. Suspected inability (eg, language problems) or unwillingness to comply with substudy procedures.

3. Experienced a life-threatening bleeding episode or had major surgery during the 3 months prior to substudy entry (Day 1).

ALLOCATION, DOSING AND ADMINISTRATION

Cohorts 1 and 2

Subjects will be sequentially assigned to a cohort, and receive a single SC dose of rIX-FP. The SC dose of rIX-FP will be administered at up to 4 injection sites, a minimum of 2.5 cm apart, with a volume of up to 4 mL per site. SC administration may occur on the stomach, thigh, or upper arm. The SC rIX-FP dose should be administered at least 14 days after the previous rIX-FP administration (21 days if subject is on a 21-day prophylaxis regimen). At Day 15 (336 hours), subjects will be administered a single IV dose of 50 IU/kg rIX-FP.

If a subject experiences a bleeding episode during the PK sampling period (prior to Day 15), the subject should treat the bleed with his standard on-demand dose of rIX-FP as prescribed in the main study, dosed IV. If LL FIX activity is ≤ 2 IU/dL, at any time point, subsequent time points may be omitted and the IV dose may be administered. If LL FIX activity is > 5 IU/dL at 336 h, up to 3 additional blood PK samples may be taken every 48 hours (384, 432, and 480 hours) until LL is < 5 IU/dL, and the IV dose delayed until completion of the additional PK sampling at the discretion of the investigator. If the treatment of a bleed occurs within 7 days of the Day 15 visit, the IV dose is optional. A subject may be treated with an additional IV dose of rIX-FP as long as the dose is given within the visit window.

Cohorts 3 and 4

Subjects will be sequentially assigned to a cohort, and receive repeated SC doses of rIX-FP for a total of 15 doses. Each SC dose of rIX-FP will be administered at up to 4 injection sites, a minimum of 2.5 cm apart, with a volume of up to 4 mL per site. SC administration may occur on the stomach, thigh, or upper arm. The first SC rIX-FP dose should be administered

at least 14 days after the previous rIX-FP administration (21 days if subject is on a 21-day prophylaxis regimen). The subject will return to their regular IV treatment schedule in the main study once they have completed the end of substudy visit 14 days after the final SC dose.

If a subject experiences a bleeding episode during the PK sampling period, the subject should treat the bleeding episode with his standard on-demand IV dose of rIX-FP as prescribed in the main study. The subject should continue in the SC substudy following the same schedule of SC injections, regardless of the IV treatment of that bleeding episode.

CONTRAINDICATIONS, PERMITTED THERAPIES AND PROHIBITED THERAPIES

Contraindications and Precautions to Further Dosing

In the event the subject experiences a hypersensitivity reaction (including anaphylaxis), the study treatment must be stopped immediately by discontinuation of the injection. In the event the subject experiences a hypersensitivity reaction or develops an inhibitor to FIX or antibodies to rIX-FP, the CSL medical monitor must be contacted before the administration of additional doses of rIX-FP.

Permitted Therapies

See Section 7.2 of the main protocol.

Prohibited Therapies

See Section 7.3 of the main protocol.

STUDY PROCEDURES

The clinical procedures that will be conducted during this study related to the evaluation of population demographics and safety are provided in Table A1. Refer to the Laboratory Manual for detailed instructions on how the laboratory assessments should be performed.

Table A1. Clinical Procedures: Safety Evaluation

Assessment	Description
Physical examination	As per the site's standard procedure
Vital signs	• Body temperature • Body weight • Blood pressure (systolic and diastolic) • Heart rate (beats per minute)
Markers of activation of coagulation	• Prothrombin fragment 1+2 • Thrombin-antithrombin (TAT) • D-dimer
Immunogenicity	Factor IX inhibitors and antibodies specific to rIX-FP and CHO cell-derived proteins.
Local tolerability	• Investigator assessment: assessment of erythema, edema or induration, and itching, local pain, or local heat after injections administered at the study site • Subject assessment: overall perception of local tolerability after injections administered at home

CHO = Chinese hamster ovary; rIX-FP = recombinant fusion protein linking coagulation factor IX with albumin; TAT = thrombin-antithrombin.

The timing and frequency of all clinical procedures are described in the Schedules of Assessments. Refer to the Laboratory Manual for details about the collection, storage, handling, and transportation of biological specimens.

Subject/Caregiver Training and SC Self-Administration at Home

At the visits for SC Dose 3, the investigator or delegate will ensure that the subject and / or caregiver has been trained sufficiently to allow for SC self-administration at home. At this time, the subject/caregiver will be instructed in the following:

- Correct reconstitution technique for rIX-FP.
- Correct selection of SC administration sites and administration technique.
- Correct drug storage.
- Adverse event reporting.
- Local tolerability assessments.
- Correct completion of eDiary.

For SC injections received by the subject at home, the subject / caregiver will report (not limited to) the following information in the eDiary:

- Details of the rIX-FP administration (eg, total actual IU per injection, number of vials used, and start date and time of injection).
- Local tolerability assessments.

For bleeding episodes:

- Type of bleeding episode (spontaneous, traumatic, unknown, or post-surgery).
- Site of the bleeding episode (ie, joint, muscle, mucosal membrane) and specific location.
- Time of start of symptoms of bleeding.
- Details of rIX-FP IV treatment of the bleeding episode (eg, total actual IU per injection, number of vials used, and start date and time of injection).

VISIT SCHEDULE

The timing and frequency of the substudy visits are described in the Schedules of Assessments.

Screening Visit (All Cohorts)

All subjects **must provide written informed consent** before any substudy-specific assessments or procedures are performed.

Written informed consent is not required for assessments or procedures performed according to standard of care (eg, for diagnosis or treatment); results from such assessments may be used in the determination of substudy eligibility.

The Day 1 visit may occur on the same day as the screening visit.

Day 1 Visit (All Cohorts)

rIX-FP SC should be administered at least 14 days after the previous rIX-FP administration in the main study (21 days if subject is on a 21-day prophylaxis regimen).

The following procedures will be performed PRIOR to the SC administration of rIX-FP on Day 1:

- Review inclusion and exclusion criteria.
- Physical examination.
- Vital signs (including weight and height).
- Blood samples for:
  - Plasma FIX activity.
  - Inhibitors against FIX.
  - Antibodies against rIX-FP.
  - Antibodies against CHO cell-derived proteins.
  - Activation of coagulation tests.
- Record AEs.
- Record concomitant therapies.

The following procedures, in addition to documenting any AEs and concomitant therapies, will be performed FOLLOWING the start of SC injection of rIX-FP:

- 30 minutes after start of injection (all cohorts):
  - Vital signs.
  - Blood sample for plasma FIX activity.
  - Blood samples for activation of coagulation tests.
  - Investigator assessment of local tolerability.

- 3 hours after start of injection (all cohorts):
  - Blood sample for plasma FIX activity.
  - Blood samples for activation of coagulation tests.
  - Investigator assessment of local tolerability.
- 8 hours after start of injection (Cohorts 3 and 4 only):
  - Blood sample for plasma FIX activity
  - Blood samples for activation of coagulation tests.

- Investigator assessment of local tolerability.

Follow-up Period for Cohorts 1 and 2

Follow-up Period: 24, 48, 72, 120, 168, and 240 Hour Visits (Days 2 to 11)

The following procedures will be performed at each visit:

- Blood sample for plasma FIX activity.
- Blood samples for activation of coagulation tests (24 hours only).
- Record AEs.
- Record concomitant therapies.

Follow-up Period: Day 15 (336 Hour) Visit

The following procedures will be performed PRIOR to the IV administration of rIX-FP:

- Physical examination.
- Vital signs (including weight).
- Blood samples for:
  - Plasma FIX activity.
  - Inhibitors against FIX.
  - Antibodies against rIX-FP.
  - Antibodies against CHO cell-derived proteins.
- Record AEs.
- Record concomitant therapies.

The following procedures, in addition to documenting any AEs and concomitant therapies, will be performed FOLLOWING the start of IV infusion of rIX-FP:

- 30 minutes after start of infusion:
  - Blood sample for plasma FIX activity.

Follow-up Period: Day 28 Visit – End of Subcutaneous Substudy

The following procedures will be performed:

- Physical examination.

- Vital signs (including weight [only if the dose is to be adjusted to return to the main study]).
- Blood samples for:
  - Plasma FIX activity (final PK sample in the SC substudy).
  - Inhibitors against FIX.
  - Antibodies against rIX-FP.
  - Antibodies against CHO cell-derived proteins.
- Record AEs
- Record concomitant therapies.
- Schedule next visit for the main study.

Repeated-dose & Follow-up Period for Cohorts 3 and 4

Visits After SC Dose 1

- Visits at 24, 48, and 72* h after SC Dose 1 for Cohort 3 (Days 2 to 4)
- Visits at 24, 48, 72, and 120* hours after SC Dose 1 for Cohort 4 (Days 2 to 6)

  * Note: For Cohort 3, the 72-h FIX activity sample represents the predose sample for SC Dose 2. For Cohort 4, the 120-h FIX activity sample represents the predose sample for SC Dose 2.

The following procedures will be performed at each of these visits:

- Blood sample for plasma FIX activity.
- Blood samples for activation of coagulation tests (at 24 hours only).
- Investigator assessment of local tolerability.
- Record AEs.
- Record concomitant therapies.

Visits for SC Doses 2 and 3

Subjects in Cohorts 3 and 4 will return to the study site for SC Doses 2 and 3 and the associated assessments. The following procedures will be performed PRIOR to SC Doses 2 and 3:

- Review eDiary.
- Record AEs.
- Record concomitant therapies.

In addition, the following procedure will be performed PRIOR to SC Dose 3:

- Blood sample for plasma FIX activity

The following procedures will be performed AFTER SC Doses 2 and 3:

- Investigator assessment of local tolerability (at 30 min).
- Record AEs.
- Record concomitant therapies.

In addition, the following procedures will be performed at the visit for SC Dose 3:

- Provide training to subject (and caregiver, if applicable) for SC self-administration at home.
- Dispense IMP for self-administration of SC Doses 4 to 12 at home, and IV IMP for on-demand treatment of bleeding episodes.
- Instruct subject (and caregiver, if applicable) on subject assessment of local tolerability.
- Instruct subject (and caregiver, if applicable) on correct completion of eDiary.
- Schedule the next study site visit for SC Dose 13.

SC Self-administration at Home, Doses 4 to 12 and Dose 14

Subjects in Cohorts 3 and 4 will administer SC Doses 4 to 12 and SC Dose 14 at home (every 3 days for Cohort 3, every 5 days for Cohort 4). Subjects will assess the following after each SC dose and will record the information in their eDiary:

- Local tolerability assessment at 30 min, at 8 h, and at 24 h.
- If bleeding episodes occur:
  - Details on bleeding episodes.
  - Details of rIX-FP IV treatment of bleeding episodes (if applicable).

Visit for SC Dose 13

Subjects will return to the study site for SC Dose 13. The following procedures will be performed PRIOR to SC Dose 13:

- Blood sample for plasma FIX activity.
- Review subject eDiary

The following procedures will be performed AFTER SC Dose 13:

- Investigator assessment of local tolerability (at 30 min).
- Record AEs.
- Record concomitant therapies.

The following procedures will be performed at any time at this visit:

- Review subject eDiary.
- IMP return and accountability.
- Dispense IMP for self-administration of SC Dose 14 at home, and IV IMP for on-demand treatment of bleeding episodes.
- Schedule the next study site visit for SC Dose 15.

Visit for SC Dose 15 (Or Final Dose for Subjects Who Discontinue from Substudy)

The following procedure will be performed PRIOR to SC Dose 15 (or final dose for subjects who discontinue from the substudy):

- Blood sample for plasma FIX activity.
- Blood samples for activation of coagulation tests.
- Review subject eDiary.
- SBP, DBP, heart rate, body temperature.

The following procedures will be performed at 30 min AFTER the dose:

- Blood sample for plasma FIX activity.
- Blood samples for activation of coagulation tests.
- SBP, DBP, heart rate, body temperature.
- Investigator assessment of local tolerability.
- Record AEs.
- Record concomitant therapies.

The following procedures will be performed at 3 hours and at 8 hours AFTER the dose:

- Blood sample for plasma FIX activity.
- Blood samples for activation of coagulation tests.
- Investigator assessment of local tolerability.
- Record AEs.
- Record concomitant therapies.

The following procedures will be performed at any time at this visit:

- eDiary review of recorded data.
- IMP return and accountability.

Visits at 24, 48, 72, 96, and 240 hours after SC Dose 15 (or Final Dose)

The following procedures will be performed at each of these visits:

- Blood sample for plasma FIX activity.

- Blood samples for activation of coagulation tests (at 24 hours only).
- Investigator assessment of local tolerability.
- Review subject eDiary.
- Record AEs.
- Record concomitant therapies.

Visit at 336 Hours (14 Days) after SC Dose 15 (or Final Dose)– End of Subcutaneous Substudy

The following procedures will be performed at this end of substudy visit:

- Physical examination.
- Vital signs (except height)
- Blood samples for:
  - Plasma FIX activity (final PK sample in the SC substudy).
  - Inhibitors against FIX.
  - Antibodies against rIX-FP.
  - Antibodies against CHO cell-derived proteins.
  - Activation of coagulation tests.
- Investigator assessment of local tolerability.
- Review subject eDiary.
- Record AEs.
- Record concomitant therapies.
- Schedule next visit for the main study.

Unscheduled Visits

Unscheduled visits, including brief PK assessments, may be arranged at any time point during the substudy, at the discretion of the investigator or upon request of the subject.

ASSESSMENTS

Safety Assessments

Safety will be assessed based on the following variables:

- AEs and SAEs.
- Investigator's assessment of local tolerability.
- Subject's assessment of local tolerability.
- Physical examination.
- Vital signs.
- Inhibitors against FIX.
- Antibodies against rIX-FP.
- Antibodies against CHO cell-derived proteins.
- Activation of coagulation tests.

Clinical laboratory tests will be performed at time points as detailed in the Schedule of Assessments for the SC substudy. More frequent evaluations may be performed, if clinically indicated, at the discretion of the investigator.

Pharmacokinetic Analyses

Pharmacokinetic Evaluation of rIX-FP

Cohorts 1 and 2:

If during the PK assessment period, a subject experiences a bleeding episode, no further blood samples will be taken as part of PK assessment, regardless of whether the bleeding episode is treated or not. The PK may or may not need to be repeated.

If LL FIX activity is ≤ 2 IU/dL, at any time point, subsequent time points may be omitted and the IV dose may be administered.

If LL FIX activity is > 5 IU/dL at 336 hours, up to 3 additional blood PK samples may be taken every 48 hours (384, 432, and 480 hours) until LL is < 5 IU/dL, and the IV dose delayed until completion of the additional PK sampling at the discretion of the investigator.

Cohorts 3 and 4:
If a subject experiences a bleeding episode during the PK assessment period, the subject should treat the bleeding episode with his standard on-demand IV dose of rIX-FP as prescribed in the main study. The subject should continue in the SC substudy following the same schedule of SC injections, regardless of the IV treatment of that bleeding episode. All PK sampling should be completed as outlined in the Schedule of Assessments for the SC substudy. See section "Substudy Pharmacokinetic Population" for details on the PK inclusion of these subjects.

Overview of Variables

The SC PK of rIX-FP and the subject's previous FIX product will be assessed on the basis of measurements of FIX activity levels in plasma. PK samples will be used to measure the following PK parameters:

Cohorts 1 and 2:

- C_{max}
- Incremental recovery (the peak level recorded 30 minutes after injection and reported as [IU/mL]/[IU/kg])
- Terminal elimination half-life ($t_{1/2}$)
- Area under the concentration-time curve ($AUC_{0\text{-last}}$)
- Clearance
- Volume of distribution at steady state (V_{ss})
- T_{max}

Cohorts 3 and 4:

- C_{max} after first dose ($C_{max,\ Dose\ 1}$) and C_{max} at steady state after final SC dose ($C_{max,ss}$)

- Incremental recovery (the peak level recorded 30 minutes after injection and reported as [IU/mL]/[IU/kg])

CCI [redacted]

- $t_{1/2}$ after final SC dose

CCI [redacted]

- Clearance
- Volume of distribution at steady state (V_{ss})

CCI [redacted]

- T_{max} after first dose ($T_{max, Dose\ 1}$) and T_{max} after final dose ($T_{max, ss}$)

Methods of Assessment

Blood samples for determination of FIX activity will be obtained before and after SC injection of rIX-FP at the time points detailed in the Schedule of Assessments for the SC substudy.

A zero-time will be assigned as the start of the injection, and the residual FIX at the predose time point will be used as the baseline value for each administration. FIX activity will be measured at a central laboratory using a validated one-stage clotting method.

Details regarding sample collection, handling, deep freezing of samples and shipment to the central laboratory are given in the Laboratory Manual in the Investigator Site File.

Local Tolerability Assessments

Investigator assessment: For the SC injections administered at the study site (Doses 1, 2, 3, 13, and 15), the investigator will perform assessments of local tolerability at the SC injection site(s). If several injection sites are used, each site will be judged but only the site with the strongest reaction will be recorded, according to the following scale:

Erythema

Description	Score
None	0
Very slight (barely perceptible)	1
Well-defined	2
Moderate to severe	3
Severe (beet redness) to slight eschar formations (injuries in depth)	4

Edema or Induration

The size of any edema or induration will be determined by measuring the smallest and largest diameters.

Itching, Local Pain, or Local Heat

The severity of any local reactions of itching, local pain, or local heat will be assessed based on the following classification: none (0), very slight (1), slight (2), moderate (3), and severe (4).

The investigator will perform local tolerability assessments at the time points detailed in the Cohort 3 Sampling Schedule and the Cohort 4 Sampling Schedule.

Subject assessment: The subject (or caregiver) will assess local tolerability at the SC injection site during SC administration at home. Subjects will record in the eDiary their judgment on the overall perception of the local reactions on a scale of none (0), very slight (1), slight (2), moderate (3), and severe (4) approximately 30 minutes, 8 hours, and 24 hours after the end of each SC dose given at home. If several injection sites are used, each site will be judged but

only the site with the strongest reaction will be recorded. The investigator will review these eDiary data at the next visit and will record local reactions as AEs.
Note: If a local reaction AE is reported, it also needs to be included in local tolerability assessment (by subject and / or investigator) to ensure consistency of reporting between AEs and local tolerability assessments.

Other Assessments

Markers of Activation of Coagulation

Activation of coagulation tests, including prothrombin fragment 1+2, thrombin-antithrombin and D-dimer, will be assessed by the central laboratory at the time points detailed in the Cohort 3 Sampling Schedule and the Cohort 4 Sampling Schedule.

STATISTICS

Sample Size Estimation

Sample size for this substudy is based upon empirical considerations and no formal sample size calculation will be performed. A maximum of up to 24 subjects will be recruited into the substudy. If a subject drops out prior to Day 1, the subject may be replaced.

Description of Analysis Datasets

Substudy Safety Population

The safety population will consist of all subjects who received at least 1 SC dose of rIX-FP in this substudy. All safety analyses will be performed on the safety population.

Substudy Pharmacokinetic Population

The PK population will comprise subjects who have received at least 1 dose of rIX-FP administered SC and have blood samples drawn for PK assessment. Subjects will be excluded from analysis if an insufficient number of analyzable PK samples were obtained to permit the evaluation of at least 1 PK parameter for rIX-FP, excluding samples obtained after receiving an IV dose of rIX-FP or any other FIX product for the treatment of a bleeding episode during the PK sampling period.

The FIX activity in subjects receiving on-demand IV treatment for bleeding episodes during the SC substudy will not be utilized from the IV treatment onward in the PK summary statistics, but may be included in the Population PK analysis if dose records are available.

Statistical Analyses and Methods

All safety data will be summarized separately for the substudy. Continuous data will be summarized using descriptive statistics including means, standard deviations, medians, first and third quartiles, and minimums and maximums. Categorical variables will be summarized with frequencies and percentages.

Safety Analyses

Safety data from the SC substudy will be summarized using descriptive statistics and will include AEs, vital signs, physical examination, investigator's and subject's assessments of local tolerability, neutralizing antibodies against FIX, antibodies against rIX-FP and CHO cells, and markers of activation of coagulation (prothrombin fragment 1+2, TAT, and D-dimer). (See Section 11.3.3 of the main protocol.)

Substudy Pharmacokinetics Data

A noncompartmental analysis will be performed to allow individual PK data analysis. Noncompartmental PK analysis will be performed for FIX activity in plasma, and PK parameters will be listed and summarized by treatment group. Individual subject and subgroup mean plasma concentration-time data will be plotted for each treatment group on linear and semi-logarithmic scales.

Population PK methodology will be applied for derivation of some of PK parameters, including calculation of bioavailability. Prior rIX-FP IV PK data (from Studies CSL654_2001, CSL654_2004, CSL654_3001, CSL654_3002, and / or CSL654_3003) will be utilized for Population PK modeling purposes that will be documented separately.

Substudy SRC Data Review

Safety and SC exposure (FIX activity levels) will be analyzed and reviewed by an SRC following Cohorts 1, 2, and 3. The final analysis of the SC substudy will be performed when all subjects have completed the SC substudy.

Appendix 3. WORLD FEDERATION OF HEMOPHILIA RECOMMENDED PLASMA FACTOR LEVEL AND DURATION OF ADMINISTRATION FOR ON-DEMAND TREATMENT AND SURGERY

Type of Hemorrhage	Desired level of FIX	Duration (days)
Joint	40% – 60%	1 – 2
Muscle (except iliopsoas)	40% – 60%	2 – 3
Iliopsoas		
• Initial	60% – 80%	1 – 2
• Maintenance	30% – 60%	3 – 5
CNS/head		
• Initial	60% – 80%	1 – 7
• Maintenance	30%	8 – 21
Throat and neck		
• Initial	60% – 80%	1 – 7
• Maintenance	30%	8 – 14
Gastrointestinal		
• Initial	60% – 80%	7 – 14
• Maintenance	30%	
Renal	40%	3 – 5
Deep laceration	40%	5 – 7
Surgery (minor)		
• Preoperative	50% – 80%	
• Postoperative	30% – 80%	1 – 5
Surgery (major)		
• Preoperative	60% – 80%	
• Postoperative	40% – 60%	1 – 3
	30% – 50%	4 – 6
	20% – 40%	7 – 14

World Federation of Hemophilia Guidelines, 2012

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Signed By	Date (GMT)
PPD	PPD 19:48:37
Approved-Clinical Safety Physician Approval	
PPD	PPD 20:28:59
Approved-PPD Approval	
PPD	PPD 21:13:48
Approved-PPD Approval	

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