Statistical Analysis Plan

CSL Behring GmbH

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A Phase III Open-Label, Multicenter, Extension Study to Assess the Safety and Efficacy of Recombinant Coagulation Factor VIII (r-VIII-SingleChain, CSL627) in Subjects with Severe Hemophilia A

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Abbreviations

ADA	Anti-Drug Antibodies
ABR	Annualized Bleeding Rate
AE	Adverse Event
AESI	Adverse Event of Special Interest
AsBR	Annualized Spontaneous Bleeding Rate
ATC	Anatomical Therapeutic Chemical
BMI	Body Mass Index
CVAD	Central Venous Access Device
CD4	Cluster of Differentiation 4
CHO	Chinese Hamster Ovary
ChS	Chromogenic Substrate
CI	Confidence Interval
CSP	Clinical Study Protocol
CSR	Clinical Study Report
CV	Coefficient of Variation
eCRF	Electronic Case Report Form
eDiary	electronic Diary
ED	Exposure Day
EMA	European Medicines Agency
FEIBA	Factor eight inhibitor bypassing agent
FVIII	Factor VIII
HIV	Human Immunodeficiency Virus
IR	Incremental Recovery
CCI	
IV	Intravenous
KM	Kaplan Meier
MedDRA	Medical Dictionary for Regulatory Activities
PK	Pharmacokinetic
PT	Preferred Term
PTP	Previously Treated Patient
PUP	Previously Untreated Patient
rFVIIa	Recombinant factor VIIa
rFVIII	Recombinant factor VIII
rVIII-SingleChain	Single chain recombinant factor VIII
RBC	Red Blood Cell
SAE	Serious Adverse Event
SAP	Statistical Analysis Plan
SI	Special Interest
SMQ	Standardised MedDRA Queries
SOC	System Organ Class
TEAE	Treatment Emergent Adverse Event
TEE	Thromboembolic Events
WBC	White Blood Cell
WFH	World Federation of Hemophilia
WHO	World Health Organization

List of Substantial Changes

The proposed revisions to the Version 1 of the Statistical Analysis Plan (SAP) dated 28 September 2016 and the rationale for these changes are summarised below.

SAP SECTION	REVISION	RATIONALE FOR REVISION
SAP Version 2 dated 10 September 2018		
General	**REVISIONS MADE THROUGHOUT THE DOCUMENT:** Protocol No. CSL627_3001 Amendment 2, 05 June 2015 **REVISED TO** Protocol No. CSL627_3001 Amendment 3, 27 January 2017.	To reflect the current protocol amendment.
Section 2.1 and 2.2 and accordingly throughout the document	Incidence of inhibitor formation to FVIII in Arm 2, PUPs was stated that would be performed on at least 50 PUPs. This condition has been removed.	Given that patients that develop inhibitors may be withdrawn from the study early, they would not necessarily achieve 50 exposure days. Therefore the text was adjusted to properly report the endpoint regardless of these circumstances.
Section 3.5.3	Efficacy Population definition has been changed removing the exclusive inclusion of subjects who do not have an inhibitor at any time point during the study.	Analysis by inhibitor status for PUPs will be included as a separate population and analysis.
Section 3.5.6	Region subgroups and Japanese subgoup added. Race subgroups added for inhibitors analysis.	To assess safety of CSL627 on regional and racial basis.
Section 3.5.6	Age subgroup changed to be based on age in this study.	To focus on age distribution in this study.
Section 4.1 and accordingly throughout the document	For PUPs, analyses of ABR, hemostatic efficacy, TEAE and IR will be presented overall and by inhibitor status.. Periods during which the subject receives injections for reasons different than prophylaxis are excluded.	To exclude periods in which other types of infusions might affect prophylaxis compliance.

Section 4.5.5	It has been specified that if a subject has two dose regimens on the same day, the frequency of the regimen will be summed and the doses will be averaged.	To handle mixed regimen assignment.
Section 4.5.7	Shift analysis in the current study from initial to final regimen has been added.	For completeness of analysis.
Section 4.5.9	Added the note that if there are overlapping surgeries within 14 days, when calculating the consumption for the first surgery, we will censor this surgery at the beginning of the second surgery.	To add details for the surgical consumption computation.
Section 4.6.1	The Annualized Bleeding Rate by inhibitor status (PUPs) is set to missing if the efficacy evaluation period is less than 8 weeks on the given inhibitor status.	To exclude bias due to short evaluation period.
Section 4.6.2.1	The Annualized Bleeding Rate by regimen (PTPs) is set to missing if the efficacy evaluation period is less than 8 weeks on that regimen.	To exclude bias due to short evaluation period.
Section 4.6.2.2	Details about how to derive number of infusions of CSL627 required to achieve hemostasis have been added.	To perform analysis as per protocol.
Section 4.6.3.2	Details added to handle missing times of bleeding events.	To clearly define how data will be handle in case of missing data.
Section 4.7.1	Analysis of Factor VIII inhibitor test results by reason for specimen collection deleted.	No further need of this analysis.
Section 4.7.1	It has been specified as per protocol that a positive Factor VIII inhibitor test needs to be confirmed with at least 2 positive results. In the analysis of Factor VIII inhibitor test results, ED categories for PUPs changed from 0-10 EDs, >10-15 EDs, >15-50 EDs into 0-10 EDs, >10-25 EDs, >25-50 and >50 EDs.	To be clearly consistent with the protocol. To include in a single category (i.e. >10-25 EDs) the highest risk period for PUPs.
Section 4.7.1	Analysis of the incidence of transient inhibitors added.	For completeness of analysis.

Section 4.7.4.1	Graphical analysis of the relationship between ADA and inhibitor titer added.	For completeness of analysis.
Section 4.7.4.2	In the analysis of antibodies against Chinese hamster ovary cells, ED categories for PUPs changed from 0-10 EDs, >10-15 EDs, >15-50 EDs into 0-10 EDs, >10-215 EDs, >215-50, and > 50 EDs.	To be consistent with other ED categories.
Section 4.7.5	Potentially clinically significant vital signs analysis has been removed.	Summaries of vital sign results and change from baseline are considered as exhaustive.
SAP Version 3		
Section 2.3	Changed "complete response" to "eradication"	To show transition of terminology between protocol amendments.
Section 4.5.3	Analysis of extent of exposure to rVIII-SingleChain has been stated to be also on Surgery population.	For consistency with Section 4.1.
Section 4.6.1.1	In the last bullet point, ABR analysis by final and initial prophylaxis regimen has been replaced with analysis within prophylaxis regimen.	For consistency throughout the section.
Section 4.6.3.1	Analysis of number of bleeding episodes over time has been removed.	No further need of this analysis.
Section 4.7.1	Analysis of Factor VIII inhibitor test results by Total EDs and EDs in the current study has been deleted for PTPs. Analysis of time to inhibitor occurrence has been changed to consider number of EDs rather than time in months. Cumulative Incidence Curve presented rather than KM curve.	No further need of this analysis. To focus on actual days of exposure.
Section 4.7.2	Summary table of all TEAEs occurred during the study and substudies including all PTPs and PUPs has been deleted.	No further need of this analysis.
Section 4.7.2.2	Positive test result for inhibitors performed at local laboratory removed from Medical events of SI	To include back due possible site differences in

		implementing the standardized methods.
Section 4.4, 4.7.1, 4.7.2.2 and 5.1	Minor typo errors have been edited.	NA
Header and signature pages	Company and contact details updated	
Interim analysis section	PTP CSR completed on Nov 2019	
General	**REVISIONS MADE THROUGHOUT THE DOCUMENT:** Protocol No. CSL627_3001 Amendment 3, 27 January 2017 **REVISED TO** Protocol No. CSL627_3001 Amendments 4, 01 October 2019 & Amendments 5, 26 May 2020.	To reflect the latest protocol amendments.
Section 4.1.2	Section added to summarize all sections impacted by Covid-19 amendment	To summarize contingency Covid-19 amendment.

1 Introduction

This document presents the Statistical Analysis Plan (SAP) for CSL Behring GmbH, Protocol No. CSL627_3001: A Phase III Open Label, Multicenter, Extension Study to Assess the Safety and Efficacy of Recombinant Coagulation Factor VIII (rVIII-SingleChain, CSL627) in Subjects with Severe Hemophilia A.

The analyses to be conducted for the final complete Clinical Study Report (CSR) are described.

This SAP is based on the Clinical Study Protocol Amendment 5 dated 26 May 2020. The contingency amendment for Covid-19 dated from 18 June 2020 has been also included.

This SAP is based on the CRF Final Version 8 dated 03May2017.

This SAP provides additional details, e.g., data handling conventions, reporting conventions, and key data derivations.

2 Study Objectives

The objectives and endpoints as stated in the Clinical Study Protocol (CSP) Amendment 5 dated 26 May 2020 are presented below. Eligible subjects are males who have been diagnosed with severe hemophilia A (FVIII activity levels < 1%). There are 3 treatment arms in this study:

- Arm 1 (Previously Treated Patients [PTPs]): subjects of all ages who participated in a previous CSL-sponsored study with rVIII-SingleChain.
- Arm 2 (Previously Untreated Patients [PUPs]): subjects 0 to < 18 years of age who have not been exposed to any FVIII product (except for short-term use of blood products).
- Arm 3 (PTPs): subjects < 65 years of age with at least 50 exposure days (EDs) to any FVIII product and not currently enrolled in an rVIII-SingleChain study.

Arm 2 PUPs can enter this study either at the time of their first bleeding episode or previously diagnosed with hemophilia A in a non-bleeding state.

A surgery substudy (open to all study arms) will investigate the use of rVIII-SingleChain in surgery. CCI [redacted]

Overall, the study objectives in all 3 study arms are to gain additional safety information on the incidence of FVIII inhibitors (including in PUPs), frequency of adverse events (AEs), and serious AEs (SAEs) associated with the use of rVIII-SingleChain, and to gain additional information on the efficacy of rVIII-SingleChain in PTPs and PUPs with severe hemophilia A. This study will collect information on subjects undergoing surgery during the study, thereby providing information on the safety and efficacy of rVIII-SingleChain during surgery.

The primary objectives of the study are:

In **Arms 1 and 3 (PTPs),** the primary objective is

- To characterize the long-term safety profile of rVIII-SingleChain with respect to inhibitor development in PTPs.

In **Arm 2 (PUPs)** the primary objectives are:

- To characterize the safety with respect to inhibitor development in PUPs.
- To evaluate the efficacy of on-demand and prophylaxis treatment of rVIII-SingleChain in PUPs.

In **Arms 1 and 3 (PTPs)**, the secondary objectives are:

- To characterize the safety profile of rVIII-SingleChain with respect to inhibitor development after 10 EDs and after 50 EDs.
- To characterize the safety profile of rVIII-SingleChain with respect to antibodies against rVIII-SingleChain, and antibodies to Chinese Hamster Ovary (CHO) proteins.
- To collect and evaluate efficacy information on the prophylaxis and treatment of bleeding episodes.
- To assess the hemostatic efficacy of rVIII-SingleChain for PTPs who undergo surgery, using the 4-point evaluation of surgical treatment scale.

In **Arm 2 (PUPs)** the secondary objectives are:

- To further characterize the safety profile of rVIII-SingleChain with respect to inhibitor development.
- To characterize the safety profile of rVIII-SingleChain with respect to antibodies against rVIII-SingleChain, and antibodies to CHO proteins.
- To collect and evaluate the number of rVIII-SingleChain injections required for the treatment of bleeding episodes.
- To characterize consumption of rVIII-SingleChain in prophylaxis, on-demand treatment, and surgery.
- To assess the hemostatic efficacy of rVIII-SingleChain for PUPs who undergo surgery, using the 4-point efficacy evaluation of surgical treatment scale.
- To assess the occurrence of clinically significant abnormalities in vital signs after rVIII-SingleChain administration.

2.1 Primary Endpoint

In **Arms 1 and 3 (PTPs),** the primary endpoint is:

- Incidence of inhibitor formation to FVIII in at least 200 PTPs with at least 100 EDs of rVIII-SingleChain.

In **Arm 2 (PUPs)** the primary endpoints are:

- Incidence of high-titer inhibitor formation to FVIII (i.e., inhibitor titer of ≥ 5 Bethesda units/mL during the study) in at least 50 PUPs
- Treatment success for major bleeding episodes, defined as a rating of "excellent" or "good" on the investigator's clinical assessment of hemostatic efficacy 4-point scale.
- Annualized spontaneous bleeding rate (AsBR) during prophylaxis and on-demand treatment.

2.2 Secondary Endpoints

2.2.1 Secondary Efficacy Endpoints

In **Arm 1 and Arm 3 (PTPs),** the secondary efficacy endpoints are:

- Annualized bleeding rate (ABR) (traumatic and non-traumatic) during prophylaxis and on-demand treatment.
- Treatment success for all bleeding (major and minor) episodes defined as a rating of "excellent" or "good" on the investigator's clinical assessment of hemostatic efficacy 4-point scale.
- Percentage of bleeding episodes requiring 1, 2, 3, or > 3 injections of rVIII-SingleChain to achieve hemostasis.
- Mean actual dose per kg per subject per year; consumption of rVIII-SingleChain, expressed as number of injections and IU/kg per month and per year, as well as IU/kg per event (prophylaxis, on-demand and surgery).
- Treatment success for surgery, using the 4-point efficacy evaluation of surgical treatment scale.

In **Arm 2 (PUPs),** the secondary endpoints are:

- Treatment success for non-major bleeding episodes, defined as a rating of "excellent" or "good" on the investigator's clinical assessment of hemostatic efficacy 4-point scale.
- Percentage of bleeding episodes requiring 1, 2, 3 or > 3 injections of rVIII-SingleChain to achieve hemostasis.
- Annualized Bleeding Rate (ABR) during prophylaxis and on-demand treatment.
- Mean and actual dose per kg per subject per year; consumption of rVIII-SingleChain, expressed as number of injections and IU/kg per month and per year, as well as IU/kg per event (prophylaxis, on-demand, and surgery).
- Treatment success for surgery, using the 4-point efficacy evaluation of surgical treatment scale. Success is defined as a rating of 'excellent' or 'good'.

2.2.2 Secondary Safety Endpoints

The secondary Safety endpoints of the study are:

In **Arm 1 and Arm 3 (PTPs),** the secondary safety endpoints are:

- Incidence of inhibitor formation to FVIII in at least 200 PTPs after 10 EDs and after 50 EDs with rVIII-SingleChain.
- Percentage of PTPs who develop antibodies against rVIII-SingleChain.
- Percentage of PTPs who develop antibodies to CHO proteins.

In **Arm 2 (PUPs)**, the secondary safety endpoints are:

- Incidence of high-titer inhibitor formation to FVIII after 10 EDs with rVIII-SingleChain in at least 50 PUPs.
    - A positive inhibitor is defined as two consecutive positive results (>=0.6 Bethesda units (BU) /mL from the central lab.
    - The high-titer inhibitor is defined as any inhibitor tier of ≥ 5 BU/mL) during the study.
- Incidence of low-titer inhibitor formation (FVIII after 10 EDs and after 50 EDs with rVIII-SingleChain in at least 50 PUPs.

  - The low-titer inhibitor is defined as any inhibitor tier of ≥0.6 and < 5 BU/mL) during the study.

- Incidence of total (low- and high-titer) inhibitor formation to FVIII after 10 EDs and after 50 EDs with rVIII-SingleChain in at least 50 PUPs.
- Incidence of transient inhibitors (negative results within 6 months after diagnosis)
- Percentage of PUPs who develop antibodies against rVIII-SingleChain.
- Percentage of PUPs who develop antibodies to CHO proteins.
- Percentage of PUPs with clinically significant abnormal values for blood pressure, or heart rate, or body temperature at 1, 2, 3, or 6 hours after the first rVIII-SingleChain injection.
- Percentage of PUPs with treatment-emergent clinically significant abnormal values for blood pressure, heart rate, or body temperature during the course of the study.

2.3 Other Endpoints

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3 Study Design

3.1 Discussion of Study Design

This multicenter, non-randomized, open-label, multiple-arm phase 3 extension study will continue to investigate the safety and efficacy of rVIII-SingleChain in PTPs and PUPs with severe hemophilia A. This study will evaluate the prophylaxis and on-demand treatment of bleeding episodes in at least 200 PTPs who achieve at least 100 EDs as well as in at least 50 PUPs. In Arms 1 and 3 (PTPs), each PTP will stay in this study until they have achieved at least 100 EDs, which overall is expected to take up to 5 years. In Arm 2 (PUPs), each PUP will stay in this study until they have achieved at least 75EDs, which overall is expected to take up to 5 years. A surgical substudy (open to subjects from all study arms) will investigate the use of rVIII-SingleChain in surgery. CCI [Valentino et al., 2015].

Eligible subjects will be enrolled in 3 Arms, as detailed in Section 2.

This study is designed to collect data on the use of rVIII-SingleChain to assess long-term safety and efficacy beyond the outcome from pre-marketing authorization clinical studies as well as to assess inhibitor development and characterize efficacy and safety of rVIII-SingleChain in PUPs. Inhibitor development is of particular interest for the safety of rVIII-SingleChain.

The preceding lead-in clinical studies, i.e. CSL627_1001 and CSL627_3002, are referred to as pivotal studies.

3.2 Study Treatment Dosing Regimen

In all study arms, the investigator will assign subjects to either prophylaxis or on-demand treatment regimens with rVIII-SingleChain. All subjects will be dosed according to the actual potency printed on the vial label and will be treated by IV injection. On-demand and prophylaxis doses can be adjusted as necessary at the discretion of the investigator. In all study arms, changes in treatment regimens (on-demand or prophylaxis) and dose modifications are allowed and are permitted at the investigator's discretion.

3.2.1 Prophylaxis Treatment Regimen

In previous studies, most subjects received prophylaxis treatment with an initial range of 15 to 50 IU/kg rVIII SingleChain every second day or 2 to 3 times per week.

- In Arm 1 and Arm 3 (PTPs), the investigator will determine the rVIII-SingleChain prophylaxis dose and dosing schedule for the subject based upon the subject's pharmacokinetic (PK) profile, rVIII-SingleChain PK data, previous FVIII treatment regimen, bleeding phenotype (if available), and taking into consideration the World Federation of Hemophilia (WFH) guidelines [WFH, 2012].
- In Arm 2 (PUPs), the investigator will determine the rVIII-SingleChain prophylaxis dose and dosing schedule at their discretion, taking into consideration the WFH guidelines [WFH, 2012], subject's age and other disease characteristics (e.g. bleeding phenotype).

3.2.2 On-demand Treatment Regimen

Subjects assigned to the on-demand treatment regimen will treat themselves or be treated by a caregiver/guardian as needed for any bleeding episode. For the on-demand treatment of bleeding episodes, the initial treatment dose and subsequent dose(s) to achieve hemostasis will be recorded, as well as confirmation that the subject received product and was given instruction for proper use.

After each bleeding episode, the number of injections required to achieve hemostatic efficacy with rVIII-SingleChain will be documented by the subject/caregiver/guardian. The details of each bleeding episode (e.g., type, location, and severity), treatment dose per event, and time required for improvement/resolution of symptoms will be recorded.

3.2.3 Treatment Regimen for Bleeding Episodes

In the event of a bleeding episode, subjects will be treated at a dose pre-determined by the investigator based on the type and severity of the bleeding episode. All subjects should treat bleeding episodes with rVIII-SingleChain when they occur, regardless of the assigned treatment regimen. The desired FVIII level for the treatment of a bleeding episode (on-demand treatment) is based on the recommendations of the WFH [WFH, 2012].

3.2.4 Surgery Doses

In all study arms, the investigator will determine the rVIII-SingleChain dose and treatment schedule for a subject who is scheduled for surgery based on the type of surgery and the clinical status of the subject. The PK data of the study subject or population (if available) will be utilized for calculating the dose regimen of rVIII-SingleChain before, during and after surgery to achieve and maintain the FVIII activity level recommended by the WFH guidelines [WFH, 2012].

3.2.5 Preventive and Additional Doses

In all study arms, preventive doses of rVIII-SingleChain are allowed. A preventive dose is defined as a dose that is taken prior to an activity or a minor procedure to prevent or minimize a bleeding episode.

In all study arms, additional doses of rVIII-SingleChain are allowed. An additional dose is defined as a dose that is taken beyond the need to control hemostasis and does not contribute to the efficacy evaluation of the bleeding episode.

These preventive and additional doses should be captured in the subject's electronic diary (eDiary) or electronic case report form (eCRF), if administered in the hospital. They will not contribute to the haemostatic efficacy evaluation for the bleeding episode, but will contribute to EDs and consumption data.

3.2.6 Change in Treatment Regimens and Dose Modifications

In all study arms, changes in treatment regimens (on-demand or prophylaxis) and dose modifications are allowed and will be permitted at the investigator's discretion. The timing of dose adjustment should be flexible and based on the type of bleeding episode, the location of the bleeding episode, the age of the subject, and bleeding phenotype.

3.2.7 CCI

3.2.7.1 CCI

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3.2.7.2 CCI

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3.2.7.3 CCI

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3.2.7.4 CCI

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3.2.7.5 CCI

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3.3 Study Schedule

The schedule of assessments can be found in the CSP.

3.4 Concomitant Medication Information

Medications other than rVIII-SingleChain taken by a subject at enrollment and continues to be taken during the study are regarded as concomitant medication and must be documented in the eCRF.

The following therapy is permitted during the study:

- Blood product transfusion (whole blood, erythrocytes [red blood cells], or platelets) may be used as clinically indicated.
- Plasma and cryoprecipitate should be used only when clinically indicated and not as a substitute for FVIII, unless FVIII is unavailable and as a rescue medication.
- Other marketed FVIII products should be used as rescue medication only when there is poor/no response to rVIII-SingleChain or when rVIII-SingleChain is not available.

Medications known to have an effect on blood clotting are to be used with caution.

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3.5 Study Populations

Unless specify otherwise, all analyses in all study populations will be performed separately for PTPs and PUPs.

3.5.1 Enrolled Population

The Enrolled population will comprise all subjects who provided informed consent and were not screen failures.

3.5.2 Safety Population

The Safety population will consist of all Enrolled population subjects who received at least one dose of rVIII-SingleChain during the study for any reason (e.g., surgery, routine prophylaxis, on-demand treatment).

3.5.3 Efficacy Population

The Efficacy population will consist of all subjects in the Safety population who received at least 1 dose of rVIII-SingleChain for either routine prophylaxis treatment or on-demand treatment during the study.

The Efficacy population might be the same as the Safety population. In this case, analyses will not be repeated for both the populations.

3.5.4 Surgery Population

The Surgery population will include all subjects in the Safety population who received at least one dose of rVIII-SingleChain for surgical prophylaxis.

3.5.5 CCI

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3.5.6 Subgroups/Subpopulations

The following subgroups will be defined:

- Age based on age in this study:
  - For PTPs (Arm 1 and Arm 3): 0 to < 6 years, ≥ 6 to < 12 years, ≥ 12 to < 18 years and ≥ 18 to ≤ 65 years, 0 to <12 years, ≥12 to ≤ 65 years;
- By Region (Europe, US, Rest of the world, Asia)
- Japan subgroup

Efficacy endpoint will be analyzed by

- Positive vs. negative test for non-inhibitory Anti-Drug Antibodies (ADAs) during the Study.

The incidence of inhibitors will be summarized by

- Race (White, Black, Asian, and Other)

Annualized Bleeding Rates will be presented by

- ADA status (Positive and Negative)

For PUPs analyses for Annualized Bleeding Rates, hemostatic efficacy, TEAE and IR will be presented by inhibitor status (Positive and Negative) at the time of assessment.

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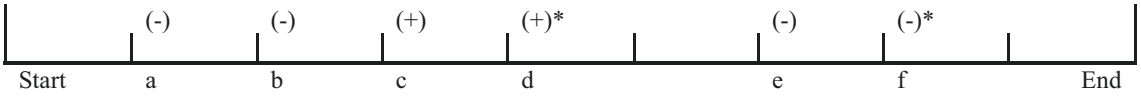
Analyses by inhibitor status or inhibitor group have been defined in this SAP within relevant sections, the definition of inhibitor status and inhibitor group are the following ones:

Inhibitor positive
A subject is inhibitor positive if he developed a titre value (from the central lab) of at least 0.6 BU/mL, and was also confirmed in the next assessment with a titre value of at least 0.6 BU/mL.

Inhibitor negative
A subject is inhibitor negative if his titre value (from the central lab) was below 0.6 BU/mL.

Inhibitor eradicated
It refers to a subject who was previously documented with a confirmed inhibitor positive titre result and at a later point in the study, his titre value decreased and became low enough to classify him as inhibitor negative (titre value < 0.6 BU/mL). However, in order to become inhibitor eradicated, an inhibitor positive subject must first present an initial inhibitor negative titre result which must be confirmed in the next assessment by another inhibitor negative titre result.

Inhibitor status
A subject's inhibitor status represents a period in the study in which he is either inhibitor positive (+) or inhibitor negative (-), depending on his titre value at a given time.



Time reference

The above schema depicts a subject starting out as a negative inhibitor (-), which is the case for all subjects in the study. At some point in the study, i.e. at Time (c), his titre level went up and met the criteria for inhibitor positive status (+), which consisted of an initial titre value of ≥ 0.6 BU/mL, represented by (+) at Time (c), and was followed by a confirmatory titre value of ≥ 0.6 BU/mL in the next assessment, represented by (+)* at Time (d). At Time (c), he is considered (+). When a subject becomes (+), the Investigator may administer an intensified prophylaxis (IP) treatment. Furthermore, he will be included in the CCI [redacted] to treat his inhibitory response to rVIII-SingleChain treatment. If the subject responds positively to IP and/or C CI, his titre values will improve (i.e. decrease) at later assessments. In the above schema, the subject became (-) at Time (e), which was followed by a confirmatory assessment (-)* at Time (f) one month later. At Time (f), the subject is considered inhibitor eradicated.

From the above schema, we can state that:
Period of (+): Time reference after Time (c) up to Time (f), or Time (c) < Time reference ≤ Time (f).
Period of (-): There will be two: on or before (+), and after (-)*.

- On or before (+): Time (start) < Time reference ≤ Time (c)
- After (-)*: Time (f) < Time reference ≤ Time (End)

By partitioning the study duration as periods of inhibitor status, analysis of time-dependent variables can be presented by inhibitor status.

Inhibitor group
An inhibitor group classifies a subject's inhibitor status overall during the study. Therefore, this classification is fixed for a subject, which differentiates itself from the classification by

inhibitor status for which a subject's inhibitor status may change from (-) to (+) over time according to his titre values.
The inhibitor positive group comprises of subjects who were confirmed (+) at any point during the study.
The inhibitor negative group comprises of subjects who were always (-) during the study.

For all subgroups defined in this section, in case of patients lower or equal than 3, the table will not be produced, data will only be provided in the listings.

3.6 Withdrawn Subjects

Subjects may withdraw, or be withdrawn, from the study for the following reasons: AEs, death, lack of efficacy, loss to follow-up, other, physician decision, protocol violation, study terminated by sponsor, or withdrawal by subject.

In addition to the general withdrawal criteria described above, PUPs in Arm 2 must be withdrawn from the study if they develop any of the following withdrawal criteria:

- Use of any FVIII product other than rVIII-SingleChain (or its marketed available version) during the study (including if used as rescue medication)
- Subject develops a confirmed high-titer inhibitor (>5 BU/mL confirmed by repeat testing at the central laboratory) but is not willing to participate in the CCI
- CCI

CCI

3.7 Randomization

This is a non-randomized study.

3.8 Blinding

This is an open-label study.

3.9 Sample Size

Planned Number of Subjects

This study will enroll a sufficient number of subjects diagnosed with severe hemophilia A to achieve a total of least 200 PTPs with at least 100 EDs (Arms 1 and 3) and at least 50 PUPs (Arm 2).

Any subject requiring surgery during the course of the study may participate in the surgery substudy. There is no predefined target number of subjects for surgery substudy.

CCI [redacted]

Sample Size Estimation

The sample size was based on the EMA guidelines for the clinical investigation of recombinant and human plasma-derived factor VIII products [EMA, 2011]. Therefore, no sample size calculations were performed. The target enrollment is at least 200 PTPs (Arms 1 and 3) completing at least 100 EDs during enrollment in all CSL-sponsored rVIII-SingleChain studies and at least 24 PUPs (Arm 2) in this study. Thus, the study will enroll at least 224 subjects with severe hemophilia A.

4 Statistical Methodology

4.1 Planned Analyses

Statistical programming and analyses will be performed by a Contract Research Organization (PPD) under the supervision of CSL Behring. Data derivations and manipulations and statistical analyses will be performed using SAS® version 9.2 or higher.

All summaries and analyses will be provided separately for PTPs and PUPs. For the separate presentation of PTPs and PUPs, all summaries and analyses will be presented as a total and by assigned treatment modality (prophylaxis, on-demand) and/or by age group for PTPs: 0 to < 6 years, ≥ 6 to < 12 years, ≥ 12 to < 18 years and ≥ 18 to ≤ 65 years, 0 to <12 years, ≥12 to ≤ 65 years.

All continuous variables will be summarized in terms of the observed sample size, mean, standard deviation, median, minimum, and maximum. Other descriptive statistics (e.g., quartiles, coefficient of variation) may be reported when appropriate. All categorical variables will be summarized using frequency counts and percentages.

Unless otherwise specified, Confidence Intervals (CIs) presented will be two-sided 95%.

Number of subjects screened will be reported. Unless otherwise stated, baseline and demographic characteristics will be summarized for the Safety, Efficacy, Surgery and CCI populations. Note: If the Safety and Efficacy populations are equal, only the safety population should be produced and a footnote added regarding the efficacy population.

Population summaries:

- Exposure and extent of exposure will be presented for the Safety and Efficacy, Surgery and CCI populations.
- Efficacy variables, compliance, adherence, preventive and additional doses and shift in modality will be presented for the Efficacy population.
- Dose Assignment, dose adjustments and consumption will be presented for the Safety and Efficacy population.
- Primary Efficacy will be generated for Efficacy population.
- The surgery substudy data will be analyzed and summarized for the Surgery population.
- CCI
- Safety variables will be presented for the Safety population.

All listings will include arm, PUP/PTP status, and age group.

4.1.1 Data Handling Conventions

4.1.1.1 Reference Date and Study Day

Timings of all safety events, interventions, and findings will be relative to the reference date. The reference date for this study will be the date of the first dose of rVIII-SingleChain defined as the date of first dose in this study.

Day 1 is the date of the Day 1 visit for this study (see CSP schedule of assessment for details).

4.1.1.2 Surgical Period

The surgical period begins when the subject receives the first dose of rVIII-SingleChain in preparation for the surgery and ends when the subject returns to the scheduled dosing regimen in the main study. If the subject does not receive rVIII-SingleChain in preparation for the surgery, then the surgical period begins on the day of surgery.

If the subject undergoes 2 surgeries, the second surgery period begins when the subject receives the first dose of rVIII-SingleChain in preparation for the second surgery, after the end of the first surgery period.

4.1.1.3 CCI

CCI

4.1.1.4 Baseline and Changes from Baseline

Baseline is defined as the last assessment before the first dose of rVIII-SingleChain in this study. Measurements obtained after the first dose of rVIII-SingleChain will be considered post-baseline values. If measurement of a variable is not made on a given subject before the first dose of rVIII-SingleChain, then that subject will be considered not to have a baseline value for that variable. Change from baseline will be defined as post-baseline assessment minus baseline assessment.

- CCI
- For the surgical substudy, baseline is defined as the last assessment before the first dose of rVIII-SingleChain for surgery.

4.1.2 Covid-19 impact

During the course of this study, the global COVID-19 pandemic occurred. All sections with specific Covid-19 analyses described how the impacts of COVID-19 will be reported. PTPs analysis was completed when COVID-19 occurred, and therefore has no impact on PTPs. Specific COVID-19 analyses apply to the following sections:

- 4.3 Disposition of Subjects
- 4.5.10 Concomitant Medication
- 4.7.2 Adverse Events

4.2 Interim Analysis

No formal efficacy or safety interim analyses are planned. In addition, safety, efficacy and / or PK data may be reported to regulatory authorities while the study is ongoing to supplement information from completed lead-in studies or the ongoing study. Those analyses do not have

an impact on the overall study design or further study conduct, and therefore are not considered to be interim analysis as defined by ICH E9.

4.3 Disposition of Subjects

Subject disposition will include a summary of the number of subjects screened and of screen failures (i.e., ineligible subjects who were screened).

Summaries of enrolled subjects overall and by source of enrollment will be provided on the enrolled population.

Summaries of enrolled subjects will be reported also by investigator. These will include a presentation of country, site ID, and number of subjects per site as a Total and by type of subject (PTP, PUP). In addition, the total number of sites will be presented.

The number of subjects in the following populations will be presented overall, by arm and by type of subject (PTP, PUP): Enrolled population, Safety population, Efficacy population, Surgery population, and [redacted] population. In addition, Efficacy population subjects who do not develop an inhibitor at any time during the study will be presented.

The number and percentage of subjects who completed/did not complete the study, and the reasons for premature withdrawal from the study will be summarized for the Safety population.

Subjects who experience either study treatment discontinuation or study discontinuation due to COVID-19 will have the reason captured in the eCRF. The reason can be either "Withdrawal by Subject," "Physician Decision," or "Other". The associated free text field entry will include "COVID-19" and will be used for flagging Covid-19 reasons. When either treatment or the study is discontinued due to an AE or death, the specific corresponding AE is collected.

Cases of study treatment discontinuation or study discontinuation due to COVID-19 will be included in the summary of subject disposition by adding in a footnote indicating the patient number for the patients concerned.

The number and percentage of subjects who had any inclusion/exclusion criteria deviation will be reported for the Enrolled population. Results will be reported also by inclusion/exclusion criterion. [redacted]

Assessments that were missed or required alternate visit modality due to COVID-19 will be reported.

4.4 Baseline and Demographic Characteristics

Unless otherwise stated, demographic characteristics will be summarized for the Safety, Efficacy, Surgery and [redacted] populations. Demographic characteristics will include: age (as collected in the eCRF, based on age in this study), race, ethnicity, country, geographic region, height, weight, and body mass index (BMI) as a continuous and/or categorical variable. Height, weight and BMI will be based on the values at the Screening visit, i.e., the screening value from this study. BMI will be derived as [weight (Kg)] / [height (m) ^2]. Treatment modality will be recorded upon entry into this study.

Baseline characteristics will be summarized for the Safety population. Baseline characteristics will include:

- Medical/surgical history summarized by System Organ Class (SOC) and Preferred Term (PT) where terms will be coded using Medical Dictionary for Regulatory Activities (MedDRA, Version 16.1 or higher). Past and active medical histories will be

displayed. Past histories are those not identified as ongoing at Screening in the current study. Active histories are those indicated as ongoing at Screening. Only the number of subjects with each history will be displayed, not the number of histories.

- Medical/surgical history related to the following viral diseases will be summarized:
  - Hepatitis B will be defined as past or active medical history mapping to a preferred term that includes "hepatitis B", or a positive test for hepatitis B at screening.
  - Hepatitis C will be defined as past or active medical history mapping to preferred term that include "hepatitis C" or a positive test for hepatitis C at screening.
  - HIV will be defined as a past or active medical history mapping to the preferred term "HIV infection".
- Hemophilia A history will be summarized by hemophilia A gene defect, blood group, number of spontaneous bleeding episodes in last 12 months (before the screening visit from the pivotal study for PTPs from Arm 1, previous to the screening visit in this study for PUPs in Arm 2 and for PTPs from Arm 3), number of trauma-induced bleeding episodes in last 12 months and number of bleeding episodes of unknown nature in last 12 months. For PUPs, summaries for the presence of bleeding at the screening visit will also be reported.
- FVIII treatment history, both the type of FVIII product (plasma product or recombinant product) and modality of treatment (prophylaxis, on-demand) will be summarized for PTPs. If there is more than 1 previous type of product or modality, then only the most recent one will be presented in the summary table. Subjects coming from the pivotal studies (1001, 3002) will automatically have FVIII treatment history. All previous FVIII products and associated modalities will be presented in the listings.
- Hemophilia social history and physical activity level questionnaire data will be presented in listings.

4.5 Exposure

4.5.1 Exposure Days and Time on Study

Exposure days (EDs) and time on study will be summarized for the Safety, Efficacy, Surgery and C CI population. Exposure for subjects coming from the pivotal studies (1001, 3002) will also be assessed cumulatively.

An ED is defined as any day that the subject receives an injection of rVIII-SingleChain regardless of the number of injections on that day. Total EDs are cumulative from previous pivotal study for PTPs in Arm 1 and are calculated from the first dose of rVIII-SingleChain, including all EDs to rVIII-SingleChain from any study or the surgical component of this study. CCI [redacted]

The number of EDs will be summarized as both a continuous and categorical variable by age group as defined in this section.

The following categories will be presented, based on first day of dosing in the pivotal study for Arm 1 and in this study for Arm 2 and Arm 3:

- PTPs: 0-10 EDs, >10-15 EDs, >15-50 EDs, >50-75 EDs, >75-100 EDs, >100 EDs
- PUPs: 0-10 EDs, >10-25 EDs, >25-50 EDs, > 50 EDs

Exposure days in the current study will be summarized as well, as both a continuous and categorical variable as described above. EDs in the current study are counted from first dose in this study or the surgical component of this study or the CCI

Total time on study (days) will be derived as:

[*Maximum* (rVIII-SingleChain last dose date, End of study visit date)] - [*Minimum* (rVIII-SingleChain first dose date considering pivotal study for PTPs Arm 1, Day 1 date in the current study)] + 1.

Time on current study (days) will be derived as:

[*Maximum* (rVIII-SingleChain last dose date, End of study visit date)] - [*Minimum* (rVIII-SingleChain first dose date during the current study, Day 1 date in the current study)] + 1.

Total time on study and time on current study in days, weeks (days/7), and months (days/30.4375) will be summarized using descriptive statistics. Time on study will be described with statistics for continuous variables. Total subject-years will be provided.

CCI

ED will also be summrized by Inhibitor Level (high/low titer) on PUPs.

In addition, a separate exposure analysis over the period of inhibitor development will be provided while subjects are inhibitor positive on PUPs.

CCI

4.5.2 Extent of Exposure to rVIII-SingleChain

The extent of exposure to rVIII-SingleChain will be summarized for the Safety, Efficacy and Surgery population overall and by modality.

The following variables will be used to characterize extent of exposure to rVIII-SingleChain:

- EDs in the current study as a continuous and categorical variable, as in Section 4.5.1
- Number of injections; and the total number of injections over all subjects
- Dose administered per injection (IU/kg); the unit of observation is the injection
- Total IU administered; the unit of observation is the subject.

CCI [redacted]

In addition, a separate extent of exposure to rVIII-SingleChain analysis over the period of inhibitor development will be provided while subjects are inhibitor positive on PUPs.

4.5.3 Compliance and Adherence

Compliance will be summarized for the Efficacy population.

Compliance will be defined in terms of:

- The prophylaxis schedule, i.e. “prophylaxis compliance”. This is applicable only to the prophylaxis regimen.
- The prescribed dose, i.e., “dose compliance”. This is applicable to both the on-demand and prophylaxis regimens.

Prophylaxis compliance will be derived as:

100 * (number of on-schedule prophylaxis injections) / (expected number of prophylaxis injections).

Expected number of prophylaxis injections will be computed considering the cumulative length of periods in which the subject has prophylaxis injections and the assigned regimen in these periods. Periods during which the subject receives injections for reasons different than prophylaxis are excluded.

Prophylaxis compliance will be categorized as 0 to < 80%, ≥80 to ≤120%, ≥120%. Subjects whose prophylaxis compliance is not between 80% and 120% will be addressed in the periodic review of protocol deviations to determine whether they should be classified as non-compliant to the prophylaxis regimen.

Dose compliance will be derived as:

100 * (number of doses within ± 20% of the prescribed dose) / (number of doses).

Dose compliance will be summarized as a continuous and categorized as 0 to < 80%, ≥80 to ≤100%. Subjects whose dose compliance is not between 80% and 100% will be addressed in the periodic review protocol deviations to determine whether they should be classified as non-complaint to prescribed dose.

Adherence will be defined as having dose compliance and prophylaxis compliance (where applicable) based on medical review and assessment of protocol deviations.

CCI [redacted]

Compliance will also be summarized while subjects are inhibitor positive on PUPs.

4.5.4 Dose Assignment and Adjustment

The following parameters will be summarized using descriptive statistics or frequency counts and percentages:

- Initial dose assignment (IU/kg)

- Final dose assignment (or assigned dose at datacut)
- Number and percentage of subjects ever assigned <20 IU/kg anytime during the study
- Number and percentage of subjects ever assigned >50 IU/kg anytime during the study
- Number and percentage of subjects with 0, 1, 2, >2 dose adjustments
- Number of dose adjustments
- Reason for dose adjustment.

The following prophylaxis regimens will be presented on dose assignment and adjustment tables:

- Every second day
- Three times per week
- Two times per week
- Other regimens

If a subject has two dose regimens on the same day, the frequency of the regimen will be summed and the doses will be averaged.

Dose assignment and adjustment for the main study will be summarized for the Safety and the Efficacy population.

4.5.5 CCI

CCI

4.5.6 Shift in modality and regimen

The shift in modality from the pivotal study to the current study will be described with shift tables, i.e. transition frequency tables, presenting number and percentages of subjects in each of the following categories:

- On-demand during the pivotal study and the current study
- Prophylaxis regimen during the pivotal study and the current study
- On-Demand during the pivotal study and Prophylaxis regimen during the current study
- Prophylaxis regimen during the pivotal study and On-Demand during the current study

The shift in modality from the pivotal study to the current study will be summarized for the Efficacy population for the PTPs Arm 1.

For prophylaxis regimen a table will be presented to summarize changes from initial to final regimen.

4.5.7 Preventive and Additional Doses

Preventive doses of rVIII-SingleChain are allowed for subjects on on-demand and prophylaxis regimens. A preventive dose is defined as a dose that is taken prior to an activity or a minor procedure to prevent or minimize a bleeding episode.

Additional doses of rVIII-SingleChain are allowed for subjects on on-demand and prophylaxis regimens. An additional dose is defined as a dose that is taken within the 72 hours from the bleeding episode and beyond the need to control hemostasis and does not contribute to the efficacy evaluation of the bleeding episode.

These preventive and additional doses will not contribute to the efficacy evaluation of the bleeding episode and should be captured as "other treatments" in the subject's eDiary if taken outside the hospital setting or eCRF (if administered in the hospital). Preventive and additional doses will contribute to EDs and consumption data.

The number and percentage of subjects with at least 1 preventive dose during the main study will be presented, and preventive doses will be summarized using descriptive statistics over the number of subjects with at least 1 preventive dose. In addition, the total number of preventive doses will be presented.

Similarly, the number and percentage of subjects with at least 1 additional dose will be presented, and additional doses will be summarized using descriptive statistics over the number of subjects with at least 1 additional dose. In addition, the total number of additional doses will be presented; and the total number of bleeding episodes requiring additional doses will be presented.

CCI [redacted]

4.5.8 Surgical Consumption

Summary statistics will be provided for the consumption of rVIII-SingleChain during surgery for the Surgery population. In particular summaries will be provided for the following time periods: pre-surgery, intra-operative, >0 to ≤72 hours, >0 to ≤168 hours, >0 to ≤336 hours and in total. Consumption for each surgery will be computed considering only doses within the corresponding surgery period. Moreover, individual consumption for each of the abovementioned time periods and in total will be listed. Results will be presented by Arm and age group. Consumption of rVIII-SingleChain on the calendar day of surgery will be also summarized for the following time periods: pre-surgery, intra-operative, post-surgery and total.

Note: If there are overlapping surgeries within 14 days, when calculating the consumption for the first surgery, we will censor this surgery at the beginning of the second surgery (indicated by pre-surgery dose, or surgery dose).

4.5.9 CCI [redacted]

CCI [redacted]

CCI [redacted]

4.5.10 Concomitant Medication

Any medications taken concurrently with rVIII-SingleChain will be regarded as concomitant medications. Concomitant medication will be summarized for the Safety, Efficacy, Surgery and CCI [redacted] populations.

For the Surgery population, only the medications that start during the surgical period will be reported.

CCI [redacted]

The analysis datasets associated with concomitant medications will contain the flags defined below:

- **Prior:** the start date is either strictly prior to the reference date; or missing.
- **Concomitant:** either the start date or the end date is on or after the reference date; or the end date is missing.
- **Prior and concomitant:** both prior and concomitant.

Partial dates will be handled as outlined in 4.12.1. Concomitant medications will be coded using the World Health Organization (WHO) Drug dictionary version Q1, 2013. These will be summarized according to the Anatomical-Therapeutic-Chemical (ATC) classifications and preferred drug name.

Concomitant (i.e., prior and concomitant, or concomitant) medications will be summarized as defined in Section 4.1. Only the number of subjects with concomitant medications (not the number of medications) will be presented.

Concomitant (i.e., prior and concomitant, or concomitant) medications will also be summarized while subjects are inhibitor positive on PUPs.

For concomitant medications which are linked to specific adverse events, the eCRF collects information to identify the specific adverse event. Concomitant medications used to treat COVID-19 associated adverse events will be summarized by ATC and preferred terms if the number of medications is at least equal to 10. Otherwise, concomitant medications used to treat COVID-19 associated adverse events will only be flagged in the listing of prior and concomitant medications.

4.6 Efficacy Analysis

The efficacy endpoints will be summarized and analyzed for the Efficacy population unless otherwise specified. The surgery substudy efficacy data will be summarized for the Surgery population. Efficacy analyses will be performed separately for the PTPs and PUPs and by modality. Efficacy results for the PUPs will be presented by inhibitor status (positive, negative) and overall.

The efficacy evaluation period begins on Treatment Day 1 date in this study and ends at the End of study Visit in this study or the last date of dose, whichever occurs later. Only those treated bleeding episodes and doses which fall within the efficacy evaluation period will count

towards the efficacy evaluation. The summary statistics to be presented are described in Section 4.1.

4.6.1 Primary Efficacy Endpoints

For PTPs, there is no primary efficacy endpoint. Efficacy endpoints for PTPs are described in Section 4.6.2 (Secondary Efficacy Endpoints).

The primary efficacy endpoints for PUPs are:

- Treatment success for major bleeding episodes, defined as a rating of "excellent" or "good" on the investigator's clinical assessment of hemostatic efficacy 4-point scale.
- Annualized spontaneous Bleeding Rate (AsBR)

4.6.1.1 Method of Analysis for the Primary Efficacy Endpoint

The primary endpoint will be summarized for the Efficacy population as described in Section 4.1.

Arm 1 and Arm 3 (PTPs)

There is no primary efficacy endpoint.

Arm 2 (PUPs)

Treatment success for major bleeding episodes

The number of bleeds and the number of treated bleeds will the presented. The percentage of bleeds treated successfully will be reported with a 95% CI. To estimate this percentage, the numerator will include the number of bleeding episodes treated with rVIII-SingleChain and rated as "excellent" or "good" (See Table 6 in Section 8.4.1 of the clinical protocol for details); and the denominator will include all treated bleeding episodes. Missing assessment will be counted as failures. With this approach, the following treated bleeds will be considered treatment failures in the primary analysis: those with ratings of "moderate", or "poor/none"; those treated with products other than rVIII-SingleChain regardless of the assessment; and those with missing investigator ratings. In order to account for within-subject correlation, generalized linear modeling using SAS' GENMOD procedure will be utilized. The model will contain only the intercept term. The binomial distribution with logit link function will be specified.

Two sensitivity analyses of the primary endpoint will be performed:

- In the first sensitivity analysis, missing investigator ratings will be excluded from the denominator.
- In the second sensitivity analysis, missing investigator ratings will be counted as treatment successes.

Results will be presented overall and by treatment modality.

Only bleeding episodes classified as major will be included in this analysis. Bleeding episodes reported by the subject in the eDiary will be excluded since major/minor classification is not collected.

Major and minor bleeds by inhibitor status will be summarized for PUPs.

CCI [redacted]

Summary of rVIII-SingleChain treated bleeding events will be listed while inhibitor positive and per patient.

rVIII-SingleChain Non-Inhibitory Anti-Drug Antibodies, patient related risk factor, treatment related risk factor will be listed for PUPs.

Treatment related risk factor and patient related risk factor will be summarized by inhibitor group.

Bleeding events not treated with rVIII-SingleChain will be listed for PUPs.

AsBR

AsBR will be derived by inhibitor status and overall as follows:

(number of bleeding events) / (observed treatment period of interest days)*365.25.

Only bleeding events requiring treatment will be included in the derivation of bleeding rates. The AsBR will be estimated for subjects who complete at least 8 weeks of treatment on the given inhibitor status using the subject's observed data. If the subject does not complete at least 8 weeks of treatment on the given inhibitor status, then the AsBR will be considered missing.

The number of spontaneous bleeding episodes per year based on a Poisson model and associated 95% CI and the number and percentage of subjects with zero bleeding episodes will be presented. In addition, the rate ratio of Prophylaxis modality to On-Demand modality (Prophylaxis- On-Demand) will be presented, along with the associated 95% CI, as obtained by the Poisson model.

Spontaneous bleeding episodes are those classified as 'Non-traumatic' in e-Diary or 'Spontaneous' in the eCRF. Annualized spontaneous bleeding rate will also be summarized for the following subgroup:

- Positive non-inhibitory Anti-Drug Antibodies (ADAs) and negative during the study
- Age based on age in this study: for PTPs: 0 to < 6 years, ≥ 6 to < 12 years, ≥ 12 to < 18 years and ≥ 18 to ≤ 65 years, 0 to <12 years, ≥12 to ≤ 65 years.
- Prophylaxis frequency: every second day, 3 times per week, 2 times per week, other regimen.

In these subgroup analyses rate ratio of Prophylaxis modality to On-Demand modality won't be displayed.

4.6.2 Secondary Efficacy Endpoints

4.6.2.1 Annualized Bleeding Rate

Annualized bleeding rate, as defined in Section 4.6.1, will be derived also by type of bleed, i.e., for total, spontaneous, traumatic, unknown and joint bleeds for PTPs. Only treated bleeds will be considered. The ABR will be estimated for subjects who complete at least 8 weeks of treatment on the given regimen using the subject's observed data. If the subject does not complete at least 8 weeks of treatment on the given regimen, or has no treated bleeding events while on the given regimen, then the ABR will be considered missing.

A summary of ABR will be performed by inhibitor status if the efficacy evaluation period is greater or equal than 8 weeks on the given inhibitor status.

For PUPs, as secondary efficacy endpoints, annualized bleeding rate, as defined in Section 4.6.1, will be presented also for traumatic, unknown and joint bleeds.

Annualized Bleeding Rates will be derived also separately for the CCI Population.

A specific analysis will be produced for annualized bleeding rates while subjects are inhibitor positive on PUPs.

Bleeding events details will be listed while subjects are inhibitor positive and for all subjects.

Subjects < 8 weeks of efficacy assessment will be listed.

4.6.2.2 Number of infusions of CSL627 required to achieve hemostasis (1, 2, 3, or >3)

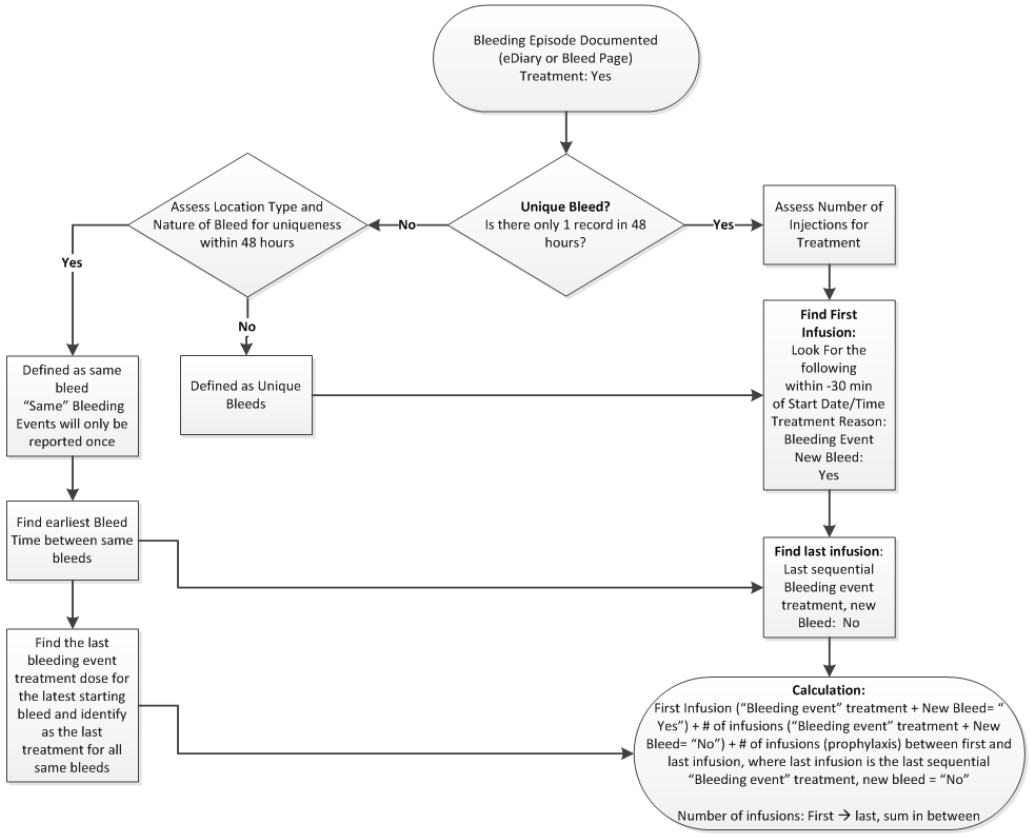
The number of bleeding episodes and the number of treated bleeds, the number and the percentages of subjects with ≥ 1 bleeding episodes and with ≥ 1 treated bleeding episodes will be presented.

The number and percentage of bleeding episodes requiring 1, 2, 3 or more than 3 infusions of CSL627 to achieve hemostasis will be summarized using frequency counts and percentages. No statistical inference will be performed on this data.

In addition, the following parameters will be presented:

- Total dose per bleeding episode in IU and IU/Kg:
  - calculated as: sum of doses (IU) per bleeding episode;
  - calculated as: sum of doses (IU/Kg) per bleeding episode;
- Total dose per injection per bleeding episode in IU and IU/Kg:
  - i.e. total dose (IU) per injection given for any bleeding episodes;
  - i.e. total dose (IU/Kg) per injection given for any bleeding episode.

Treatment Success to achieve hemostasis will be as illustrated:



4.6.2.3 Consumption of rVIII-SingleChain

Consumption will be summarized as described in Section 4.1. Consumption will be summarized for the Efficacy population and Safety population. The following parameters will be derived and summarized using frequency counts or descriptive statistics for subjects on the routine prophylaxis regimen:

- Total number of prophylaxis injections overall calculated as sum of all prophylaxis injections including all subjects;
- Prophylaxis dose administered per subject per month and per year (IU/kg):
  - per year calculated as: sum of prophylaxis doses (IU/kg) per subject*365.25/(efficacy evaluation period);
  - per month calculated as: sum of prophylaxis doses (IU/kg) per subject*(365.25/12)/(efficacy evaluation period);
- Total dose administered per subject per month and per year (IU/kg):
  - per year calculated as: sum of doses (IU/kg) per subject*365.25/(efficacy evaluation period);
  - per month calculated as: sum of doses (IU/kg) per subject*(365.25/12)/(efficacy evaluation period);
- Prophylaxis IU administered per subject per month and per year (IU):

  - per year calculated as: sum of prophylaxis doses (IU) per subject*365.25/(efficacy evaluation period);
  - per month calculated as: sum of prophylaxis doses (IU) per subject*(365.25/12)/(efficacy evaluation period);
- Total IU administered per subject per month and per year (IU):
  - per year calculated as: sum of doses (IU) per subject*365.25/(efficacy evaluation period);
  - per month calculated as: sum of doses (IU) per subject*(365.25/12)/(efficacy evaluation period).

Each dose (IU/kg) will be calculated using the total international units (IU) recorded and the most recent recorded value of weight (kg).

The following prophylaxis regimens will be presented for consumption during routine prophylaxis:

- Three times per week
- Two times per week
- All frequencies.

Prophylaxis infusions are those recorded as administered for 'Routine/Prophylaxis'. Total infusions also include those recorded as administered for 'Bleeding Event', 'Surgery', 'Post Surgery' 'Prevention Prior to Activity', and 'Additional Treatment'.

The following parameters will be derived and summarized using frequency counts or descriptive statistics for subjects assigned to on on-demand treatment:

- Number of infusions per subject per month and per year:
  - per year calculated as: sum of infusions per subject*365.25/(efficacy evaluation period);
  - per month calculated as: sum of infusions per subject*(365.25/12)/(efficacy evaluation period);
- Total dose administered per subject per month and per year (IU/kg):
  - per year calculated as: sum of doses (IU/kg) per subject*365.25/(efficacy evaluation period);
  - per month calculated as: sum of doses (IU/kg) per subject*(365.25/12)/(efficacy evaluation period);
- Total IU administered per subject per month and per year (IU):
  - per year calculated as: sum of doses (IU) per subject*365.25/(efficacy evaluation period);
  - per month calculated as: sum of doses (IU) per subject*(365.25/12)/(efficacy evaluation period).

Each dose (IU/kg) will be calculated using the total international units (IU) recorded and the most recent recorded value of weight (kg).

A specific analysis will be produced for consumption of rVIII-SingleChain while subjects are inhibitor positive on PUPs.

4.6.2.4 Treatment success for surgery

The investigator's overall clinical assessment of hemostatic efficacy for surgical prophylaxis based on the 4-point ordinal efficacy evaluation (See Table 7 of Section 8.5.2.1 of the clinical protocol for details) for surgical treatment scale (excellent, good, moderate, poor/none) will be tabulated overall and by type of surgery (i.e., emergency surgeries, non-emergency surgeries). The treatment success rate, defined as the percentage of surgical hemostasis ratings of excellent or good, will be presented. . Missing assessments will be excluded from the analysis.

Surgical prophylaxis will be summarized for the Surgery population.

4.6.3 Other Efficacy Endpoints

4.6.3.1 Time between the last injection and the next bleeding episode

The time (in hours) between the last injection and the next bleeding episode will be derived. This will only be derived for bleeding episodes that occur during the efficacy evaluation period. For bleeding events with missing time, time to most recent infusion will be derived imputing time to 00:00. Negative values will be reported as zero. Times will be grouped into the following intervals: ≤24, >24 to ≤48, >48 to ≤72, >72 to ≤96, >96 hours after the preceding injection. These will be presented in the listings, which will include as a minimum the following information: type of subject, arm, modality, cause (spontaneous, traumatic, unknown), actual time in hours, and time category.

4.6.3.2 Location of bleeding episodes

The characteristics of bleeding episodes including the type of event (traumatic or spontaneous or unknown causality) and the location of bleeding will be summarized using frequency counts and percentages. Tables will be provided separately for all bleeds, traumatic bleeds, spontaneous bleeds and bleeds with unknown causality.

4.6.4 Other Analyses for the Surgical Substudy

The following information will be summarized using descriptive statistics, or presented qualitatively as appropriate:

- Predicted and estimated blood loss during surgery.
- Predicted and actual transfusion requirements during surgery.
- Change in hemoglobin levels between baseline, during surgery, and after surgery.

These data will be presented for the Surgery population.

Surgical, postoperative details, blood loss and transfusion requirements will be listed while inhibitor positive and for all subjects.

4.7 Safety Analysis

Safety data will be summarized using the Safety population, the Surgery population and the CCI population. Unless specify otherwise, safety data will be summarized separately for the PTPs (Arm 1 and Arm 3) and PUPs (Arm 2) and by age group for PTPs: 0 to < 6 years, ≥ 6 to < 12 years, ≥ 12 to < 18 years and ≥ 18 to ≤ 65 years, 0 to <12 years, ≥12 to ≤ 65 years.

4.7.1 Incidence of Inhibitor Formation

The incidence of inhibitor formation to FVIII will be estimated for subjects in the Safety population who did not have inhibitors at baseline. Baseline assessments are defined as those assessments done before date and time or on the same date and time of the first dose. If time of inhibitors assessment or time of first dose is missing then the inhibitor result taken at the same date of the first dose will be considered as baseline. Inhibitor formation will be defined as any post-baseline inhibitor titer ≥0.6 BU/mL identified and confirmed by re-testing at a subsequent visit. Both tests must be performed by a central laboratory. A positive result not confirmed as positive by re-testing at a subsequent visit result will be considered as non positive. In the KM analysis of inhibitor occurrence, the first positive result will be considered as an event. A positive result not confirmed as positive by re-testing at a subsequent visit result will not be considered as an event. Positive FVIII inhibitors will be further categorized as low or high titer. Low-titer inhibitors are defined as positive inhibitors with a titer of ≤5 BU/mL. High-titer inhibitors are defined as positive inhibitors with a titer of > 5 BU/mL.

For the inhibitor incidence after 10 Total EDs, the numerator will include all subjects with inhibitors observed at the closest visit up to 10 EDs (≤10 EDs). The denominator will include all subjects with at least 10 EDs (≥10 EDs) plus subjects with less than 10 EDs but with inhibitors.

- Numerators = Number of PTP subjects who develop inhibitors up to 10 EDs (≤10 EDs)
- Denominators = Total number of PTPs with at least 10 EDs (≥10 EDs) + subjects with less than 10 EDs with inhibitors. Subjects not tested at ≤10 EDs will be excluded.

The Inhibitor incidence after 50 Total EDs

- Numerators = Number of PTP subjects who develop inhibitors up to 50 EDs (≤50 EDs)
- Denominators =Total number of PTPs with at least 50 EDs (≥50 EDs) + subjects with less than 50 EDs with inhibitors. Subjects not tested at ≤50 EDs will be excluded.

The Inhibitor incidence after 100 Total EDs

- Numerators = Number of PTP subjects who develop inhibitors up to 100 EDs (≤100 EDs)
- Denominators = Total number of PTPs with at least 100 EDs (≥100 EDs) + subjects with less than 100 EDs with inhibitors. Subjects not tested at ≤100 EDs will be excluded.

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Same algorithm will be applied for PUPs.

For PUPs incidence of transient inhibitors (negative results within 6 months after positive result) will be also provided.

The transient inhibitor incidence

- Numerators = Number of PUPs subjects who develop inhibitors and have subsequent negative results within 6 months, i.e. 183 days
- Denominators = Total number of PUPs who develop inhibitors

A two-sided 95% exact CI for the incidence of inhibitor formation will be calculated. If zero inhibitors are observed, then a one-sided 97.5% upper confidence limit will be calculated. SAS' FREQ procedure will be applied to produce an exact CI, which uses the Clopper-Pearson CI as the default method, however, Wald CIs will also be presented. The analysis will be performed also by race.

For PUPs, the incidence (with CI) of inhibitor formation to FVIII will be estimated also by Total EDs ranges. According to the Total EDs they were exposed at time of first positive FVIII inhibitor test PUPs will be classified into 0-10 EDs, >10-25 EDs, >25-50 and >50 EDs. Assessments at EDs=0 are defined as those assessments done before date and time or on the same date and time of first dose. If time of assessment or time of first dose is missing then the inhibitor result taken at the same date of the first dose will be considered as at EDs=0. An assessment done on the same date and time of a dose will be considered to be exposed to the number of EDs the subject has been exposed before that date and time. If time is missing for the assessment or the dose, then the assessment done on the same date of dose will be considered to be exposed to the EDs the subject has been exposed before the date of that dose.

Summaries of inhibitors assay test and inhibitor titer while subjects are inhibitor positive will be provided.

The incidence of inhibitor formation to FVIII will be also summarized at the assessment of 10, 50 and 100 EDs in the current study as collected in the eCRF.

Analysis will be performed overall, by region and considering the Japanese subgroup only.

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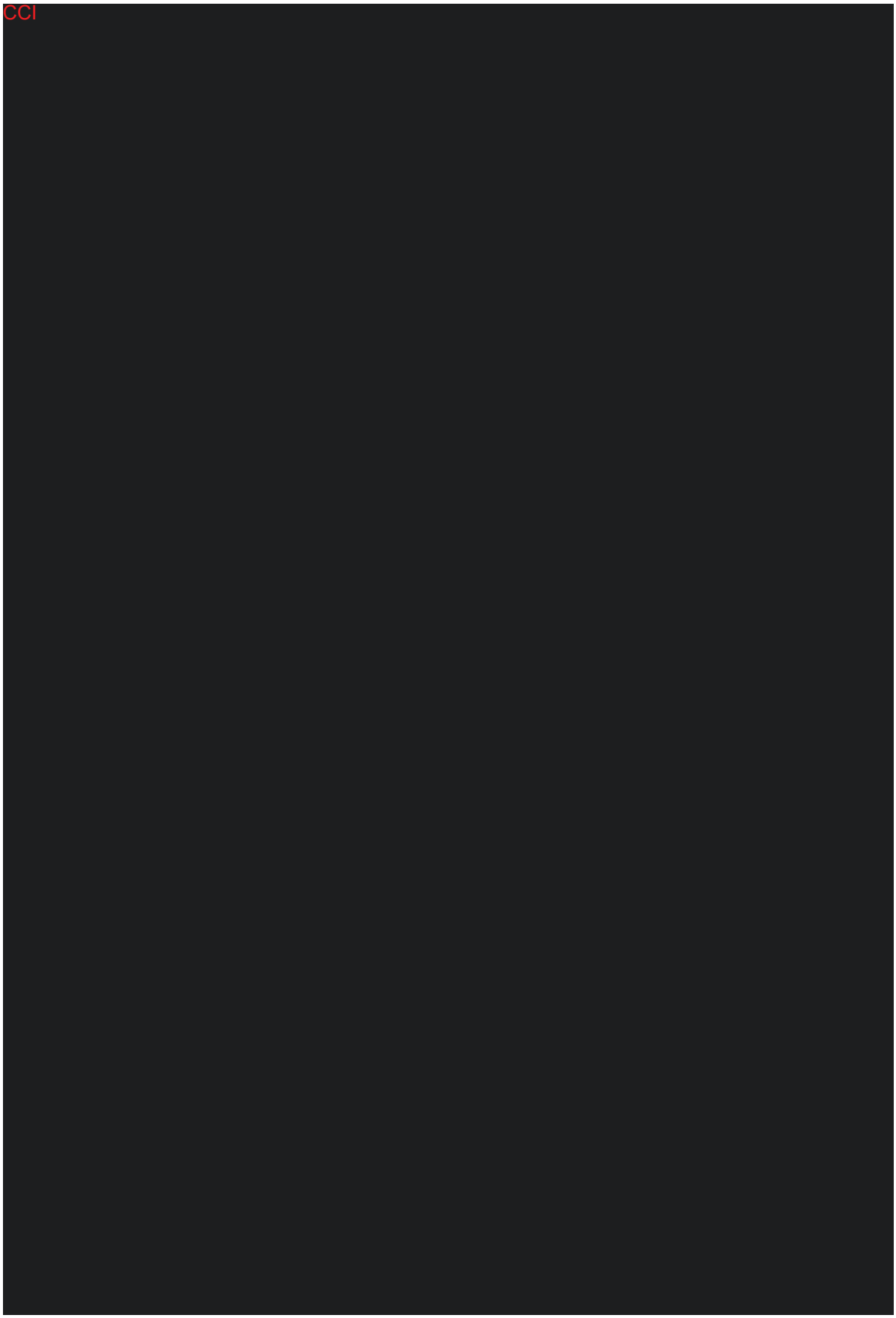

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4.7.2 Adverse Events

An AE is any untoward medical occurrence in a subject or clinical investigation subject administered a pharmaceutical product and which does not necessarily have a causal relationship with this treatment.

Adverse events will be coded and grouped by SOC and PT using the MedDRA Version 16.1 or higher.

An AE will be regarded as treatment-emergent (TEAE) if it was present prior to the first dose of rVIII-SingleChain and subsequently worsened in severity, or was not present prior to the first dose but subsequently appeared. For this determination, partially missing dates will be handled as outlined in 4.12.1. An AE will be assumed to be treatment-emergent if non-treatment emergence cannot be reasonably ruled out. All AEs reported for PTP in Arm 1 will be considered treatment-emergent.

TEAEs will include AEs that occurred during the surgical period, but will exclude TEAEs during the CCI period. A summary table with all the TEAEs that occurred during the studywill be also provided.

Summary of AEs while subjects are inhibitor positive should be performed. All AEs while subjects are inhibitor positive will be listed. Serious AEs while subjects are inhibitor positive will also be listed.

An overview summary table of COVID-19 associated treatment-emergent adverse events (TEAEs), including number and percentages of subjects as well as the number of events, will be provided if the number of Covid-19 associated TEAE is at least equal to 10. Otherwise, Covid-19 associated TEAEs will only be listed.

TEAEs with missing causality assessment will be considered as related.

TEAEs leading to withdrawal are all TEAEs reported on the AE log with “Was subject terminated from study due to the AE” as “Yes” or “Action taken with study drug” with response of “Permanently discontinued”.

The following will be summarized by SOC and PT; displaying the number and percentage of subjects who experience at least 1 event, as well as the total number of events:

- All AEs. This will include TEAEs, and AEs that are not treatment emergent.
- All SAEs. This will include TE SAEs, and SAEs that are not treatment-emergent.
- TEAEs
- Related TEAEs
- Non-serious TEAEs
- Non-serious TEAE by frequency threshold of preferred term (>1%, >2%, >3%, >4%, and >5% in either age cohort)
- TE SAEs

- Related TE SAEs
- TEAEs by maximum severity. If a subject experiences multiple events that map to a single PT, the only the most severe event will be counted.
- Covid-19 TEAEs (considering the same rule of 10 AEs described for the summary table)
- TEAEs while subjects are inhibitor positive

In addition, the SOCs and PTs will be displayed in decreasing frequency. These displays will include the number of subjects who experience at least 1 event, as well as the total number of events.

TEAEs and TE SAEs will be summarized for the Safety population. TEAEs starting during the surgical period will be summarized by SOCs and PTs for the Surgery population. TEAEs starting during the CCI period will be summarized overall and by SOCs and PTs for the CCI population.

All AEs (including all SAEs) will be presented in the individual subject listings. SAEs, deaths, and discontinuations due to AEs will be supported by separate listings.

AEs occurring within one month prior to positive inhibitor development will be listed.

4.7.2.1 Treatment-emergent Adverse Events of Special Interest

Treatment-emergent AEs of special interest (AESIs) will be summarized by category and PT; displaying the number and percentage of subjects who experience at least one event, as well as the total number of events. The treatment-emergent AESIs and how they will be identified are outlined below:

- Thromboembolic Events (TEE) - Standardised MedDRA Queries (SMQ) TEE (narrow)
- Hypersensitivity - SMQ hypersensitivity (narrow)
- Anaphylactic reactions - SMQ Anaphylactic reaction (narrow).

Note: In addition to the SMQ search, a medical review of the AEs may be performed to determine which AESI are confirmed cases.

Treatment-emergent AESIs will be summarized for the Safety population.

Separate listings of AESI data will be also provided: subject, SOC, PT, reported term, causality, seriousness, start and end date/time of events will be displayed.

4.7.2.2 Medical events of special interest

Medical events of special interest include:

- Minor surgery
- Hospital admission for less than 24 hours for events not considered as SAEs
- Positive test result for inhibitors performed at local laboratory
- Overdose
- Hypersensitivity reactions
- Thrombotic events

The number and percentage of subjects with any medical events of special interest, as well as the total number of events, will be presented.

The medical events of special interest will be summarized by category and sub-category; displaying the number and percentage of subjects who experience at least one event, as well as the total number of events (analogous to the AE display by SOC and PT).

Medical events of special interest will be summarized by inhibitor status and on overall for the Safety population.

4.7.3 Local tolerability

Local tolerability will be summarized for the Safety population. Assessments during the CCI period will be excluded from the summary on the Safety Population and presented separately for the CCI population.

4.7.3.1 Subject Assessments

In all 3 Arms, subjects' overall perception of local injection site reactions after each injection will be rated as: None (0), Very slight (1), Slight (2), Moderate (3), and Severe (4). The number and percentage of subjects with at least 1 assessment and the total number of assessments will be summarized.

The number and percentage of subjects with each rating and the number and percentage of events with each rating will be summarized. A reaction will be defined as a rating of very slight, slight, moderate, or severe. The number and percentage of subjects with any reaction, and the total number of reactions will be presented.

4.7.3.2 Investigator Assessments:

Erythema

In Arm 2 and Arm 3, investigators will assess local tolerability after each injection. These will be rated as follows: 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). The number and percentage of subjects with at least 1 assessment and the total number of assessments will be summarized. The number and percentage of subjects for each rating and the number and percentage of events for each rating will be summarized.

Itching, pain and heat

For itching, pain and heat, the number and percentage of subjects with each severity and the number of events with each severity will be presented.

Edema or induration

The size of any edema or induration will be determined by measuring the smallest and largest diameters. For the smallest and largest size of edema or induration, the maximum size across all assessments will be summarized using descriptive statistics.

A separate analysis will be produced on overall investigator assessments while subjects are inhibitor positive on PUPs.

4.7.4 Laboratory findings

Laboratory safety parameters will be measured at the following timepoints:

- For PUPs assigned to Prophylaxis regimen: during Screening, every month until 25 EDs, and every 3 months after 25 EDs and/or End-of-Study Visit.
- For PUPs assigned to On-Demand regimen: during Screening, during Follow-up visits 1 month after each rVIII-SingleChain dose and/or End-of-Study Visit.
- For PTPs: during screening, every 3 months until the subject reaches 50 EDs, and then yearly until End-of-Study Visit as detailed in the Schedule of Assessment in the Clinical Study Protocol (CSP) Amendment 3 dated 27 January 2017.
- CCI [redacted]

Laboratory results (hematology and biochemistry) along with the change from baseline will be summarized by parameter and study visit. CCI [redacted] Baseline is the last non-missing result prior to the first infusion in the current study. Only scheduled visits will be displayed. 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. All visits (including unscheduled, pre/post-surgery visits, CCI [redacted]) will be included in the determination of these maximum/minimum changes from baseline. The number and percentage of subjects with treatment-emergent abnormal hematology and biochemistry values (baseline value normal and post-baseline value abnormal) as assessed by the investigator and recorded on the database as Clinically Significant (CS) will be tabulated by scheduled visit, as well overall. A subject will be counted as having a CS abnormal result as overall result the subject has at least one clinically significant abnormal result after baseline, including unscheduled visits. Laboratory values will be converted to the standard units and this will be documented in the study data tabulation model (SDTM) documentation.

Laboratory results will be provided in the Safety population and presented overall and subgroups based on age in this study. For PTPs: 0 to < 6 years, ≥ 6 to < 12 years, ≥ 12 to < 18 years and ≥ 18 to ≤ 65 years, 0 to <12 years, ≥12 to ≤ 65 years.

Notes:

- All results outside predefined normal ranges will be flagged in the data listings.
- Repeat laboratory results within a visit will not be used in any summary calculations. Repeat results will be listed only.

4.7.4.1 Non-inhibitory Anti-Drug Antibodies (ADAs)

Non-inhibitory anti-drug antibodies (ADAs) screening test results and the confirmatory ADAs IgG and ADAs IgM test results will be tabulated by scheduled visit and inhibitor group. The percentages (positive or negative) at each visit will be based on the number of subjects who were tested at the visit. The final result will be positive if one of the confirmatory tests is positive; otherwise the final result will be negative. The final result over all visits will be based on the final assessment at EOS.

In addition, a shift analysis showing the change in status between baseline and anytime during the study, as well as between baseline and final assessment (EOS) will be provided.

The following information will be summarized, displaying the number and percentage of subjects:

- Positive anytime during the study
- Positive at baseline
- Positive at baseline and anytime after baseline
- Positive at baseline and at the end-of-study visit
- Negative at baseline and positive anytime post-baseline
- Negative at baseline and positive at the End-of-study Visit.

Baseline is the baseline visit of the current study.

Anti-rVIII antibody test results will be summarized for the Safety population overall and by age.

The relationship between ADA and inhibitor titer will be explored graphically overall and by subject displaying in a scatter plot inhibitor titer values along visits stratifying by ADA status.

4.7.4.2 Antibodies against Chinese Hamster Ovary cells

Test results for antibodies against CHO cells will be summarized by reason for specimen collection. If more than one assessment has the same reason, then the most recent one will be considered. The number of subjects tested, and the results (positive or negative) will be displayed. The percentages (positive or negative) will be based on the number of subjects who were tested within reason.

In addition, to the results by reason for specimen collection a "final" result will be derived and presented. A subject's final result will be counted as positive if the subject had a positive test at least once anytime during the study (i.e., at any time on or after screening, including at unscheduled visits). Otherwise, the "final" result will be negative.

The results for antibodies against CHO cells will be summarized also by Total EDs ranges based on first dose in the pivotal study (PTPs, Arm 1) or on first dose in this study (PTPs, Arm 3 and PUPs). According to the Total EDs they were exposed at time of assessment PTPs will be classified into 0-10 EDs, >10-15 EDs, >15-50 EDs, >50-75 EDs, >75-100 EDs, >100 EDs. PUPs will be classified into 0-10 EDs, >10-25 EDs, >25-50, and > 50 EDs. If more than one assessment is included in the same EDs range, then the most recent one will be considered. Definition of assessments at EDs=0 and handling of assessments done on the same date and time of a dose will be as detailed in Section 4.7.1. Analysis will be repeated considering EDs achieved in the current study only.

The results for antibodies against CHO cells will be also summarized at the assessment of 10, 50 and 100 EDs in the current study as collected in the eCRF.

Tests for antibodies against CHO will be summarized for the total Safety population.

4.7.4.3 CD4 Lymphocyte Count

Cluster of Differentiation 4 (CD4) lymphocyte count will also be tested for known HIV-positive subjects using a blood sample taken at Screening if a result is not available in the subject's medical record or the result available is older than 1 year. Results will be listed only.

4.7.4.4 Virology

Retention samples for virology will be obtained at Screening and at the End-of-Study Visit. Results will be listed only.

4.7.5 Vital Signs

Vital signs including blood pressure, heart rate, temperature, and respiratory rate will be documented:

- For PTPs during the screening period, every 3 months until the subject reached 50 EDs and then yearly until End of Study visit.
- For PUPs during the screening period, before and at 1, 2, 3, and 6 hours after the first rVIII-SingleChain injection, every 3 months until the subject reached 50 EDs, then yearly until End of Study visit. For PUPs enrolled into the CCI vital signs will be collected also during enrolment into the CCI, at the following monthly visits and at the end of the CCI.
- CCI

Vital sign results along with the change from baseline will be summarized by scheduled visit. CCI

Vital signs results will be summarized for the Safety population and will be presented by PUPs and PTPs separately and by age subgroups based on age in this study: for PTPs: 0 to < 6 years, ≥ 6 to < 12 years, ≥ 12 to < 18 years and ≥ 18 to ≤ 65 years, 0 to <12 years, ≥12 to ≤ 65 years.

4.7.6 Physical Examination

A physical examination will be conducted by the investigator or delegate according to the schedule of events as in the CSP. A standard of care physical examination for each subject will be performed. Any unfavorable findings considered by the investigator as clinically significant at any point in the study will be documented in the eCRF as an AE.

At Screening clinically significant abnormal findings are to be reported on the Medical/Surgical History form. For all other visits, new clinically significant abnormal findings or clinically significant deteriorations are to be reported on the Adverse Events form. Results will be listed in the corresponding listing.

4.7.7 Incremental Recovery

Incremental recovery (IR) will be calculated with and without adjustment for any baseline endogenous predose FVIII activity levels. Baseline-uncorrected analysis will be done with the unchanged concentration FVIII activity level profiles, while baseline-corrected analysis will be done with transformed values (baseline or pre-dose activity levels subtracted from all the post-infusion measurements).

Only central laboratory FVIII concentration/activity levels quantified using validated chromogenic substrate assay (ChS) will be used in the analysis. IR will be derived using the concentrations FVIII activity levels obtained from the ChS assay.

IR is defined as FVIII activity obtained 30 minutes after injection, divided by the dose of rVIII-SingleChain (IU/dL / IU/kg). The exact time of blood draw after infusion will be recorded and used in the analysis (if needed). All values below the limit of quantification will be treated as zero (0) values.

Descriptive statistics (n, mean, standard deviation [SD], coefficient of variation [CV], median, minimum, and maximum, along with geometric mean, and 95% CIs around the geometric mean) will be presented for IR.

Individual FVIII activity levels will be presented to the significant digits available in the source data and IR will be formatted to 3 significant digits. Parameters or statistics which cannot be determined will be represented in the tables by "-" for not applicable.

FVIII measured before dose and after dose at Day 1, ED 10, ED 50 and ED 100 will be summarized by age group for PTPs (0 to < 6 years, ≥ 6 to < 12 years, ≥ 12 to < 18 years and ≥ 18 to ≤ 65 years, 0 to <12 years, ≥12 to ≤ 65 years)

IR will be also summarized in the following Total ED ranges based on first dose in the pivotal study (PTPs) or on first dose in this study (PUPs): 0-10 EDs, >10-15 EDs, >15-50 EDs, >50-75 EDs, >75-100 EDs, >100. For PUPs only the ranges 0-10 EDs, >10-25 EDs, >25-50, and > 50 EDs will be reported. If more than one assessment is included in the same EDs range, then the most recent one will be considered. Definition of assessments at EDs=0 and handling of assessments done on the same date and time of a dose will be as detailed in Section 4.7.1.

Analysis will be repeated considering EDs achieved in the current study only.

IR will be also summarized by reason for specimen collection. If more than one assessment has the same reason, then the most recent one will be considered.

For PUPs, results will be presented overall and by inhibitor status at time of the assessment.

CCI [redacted]

4.8 Adjustment for Covariates

Not applicable.

4.8.1 Center Effects

There are no plans to display results by center.

4.9 Protocol Deviations

Deviations from the protocol will be documented on an ongoing basis throughout the study period. All protocol deviations will be summarized and listed with type and details of deviation.

4.10 Deviations from SAP

Any deviations from the original statistical plan will be described and justified in the final clinical study report,.

4.11 Changes in Conduct or Planned Analyses from the Protocol

Section 2.1 and 2.2: In the protocol, incidence of inhibitor formation to FVIII in Arm 2, PUPs is stated that would be performed on at least 50 PUPs. However, this condition has been removed. Given that patients that develop inhibitors may be withdrawn from the study early, they would not necessarily achieve 50 exposure days but we would definitely have to include them in the calculation. Therefore the text was adjusted to ensure the option to properly report the endpoint regardless of these circumstances.

CCI [redacted]

Section 3.5.3: Efficacy Population definition has been changed removing the exclusive inclusion of subjects who do not have an inhibitor at any time point during the study.

CCI [redacted]

Section 4.6.1 and 4.6.2.1: In the Annualized Bleeding Rate analysis it has been added that subjects with an efficacy evaluation period less than 8 weeks (56 days) will be excluded from the analysis to exclude bias due to short evaluation period.

Section 4.6.2.2: The analysis of number of infusions of CSL627 required to achieve hemostasis has been added for completeness of analysis.

Section 4.7.1: Incidence of transient inhibitors has been added for completeness of analysis.

Section 4.7.2.1: Analysis of AESIs has been added for completeness of analysis.

4.12 Missing Values

4.12.1 Handling Partial Dates

A date is a valid partial date if the day is missing, or the day and the month are missing. Where appropriate, the algorithm outlined in Table 2 will be applied to accommodate partial dates.

Table 2: Handling Partial Dates

Date	Missing Element(s)	Imputation
Start date	Day and Month	First day of the year
	Day	First day of the month
Stop date	Day and Month	Last day of the year
	Day	Last day of the month

4.12.2 Early Withdrawal or Missing data

Refer to the handling of partial dates in Section 4.12.1 and method of analysis for the primary efficacy endpoint in Section 4.6.1.1. Other than these two items, no imputation due to withdrawals or missing data will be applied.

4.13 Algorithms/SAS Codes

- **Tables that need descriptive statistics – continuous variables:**
  PROC UNIVARIATE DATA=dset NOPRINT;
  VAR var1 var2 var3 …varn;
  BY byvar; (optional)
  OUTPUT OUT=outname
  N=n MEAN=mean MIN=min MAX=max MEDIAN=median STD=std Q1=q1 Q3=q3;
  RUN;

- **Tables that need frequency counts:**
  PROC FREQ DATA=dset NOPRINT;
  BY byvar; (optional)
  *TABLES var1*var2;*
  OUTPUT OUT=outname;
  RUN;

- **Tables that need 95% CIs within group for binomial proportions:**
  PROC FREQ DATA=dset;
  BY byvar; (optional)

TABLES var1;
EXACT BINOMIAL; RUN;

- **Tables that require generalized linear modelling, including 95% CIs:**

PROC GENMOD DATA= dset;
CLASS subject;
MODEL 'bleeding events / time on csl = < treatment> /CL DIST=POISSON offset=logtime link=log;
LSMEANS < treatment> /diff=control exp cl;
WHERE wherever; (optional)
RUN;

- **The geometric mean is the antilog of the arithmetic mean of the logs:**

DATA dset;
SET dset old;
LOGx = LOG(x);
RUN;

PROC UNIVARIATE DATA=dset NOPRINT;
VAR LOGx;
OUTPUT OUT=outname
MEAN=logmean;
RUN;

DATA outname;
SET outname;
geomean = EXP(logmean);
RUN;

5 Tables and Listings

5.1 Format

The following conventions will be adopted for the outputs. These conventions will enhance the review process and help to standardize presentations.

- All tables, figures, and listings (where appropriate) will be presented in Landscape Orientation. A 9-*point* font size using the *Courier New* font is proposed.
- Legends will be used for all figures with more than 1 variable or item displayed.
- Only standard keyboard characters will be used in tables and figures. Special characters, such as non-printable control characters, printer specific or font specific characters, will not be used on a table or figure.
- All footnotes will be left justified and at the bottom of a page. Footnotes must be present on the page where they are first referenced. Footnotes will be used sparingly and only to add value to the table or figure. If more than four footnotes are planned then a cover page may be used to display the footnotes.
- All laboratory data will be presented in the Standard Units.
- All date values will be presented as DDMMMYYYY (e.g., 08SEP2008) format.
- All observed time values will be presented using a 24-hour clock HH:MM:SS format (e.g., 13:35:56 or 14:22). Seconds will only be reported if measured.
- Time durations will be reported in mixed HHh MMm SSs notation (e.g., 5h 32m, or 27h 52m 20s). Decimal notations will not be used to present time durations.
- All tables and figures will have the name of the program and a date/time stamp on the bottom of each output.
- Populations represented on the tables or figures will be clearly identified in the last title of the Table.
- Consistent terminology will be used to define and identify a population.
- Population sizes will be presented for as totals in the column heading as (N=xxx), where appropriate.
- All study population and baseline characteristics and safety summaries will include a Total column where appropriate.
- All population summaries for continuous variables will include n, mean, SD, median, minimum, and maximum. Other descriptive statistics (e.g., quartiles, coefficient of variation) may be reported when appropriate.
- The minimum and maximum values will be presented with the same number of decimal places as the raw data collected. The mean and percentiles (e.g. median, Q1, and Q3) will be presented using one additional decimal place. The standard deviation and standard error will be presented using two additional decimal places. PK parameters should have a minimum of 3 significant figures.
- Percentages will be presented to 1 significant decimal place in general. The denominator will be the total size of the sample, N, unless otherwise noted.

- Any p-values reported on default output from statistical software may be reported at the default level of precision, with one exception: p-values of 0.0000 or 10E-4 or below will be reported as <0.0001.
- The *left* and *right margins* of all tables and listings will be a minimum of 2.1 cm from the left and 1.9cm from the right. The *top and bottom margins* will be a minimum 2.92cm. *Header and footer* will be both 1.27 cm.

5.2 Tables

The list of tables and associated shells are provided in a separate document.

5.3 Figures

The list of figures and associated shells are provided in a separate document.

5.4 Listings

The list of listings and associated shells are provided in a separate document.

5.5 Appendices

NA

5.6 References

CSL Behring GmbH, Protocol No. CSL627_1001: A Phase I/III Open-label, Multicenter, Crossover Safety, Efficacy and Pharmacokinetic Study of Recombinant Coagulation Factor VIII (rFVIII) Compared to Recombinant Human Antihaemophilic Factor VIII (rFVIII; INN: octocog alfa) in Subjects with Hemophilia A, and a Repeat PK, Safety and Efficacy Study.

CSL Behring GmbH, Protocol No. CSL627_3001: A Phase III Open Label, Multicenter, Extension Study to Assess the Safety and Efficacy of Recombinant Coagulation Factor VIII (rVIII-SingleChain, CSL627) in Subjects with Severe Hemophilia A.

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