2 SYNOPSIS

Name of Sponsor: CSL Behring GmbH	Individual Study Table Referring to Part of the Dossier Volume: Page:	(For National Authority Use Only)
Name of Finished Product: rVIII-SingleChain (CSL627)		
Name of Active Ingredient: FVIII (lonoctocog alfa)		

Title of Study:
A Phase 3 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
(Synopsis for Previously Untreated Patients Only; Arm 2)

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Publication (reference):
None

Study Period Arm 2 (For Previously Untreated Patients [PUPs] Only): *First Subject Visit*: 26 August 2015 *Last Subject Visit*: 19 January 2021	**Phase of Development:** Phase 3

Objectives CSL627-3001 Arm 2 Study:
Primary Objectives: The primary objectives in previously untreated patients (PUPs [Arm 2]) were:

- To characterize the safety with respect to inhibitor development.
- To evaluate the efficacy of on-demand and prophylaxis treatment of Single chain recombinant coagulation factor VIII (rVIII-SingleChain).

Secondary Objectives: The secondary objectives in PUPs (Arm 2) were:

- 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 Chinese hamster ovary (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.

Exploratory Objectives: The exploratory objectives in PUPs (Arm 2) were:

- To characterize the relationship between inhibitor development and exposure to rVIII-SingleChain in PUPs.
- Immune tolerance induction (ITI) substudy: to investigate the use of rVIII-SingleChain in ITI in PUPs who develop an inhibitor to rVIII-SingleChain.

Methodology:

This multicenter, nonrandomized, open-label, multiple-arm phase 3 extension study continued to investigate the safety and efficacy of rVIII-SingleChain in PUPs with severe hemophilia A. This study evaluated the prophylaxis and on-demand treatment of bleeding episodes in PUPs who achieved at least 75 exposure days (EDs). A surgical substudy (open to subjects from all study arms) investigated the use of rVIII-SingleChain in surgery. In addition, an ITI substudy (open to subjects who developed a confirmed inhibitor to rVIII-SingleChain) investigated the use of rVIII-SingleChain as ITI therapy.

Eligible subjects were males (0 to < 18 years of age) diagnosed with severe hemophilia A (coagulation factor VIII [FVIII] activity levels < 1%).

The results of previously treated patients (PTPs) (Arm 1 and Arm 3) were presented previously in a separate report. Subjects in Arm 2 were PUPs who had not participated in any clinical study with rVIII-SingleChain and had no other prior exposure to any FVIII product.

Number of Subjects:

The target enrollment was at least 50 PUPs based on the European Medicines Agency guidelines for the clinical investigation of recombinant and human plasma-derived FVIII products.

Diagnosis and Main Criteria for Inclusion:

Subjects aged 0 to < 18 years with severe congenital hemophilia A (FVIII activity < 1%, determined in local laboratory before enrollment or documented in subject's medical record) with no prior exposure to any FVIII product (with the exception of short-term use of blood products).

Investigational Product, Dose and Mode of Administration, Batch Number(s):

The study drug, rVIII-SingleChain, was supplied as a powder in single-use vials and administered as an intravenous injection. Each vial of rVIII-SingleChain powder was reconstituted with 1 vial of sterile water for injection (2.5 mL for 250, 500, or 1000 IU vials; 5.0 mL for 2000 or 3000 IU vials). In Arm 2 (PUPs), the investigator determined the rVIII-SingleChain dose and dosing schedule at their discretion, taking into consideration the World Federation of Hemophilia (WFH) guidelines, subject age, and other disease characteristics (eg, bleeding phenotype).

In the event of a bleeding episode, subjects were treated at a dose predetermined by the investigator based on the type and severity of the bleeding episode. The desired FVIII level for the treatment of a bleeding episode (on-demand treatment) was based on the WFH guidelines.

Changes in treatment regimen (on-demand or prophylaxis) and dose modifications were allowed at the investigator's discretion. The timing of dose adjustment was to be flexible and based on the type and location of the bleeding episode, age of subject, and bleeding phenotype. Preventive and additional doses of rVIII-SingleChain were also allowed.

The investigator determined the rVIII-SingleChain dose and treatment schedule for subjects who were scheduled for surgery based on the type of surgery and the clinical status of the subject. The pharmacokinetic data from subjects (if available) were 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.

The use of bypassing agents (ie, activated recombinant FVII or activated prothrombin complex concentrate / FVIII inhibitor bypassing agent) was permitted in subjects with inhibitors.

Duration of Treatment:

Inhibitor negative subjects remained in the study until they achieved 75 EDs with rVIII-SingleChain. The overall study duration was expected to be up to 6 years. Additional time of up to 3 years in the study could occur for subjects who developed an inhibitor.

Criteria for Evaluation (in PUPs [Arm 2]):

Efficacy

Primary Endpoints: The primary efficacy analysis endpoints included:

- 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.

Secondary Endpoints: The secondary efficacy analysis endpoints included:

- Treatment success for nonmajor 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 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.

Exploratory Endpoints: The exploratory efficacy analysis endpoints in the ITI substudy included:

- Complete response to ITI treatment with rVIII-SingleChain, overall and per regimen.
- Time to complete response to ITI treatment with rVIII-SingleChain, overall and per regimen.
- Consumption of rVIII-SingleChain for ITI treatment, overall and per regimen.

Safety

Primary Endpoint: The primary safety endpoint included:

- Incidence of high-titer inhibitor formation to FVIII (ie, inhibitor titer of > 5 Bethesda unit [BU]/mL) in PUPs with at least 50 EDs of rVIII-SingleChain.

Secondary Endpoints: The secondary safety endpoints included:

- Incidence of high-titer inhibitor formation to FVIII (ie, inhibitor titer of > 5 BU/mL) after 10 EDs with rVIII-SingleChain.
- Incidence of low-titer inhibitor formation (ie, inhibitor titer of ≤ 5 BU/mL) to FVIII after 10 EDs and after 50 EDs with rVIII-SingleChain.
- Incidence of total (low- and high-titer) inhibitor formation to FVIII after 10 EDs and after 50 EDs with rVIII-SingleChain.
- Incidence of transient inhibitors (negative results within 6 months after diagnosis).
- Percentage of subjects who developed antibodies against rVIII-SingleChain.
- Percentage of subjects who developed antibodies to CHO proteins.

Exploratory Endpoints: The exploratory safety endpoints included:

- Cumulative risk of low-titer and high-titer inhibitors over increasing exposure to rVIII-SingleChain.
- Incidence of high-titer inhibitor formation after 10 EDs up to 50 EDs with rVIII-SingleChain.
- Incidence of low-titer inhibitor formation after 10 EDs up to 50 EDs with rVIII-SingleChain.
- Incidence of high- and low-titer inhibitor formation after 10 EDs up to 50 EDs with rVIII-SingleChain.

Statistical Methods:

All safety and efficacy endpoints were summarized or listed as appropriate. Continuous data were summarized using descriptive statistics, and categorical data were summarized using frequency counts and percentages. No formal interim analyses were planned.

Efficacy Analysis:

The PUP Efficacy Population comprised all enrolled subjects who received at least 1 dose of rVIII-SingleChain for either routine prophylaxis treatment or on-demand treatment during the study.

The PUP Surgery Population comprised all enrolled subjects who received at least 1 dose of rVIII-SingleChain for surgical prophylaxis.

The ITI Population included all PUPs who received at least 1 dose of rVIII-SingleChain to treat their inhibitor.

The number of bleeds and the number of treated bleeds were presented.

The investigator's clinical assessment of hemostatic efficacy for the treatment of major bleeding episodes, based on the 4-point ordinal scale ("excellent", "good", "moderate", "poor / no response"), was tabulated. The percentage of major bleeding episodes treated successfully (defined as ratings of "excellent" or "good") was summarized and reported together with a 2-sided 95% CI. To estimate the proportion, the denominator included all treated bleeding episodes categorized as major. To account for within-subject correlation, generalized linear modeling using SAS' GENMOD procedure was utilized. The model contained only the intercept term. The binomial distribution with logit link function was specified.

The investigator's clinical assessment of hemostatic efficacy for the treatment of nonmajor bleeding episodes was analyzed as described for major bleeding episodes above.

ABR was presented for total, traumatic, unknown, and joint bleeds. A summary of ABR by inhibitor status was performed if the efficacy evaluation period was ≥ 8 weeks for the given inhibitor status. The AsBR was summarized by regimen (on-demand or prophylaxis) using descriptive statistics. In addition, the number of spontaneous bleeding episodes per year and associated 95% CI was estimated based on a Poisson distribution. Generalized linear modeling using SAS' GENMOD procedure was utilized. The Poisson distribution with log link function and log_time offset was specified.

The number and percentage of bleeding episodes requiring 1, 2, 3, or > 3 injections of rVIII-SingleChain to achieve hemostasis were summarized using frequency counts and percentages. The consumption of rVIII-SingleChain, was derived and expressed in terms of IU/kg per month, IU/kg per year, total IU per injection, per month and per year. Consumption was summarized using descriptive statistics for on-demand, prophylaxis, and surgery.

Surgical Substudy

The investigator's overall clinical assessment of hemostatic efficacy for surgical prophylaxis based on the 4-point ordinal efficacy evaluation for surgical treatment scale (excellent, good, moderate, poor / no response) was tabulated overall and by type of surgery (ie, emergency surgeries, nonemergency surgeries). The treatment success rate, defined as the percentage of surgical hemostasis ratings of excellent or good, was presented.

The following information was 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.

ITI Population

A summary of the consumption of rVIII-SingleChain for inhibitor treatment period was provided. Number and percentages of subjects achieving an eradication to ITI treatment with rVIII-SingleChain was presented with a 2-sided exact 95% CI. The percentage of subjects achieving an eradication was calculated based on the ITI Population.

Other Efficacy Analyses

The characteristics of bleeding episodes including the type of event (traumatic or spontaneous or unknown causality) and the location of bleeding (joint, muscle, mucosal or other) were summarized using frequency counts and percentages.

Safety Analysis:

Safety analysis was based on Safety Population. The Safety Population comprised all the PUP Enrolled Population who received at least 1 dose of rVIII-SingleChain during the study for any reason (eg, surgery, routine prophylaxis, on-demand treatment).

Incidence of transient inhibitors (negative results within 6 months after positive result) in PUPs was also provided.

Kaplan-Meier (KM) estimates were used to analyze the cumulative risk of occurrence overall, for subjects with low-titer (ie, inhibitor titer of ≤ 5 BU/mL) and high-titer (> 5 BU/mL) inhibitor formation over increasing exposure to rVIII-SingleChain.

The number of subjects at risk and the rate of both low-titer and high-titer occurrence were summarized.

The number and percentage of subjects who experienced at least 1 adverse event (AE) and the number of events were summarized by System Organ Class (SOC) and Preferred Term (PT). Additional treatment-emergent AE (TEAE) summaries included all AEs (including TEAEs and AEs that were not treatment-emergent), related TEAEs, TEAEs by

maximum severity, TEAEs leading to death, treatment-emergent serious adverse events (TE SAEs), related SAEs, and TEAEs leading to withdrawal.

Laboratory parameters (hematology and biochemistry), noninhibitory antidrug antibodies (ADAs) screening test results, and test results for antibodies against CHO cells were summarized. All other safety data (cluster of differentiation 4 [CD4] lymphocyte count, virology, vital signs, physical examination, and incremental recovery [IR]) were summarized using descriptive statistics and were listed.

For subjects enrolled in the ITI substudy and included in the ITI Population, inhibitor titer over time was summarized. The historical peak titer (ie, the highest inhibitor titer before initiation of ITI treatment) and the peak titer during ITI treatment were identified for each subject and summarized separately.

Results: Results are only presented for the PUPs (Arm 2).

Subject Disposition

A total of 24 subjects were enrolled in the study and exposed to treatment with rVIII-SingleChain. Overall, 19 subjects (79.2%) completed the study, and 5 subjects (20.8%) discontinued the study. Three subjects (12.5%) discontinued the study as per physician's decision, 1 subject (4.2%) discontinued because of an AE (high-titer inhibitor) before the ITI substudy was implemented, and 1 subject (4.2%) discontinued because of overseas relocation.

Demographics

Only male subjects were enrolled into this study. Overall, the majority of subjects were White (62.5% of subjects); 29.2% of subjects were Black or African American and 8.3% were Asian. With regard to ethnicity, 4.2% of subjects were Hispanic or Latino and 95.8% of subjects were not Hispanic or Latino. The mean age was 1.4 years.

Efficacy

Efficacy - Main Study

The key efficacy findings from the main study were as follows:

- Overall, 92.1% (290 of 315) treated bleeding episodes had a hemostatic response rated as "excellent" or "good", with similar treatment success for bleeding episodes on the on-demand and prophylaxis regimens. Overall, 88.9% of bleeding episodes were controlled with 1 or 2 injections of rVIII-SingleChain.
- Treatment success was 93.6% while subjects were inhibitor negative and was 68.4% while subjects were inhibitor positive.
- There was 1 major bleeding episode (spontaneous bleeding event in right knee) that was treated with rVIII-SingleChain, with a hemostatic efficacy rating of "excellent".

- Overall, 90.0% (54 of 60) of treated nonmajor bleeding episodes had a response rated as "excellent" or "good"; the treatment success rate was 92.0% and 88.6% for the on-demand and prophylaxis treatment regimens, respectively.
- The median (range) ABR was 3.76 (0.0 to 17.1) for all bleeds and 1.15 (0.0 to 5.6) for spontaneous bleeds for the on-demand treatment regimen and was 1.84 (0.0 to 23.6) for all bleeds and 0.88 (0.0 to 19.7) for spontaneous bleeds for the prophylaxis treatment regimen.
- There was no apparent clinically relevant difference in ABRs and AsBRs while the subjects were inhibitor-positive compared with while they were inhibitor negative.

Efficacy in Subjects While Inhibitor Positive

- The mean (SD) total ITI dose of rVIII-SingleChain was 183.84 IU/kg (102.385) per subject per week. The mean (range) number of injections administered during inhibitor treatment period was 124.6 (16 to 287).
- Nine out of 11 subjects (81.8%; 95% CI: 0.482, 0.977) who were treated for inhibitor eradicated their inhibitor. The median (range) EDs to inhibitor eradication was 37.00 (16.0 to 194.0). The median (range) time to inhibitor eradication was 14.29 (7.7 to 64.4) weeks. Six peak low-titer subjects and 3 peak high-titer subjects achieved inhibitor eradication.

Efficacy - Surgery

The key efficacy findings relating to the use of rVIII-SingleChain in surgical prophylaxis were as follows:

- There were 3 surgeries during the study and all 3 were nonemergency surgeries. The treatment success rate of rVIII-SingleChain in these surgeries was 100%.
- No blood transfusion was given for any surgeries.

Safety

The key safety findings from the Main study were as follows:

- Of the 24 subjects, 12 subjects tested positive for inhibitor development. Of these, 6 subjects had a peak inhibitor value in the high-titer range (> 5 BU/mL), and 6 subjects had a peak inhibitor value in the low-titer range (≤ 5 BU/mL).
- Twelve subjects developed non-inhibitory ADAs during the study. Eight of the 12 subjects who developed non-inhibitory ADAs were positive for inhibitors; 6 subjects had high-titer and 2 subjects had low-titer inhibitors. Two of these 12 subjects were confirmed to be positive for non-inhibitory ADAs by the End of Study (EOS).
- There were no reports of development of antibodies against CHO host cell proteins. There were no reports of anaphylactic reactions or TEEs. No AEs related to rVIII-SingleChain associated with double or higher dose than prescribed were

reported.

- Ten subjects experienced 15 AESIs that could be considered as symptoms or manifestations of hypersensitivity reactions. All the AESIs were either mild or moderate in severity and none of these were related to rVIII-SingleChain. Upon medical review, none of these AESIs were confirmed as hypersensitivity reactions.
- Overall, 14 subjects in the PUP Safety Population experienced 21 treatment-emergent serious adverse event (TE SAEs). Thirteen SAEs were related to rVIII-SingleChain, with 12 of these comprising PTs summarized as Inhibitor Development.
- One subject was withdrawn from the study due to an SAE of inhibiting antibodies positive (high titer), as per protocol requirement. After this SAE, the clinical study protocol was amended to allow subjects diagnosed with inhibitor to continue in the study and enroll into the ITI substudy.
- There were no notable findings relating to clinical laboratory or vital signs parameters.

Safety in ITI Population

The ITI population comprised of 11 subjects. The key safety findings were as follows:

- Of the 11 subjects in the ITI Population, 5 subjects had a peak high-titer (> 5 BU/mL) inhibitor, and 6 subjects had a peak low-titer (≤ 5 BU/mL) inhibitor. Six subjects were enrolled in the ITI substudy. At the time of enrollment into the ITI substudy, 2 subjects had a high-titer inhibitor, and 4 subjects had a low-titer inhibitor.
- All subjects in the ITI Population reported at least 1 TEAE during the inhibitor treatment period.
- A total of 5 TE SAEs were reported in 4 subjects in the ITI Population during the inhibitor treatment period.
- Two of the 4 subjects had 1 SAE each that was considered related to rVIII-SingleChain. All the SAEs during the inhibitor treatment period had resolved at the EOS.
- There were no AEs leading to discontinuation from the ITI substudy. Three subjects had AESIs considered as symptoms or manifestations of hypersensitivity reactions during the inhibitor treatment period. None of these AESIs were confirmed as hypersensitivity reactions on medical review.

Conclusions:

The overall treatment success was 92.1% for all rVIII-SingleChain-treated bleeds. The high-titer and low-titer inhibitor rate in PUPs was 25% each. Immunological analyses suggested a low-affinity antibody population in PUPs with hemophilia A. The majority of PUPs (81.8%) who continued treatment with rVIII-SingleChain achieved inhibitor eradication. Considering safety, efficacy, inhibitor eradication rate, and the immunological analyses, the benefit-risk profile for rVIII-SingleChain in PUPs is largely consistent with that observed in PTPs. No new safety signals were identified.

Date of Report: 25 June 2021