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 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		
Coordinating Investigator: PPD UMCU, Heidelberglaan 100, Utrecht, 3584 CX, Netherlands		
Publication (reference): None		
Study Period: *First Subject Visit*: 13 October 2014 *Last Subject Visit*: 04 December 2018	**Phase of Development:** Phase 3	

Objectives:

Primary Objective: The primary objective in previously treated patients (PTPs) (Arms 1 and 3) was to characterize the long-term safety profile of rVIII-SingleChain with respect to inhibitor development.

Secondary Objectives:

In PTPs, the secondary objectives were:

- To characterize the safety profile of rVIII-SingleChain with respect to inhibitor development after 10 exposure days (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 efficacy evaluation of surgical treatment scale.

Exploratory Objectives:

In PTPs, the exploratory objective was to further characterize the safety profile of rVIII-SingleChain with respect to inhibitor development.

Methodology:

This multicenter, non-randomized, open-label, multiple-arm phase 3 extension study continued to investigate the safety and efficacy of rVIII-SingleChain in PTPs with severe hemophilia A (factor VIII [FVIII] activity levels < 1%). The study aimed to evaluate routine prophylaxis and on-demand treatment of bleeding episodes in at least 200 PTPs who achieved at least 100 EDs to rVIII-SingleChain. A surgical substudy (open to subjects from all study arms) investigated the use of rVIII-SingleChain in surgery.

Subjects in Arm 1 were PTPs of any age who had participated in a previous CSL Behring-sponsored clinical study with rVIII-SingleChain. Subjects in Arm 3 were PTPs 0 to < 65 years of age previously exposed to FVIII products (which may include rVIII-SingleChain), but who had not been enrolled in a rVIII-SingleChain study. Arm 2 includes previously untreated patients (PUPs) for whom the study is currently ongoing. Results for PUPs will be presented in a separate Clinical Study Reports after the completion of the study.

Number of Subjects:

The target enrollment was at least 200 PTPs (Arms 1 and 3) completing at least 100 EDs during enrollment in all CSL Behring-sponsored rVIII-SingleChain studies, based on the European Medicines Agency guidelines for the clinical investigation of recombinant and human plasma-derived factor VIII products. A total of 222 subjects were enrolled.

Diagnosis and Main Criteria for Inclusion:

Arm 1: Subjects who had participated in a previous CSL Behring-sponsored rVIII-SingleChain investigational study (ie, Studies CSL627_1001 and CSL627_3002; hereafter referred to as Studies 1001 and 3002, respectively).

Arm 3: Subjects aged 0 to < 65 years at the time of providing informed consent, with a diagnosis of severe congenital hemophilia A (FVIII activity < 1%, determined in local laboratory before enrollment or documented in subject's medical record) and a minimum of 50 EDs to any FVIII product.

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 all study arms in Study CSL627_3001 (hereafter referred to as Study 3001), the dose was based on the subject's most current body weight prior to administration and the actual FVIII potency (units) as indicated on the vial label.

The investigator determined 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 took into consideration the World Federation of Hemophilia (WFH) guidelines.

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. All subjects treated bleeding episodes with rVIII-SingleChain when they occurred, regardless of the assigned treatment regimen. The desired FVIII level for the treatment of a bleeding episode (on-demand treatment) was based on the WFH guidelines.

Duration of Treatment:

The duration of the study for an individual PTP subject was approximately 5 years. PTPs in Arm 1 could enroll immediately after participation in previous rVIII-SingleChain studies and continue treatment until achieving at least 100 EDs (including EDs from any previous rVIII-SingleChain study). PTPs in Arm 3 received treatment in the study until they achieved at least 100 EDs with rVIII-SingleChain (excluding EDs from any previous rVIII-SingleChain study that the subject may have participated in).

Criteria for Evaluation:

Efficacy Endpoints:

There were no primary efficacy endpoints for PTPs.

Secondary efficacy endpoints included:

- Annualized bleeding rate (traumatic and nontraumatic) during prophylaxis and on-demand treatment.
- Treatment success for bleeding episodes defined as a rating of "excellent" or "good" on the investigator's clinical assessment of hemostatic efficacy 4-point scale.
- Number of injections of rVIII-SingleChain required to achieve hemostasis (1, 2, 3, or > 3)
- 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.

Other efficacy endpoints for PTPs were as follows:

- Number of bleeding episodes over time.
- Time between the last injection and the next bleeding episode.
- Location of bleeding episodes.

Safety Endpoints:

For PTPs, the primary endpoint was the incidence of inhibitor formation to FVIII in at least 200 PTPs with at least 100 EDs of rVIII-SingleChain.

The secondary safety endpoints for PTPs were as follows:

- 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 developed antibodies against rVIII-SingleChain.
- Percentage of PTPs who developed antibodies to CHO proteins.

Other safety endpoints for PTPs were as follows:

- Incidence of inhibitor formation after 10 EDs up to 50 EDs with rVIII-SingleChain.
- Incidence of inhibitor formation after 50 EDs up to 100 EDs with rVIII-SingleChain.

Statistical Methods:

All safety and efficacy data were summarized or listed as appropriate. Continuous data were summarized using descriptive statistics and categorical data summarized using frequency counts and percentages. No formal interim analyses were planned. The final analysis of PTPs was planned to be conducted when all PTPs had completed the study to support the production of this study report on PTPs while the study is still ongoing for the PUP arm.

Efficacy analysis:

Efficacy endpoints were summarized for the Efficacy population unless otherwise specified. Surgery substudy efficacy data were summarized for the Surgery population. The efficacy evaluation period started on the Treatment Day 1 date in this study and ended at the End of Study Visit in this study or the last date of dose, whichever occurred later. Only those treated bleeding episodes and doses that fell within the efficacy evaluation period were included in the efficacy evaluation.

Control and prevention of bleeding episodes

The number of bleeds and the number of treated bleeds were presented. The percentage of bleeds treated successfully were reported with a 95% CI. To estimate this percentage, the numerator included the number of bleeding episodes treated with rVIII-SingleChain and rated as "excellent" or "good"; and the denominator included all treated bleeding episodes. Missing assessment was counted as failures. With this approach, the following treated bleeds were 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. Two sensitivity analyses were performed (ie, a) missing investigator ratings were excluded from the denominator and b) missing investigator ratings were counted as treatment successes). Results were presented overall and by treatment modality.

The number and percentage of bleeding episodes requiring 1, 2, 3 or more than 3 injections of rVIII-SingleChain to achieve hemostasis were summarized using frequency counts and percentages. No statistical inferences were performed on these data.

Routine prophylaxis

Annualized bleeding rates (ABR) were derived by type of bleed, ie, for total, spontaneous, traumatic, unknown and joint bleeds for PTPs. Only treated bleeds were considered. The ABR was estimated for PTPs who completed at least 8 weeks of treatment on the given regimen using the subject's observed data. If the subject did 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 was considered missing. However, the ABRs for subjects who completed at least 8 weeks of treatment but did not receive any treatment for bleeding events within a regimen were set to zero.

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 / none) was tabulated overall and by type of surgery (ie, emergency surgeries, non-emergency 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.

PK analysis:

Incremental recovery (IR) was calculated with and without adjustment for any baseline endogenous predose FVIII activity levels. Baseline-uncorrected analysis were performed with the unchanged concentration FVIII activity level profiles, while baseline-corrected analysis were performed with transformed values (baseline or predose activity levels subtracted from all the postinjection measurements). Only central laboratory FVIII concentration / activity levels quantified using validated chromogenic substrate assay were used in the analysis. IR was derived using the concentrations of FVIII activity levels obtained from the chromogenic substrate assay.

Descriptive statistics (n, mean, standard deviation [SD], coefficient of variation, median, minimum, and maximum, along with geometric mean, and 95% CIs around the geometric mean) were presented for IR. Individual FVIII activity levels were presented to the significant digits available in the source data and IR were formatted to 3 significant digits. Parameters or statistics which could not be determined were represented in the tables by "-" for not applicable.

Safety analysis:

To calculate the inhibitor incidence after 10 EDs (ie, after 50 EDs and after 100 EDs), the numerator included all subjects with inhibitors observed at the closest visit up to 10 EDs (≤ 10 EDs; ie, up to 50 EDs and up to 100 EDs). The denominator included all subjects with at least 10 EDs (≥ 10 EDs; ie, at least 50 EDs and at least 100 EDs) plus subjects with less than 10 EDs (< 10 EDs; ie, less than 50 EDs and less than 100 EDs) but with inhibitors.

The incidence of inhibitor formation to FVIII was estimated for subjects in the Safety population who did not have inhibitors at baseline. Baseline assessments were defined as those assessments performed 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 was missing then the inhibitor result taken at the same date of the first dose was considered as baseline. Inhibitor formation was defined as any postbaseline inhibitor titer ≥ 0.6 BU/mL identified and confirmed by re testing at a subsequent visit. Both tests were performed by a central laboratory. A positive result not confirmed as positive by retesting at a subsequent visit result was considered as nonpositive.

In the Kaplan Meier analysis of inhibitor occurrence, the first positive result was considered as an event. A positive result not confirmed as positive by retesting at a subsequent visit result was not considered as an event. Positive FVIII inhibitors were further categorized as low or high titer. Low-titer inhibitors were defined as positive inhibitors with a titer of ≤ 5 BU/mL. High-titer inhibitors were defined as positive inhibitors with a titer of > 5 BU/mL**.**

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 and Preferred Term. Additional treatment-emergent AE summaries included related AEs, AEs by maximum severity, AEs leading to death, serious adverse event (SAEs), related SAEs, and AEs leading to withdrawal.

The subjects' assessments of local tolerability and the investigator's assessment of erythema were summarized using frequency counts and percentages based on the total number of rVIII-SingleChain injections.

Laboratory parameters, non-inhibitory antidrug antibodies (ADAs) and CHO host cell protein, and vital sign results were summarized. The number and proportion of subjects with treatment-emergent abnormal laboratory values or potentially clinically significant vital sign values were tabulated.

Results:

Subject Disposition and Demographics

A total of 222 PTP subjects were enrolled into the study and exposed to treatment with rVIII-SingleChain, including 204 PTPs from the lead-in studies that were enrolled in Arm 1. Arm 3 of the study comprised a total of 18 subjects.

Overall, 197 of 222 (88.7%) enrolled PTP subjects completed the study and 25 (11.3%) discontinued the study. Ten subjects (4.5%) elected to withdraw from the study for unspecified reasons, 4 (1.8%) subjects discontinued due to AEs, 5 (2.3%) subjects discontinued for 'other' reasons, 1 subject discontinued due to lack of efficacy, 1 subject was lost to follow-up, 3 subjects discontinued due to the physician's decision, and there was 1 unrelated subject death that was associated a treatment-emergent adverse event (TEAE) of Generalised Tonic-clonic Seizure.

rVIII-SingleChain Administration and Exposure

The cumulative mean (SD) number of EDs for PTPs (ie, in the lead-in studies and the current study) was 416.5 (163.74) and was highest in the ≥ 18 to ≤ 65 years age group at 442.9 (175.94). The mean (SD) number of EDs was comparable across the remaining 3 age groups: < 6 years (343.0 [144.45]), ≥ 6 to < 12 years (389.1 [140.40]), and ≥ 12 to < 18 years (394.6 [11.08]).

The mean (SD) number of EDs for PTPs in the current study was 341.9 (135.48). A total of 216 subjects (97.3%) and 212 subjects (95.5%) attained > 100 EDs cumulatively and in the current study, respectively.

Pharmacokinetic Results

PK analyses in Study CSL627_3001 (Arms 1 and 3) were consistent with findings from Study 1001. In the overall PTP Safety Population, mean FVIII activity increased from predose levels of 3.33 IU/dL to 66.6 IU/dL approximately 30 to 60 after injection of rVIII-SingleChain. Subjects in the 2 pediatric age groups of < 6 years (53.6 IU/dL) and ≥ 6 to < 12 years (60.4 IU/dL) attained slightly lower mean FVIII activities compared to the adolescent age group of ≥ 12 to < 18 years (69.2 IU/dL) and the adult age group of ≥ 18 to ≤ 65 years (70.8 IU/dL).

The mean IR for subjects in the overall PTP Safety Population was 1.79 (IU/Dl)/(IU/kg), with similar age based observations as noted for the FVIII activity levels. Of note, IR for subjects in the overall PTP Safety Population in Study 3001 remained consistent after long-term use of rVIII-SingleChain, and was comparable after 10 EDs, 50 EDs, and 100 EDs.

Efficacy

Control and prevention of bleeding episodes

Data from Study 3001 (Arms 1 and 3) were consistent with those previously reported in Studies 1001 and 3002 with respect to the control and prevention of bleeding episodes, and showed that treatment success rates were not affected by subject age group. In the current study, 2413 bleeding episodes were treated with rVIII-SingleChain, 87.1% of all treated bleeding events had a response rated as 'excellent' or 'good', demonstrating consistency with data from Study 1001, in which 92.3% of treated bleeding episodes had a response rate rated as 'excellent' or 'good'.

Based on the investigator's overall assessment of hemostatic efficacy, data from Study 3001 also extended knowledge from the pivotal Study 1001, by demonstrating that use of different prophylaxis regimens (every 2nd day [87.3%], 3 times per week [94.6%], 2 times per week [89.6%] or based on 'other' regimens [95.5%]) does not affect outcomes rated as 'excellent' or 'good' for the treated bleeding events.

In line with data from the pivotal registration Study 1001, the majority of treated bleeding events (86.2%) were controlled with 1 or 2 injections of rVIII-SingleChain.

Routine prophylaxis

Data from Study 3001 (Arms 1 and 3) were also in line with the pivotal registration Study 1001 with regard to the use of rVIII-SingleChain in routine prophylaxis, as the ABR was reduced by 90% with prophylaxis, when compared to the on-demand treatment group.

Data from Study 3001 extended knowledge of the product by demonstrating that subject age did not impact the ABR (95% CI), except as expected for the pediatric age group of ≥ 6 to < 12 years due to higher FVIII clearance compared with the adolescents and adults, lifestyle characteristics, weight and bleeding profiles.

Review of data by treatment regimen also showed no difference in the ABR (95% CI) for subjects receiving rVIII-SingleChain every 2nd day, 2 times or 3 times per week; 2.1 (1.7, 2.6), 2.5 (2.3, 2.7), and 2.7 (2.5, 2.9), respectively.

In Study 3001 (Arms 1 and 3), the development of rare non-inhibitory ADAs did not impact the ABR, which remained similar in subjects with and without non-inhibitory ADAs. Furthermore, the type of prophylaxis treatment regimen (ie, rVIII-SingleChain every 2nd day, 2 times or 3 times per week) did not appear to impact the efficacy of treatment as assessed by the ABR.

Surgical prophylaxis

The data from Study 3001 (Arms 1 and 3) were also consistent with those previously reported in Study 1001 with respect the use of rVIII-SingleChain in perioperative (surgical) prophylaxis, as demonstrated by the 100% treatment success rate in the surgical prophylaxis, for both emergency and non-emergency surgeries. There were a total of 32 surgical procedures performed with 87.5% rated as excellent and 12.5% as good. In addition, the transfusion requirements and hemoglobin levels of the subjects were within expected margins for the type of surgeries undertaken in the study.

Safety

In Study 3001, the safety profile of rVIII-SingleChain was consistent with the documented profile of rVIII-SingleChain in adult and pediatric PTPs with hemophilia A investigated in lead-in Studies 1001 and 3002.

Key safety findings from the study were as follows:

- There were no reports of inhibitor formation to FVIII. A small proportion of subjects (3.2%) that were negative for non-inhibitory ADAs at baseline were confirmed as positive for non-inhibitory ADAs during the study; however, these patients were all negative for non-inhibitory ADA by the end of the study.
- There were no reports of development of antibodies against CHO host cell proteins. There were no reports of anaphylactic reactions, TEEs, and TEAEs related to rVIII-SingleChain associated with double or higher dose than prescribed.
- One PTP experienced 3 nonserious related TEAEs of Drug Hypersensitivity. The subject made a complete recovery but discontinued rVIII-SingleChain after the third occurrence of Drug Hypersensitivity.
- Overall, 9.9% of the PTPs experienced treatment-emergent SAEs, none of which were considered related to rVIII-SingleChain.
- Four PTPs experienced 6 TEAEs that resulted in study discontinuation, 3 of which (Preferred Term: Drug Hypersensitivity; all in 1 subject) were considered related to rVIII-SingleChain.
- There was a single unrelated death in the study (due to an event of Generalised Tonic-clonic Seizure).
- There were no notable findings relating to clinical laboratory or vital signs parameters.
- The AEs that started during the surgical period were consistent with events associated with the surgical procedure (eg, Procedural Pain) and none were considered by the investigator as related to rVIII-SingleChain.

Conclusions:

The postmarketing requirement from the European Medicines Agency guideline for 200 PTPs with ≥ 100 EDs to rVIII-SingleChain was fulfilled. A total of 222 PTP subjects were enrolled into the study and exposed to treatment with rVIII-SingleChain. The mean (SD) number of EDs for all PTPs in the current study was 341.9 (135.48). A total of 216 subjects (97.3%) and 212 subjects (95.5%) attained > 100 EDs overall and in the current study, respectively.

Data from Study 3001 (Arms 1 and 3) were consistent with those previously reported in Studies 1001 and 3002 with respect to the control and prevention of bleeding episodes, use in routine prophylaxis, and surgical prophylaxis. No new safety signals or concerns were identified from this extension study.

This extension study has demonstrated the long-term efficacy and safety of rVIII-SingleChain in PTPs with severe hemophilia A when used for routine prophylaxis, on-demand treatment, and for surgical prophylaxis, and supports the current dosing regimen as detailed in the product label.

Date of Report: 28 November 2019