Amsterdam, 11 November 2021
EMA/456459/2021
Committee for Medicinal Products for Human Use (CHMP)

Assessment report for paediatric studies submitted according to Article 46 of the Regulation (EC) No 1901/2006

Afstyla

lonoctocog alfa

Procedure no: EMEA/H/C/004075/P46/003

Note

Assessment report as adopted by the CHMP with all information of a commercially confidential nature deleted.

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1. Introduction

On 2nd July 2021, the MAH submitted a completed paediatric study for Afstyla, in accordance with Article 46 of Regulation (EC) No1901/2006, as amended.

This submission is a post-authorisation measure in accordance with Article 46 of the paediatric regulation with no change to PI.

The MAH submitted the PUP CSR for study CSL627_3001.
The PTP CSR for study CSL627_3001 was submitted in sequence 68 already.

The MAH also requests for a full PIP compliance check, which will be assessed by PDCO, separately.

A short critical expert overview has also been provided.

2. Scientific discussion

2.1. Information on the development program

Afstyla was evaluated within three clinical studies:

CSL627_1001: This was a completed pivotal Phase I/III, prospective, multicenter, open label study to evaluate the PK, efficacy (on-demand, routine prophylaxis, surgical prophylaxis), and safety in 175 adolescents and adult subjects (aged 12 to 65 years) with severe haemophilia A.

CSL627_3002: This was a completed Phase III, prospective, multicenter, open label, paediatric study to evaluate the PK, efficacy (on-demand and routine prophylaxis), and safety in 85 children aged less than 12 years with severe haemophilia A.

CSL627_3001: This was a completed Phase III, prospective, multicenter, open label, extension study to evaluate the safety (long-term safety and inhibitor development) and efficacy (on-demand, routine prophylaxis, surgery, Immune tolerance induction (ITI) substudy) in previously treated patients (PTPs) and previously untreated patients (PUPs). The extension study 3001 was conducted to fulfill the European Medicines Agency (EMA) postmarketing requirement of at least 200 PTPs with at least 100 exposure days (EDs) as stipulated in the EMA "Guideline on the clinical investigation of recombinant and human plasma-derived factor VIII products", adopted 21 July 2011.

comment:

A line listing of all the concerned studies is requested (RSI).

2.2. Information on the pharmaceutical formulation used in the study

Afstyla (Recombinant Single-Chain Factor VIII or rVIII-SingleChain) is used for the treatment and prevention of bleeding in patients with haemophilia A as replacement therapy. The active substance, lonoctocog alfa, is expressed and secreted by Chinese hamster ovary cells. It is a B-domain truncated variant of human factor VIII defined by covalently bonded FVIII heavy and light chains within a single polypeptide structure. It is formulated as a sterile, non-pyrogenic, preservative-free, lyophilized, powder for intravenous administration provided in a single-use vial. Each single-use vial contains nominally 250 IU, 500 IU, 1000 IU, 2000 IU or 3000 IU (International Units) of rVIII-SingleChain for reconstitution with sterile water for injection (2.5 ml sWFI: 250 IU, 500 IU, 1000 IU; 5.0 ml sWFI: 2000 IU, 3000 IU).

2.3. Clinical aspects

2.3.1. Introduction

The MAH submitted a final report from PUPs of the Study CSL627_3001 (Arm 2). This study was completed for PUPs (last subject visit) in January 2021, the completed Clinical Study Report (CSR) dated June 2021.

A summary of the final results from PTPs in this study (Arms 1 and 3, completed for PTPs in December 2018) was submitted to EMA in January 2020 (eCTD sequence 68 / procedure reference EMEA/H/C/004075/MEA/002.1). The final report for PTPs dated 28 November 2019.

2.3.2. Clinical study

Clinical study number and title

CSL 627_3001 **-** 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.

Description

Study 3001 was a multicenter, non-randomized, open-label, multiple-arm, phase 3 extension study to investigate the safety and efficacy of rVIII-SingleChain in PTPs and PUPs with severe hemophilia A (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 (Study Arms 1 and 3) as well as in PUPs who achieved at least 50 EDs (Study Arm 2).

A main objective of this study was to collect information on inhibitor formation in PUPs 0 to < 18 years of age. In this regard, the EMA guideline in effect in 2011 stated that approval of the indication in PUPs will be based on a clinical trial in a minimum of 50 PUPs evaluated for efficacy and safety during at least 50 EDs. Thus, in line with the guideline in effect at time of study planning and implementation of Study Amendment 3, this extension study was planned to a) fulfill the EMA requirements for a postmarketing investigation to attain 100 EDs in at least 200 PTPs (completed) and b) acquire efficacy and safety data in at least 50 PUPs attaining at least 50 EDs to rVIII-SingleChain. Per Protocol Amendment 4, the number of PUPs was reduced to at least 24, with each PUP remained in the study until they achieved at least 75 EDs (Study Amendment 5).

A surgical substudy (open to subjects from all study arms) investigated the use of rVIII-SingleChain in surgery. Additionally, an immune tolerance induction (ITI) substudy in PUPs was implemented to investigate the use of rVIII-SingleChain as ITI therapy in PUPs who develop an inhibitor to rVIII-SingleChain in the main study.

Study Period (for PUPs):

- First Subject Visit: 26 August 2015

- Last Subject Visit: 19 January 2021

- Clinical Study Report (for PUPs; Arm 2) Version 1.0 dated 25 June 2021

Methods

Objectives (Arm 2)

Primary Objectives (PUPs [Arm 2]):

- 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 (PUPs [Arm 2]):

- 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.

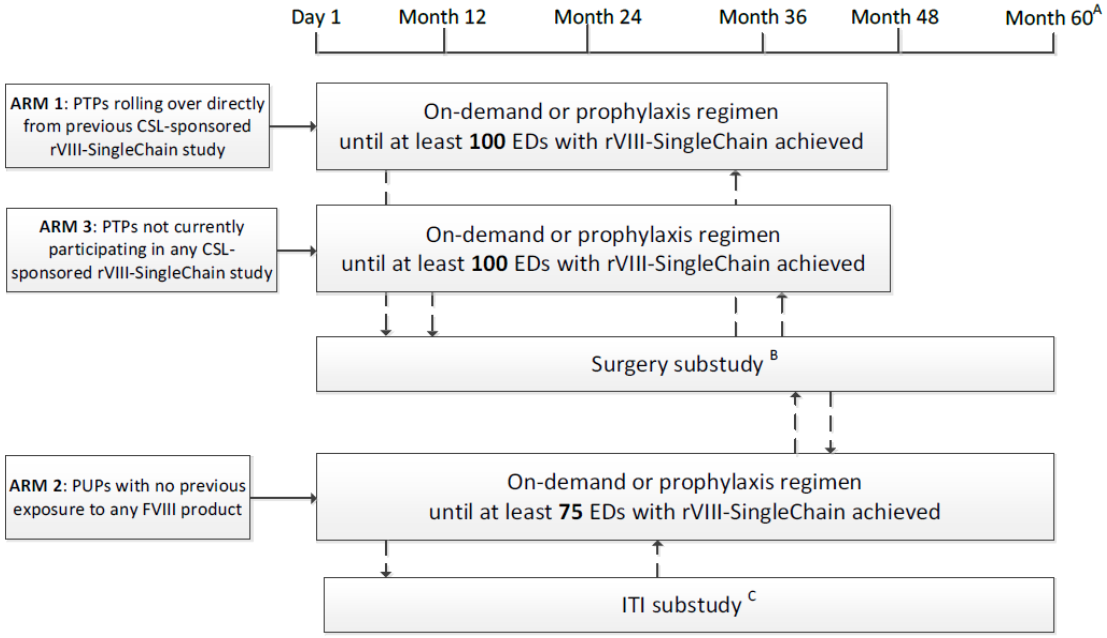
Exploratory Objectives (PUPs [Arm 2]):

- 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.

Study design

The study was a multicenter, nonrandomized, open-label, multiple-arm extension study. It was performed at study sites in 7 countries (Italy, Lebanon, Malaysia, Netherlands, Portugal, South Africa, United States). Eligible subjects were males diagnosed with severe hemophilia A (FVIII activity levels < 1%). Subjects in Arm 1 were PTPs who had participated in a previous CSL-sponsored clinical study with rVIII-SingleChain. Subjects in Arm 3 were PTPs who had not participated in a previous CSL-sponsored clinical study with rVIII-SingleChain. 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.

Figure 1: Study Overview of CSL627_3001



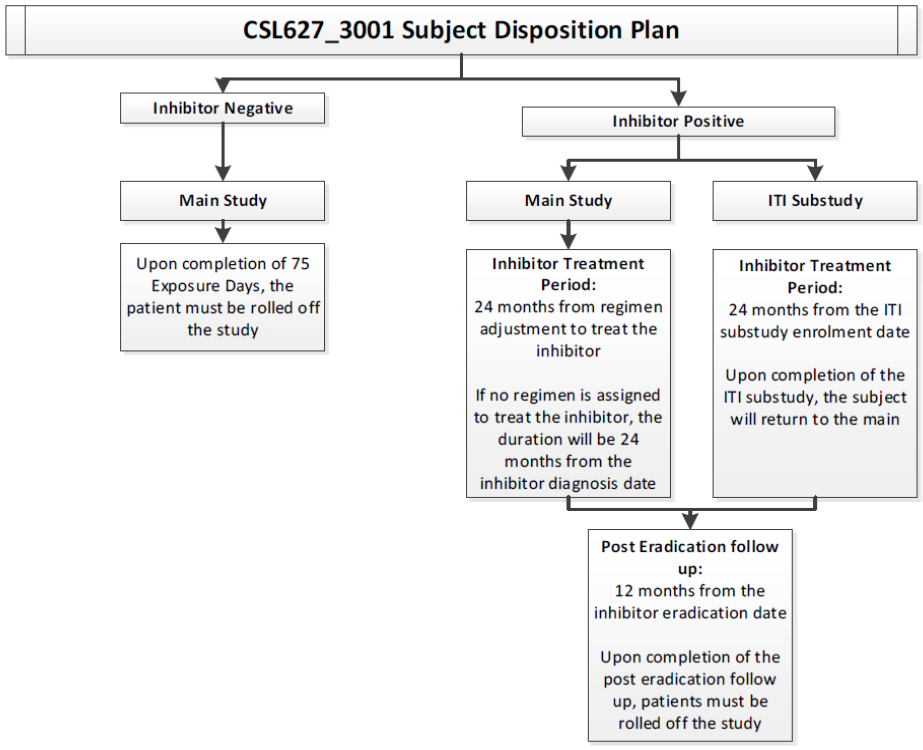
Abbreviations: ED = exposure day; PTP = previously treated patient; PUP = previously untreated patient.

A: Estimated duration of study participation to achieve the indicated number of EDs to rVIII-SingleChain.

B: All subjects who participate in Study CSL627_3001 are eligible for the surgery substudy at any time during the study.

C: The ITI substudy is open to Arm 2 PUPs who develop a confirmed inhibitor to rVIII-SingleChain during on-demand or prophylaxis treatment.

Figure 2: Disposition Plan for PUPs



Abbreviations: ITI = immune tolerance induction; PUP = previously untreated patient.

Study population /Sample size

For study Arm 2, eligible subjects aged 0 to < 18 years with severe congenital hemophilia A (FVIII activity < 1%) with no prior exposure to any FVIII product (with the exception of short-term use of blood products). Exclusion criteria include family history of FVIII inhibitors, known other coagulations disorder, receiving non-permitted therapy, prior evidence of thrombosis, hypersensitivity to rVIII-SingleChain or any excipients or CHO proteins, low platelet count at screening, HIV-positive subjects (exceptions possible).

For the ITI substudy, eligible PUPs of Arm 2 had to show an inhibitor titer ≥ 0.6 BU/mL (confirmed by repeat testing at the central laboratory). PTPs, subjects with evidence of thrombosis or planned immunosuppressive therapy or inhibitor relapse (2 consecutive inhibitor samples with an inhibitor titer ≥ 0.6 BU/mL, analyzed by the central laboratory after a successful first ITI attempt) were not to be enrolled.

As per Protocol Amendment 4, dated 01 October 2019, this study was planned to enroll a total of at least 200 PTPs with at least 100 EDs (Arms 1 and 3) and at least 24 PUPs (Arm 2). Any subject requiring surgery during the course of the study could participate in the surgery substudy, with the exception of inhibitor positive PUPs as the surgical procedure should be covered by a bypassing agent and not by rVIII-SingleChain.

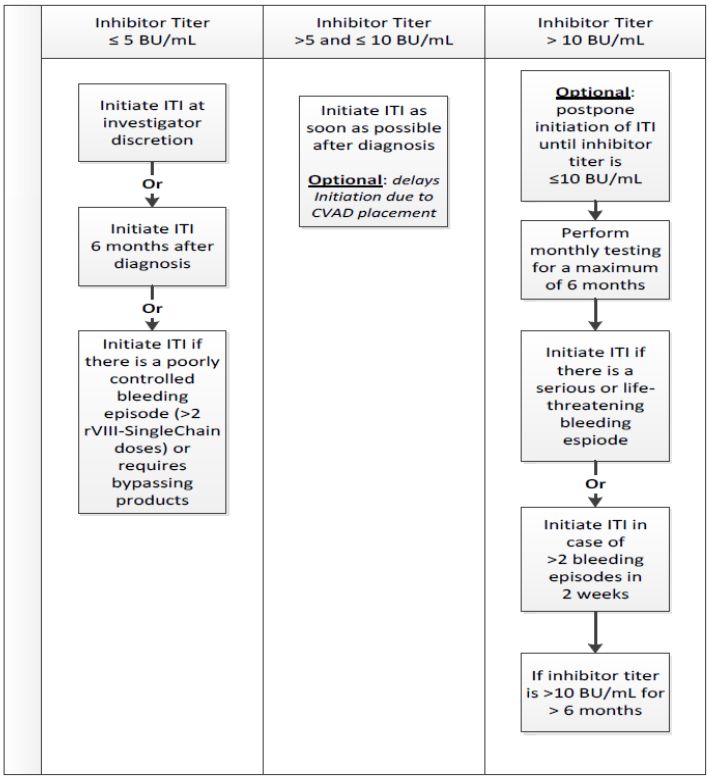
Treatments

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 (2012), 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 (2012).

Inhibitor negative subjects remained in the study until they achieved 75 EDs with rVIII-SingleChain.

For ITI therapy, the timepoint of initiation was determined by the investigator based on the inhibitor titer and taking into account the criteria outlined below. At the investigator's discretion, the following subjects could have an optional waiting period of up to 6 months prior ITI therapy (inhibitor titer of > 10 BU/mL and to allow the inhibitor titer to decrease to ≤ 10 BU/mL, need for a central venous access device for ITI therapy). During the waiting period, the subject must not receive any dose of rVIII-SingleChain, and bleeding episodes had to be treated with bypassing agents. Subjects eligible for ITI were to assign either low-dose regimen of 50 IU/kg 3 times weekly or intermediate-dose regimen of 100 IU/kg daily, or High-dose regimen of 200 IU/kg daily (may be split into 2 doses of 100 IU/kg daily). A change to a less intense regimen if the subject's inhibitor titer showed a decrease was permitted to avoid excessively high FVIII levels. ITI treatment was to continue until ITI success (inhibitor titer of < 0.6 BU/mL at 2 consecutive visits), ITI therapy failure (24 months of ITI therapy without achieving inhibitor eradication), or subject discontinuation, whichever occurred first.

Figure 5: Criteria for Timing of ITI Therapy Initiation



Abbreviations: BU = Bethesda unit; CVAD = central venous access device; ITI = immune tolerance induction.

Outcomes/endpoints

Efficacy

Primary Endpoints:

- 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:

- 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 (ITI substudy):

- 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:

- 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:

- 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:

- 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

Recruitment/ Number analysed

Overall, Arm 2 of Study 3001 included 24 PUPs aged 0 to 5 years, of whom 21 subjects (87.5%) attained > 50 EDs.

19 subjects completed the study, and 5 subjects discontinued the study. Three subjects discontinued the study as per physician's decision, 1 subject discontinued because of an AE (high-titer inhibitor) before the ITI substudy was implemented, and 1 subject (4.2%) discontinued because of overseas relocation. Of the 24 PUPs, 12 were initially assigned to on-demand treatment. 11 on-demand subjects switched to a once-weekly prophylaxis regimen, and this switch occurred between 9 and 650 days (1.78 years) after receiving the initial on-demand treatment.

Table 11-1 Subject Populations (PUPs - Enrolled Population)

Category	Total
Enrolled	24
Safety Population	24
Efficacy Population	24
Surgery Population	3
ITI Population	11

ITI = immune tolerance induction; PUP = previously untreated patient; rVIII-SingleChain = single chain recombinant coagulation factor VIII.

Baseline data

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 (range 0-5). Mean weight was 10.1 kg (range 3.8-20.0), mean height 76.3 cm (range 54-110). 8 subjects were enrolled in South Africa, 2 in Malaysia, 1 in the United States, and 3 each the Lebanon, Netherlands, and Portugal.

Two subjects in the Surgery Population (N=3) were Black or African American and 1 was White. The mean age was 1.7 years. The majority of subjects in the ITI Population (N=11) were White (9 subjects) the remaining 2 subjects were Black or African American. The mean age of the subjects was 1.2 years (range 0-3).

In the 12 months before study entry, the incidence of bleeding episodes in the PUP Safety Population (N=24) was low (5 out of 24 (20.8%) had reported bleeding events at screening). The mean incidence of spontaneous and traumatic bleeding episodes in the last 12 months calculated for all (N=24) subjects before study entry was 0.2 and 0.4.

Efficacy results

There were a total of 385 bleeding episodes during the study in PUPs. Of these, 315 bleeding episodes were treated with rVIII-SingleChain, of which 312 were treated with rVIII-SingleChain alone, and 3 were treated with rVIII-SingleChain and bypassing agent; 50 bleeding events did not require any treatment, 20 were treated with bypassing agent alone. Of the 315 treated bleeding episodes, 1 was major and 60 were nonmajor. The majority of spontaneous bleeding episodes that required treatment were located in other locations (75 bleeding episodes), followed by muscle (65 bleeding episodes), and joint (57 bleeding episodes).

Overall Haemostatic Efficacy

92.1% (290 of 315) treated bleeding episodes had a response rated as "excellent" or "good" (95% CI: 87.0 to 95.3). The percentage of bleeding events rated as "excellent" or "good" was similar on the on-demand and prophylaxis regimens (91.2% and 92.2%, respectively). The results from the sensitivity analyses (ie, all missing data excluded, or all missing data counted as treatment success) were similar to the primary analysis results.

Table 11-6 Investigator's Overall Assessment of Hemostatic Efficacy (PUPs - Efficacy Population)

Bleeding type assessment	On-demand (N = 12)	Prophylaxis (N = 23) *	Overall (N = 24)
Number of bleeding events	40	345	385
Number of treated bleeding events	34	281	315
Excellent (n [%])	26 (76.5)	252 (89.7)	278 (88.3)
Good (n [%])	5 (14.7)	7 (2.5)	12 (3.8)
Moderate (n [%])	3 (8.8)	18 (6.4)	21 (6.7)
Poor / no response (n [%])	0	3 (1.1)	3 (1.0)
Missing (n [%])	0	1 (0.4)	1 (0.3)
Treatment success (a)	31	259	290
Rate of treatment success	91.2	92.2	92.1
95% CI for rate	(79.3, 96.5)	(86.7, 95.5)	(87.0, 95.3)
Treatment success (b)	31	259	290
Rate of treatment success	91.2	92.5	92.4
95% CI for rate	(79.3, 96.5)	(87.0, 95.8)	(87.3, 95.5)
Treatment success (c)	31	260	291
Rate of treatment success	91.2	92.5	92.4
95% CI for rate	(79.3, 96.5)	(87.0, 95.8)	(87.3, 95.5)

CI = confidence interval; PUP = previously untreated patient.

Notes:

[1] Success was defined as a rating of "excellent" or "good". [a] Primary analysis: missing counted as failure; [b] Sensitivity analysis: all missing excluded; [c] Sensitivity analysis: missing counted as success.

[2] 95% CI based on a generalized linear model to account for within-subject correlation.

[3] Table presents number and percentage of bleeding events (n [%]).

[4] Percentages were based on the number of treated bleeding events.

[5] Regimens are actual regimens.

[6] * Prophylaxis subject total included 12 subjects assigned to prophylaxis plus 11 of 12 on-demand subjects who later switched to prophylaxis, per Investigator decision.

Source: Table 14.2.1.1

comment:

A total of 315 bleeding events have been treated with Afstyla with a treatment succes rate of 92.4%. 1 major bleeding episode occurred and was succesfully treated. 54 of 60 treated nonmajor bleeding episodes were succesfully treated. It is unclear why only a minority of bleeding episodes were classified according to severity (major and nonmajor). Also, occurrence of only 1 major bleeding episode among 315 treated bleeds appears rather unusual. The Applicant is asked for clarification.

Efficacy in inhibitor-positive subjects

Of the 24 subjects who were enrolled to Arm 2 and exposed to rVIII-SingleChain, 12 subjects tested positive for inhibitors (6 had a high-titer range peak inhibitor, and 6 had a low-titer range peak inhibitor value). 73 bleeding events occurred in 9 inhibitor-positive subjects while their inhibitor status was positive. 19 bleeding events were treated with rVIII-SingleChain in 6 of 9 inhibitor-positive subjects while their inhibitor status was positive and were rated for hemostatic efficacy.

Of the 19 treated bleeding events:

- Three were rated as "poor / no response" (closest inhibitor titer result before the bleeding event) (proximal titers: 2.55, 28.5, and 5.90 BU/mL).
- Three were rated as "moderate" (proximal titers: 1.35, 4.02, and 1.82 BU/mL).
- Three were rated as "good" (proximal titers: 1.78, 1.78, and 1.30 BU/mL).
- Ten were rated as "excellent" (proximal titers: 0.66, 1.06, 1.49, 0.92, 0.71, 0.68, 4.0, 15.5, 14.5, and 7.80 BU/mL).

Treatment success by inhibitor status was 93.6% (95% CI: 89.1 to 96.3) while subjects were inhibitor negative and 68.4% (95% CI: 35.5 to 89.5) while subjects were inhibitor positive.

Primary Endpoint - Treatment Success for Major Bleeding Episodes

There was 1 major bleeding episode (spontaneous bleeding event in right knee) treated with rVIII-SingleChain, which had a hemostatic efficacy rating of "excellent". For this bleeding, no other medication was taken aside from Afstyla and 1 infusion was required to achieve haemostasis.

Primary Endpoint - Annualized Spontaneous Bleeding Rate

For spontaneous bleeding episodes, median (range) AsBR was 1.15 (0.0 to 5.6) in the on-demand treatment regimen and 0.88 (0.0 to 19.7) in the prophylaxis treatment regimen. Mean (SD) AsBR was 1.90 (2.25) and 4.04 (6.37), respectively.

Table 11-8 Summary of ABRs (PUPs - Efficacy Population)

Type of bleeding event	On-demand (N = 12)	Prophylaxis (N = 23) *	Prophylaxis / On-demand
Subjects with an efficacy evaluation period ≥ 8 weeks [n (%)]	10 (83.3)	23 (100)	
Total bleeding events			
n	10	23	
Mean (SD)	5.12 (5.331)	5.94 (7.705)	
Median (Min, Max)	3.76 (0.0, 17.1)	1.84 (0.0. 23.6)	
Number of bleeding events per year (95% CI)	3.4 (2.4, 4.7)	5.7 (5.1, 6.4)	1.71 (1.19, 2.46)
Spontaneous bleeding events			
n	10	23	
Mean (SD)	1.90 (2.252)	4.04 (6.374)	
Median (Min, Max)	1.15 (0.0, 5.6)	0.88 (0.0, 19.7)	
Number of bleeding events per year (95% CI)	2.2 (1.4, 3.5)	4.9 (4.2, 5.6)	2.23 (1.36, 3.67)
Traumatic bleeding events			
n	10	23	
Mean (SD)	2.15 (4.016)	1.70 (2.899)	
Median (Min, Max)	0.00 (0.0, 11.4)	0.73 (0.0, 12.3)	
Number of bleeding events per year (95% CI)	4.4 (2.4, 7.9)	2.2 (1.8, 2.7)	0.50 (0.27, 0.94)
Unknown bleeding events			
n	10	23	
Mean (SD)	1.06 (1.967)	0.21 (0.388)	
Median (Min, Max)	0.00 (0.0, 5.7)	0.00 (0.0, 1.2)	
Number of bleeding events per year (95% CI)	1.1 (0.4, 3.0)	0.6 (0.4, 1.1)	0.57 (0.19, 1.72)
Joint bleeding events			
n	10	23	
Mean (SD)	1.63 (1.787)	1.35 (1.341)	
Median (Min, Max)	1.21 (0.0, 4.5)	1.39 (0.0, 4.9)	
Number of bleeding events per year (95% CI)	2.7 (1.6, 4.7)	1.5 (1.2, 1.9)	0.56 (0.31, 1.00)
Number of subjects with zero treated bleeding events [n (%)]	3 (25.0)	3 (13.0)	

ABR = annualized bleeding rate; CI = confidence interval; Max = maximum; Min = minimum; PUP = previously untreated patient; SD = standard deviation.

Notes:

[1] Number of bleeds per year (95% CI) and ratio were based on a Poisson distribution.

[2] Subjects with an efficacy evaluation period less than 8 weeks (56 days) were excluded from bleeding rates.

[3] Regimens are actual regimens.

[4] * Prophylaxis subject total included 12 subjects assigned to prophylaxis plus 11 of 12 on-demand subjects who later switched to prophylaxis, per Investigator decision.

Source: Table 14.2.2.1

There was no apparent clinically relevant difference in AsBRs while the subjects were inhibitor positive compared with while they were inhibitor negative. Of note, 20 of the 73 bleeding events while inhibitor positive were treated with bypassing agents alone and 34 bleeding events did not require treatment. In addition, there was no apparent clinically relevant difference in AsBRs between subjects with noninhibitory antidrug antibodies (ADAs) and subjects without ADA.

Table 11-9 Summary of ABRs by Inhibitor Status (PUPs - Efficacy Population)

Type of bleeding event	On-demand (N = 12)	Prophylaxis (N = 23) *	Prophylaxis / On-demand
While inhibitor positive			
Subjects with an efficacy evaluation period ≥ 8 weeks [n (%)]	0	11 (47.8)	
Total bleeding events			
n	0	11	
Mean (SD)		2.37 (3.276)	
Median (Min, Max)		0.47 (0.0, 10.1)	
Number of bleeding events per year (95% CI)		3.1 (2.0, 4.9)	
Spontaneous bleeding events			
n	0	11	
Mean (SD)		2.08 (3.273)	
Median (Min, Max)		0.47 (0.0, 10.1)	
Number of bleeding events per year (95% CI)		2.5 (1.5, 4.1)	
Traumatic bleeding events			
n	0	11	
Mean (SD)		0.21 (0.693)	
Median (Min, Max)		0.00 (0.0, 2.3)	
Number of bleeding events per year (95% CI)		2.3 (0.7, 7.1)	
Unknown bleeding events			
n	0	11	
Mean (SD)		0.08 (0.271)	
Median (Min, Max)		0.00 (0.0, 0.9)	
Number of bleeding events per year (95% CI)		0.9 (0.1, 6.4)	
Joint bleeding events			
n	0	11	
Mean (SD)		0.51 (1.011)	
Median (Min, Max)		0.00 (0.0, 3.0)	
Number of bleeding events per year (95% CI)		1.6 (0.7, 3.9)	
Number of subjects with zero treated bleeding events [n (%)]	0	6 (26.1)	
While inhibitor negative			
Subjects with an efficacy evaluation period ≥ 8 weeks [n (%)]	10 (83.3)	21 (91.3)	
Total bleeding events			
n	10	21	
Mean (SD)	5.12 (5.331)	6.63 (8.251)	
Median (Min, Max)	3.76 (0.0, 17.1)	1.98 (0.0, 23.6)	
Number of bleeding events per year (95% CI)	3.4 (2.4, 4.7)	6.5 (5.8, 7.4)	1.94 (1.35, 2.81)
Spontaneous bleeding events			
n	10	21	
Mean (SD)	1.90 (2.252)	4.31 (7.028)	
Median (Min, Max)	1.15 (0.0, 5.6)	0.52 (0.0, 19.7)	
Number of bleeding events per year (95% CI)	2.2 (1.4, 3.5)	5.8 (5.0, 6.7)	2.66 (1.62, 4.39)
Traumatic bleeding events			
n	10	21	
Mean (SD)	2.15 (4.016)	2.07 (3.015)	
Median (Min, Max)	0.00 (0.0, 11.4)	1.24 (0.0, 12.3)	
Number of bleeding events per year (95% CI)	4.4 (2.4, 7.9)	2.5 (2.0, 3.2)	0.58 (0.31, 1.08)
Unknown bleeding events			
n	10	21	
Mean (SD)	1.06 (1.967)	0.24 (0.413)	
Median (Min, Max)	0.00 (0.0, 5.7)	0.00 (0.0, 1.2)	
Number of bleeding events per year (95% CI)	1.1 (0.4, 3.0)	0.7 (0.4, 1.2)	0.62 (0.20, 1.90)
Joint bleeding events			
n	10	21	
Mean (SD)	1.63 (1.787)	1.71 (1.454)	
Median (Min, Max)	1.21 (0.0, 4.5)	1.47 (0.0, 4.9)	
Number of bleeding events per year (95% CI)	2.7 (1.6, 4.7)	1.7 (1.4, 2.2)	0.63 (0.35, 1.14)
Number of subjects with zero treated bleeding events [n (%)]	3 (25.0)	3 (13.0)	

ABR = annualized bleeding rate; CI = confidence interval; Max = maximum; Min = minimum; PUP = previously untreated patient; SD = standard deviation.

Notes:

[1] Number of bleeds per year (95% CI) and ratio were based on a Poisson distribution.

[2] Subjects with an efficacy evaluation period less than 8 weeks (56 days) were excluded from bleeding rates.

[3] Regimens are actual regimens.

[4] * Prophylaxis subject total included 12 subjects assigned to prophylaxis plus 11 of 12 on-demand subjects who later switched to prophylaxis, per Investigator decision.

Secondary Endpoint - Treatment Success for Nonmajor Bleeding Episodes

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.

Secondary Endpoint - Number of Single Chain Recombinant Coagulation Factor VIII Injections to Achieve Hemostasis

315 of 385 (81.8%) bleeding episodes were treated with rVIII-SingleChain (312 alone with rVIII-SingleChain and 3 in combination with bypassing agents) during the study. In 88.9% of all treated bleeding episodes, 1 or 2 injections of rVIII-SingleChain were sufficient to achieve hemostasis. 8.9% of treated bleeding episodes required ≥ 3 injections of rVIII-SingleChain to achieve hemostasis. Of note, 20 of 385 (5.2%) bleeding events were treated with only bypassing agents.

Secondary Endpoint - Annualized Bleeding Rate

For all bleeds, the median (range) ABR was 3.76 (0.0 to 17.1) for the on-demand treatment regimen and 1.84 (0.0 to 23.6) for the prophylaxis treatment regimen. There was no clinically relevant difference in ABRs while the subjects were inhibitor positive compared with while they were inhibitor

negative. There was no clinically relevant difference in ABRs between subjects with ADAs and subjects without ADAs (see tables 11-8 and 11-9 above).

Secondary Endpoint - Consumption of rVIII-SingleChain

The mean total dose administered per subject per week in the on-demand treatment regimen (N=12) was 9.64 IU/kg. On-demand treated subjects received a mean total dose per infusion per bleed of 35.0 IU/kg (median 32.1) and received a mean of 1.23 infusions per subject per months.

The mean dose per prophylactically infusion was 51.56 IU/kg among all treatment regimen (median 50.00, range 18.2-429.6). The mean prophylaxis dose administered per subject week (year) in different treatment regimens was as follows:

- 32.60 IU/kg (1701.23 IU/kg per year) in the 1 time per week regimen (N=22).
- 71.23 IU/kg (3716.48 IU/kg per year) in the 2 times per week treatment regimen (N=15).
- 161.04 IU/kg (8402.83 IU/kg per year) in the 3 times per week treatment regimen (N=12).
- 283.60 IU/kg (14798.09 IU/kg per year) in the other treatment regimen (N=5).

For all prophylactic treatment regimen (N=23) mean consumption was 4671.54 IU/kg per year (median 4029.99, range 1088.4-10202.5).

The mean total dose administered per subject per week (year) in different treatment regimens was as follows:

- 45.42 IU/kg (2369.83 IU/kg per year) in the 1 time per week regimen (N=22).
- 87.84 IU/kg (4583.45 IU/kg per year) in the 2 times per week treatment regimen (N=15).
- 166.62 IU/kg (8694.24 IU/kg per year) in the 3 times per week treatment regimen (N=12).
- 317.38 IU/kg (16560.25 IU/kg per year) in the other treatment regimen (N=5).

Total mean consumption for all prophylactically treated subjects (N=23) was 5346.86 IU/kg per year (median 4784.00, range 1383.2-12520.8).

Total mean dose per infusion per bleed for all prophylactically treated subjects (N=23) was 79.8 IU/kg (median 49.63).

Secondary Endpoint - Treatment success for surgery, using the 4-point efficacy evaluation of surgical treatment scale

There were 3 surgeries in the PUPs during the study, 2 circumcisions and 1 port placement surgery (all nonemergency).

The 2 circumcision surgeries required 13 injections (15,693 IU, assigned dose 100 IU/kg) and 4 injections (5631 IU, assigned dose 100 IU/kg) of rVIII-SingleChain. The port replacement surgery required 8 injections (7330 IU, assigned dose 49 IU/kg) of rVIII-SingleChain. The treatment success rate of rVIII-SingleChain for the 3 nonemergency surgeries was 100% (i.e. haemostatic efficacy was rated excellent for all surgeries). The volume of blood loss during the surgical substudy (mean 3.3 mL) was higher than the predicted average levels (0.5 mL), no blood transfusion was given for any of the surgeries. During the surgical substudy, hemoglobin levels were maintained close to baseline levels, with a slight increase during the postoperative period.

Table 14.2.6.1 Comparison of Predicted and Observed Intraoperative Estimated Blood Loss (PUPs - Surgery Population)

	On-Demand (N=2)	Prophylaxis (N=1)	Total (N=3)
Predicted Average Blood Loss (mL)			
n	2	0	2
Mean (SD)	0.5 (0.71)		0.5 (0.71)
Median	0.5		0.5
Min, Max	0, 1		0, 1
Predicted Maximum Blood Loss (mL)			
n	2	0	2
Mean (SD)	1.0 (1.41)		1.0 (1.41)
Median	1.0		1.0
Min, Max	0, 2		0, 2
Observed Blood Loss (mL)			
n	2	1	3
Mean (SD)	5.0 (7.07)	0.0 ()	3.3 (5.77)
Median	5.0	0.0	0.0
Min, Max	0, 10	0, 0	0, 10

CSL BEHRING GMBH: CSL627_3001/CIL-MJ/FINAL/SUR01P.SAS
Produced: 21 April 2021, 5:58; Data Cut: 12 Feb 2021 Page 1 of 1
Source data: Listing 16.2.9.3.3

comment:

Taken into account the body weight at date at screening, the WHO child growth standards, and the date of surgery, the surgery dosing appears reasonable. According to the study protocol, any subject required to have surgery needed to suspend regular rVIII-SingleChain treatment. Subjects were to be treated with rVIII-SingleChain before, during, and after surgery, under the supervision of and as prescribed by the treating physician according to factor maintenance levels und treatment duration recommended by the WFH 2012 treatment guidelines.

It is unclear, how the surgery ratings of excellent haemostatic efficacy were achieved. According to the rating scale, estimated blood loss should be not more than 20% higher than the estimated predicted blood loss to achieve an excellent rating. Apparently, this criterion was not met according to Table 14.2.6.1 of the final CSR [predicted mean (SD) average blood loss 0.5 (0.71) mL, predicted mean (SD) maximum blood loss 1.0 (1.41) mL, observed mean (SD) blood loss 3.3 (5.77) mL.

ITI - exploratory endpoint: Consumption of rVIII-SingleChain for Inhibitor Treatment

The mean (SD) total ITI dose administered per subject per week was 183.84 IU/kg (102.385). The mean (range) number of injections administered during inhibitor treatment period was 124.6 (16 to 287), the mean (range) number of EDs equally was 124.2 (16 to 287) EDs.

ITI - exploratory endpoint: Inhibitor Eradication

Time to inhibitor eradication was defined as the time between start of the first ITI dose (ie, first dose adjusted to treat the inhibitor, as defined by the investigator) to the complete response (ie, a confirmed inhibitor titer < 0.6 BU/mL at 2 consecutive visits, analyzed at the central laboratory).

11 subjects were treated for their inhibitor (ITI population was defined as all subjects who received at least 1 dose of rVIII-SingleChain for the ITI substudy). Of these, 9 subjects had low-titer inhibitors and 2 had high-titer inhibitors at the time they began treatment for their inhibitor. In the end, 6 peak low-titer inhibitor subjects and 5 peak high-titer inhibitor subjects were treated for their inhibitor.

Nine of 11 subjects (81.8%; 95% CI: 0.482, 0.977) achieved inhibitor eradication with rVIII-SingleChain (3/5 subjects with peak high-titer inhibitor and 6/6 subjects with peak low-titer inhibitor, 2 subjects with initial high-titer inhibitor did not achieve inhibitor eradication). The median (range) EDs to inhibitor eradication was 37.00 (16.0 to 194.0) for the 9 subjects who had low-titer inhibitors at the time they began treatment for their inhibitor. The median (range) time to inhibitor eradication was 14.29 (7.7 to 64.4) weeks for these subjects.

Of note, six of the 11 subjects received ITI treatment with rVIII-SingleChain in the ITI substudy. Of these, 5 subjects received low-dose (50 IU/kg 3 times weekly) and 1 subject received a high-dose (200 IU/kg daily) ITI regimen with rVIII-SingleChain (see also extent of exposure in the safety results).

comment:

The ITI population was defined as all subjects who received at least 1 dose of rVIII-SingleChain for the ITI substudy. 11 subjects were included in the ITI population but 6 subjects received ITI treatment (N=5 low-dose and N=1 high-dose regimen). Overall, 9 subjects, all with initial low-titer inbhibitor, received inhibitor eradication. There is uncertainty regarding treatment regimen and treatment success.

Safety results

Extent of Exposure

The mean (SD) number of EDs for 24 enrolled and treated PUPs was 245.5 (161.56) EDs; the median (interquartile range) number of EDs was 230 (142, 323) EDs. A total of 21 subjects (87.5%) attained > 50 EDs. The mean (SD) dose administered per infusion was 53.3 (26.34) IU/kg. The mean number of EDs in inhibitor-positive was 109.3 EDs and inhibitor-negative subjects was 190.8 EDs. Of note, preventive and additional doses of rVIII-SingleChain were permitted during the study (overall 10 subjects in the on-demand group received a mean of 5 additional doses).

Table 12-1 Extent of Exposure to rVIII-SingleChain (PUPs - Efficacy Population)

	Total (N = 24)
All subjects	24
EDs in the current study	
n	24
Mean (SD)	245.5 (161.56)
Median	230.0
Q1, Q3	142.0, 323.0
Min, Max	5, 639
0 to 10 EDs [n (%)]	2 (8.3)
> 10 to 25 EDs [n (%)]	1 (4.2)
> 25 to 50 EDs [n (%)]	0
> 50 EDs [n (%)]	21 (87.5)
Number of injections	
n	24
Mean (SD)	246.4 (162.37)
Median	231.0
Q1, Q3	142.0, 323.5
Min, Max	5, 641
Total number of injections	5914
Dose Per Injection Administered (IU/kg)	
n	5914
Mean (SD)	53.3 (26.34)
Median	50.0
Q1, Q3	40.6, 57.5
Min, Max	5, 660
Total IU Administered	
n	24
Mean (SD)	188,716.4 (170,073.95)
Median	169,039.5
Q1, Q3	82,419.0, 255,435.5
Min, Max	2552, 788,293

ED = exposure day; Max = maximum; Min = minimum; PUP = previously untreated patient; Q1, Q3 = interquartile range; rVIII-SingleChain = single chain recombinant coagulation factor VIII; SD = standard deviation.

Notes:

[1] Percentages, where indicated, were based on the number of subjects in specified population.

[2] Exposure during the surgical period was excluded.

[3] The Safety Population table was not generated as there was no difference between the Efficacy and Safety Populations.

comment:

The Applicant concluded that the mean number of EDs in inhibitor-positive and inhibitor-negative subjects was comparable. Given an almost 2-fold difference, this statement requires further explanation.

In the ITI Population, 11 subjects received treatment with rVIII-SingleChain; 6 of the 11 subjects were enrolled in the ITI substudy: 5 subjects received a low-dose (50 IU/kg 3 times weekly) regimen and 1 subject received high-dose (200 IU/kg daily) ITI regimen. The mean (SD) number of EDs was 124.2 (98.79) EDs and 7 subjects (63.6%) attained > 50 EDs during their inhibitor treatment period.

Primary Endpoint: Inhibitor against FVIII

The primary safety endpoint was 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.

Twenty-four subjects were enrolled and exposed to rVIII-SingleChain during the study, and 12 subjects (50.0%) tested positive for inhibitors. Of these, 6 subjects (25.0% of total, primary safety endpoint) had a peak inhibitor value in the high-titer range, and 6 subjects (25.0% of total) had a peak inhibitor value in the low-titer range. The overall median EDs for initial inhibitor development was 10 EDs (range 4 to 23 EDs). Median EDs for initial inhibitor development in high titer subjects was 9.0 EDs (range 4 to 23 EDs) and in low titer subjects was 10 EDs (range 5 to 23 EDs). Of the 12 inhibitor-positive subjects, 1 subject was withdrawn from the study because of protocol requirement as a result of high inhibitor titer at diagnosis (8.50 BU/mL); following this the protocol was amended to allow subjects diagnosed with inhibitor to continue participation in the study and enroll into the ITI substudy. 1 subject was withdrawn after entering the ITI substudy (physician's decision), and 1 subject had inhibitor-positive status at study end.

Secondary Endpoint: Noninhibitory Antidrug Antibodies (ADAs)

Twelve subjects (50.0%) developed noninhibitory ADAs during the study. Eight of the 12 subjects who developed noninhibitory ADAs were positive for inhibitors; 6 subjects had high-titer and 2 subjects had low-titer. Two of these 12 subjects (8.3%) were confirmed to be positive for noninhibitory ADAs by the EOS (1 subject had high-titer inhibitor and the other subject was not positive for inhibitor).

Secondary Endpoint: Antibodies to Chinese Hamster Ovary Host Cell Proteins

None of the subjects developed antibodies against CHO host cell proteins

Adverse events

Treatment-emergent adverse events (TEAEs): All subjects in the PUP Safety Population experienced at least 1 TEAE. A total of 320 TEAEs were reported (12 severe, 93 moderate, 208 mild). The highest frequency of TEAEs were in the System Organ Class: Infections and Infestations (91.7%), General Disorders and Administrative Site Conditions (66.7%), Investigations (50.0%, N=12/24 of which were N=12 Inhibiting antibodies positive and N=6 Anti-factor VIII antibody positive), Injury, Poisoning and Procedural Complications (37.5%), Respiratory, Thoracic, and Mediastinal Disorders (33.3%), Gastrointestinal Disorders (33.3%), Musculoskeletal and Connective Tissue Disorders (33.3%), Skin and Subcutaneous Tissue Disorders (29.2%), Blood and Lymphatic System Disorders (25.0%), Vascular Disorders (12.5%). Of the TEAEs reported in ≥ 10% of subjects in the overall PUP Safety Population, the most commonly reported TEAEs were Pyrexia (44 TEAEs) in 15 subjects, Upper respiratory Tract Infection (18) in 7 subjects, Nasopharyngitis (15) in 9 subjects, and Inhibitor Development (14 TEAEs; Inhibiting Antibodies Positive [7], Anti-factor VIII Antibody Positive [6], and Factor VIII Inhibition [1]) in 13 subjects.

Related TEAEs: Twelve subjects (50%) had a total of 17 TEAEs related to rVIII-SingleChain, the majority of which were Inhibitors Development (14 TEAEs, 82.4%). The other were fatigue (n=1), pyrexia (n=1), and haemorrhage (n=1). One severe TE SAE of Inhibiting Antibodies Positive (high titer) led to study discontinuation, which was related to rVIII-SingleChain and had not resolved at the end of study.

Adverse Events of Special Interest (AESI): Potential events of hypersensitivity reactions were identified. Ten subjects (41.7%) experienced 15 TEAEs that could be considered as symptoms or manifestations of Hypersensitivity reactions. These TEAEs were eczema (n=3 in 3 subjects), rash (n=3 in 3 subjects), bronchospasm (n=4 in 2 subjects), and conjunctivitis allergic, dermatitis allergic, eye swelling, rash erythematous, rhinitis allergic (each occurring once in a single subject). Upon medical review, none of these TEAEs of special interest were confirmed as hypersensitivity reactions.

Local tolerability: 21 subjects reported at least 1 self-assessment. No local reactions were reported for 99.7% of subject-assessed rVIII-SingleChain injections. A small proportion of injections were reported as being associated with very slight to moderate local reactions, and there were no injections associated with severe local reactions. The investigator's assessment of erythema identified no reaction in any of the assessed injections.

No deaths were reported in this study. No anaphylactic reactions or thromboembolic events were reported. There were no notable findings relating to clinical laboratory or vital signs parameters.

Of note, two subjects who experienced unrelated TEAEs of Coronavirus test positive recovered.

Other endpoint: Incremental Recovery

Incremental recovery (IR) was assessed as a PK (and safety) parameter in 6 PUPs who participated in the ITI substudy to monitor inhibitor development. Incremental recovery was assessed in the 6 PUPs in the ITI substudy. As expected for subjects with inhibitors, all subjects had at least 1 post-dose FVIII activity level that was below the limit of quantification or much lower than normal. Three subjects had low IR values that increased over time as the inhibitor was eradicated.

2.3.3. Discussion on clinical aspects

Afstyla is a recombinant single-chain Factor VIII (rVIII-SingleChain, INN: lonoctocog alfa) indicated for the treatment and prevention of bleeding in patients of all age groups with haemophilia A as replacement therapy. The active substance is a B-domain truncated variant of human factor VIII defined by covalently bonded FVIII heavy and light chains within a single polypeptide structure. Marketing authorisation valid throughout the European Union was granted on 04 January 2017 on the basis of two main studies. The first study was conducted in previously treated adult/adolescent subjects with severe haemophilia A, the second study involved paediatric PTPs below 12 years of age.

In accordance with the EMA requirements for the postmarketing investigation and the clinical guideline on FVIII products in effect in 2011, a third study, coded CSL 627_3001, was conducted to evaluate routine prophylaxis and on-demand treatment of bleeding episodes in at least 200 PTPs who achieved at least 100 EDs and in PUPs who achieved at least 50 EDs. The study was titled "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". A summary of the final results from PTPs in this study (Arms 1 and 3, completed for PTPs in December 2018) was already submitted to EMA in January 2020 (eCTD sequence 68 / procedure reference EMEA/H/C/004075/MEA/002.1). The final report for PTPs dated 28 November 2019.

Now, the MAH submitted a final report from PUPs of this study (Arm 2), in accordance with Article 46 of Regulation (EC) No1901/2006. The main goal of this study arm was to acquire efficacy and safety data in at least 50 PUPs treated at least for 50 EDs with rVIII-SingleChain. The number of PUPs was reduced to at least 24 per Protocol Amendment 4. and the study was completed in January 2021 (last subject visit, CSR dated June 2021). It is noted that no change to product information is planned.

Arm 2 of Study 3001 included 24 PUPs with a mean age of 1.4 years (range 0-5), 21 subjects (87.5%) achieved > 50 EDs. 11/12 initially on-demand treated subjects switched to prophylaxis regimen giving a total of N=23 subjects in the prophylaxis group. 19 subjects completed the study, 5 discontinued. Of note, not all pre-planned secondary or explorative analyses have been appropriately described in the final report. It should be noted that due to the early stop of enrolment, the significance of some endpoints is compromised anyway. There is no serious concern for study conduct, ten major protocol deviations were found (3x dosing, 2x visit/procedural, 2x laboratory noncompliance, 1x visit schedule, 2x other), none led to study discontinuation.

A primary efficacy endpoint was treatment success for major bleeding episodes. A total of 315 bleeding episodes were treated with rVIII-SingleChain (312 were treated with rVIII-SingleChain alone, 3 were additionally treated with bypassing agent). One bleeding episode was a major bleeding, i.e. a spontaneous bleeding in right knee, and this was successfully treated ("excellent" rating on a 4-point efficacy scale, no other medication was taken aside from Afstyla and 1 infusion was required to achieve haemostasis). 54 of 60 (90.0%) nonmajor classified bleeding episodes have been successfully treated. In total, 290 of 315 (92.1%) bleeding episodes had a response rated as "excellent" or "good". In 88.9% of all treated bleeding episodes 1-2 injections of Afstyla were sufficient to achieve hemostasis, 8.9% of treated bleeding episodes required ≥ 3 injections to achieve hemostasis. In addition, haemostatic efficacy was evaluated by inhibitor status and treatment success was 93.6% in the absence and 68.4% in the presence of inhibitory antibodies. Annualized bleeding rates in the PUPs were further study objectives. The median ABR for the on-demand treatment regimen was 3.76 (range 0.0-17.1, mean: 5.12) for all bleeds (spontaneous bleeds median ABR 1.15, range 0.0-5.6, mean ABR 1.9). The median ABR for the prophylaxis treatment regimen was 1.84 (range 0.0-23.6, mean 5.94) for all bleeds (spontaneous bleeds median ABR 0.88, range 0.0-19.7, mean ABR 4.04).

Treatment of inhibitor-positive subjects was an exploratory objective, and therefore does not necessarily has further implications for the product labelling. However, to briefly brief summarize this effort, consumption data during ITI are provided and inhibitor eradication is described. 9/11 subjects (81.8%) who were treated for their inhibitors achieved inhibtor eradication which was achieved at a median of 37 EDs (range 16-194) and median of 14 weeks (range 7.7-64.4). Of note, only 6/11 subjects received a low-dose (50 IU/kg 3 times weekly, N=5) or high-dose (200 IU/kg daily, N=1) ITI regimen. Clarification is requested regarding the correlation of treatment regimen and treatment succes, and whether ITI could be reflected in the product information.

Overall, favourable efficacy was demonstrated in the on-demand and prophylactic treatment of PUPs and the data are line with the benefits shown in other Afstyla studies. On-demand treatment of bleeding episodes was efficacious, the vast majority of treated bleedings was sufficiently controlled by 1 or 2 injections of Afstyla. No concerns arise from consumption data, total consumption for all prophylactically treated subjects was 5346 IU/kg per year (median 4784, range 1383-12520) which is a common range for Haemophilia A subjects, including PUPs. No firm conclusion can be drawn from the ABR data due to the small sample size, yet the reported rates do not give cause for concern and commonly reflect typical ranges for the PUPs (Keipert, Müller-Olling et al. 2020; Yaish et al. 2020). Treatment success during surgery was evaluated in 3 cases (2x circumcision, 1x port placement). Further clarifications are requested regarding the surgery efficacy ratings, yet despite its small size data rather support a favourable profile.

The primary safety objective was to evaluate the development of FVIII inhibitory antibodies. In total, 12/24 (50%) PUPs were positive for inhibitors. 6 Subjects each (25% of total) had inhibitor values in the high-titer and in the low-titer range, respectively. Initial all-titer inhibitor development was observed at a median of 10 EDs (range 4-23). For high-titer and low-titer development, initial occurrence was observed at median of 9 and 10 EDs, respectively. This is considered a typical time course for inhibitor development. In fact, most inhibitors develop within the first 50 EDs with 50% of inhibitor already presenting within the first 15 EDs (van den Berg et al. 2018; Keipert et al. 2018). Of note, the mean number of EDs for all PUPs was 245.5 (median 230, min-max range 5-639). 21 subjects (87.5%) achieved at least 50 EDs, 2 subjects achieved <10 EDs and 1 subject >10 EDs. Further clarification is requested for inhibitor status in the 3 subjects not having achieved 50 EDs.

In line with the EMA FVIII referral, it is acknowledged that the lack of direct comparative data is stressing the significance of reported inhibitor incidence rates and inhibitor frequency for PUPs is reported as 'very common' in the current SmPC of Afstyla. With further reference made to EMA Assessment report of the FVIII Referral (EMA/763977/2017), for most recombinant FVIII products all-titer inhibitor frequencies range from 15 to 38% and high-titer inhibitors are in the range of 9-22.6%. A recent meta-analysis likewise showed that all-titer inhibitor rates are in the range of 26-40% for recombinant FVIII products, with an estimated frequency of 22% (95%CI: 18-27%) for high-titer inhibitors (Keipert et al. 2021). Therefore, it is considered that the rates estimated in this study for both all-titer and high-titer inhibtors are in the upper range or above the frequencies already described. The clinical relevance of this finding remains uncertain.

Other safety endpoints referred to non-inhibitory ADAs and adverse events including the potential for hypersensitivity reaction. 12 subjects had noninhibitory ADAs with strong intra-subject overlap of also having inhibitory antibodies. Events potentially related to hypersensitivity reactions were identified, i.e. 10 subjects experienced 15 such TEAEs including eczema, rash, and bronchospasm. These events were not confirmed as related after medical review; however, the applicant is requested to provide further details in this regard. No other important or new safety issues were identified. No deaths, no anaphylactic reactions, no thromboembolic events were reported.

For regulatory consideration, the applicant has stated that the study objective was in accordance with the EMA guideline in effect at date of study initiation. Of note, the study period for PUPs was August 2015 (first subject visit) until January 2021 (last subject visit). The guideline on the clinical investigation of recombinant and human plasma-derived factor VIII products currently into effect, i.e. since 01 February 2019 (EMA/CHMP/BPWP/144533/2009 rev. 2), removed the obligation to perform clinical trials in PUPs and instead requests post-authorisation studies based on a set of core data elements to be collected in haemophilia registries. It is further stated that the applicant has reached an agreement with the EMA Paediatric Committee through a request for modification of the pediatric investigational plan (PIP) to stop enrolling subjects into Study CSL627_3001. Accordingly, the ITI substudy had been extended to sufficiently follow up all inhibitor-positive PUPs.

Overall, post-authorisation PUP data were submitted in accordance with Article 46 of the paediatric regulation and support the favourable benefit-risk balance of Afstyla. Given the change of the regulatory landscape from conducting clinical trials in PUPs to collecting such data within haemophilia registries, the stop of this study and final report of PUP data is considered acceptable. The disadvantage, however, is that statistical significance of the submitted data is compromised. Additional minor clarifications are requested to address identified issues in the efficacy and safety assessments. Currently, it remains unclear whether ITI should be reflected in the product information. Clarification is requested in this regard as no change to the SmPC has been proposed.

References:

- Keipert, Christine, et al. "Annual Bleeding Rates: Pitfalls of Clinical Trial Outcomes in Hemophilia Patients." Clinical and Translational Science 13.6 (2020): 1127-1136;

- Yaish, Hassan, et al. "Safety and efficacy of turoctocog alfa in the prevention and treatment of bleeds in previously untreated paediatric patients with severe haemophilia A: Results from the guardian 4 multinational clinical trial." Haemophilia 26.1 (2020): 64-72

- van den Berg, H. Marijke, et al. "Timing of inhibitor development in more than 1000 previously untreated patients with severe hemophilia A." Blood, The Journal of the American Society of Hematology 134.3 (2019): 317-320.

- Keipert, C., et al. "Clinical trials and registries in haemophilia: Opponents or collaborators? Comparison of PUP data derived from different data sources." Haemophilia 24.3 (2018): 420-428.

- Keipert, Christine, et al. "Epidemiological Challenges in Rare Bleeding Disorders: FVIII Inhibitor Incidence in Haemophilia A Patients—A Known Issue of Unknown Origin." International Journal of Environmental Research and Public Health 18.1 (2021): 225)

- Assessment report - Referral under Article 31 of Directive 2001/83/EC resulting from pharmacovigilance data (EMA/763977/2017; https://www.ema.europa.eu/en/documents/referral/factor-viii-article-31-referral-assessment-report_en.pdf)

- Guideline on the clinical investigation of recombinant and human plasma-derived factor VIII products (EMA/CHMP/BPWP/144533/2009 rev. 2; https://www.ema.europa.eu/en/documents/scientific-guideline/guideline-clinical-investigation-recombinant-human-plasma-derived-factor-viii-products-revision-2_en.pdf)

3. Overall conclusion and recommendation

Overall, post-authorisation PUP data, submitted in accordance with Article 46 of the paediatric regulation, support the favourable benefit-risk balance of Afstyla. Minor clarifications are requested on several aspects of the final analysis which need to be sufficiently addressed by the Applicant. However, it is acknowledged that regulatory changes during the study conduct, and subsequently a small number of PUPs included, compromise the significance of the final study results.

☒ Not fulfilled:

Based on the data submitted, the MAH should provide description of the additional clarifications requested as part of this procedure. (see section "Additional clarification requested")

4. Additional clarification requested / RSI

Based on the data submitted, the MAH should address the following questions as part of this procedure:

1) Line listing of all the non-clinical and clinical studies included in the development program should be provided (refer to Annex).

2) Subjects eligible for study arm 2 were not allowed to have had prior exposure to any FVIII product, with the exception of short-term use of blood products. The Applicant should comment on any potential issues regarding prior use of blood products, in particular whether this might have resulted in any bias on the estimation of inhibitor development.

3) A total of 315 bleeding events have been treated with Afstyla with a treatment succes rate of 92% i.e. 290 of 315 bleeding episodes had a response rated as "excellent" or "good". One major bleeding episode occurred and was succesfully treated. 54 of 60 treated nonmajor bleeding episodes were succesfully treated. It is unclear why only a minority of bleeding episodes were classified as major or nonmajor. Also, frequency of only 1 major bleeding episode among 315 treated bleeds appears rather low. The Applicant is asked for clarification.

4) The mean dose per prophylactically infusion was 51.56 IU/kg among all treatment regimen (median 50.00, range 18.2-429.6). The Applicant is requested to comment on the upper range maximum of dosing up to 429 IU/kg for prophylactic infusion.

5) Subject exposure for inhibitor analysis: Of the 24 subjects included in the analysis, 2 subjects achieved <10 EDs and 1 subject >10 EDs. The Applicant should clarify whether these 3 subjects had already developed FVIII inhibitory antibodies. In case these did not, an additional inhibitor frequency analysis is requested (all-titer frequency, high-titer frequency, low-titer frequency) by only including subjects with at least 50 EDs.

6) It is unclear, how the surgery ratings of excellent haemostatic efficacy were achieved. According to the rating scale, estimated blood loss should be not more than 20% higher than the estimated predicted blood loss to achieve an excellent rating. Apparently, this criterion was not met according to Table 14.2.6.1 of the final CSR [predicted mean (SD) average blood loss 0.5 (0.71) mL, predicted mean (SD) maximum blood loss 1.0 (1.41) mL, observed mean (SD) blood loss 3.3 (5.77) mL. Further clarification is requested.

7) ITI substudy: 11 subjects were included in the ITI population but only 6 subjects received ITI treatment (N=5 low-dose and N=1 high-dose regimen). Overall, 9 subjects, all with initial low-titer inbhibitor, received inhibitor eradication. There is uncertainty regarding treatment regimen and treatment success. Further explanation is requested in particular on the subjects not receiving ITI treatment. The Applicant is also asked, whether ITI data will be reflected in the SmPC according to the EMA Reflection paper on Immune Tolerance Induction in haemophilia A patients with inhibitors (EMA/CHMP/BPWP/153137/2011).

8) Events potentially related to hypersensitivity reactions were identified, i.e. 10 subjects experienced 15 such TEAEs including eczema, rash, and bronchospasm. These events were not confirmed after medical review. The Applicant is requested to provide further details in this regard.

9) Aside from the 14 related TEAEs of inhibitor development, fatigue (n=1), pyrexia (n=1), and haemorrhage (n=1) have been reported. Pyrexia is already included in the tabulated list of adverse reactions of the Afstyla SmPC, however, fatigue and haemorrhage are not. Further clarification is requested.

10) Three subjects discontinued the study as per physician's decision. The Applicant is asked to provide additional details for the underlying reason(s).

The timetable is a 30 day response timetable with clock stop.

5. MAH's responses and assessment of the responses to the additional clarifications requested/RSI

Question 1

Line listing of all the non-clinical and clinical studies included in the development program should be provided (refer to Annex).

MAH's responses

Please refer to Annex. Line listing of all the studies included in the development program

Assessment of the MAH's responses

The requested information has been provided.

Point clarified

Question 2

Subjects eligible for study arm 2 were not allowed to have had prior exposure to any FVIII product, with the exception of short-term use of blood products. The Applicant should comment on any potential issues regarding prior use of blood products, in particular whether this might have resulted in any bias on the estimation of inhibitor development.

MAH's responses

CSL has checked the medications taken prior to the first dose with Afstyla. These data show that none of the subjects enrolled in the study have had prior exposure to any FVIII-containing blood products. Any possible bias on the development of an inhibitor can be excluded. Details regarding subjects who took any prior medications before the first Afstyla dose are provided in the table below.

Assessment of the MAH's responses

Data provided for the subjects' medications prior the first dose of Afstyla do not raise concerns regarding potential bias on the estimation of FVIII inhibitor development.

Point clarified.

Question 3

A total of 315 bleeding events have been treated with Afstyla with a treatment succes rate of 92% i.e. 290 of 315 bleeding episodes had a response rated as "excellent" or "good". One major bleeding episode occurred and was succesfully treated. 54 of 60 treated nonmajor bleeding episodes were succesfully treated. It is unclear why only a minority of bleeding episodes were classified as major or nonmajor. Also, frequency of only 1 major bleeding episode among 315 treated bleeds appears rather low. The Applicant is asked for clarification.

MAH's responses

The reason that only a minority of the bleeding episodes were classified as major or nonmajor by the investigators was because the classification was done as per the protocol. The protocol describes the classification as follow (CSR Section 9.5.1.2): Major bleeding episodes are defined as bleeding episodes for which a subject was required to seek treatment at the hemophilia center from the treating

physician for any episode that threatened the subject's life or a loss of limb. Examples of major bleeding episodes included intracranial hemorrhage, gastrointestinal bleeding, and severe bleeding. All other bleeding episodes were classified as nonmajor unless the investigator assessment noted otherwise.

Only 1 bleeding episode was considered as a major bleeding episode according to this definition and this subject was treated successfully by the investigator at the site. For treatment of minor bleeding episodes at home, the subjects or their caregivers recorded the information in the eDiary and discussed those bleeds at their next doctor appointment. In case of these minor bleeding episodes, the eDiary data were captured in the electronic study database without interference by the investigator. This explains why not all bleeding episodes were classified by the investigator in the electronic case report form (eCRF).

Assessment of the MAH's responses

It is noted that a large number of home-treated minor bleeding episodes has not been classified by a study investigator.

Point not further pursued.

Question 4

The mean dose per prophylactically infusion was 51.56 IU/kg among all treatment regimen (median 50.00, range 18.2-429.6). The Applicant is requested to comment on the upper range maximum of dosing up to 429 IU/kg for prophylactic infusion.

MAH's responses

The 429 IU/kg dose taken for routine prophylaxis may have resulted from a data entry error in the total dose by the caregiver, but it was not verified by CSL because it was an eDiary collected data. Please see below Background information for further details.

Background

In addition to the bleeding information, the actual Afstyla total dose given and specific reason for treatment were collected using eDiary. The actual dose was entered in a device by the caregiver, and the entered information are later linked to the electronic study database. All bleeding and dosing information entered in the eDiary were medically reviewed on a regular basis during the course of the study. Although most fields in the eDiary can be automatically queried based their fixed number of responses provided by the pull-down menus, other fields, like the total dose, were entered as a free text. No range check could be applied automatically to total dose because it is based on the reason for treatment. The Investigator could either administer an assigned dose for routine prophylaxis or a high bolus dose to treat a bleeding event. The challenge arises from verifying the total dose entered when there is no source documentation. Furthermore, if we were able to contact the caregiver, his/her anecdotal response could be inaccurate due to the amount of time since the total dose was entered. Therefore, the total dose and other free text fields entered in the eDiary remained unverified in our study database.

Although CSL has initially considered to exclude the extreme values entered for total doses as possible data entry errors in the descriptive summary statistics, this was not done because it could lead to selection bias due to not fully understanding the nature and extent of inaccuracies in total doses. Therefore, CSL analyzed total doses as entered by the caregiver, and based any conclusions related to

the total dose (e.g. consumption) on the median, which is less affected by extreme values, compared to the mean.

Assessment of the MAH's responses

It is noted that the maximum dosing of 429 IU/kg for prophylactic infusion is likely to be an data entry error. Mean, median, and Q3 consumptions data generally do not give cause for concern.

Point clarified.

Question 5

Subject exposure for inhibitor analysis: Of the 24 subjects included in the analysis, 2 subjects achieved <10 EDs and 1 subject >10 EDs. The Applicant should clarify whether these 3 subjects had already developed FVIII inhibitory antibodies. In case these did not, an additional inhibitor frequency analysis is requested (all-titer frequency, high-titer frequency, low-titer frequency) by only including subjects with at least 50 EDs.

MAH's responses

1 subject < 10 EDs was inhibitor positive, the remaining two subjects (one < 10 EDs and one >10 EDs) were inhibitor negative.

In subjects with at least 50 EDs, 11 developed an inhibitor (see Table 14.1.8.3.1.1).

Table 14.1.8.3.1.1 Extent of Exposure to rVIII-SingleChain with at least 50 EDs and who developed an inhibitor (PUPs - Efficacy Population)

	Total (N=24)
All Subjects	
Exposure Days in the current study	
n	11
Mean (SD)	320.0 (109.09)
Median	317.0
Q1, Q3	236.0, 396.0
Min, Max	166, 539
Number of Infusions	
n	11
Mean (SD)	321.2 (110.87)
Median	317.0
Q1, Q3	236.0, 396.0
Min, Max	166, 543
Total Number of Infusions	3533

CSL BEHRING GMBH: CSL627_3001/CIL-MJ/FINAL/EXTT01P.SAS
Produced: 8 September 2021, 9:45; Data Cut: 12 Feb 2021 Page 1 of 4
Source: Listing 16.2.5.6
Notes: [1] Percentages where indicated, are based on the number of subjects in specified population.
[2] Exposure during the surgical period is excluded.
[3] The Safety population table has not be generated as there is no difference between efficacy and safety population.
[4] Regimens are actual regimens.

In subjects with at least 50 EDs, 5 subjects developed a high titer inhibitor (see Table 14.1.8.3.1.2)

Table 14.1.8.3.1.2 Extent of Exposure to rVIII-SingleChain with at least 50 EDs and who developed high titer inhibitor (PUPs - Efficacy Population)

	Total (N=24)
All Subjects	
Exposure Days in the current study	
n	5
Mean (SD)	305.6 (122.99)
Median	317.0
Q1, Q3	198.0, 396.0
Min, Max	166, 451
Number of Infusions	
n	5
Mean (SD)	307.2 (125.39)
Median	317.0
Q1, Q3	198.0, 396.0
Min, Max	166, 459
Total Number of Infusions	1536

CSL BEHRING GMBH: CSL627_3001/CIL-MJ/FINAL/EXTT01P.SAS
Produced: 8 September 2021, 9:45; Data Cut: 12 Feb 2021 Page 1 of 4
Source: Listing 16.2.5.6
Notes: [1] Percentages where indicated, are based on the number of subjects in specified population.
[2] Exposure during the surgical period is excluded.
[3] The Safety population table has not be generated as there is no difference between efficacy and safety population.
[4] Regimens are actual regimens.

In subjects with at least 50 EDs, 6 subjects developed a low titer inhibitor (see Table 14.1.8.3.1.3).

Table 14.1.8.3.1.3 Extent of Exposure to rVIII-SingleChain with at least 50 EDs and who developed an low titer inhibitor and never became high titer (PUPs - Efficacy Population)

	Total (N=24)
All Subjects	
Exposure Days in the current study	
n	6
Mean (SD)	332.0 (106.40)
Median	302.0
Q1, Q3	285.0, 328.0
Min, Max	236, 539
Number of Infusions	
n	6
Mean (SD)	332.8 (107.93)
Median	302.5
Q1, Q3	285.0, 328.0
Min, Max	236, 543
Total Number of Infusions	1997

CSL BEHRING GMBH: CSL627_3001/CIL-MJ/FINAL/EXTT01P.SAS
Produced: 8 September 2021, 9:45; Data Cut: 12 Feb 2021 Page 1 of 4
Source: Listing 16.2.5.6
Notes: [1] Percentages where indicated, are based on the number of subjects in specified population.
[2] Exposure during the surgical period is excluded.
[3] The Safety population table has not be generated as there is no difference between efficacy and safety population.
[4] Regimens are actual regimens.

Assessment of the MAH's responses

Information provided by the Applicant regarding subjects' exposure for inhibitor analysis do not give cause for concern.

Point clarified.

Question 6

It is unclear, how the surgery ratings of excellent haemostatic efficacy were achieved. According to the rating scale, estimated blood loss should be not more than 20% higher than the estimated predicted blood loss to achieve an excellent rating. Apparently, this criterion was not met according to Table 14.2.6.1 of the final CSR [predicted mean (SD) average blood loss 0.5 (0.71) mL, predicted mean (SD) maximum blood loss 1.0 (1.41) mL, observed mean (SD) blood loss 3.3 (5.77) mL. Further clarification is requested.

MAH's responses

CSL acknowledges that the actual mean blood loss of surgeries was higher than 20% than the predicted blood loss (Table 14.2.6.1).

Table 14.2.6.1 Comparison of Predicted and Observed Intraoperative Estimated Blood Loss (PUPs - Surgery Population)

	On-Demand (N=2)	Prophylaxis (N=1)	Total (N=3)
Predicted Average Blood Loss (mL)			
n	2	0	2
Mean (SD)	0.5 (0.71)		0.5 (0.71)
Median	0.5		0.5
Min, Max	0, 1		0, 1
Predicted Maximum Blood Loss (mL)			
n	2	0	2
Mean (SD)	1.0 (1.41)		1.0 (1.41)
Median	1.0		1.0
Min, Max	0, 2		0, 2
Observed Blood Loss (mL)			
n	2	1	3
Mean (SD)	5.0 (7.07)	0.0 ()	3.3 (5.77)
Median	5.0	0.0	0.0
Min, Max	0, 10	0, 0	0, 10

CSL BEHRING GMBH: CSL627_3001/CIL-MJ/FINAL/SUR01P.SAS
Produced: 21 April 2021, 5:58; Data Cut: 12 Feb 2021 Page 1 of 1
Source data: Listing 16.2.9.3.3

According to this definition it should not have been rated as excellent. However, in 2 of the 3 surgeries, both the predicted and actual blood loss was 0mL and could be rated as excellent (Listing 16.2.9.3.3).

The actual blood loss during the port placement in the third patient exceeded the predicted blood loss although the total loss was still a very small volume (10 mL, Listing 16.2.9.3.1 and 16.2.9.3.3).

Assessment of the MAH's responses

The Applicant admits an erroneous assessment and the validity of these surgical efficacy data is thus in doubt. However, due to the very small number of cases, the data are not meaningful anyway.

Issue not further pursued.

Question 7

ITI substudy: 11 subjects were included in the ITI population but only 6 subjects received ITI treatment (N=5 low-dose and N=1 high-dose regimen). Overall, 9 subjects, all with initial low-titer inbhibitor, received inhibitor eradication. There is uncertainty regarding treatment regimen and treatment success. Further explanation is requested in particular on the subjects not receiving ITI treatment. The Applicant is also asked, whether ITI data will be reflected in the SmPC according to the EMA Reflection paper on Immune Tolerance Induction in haemophilia A patients with inhibitors (EMA/CHMP/BPWP/153137/2011).

MAH's responses

Given the flexibility in the dosing options in the main study investigators had the option to increase the dose of rVIII-SingleChain to attempt to treat the inhibitor and achieve eradication without formally enrolling the patient in the ITI study.

The ITI sub study allowed the investigator to assign either a low dose (50 IU/kg, 3x weekly), intermediate dose (100 IU/kg daily), and high (200 IU/kg daily) regimen. The main study allowed the investigator to increase the subject's regimen to treat the inhibitor. CSL decided to include all the subjects who had any dose adjustment as ITI population in order to evaluate the treatment response.

Of the 11 subjects included in the ITI population, 5 were enrolled into the ITI sub-study on the low dose regimen (50IU/kg, 3 times a week) and 1 received a high dose regimen (200 IU/kg daily). The remaining 5 subjects remained in the main study; 4 received intensified prophylaxis regimens (3 received low dose of ITI (50 IU/kg 3x weekly, 58 IU/kg 3x weekly, and 50 IU/kg 2x weekly and 1 42 IU/kg 3x weekly) to treat the inhibitor and 1 subject continued on their current regimen without modification (30 IU/kg once weekly). The 5 subjects who remained in the main study had all achieved inhibitor eradication.

Regarding the addition of the ITI information, CSL is committed to update the EU-SmPC in upcoming variation procedures (planned for December 2021) to include ITI information according to the EMA reflection paper on Immune Tolerance Indication in Haemophilia A patients with inhibitors (EMA/CHMP/BPWP/153137/2011). CSL also proposes to update the introductory paragraph in Section 5.1 to include demographic information from study CSL627_3001.

Assessment of the MAH's responses

Provided information sufficiently clarify treatment regimens for the 11 subjects included in the ITI population. A variation is planned to also include ITI related information in the EU SmPC.

Point clarified.

Question 8

Events potentially related to hypersensitivity reactions were identified, i.e. 10 subjects experienced 15 such TEAEs including eczema, rash, and bronchospasm. These events were not confirmed after medical review. The Applicant is requested to provide further details in this regard.

MAH's responses

CSL acknowledges the assessor's request to provide further clarification regarding the 15 TEAEs that could be considered as symptoms or manifestations of hypersensitivity reactions.

A total of 15 TEAEs were identified using the SMQ* Hypersensitivity (narrow). Two subjects (8.3%) experienced a total of 4 events of Bronchospasm (1 subject had 3 events of Bronchospasm, 1 subject had 1 event), 3 subjects (12.5%) experienced 1 event each of Eczema and 3 subjects (12.5%) experienced 1 event each of Rash. The remaining 5 events were Conjunctivitis allergic Dermatitis allergic, Eye swelling, Rash erythematous and Rhinitis allergic; all reported in 1 subject each. All the events were non-serious and of either mild or moderate severity. rVIII-SingleChain dose was not changed following 12 of the events, while the action taken with the study treatment was reported as not applicable for the remaining 3 events. For the latter 3 events, concomitant medication was prescribed to treat them. The outcome was reported as recovered for all but one event (Rash). All the events were assessed as not related to rVIII-SingleChain by the investigator.

CSL would like to clarify that these were confirmed TEAEs. However, upon medical review, none of these TEAEs were confirmed as hypersensitivity reactions related to rVIII-SingleChain.

*SMQ: Standardised MedDRA Query

Assessment of the MAH's responses

The Applicant's comments are acknowledged, the concerned TEAEs were assessed as not related by the study investigator. The potential for hypersensitivity reactions is flagged within the SmPC (Section 4.4 Special warnings and precautions for use, Section 4.8 Undesirable effects - Summary of the safety profile) and these occur at common frequency (Section 4.8 Undesirable effects - Tabulated list of adverse reactions).

Point clarified.

Question 9

Aside from the 14 related TEAEs of inhibitor development, fatigue (n=1), pyrexia (n=1), and haemorrhage (n=1) have been reported. Pyrexia is already included in the tabulated list of adverse reactions of the Afstyla SmPC, however, fatigue and haemorrhage are not. Further clarification is requested.

MAH's responses

CSL acknowledges the assessor's request and would like to provide further clarification.

One subject experienced intermittent fatigue of mild severity assessed as nonserious and related to rVIII-SingleChain by the investigator. The dose of rVIII-SingleChain was not changed and no other action was taken. The outcome was reported as not recovered. A month prior to this event, the subject had experienced malaise and within the following month, he also experienced Pyrexia and Inhibitor development. Approximately 4 months later, the subject experienced Iron deficiency anaemia. Of note, the underlying haemophilia, development of FVIII inhibitors, and the difficulty in diagnosing fatigue in this 1-year-old subject, were considered as confounders. Furthermore, fatigue could be an early symptom of Iron deficiency anaemia that was later diagnosed.

Throughout the clinical development program of rVIII-SingleChain, 1 additional event of Fatigue has been reported in a PTP. That was a non-serious event of mild severity that was assessed as not related to rVIII-SingleChain by the investigator.

After medical review of this single event of Fatigue with plausible other root cause, an update of the SmPC was not deemed necessary.

One subject experienced severe haemorrhage which was assessed as serious and related to rVIII-SingleChain by the investigator. Of note, the subject was tested positive for high titer FVIII inhibitors (5.90 BU/ml) one week before the occurrence of haemorrhage. rVIIISingleChain dose was increased, rFVII (NovoSeven) was administered and the subject recovered from the event. CSL assessed this event as related to rVIII-SingleChain. The presence of FVIII inhibitors was likely the main cause of haemorrhage. Haemorrhage itself is a clinical sign that allows for early suspicion and testing for FVIII inhibitors, as described in section 4.4 of the EU-SmPC:

Inhibitors

The formation of neutralising antibodies (inhibitors) to factor VIII is a known complication in the management of individuals with haemophilia A. These inhibitors are usually IgG immunoglobulins directed against the factor VIII procoagulant activity, which are quantified in Bethesda Units (BU) per

ml of plasma using the modified assay. The risk of developing inhibitors is correlated to the severity of the disease as well as the exposure to factor VIII, this risk being highest within the first 50 exposure days but continues throughout life although the risk is uncommon.

The clinical relevance of inhibitor development will depend on the titre of the inhibitor, with low titre posing less of a risk of insufficient clinical response than high titre inhibitors.

In general, all patients treated with coagulation factor VIII products should be carefully monitored for the development of inhibitors by appropriate clinical observations and laboratory tests. If the expected factor VIII activity plasma levels are not attained, or if bleeding is not controlled with an appropriate dose, testing for factor VIII inhibitor presence should be performed. In patients with high levels of inhibitor, factor VIII therapy may not be effective and other therapeutic options should be considered. Management of such patients should be directed by physicians with experience in the care of haemophilia and factor VIII inhibitors.

Therefore, after medical review of this single case of Haemorrhage in the context of FVIII inhibitors, an update of the Afstyla SmPC was not deemed necessary.

Assessment of the MAH's responses

The Applicant's explanations are acknowledged.

Point not further pursued.

Question 10

Three subjects discontinued the study as per physician's decision. The Applicant is asked to provide additional details for the underlying reason(s).

Assessment of the MAH's responses

Additional information provided for subjects' discontinuation per physician's decision do not raise concerns.

Point clarified.

6. Overall conclusion and recommendation on the responses to the additional clarifications requested/RSI

☒ **Fulfilled:** No further action required

Annex. Line listing of all the studies included in the development program

The studies should be listed by chronological date of completion:

Non clinical studies

Product Name: CSL627 (rVIII-SingleChain)

Study title	Study number	Date of completion*	Date of submission of final study report
Pharmacodynamic efficacy of CSL627 in preclinical tox species using thrombin generation	IVR 14-03	04 December 2014	04 December 2015
Pharmacodynamic efficacy of rVIII-Single Chain in monkey plasma using thrombin generation	IVX 14-10	03 February 2015	04 December 2015
Pharmacodynamic comparison of rVIII-SingleChain (CSL627) and Advate® regarding thromboelastography and thrombin generation parameters following a single intravenous injection to Hemophilia A mice	PSM 12-18	25 March 2015	04 December 2015
Pharmacodynamic comparison of rVIII-SingleChain (CSL627) and Advate® regarding aPTT following a single intravenous injection to Hemophilia A mice	PSM 12-23	23 March 2015	04 December 2015
Correction of hemostasis in FVIII ko mice following treatment with rVIII SingleChain, Helixate®, ReFacto® AF, Advate® and Humate® P	ABM 03/10 and ABM 01/11	20 February 2015	04 December 2015
CSL 627 (rFVIII): Effects on General Haemodynamics and Respiratory Variables in Anaesthetised Beagle Dogs (Intravenous Infusion Administration)	APQ0016	21 December 2011	04 December 2015
CSL 627 (rFVIII): Telemetric Evaluation of Cardiovascular Effects in the Conscious Beagle Dog (Intravenous Infusion Administration)	APQ0018	20 December 2011	04 December 2015
CSL 627 (rFVIII): Telemetric Evaluation of Cardiovascular Effects in the Conscious Cynomolgus Monkey (Intravenous Infusion Administration)	APQ0019	20 December 2011	04 December 2015
Validation of an ELISA method for the determination of CSL627 in rat plasma	10087	06 January 2011	04 December 2015

Validation of an ELISA method for the determination of antibodies against CSL627 in rat plasma	10097	20 January 2011	04 December 2015
Validation of an ELISA method for the determination of antibodies against CSL627 in monkey plasma	10098	20 January 2011	04 December 2015
Validation report for chromogenic determination of FVIII activity in plasma samples using Behring Coagulation System	MEV-83r	29 October 2009	04 December 2015
Pharmacokinetic evaluation of rFVIII/CSL627, Helixate®, ReFacto AF® and Advate® in FVIII ko mice	PSM 06/11	21 June 2016	11 October 2016
CSL627: PK Study and Tool Antibody Production in Cynomolgus Monkeys	APQ0015	05 April 2011	04 December 2015
CSL627: PK Study in Cynomolgus Monkeys	APQ0020	20 June 2012	04 December 2015
CSL627: Single Dose Toxicity Study by Intravenous Bolus Administration to CD Rats	APQ0010	31 May 2011	04 December 2015
CSL627: Single Dose Toxicity Study by Intravenous Bolus Administration to Cynomolgus Monkeys	APQ0011	05 May 2011	04 December 2015
CSL627: Toxicity Study by Intravenous Bolus Administration to CD Rats for 4 Weeks Followed by a 14 Day Recovery Period	APQ0013	31 May 2011	04 December 2015
CSL627: Toxicity Study by Intravenous Bolus Administration to Cynomolgus Monkeys for 4 Weeks Followed by a 14 Day Recovery Period	APQ0014	17 June 2011	04 December 2015
CSL627: Local Tolerance Study in the Rabbit following Intravenous, Intra-arterial or Perivenous Injection	APQ0012	19 May 2011	04 December 2015
In Vivo Thrombogenicity Test in the Rabbit (Modified Wessler Test as Described by Giles, A.R. 1980)	S30668	19 May 2011	04 December 2015
Validation report for determination of FVIII activity in plasma samples using Behring Coagulation Timer and Behring Coagulation System	MEV-68r	17 November 2008	04 December 2015
Validation report for modified chromogenic determination of FVIII activity in plasma samples using Behring Coagulation System	020200021r	15 November 2011	04 December 2015
Validation report for determination of inhibitory antibodies against FVIH	MEV-70r	10 March 2009	04 December 2015
Validation report for determination of antibodies against rFVIII in human plasma samples	020200023r	01 February 2012	04 December 2015
Validation report for determination of antibodies against rFVIII (CSL627), Isotype IgG with Dianova conjugate in human plasma samples	020200034r	12 July 2013	04 December 2015

Validation report for determination of antibodies against rFVIII-CHO cell proteins using ELISA	020200030r	17 January 2014	04 December 2015
DETECTION OF ANTIBODIES AGAINST RVIII CHO HCP IN CITRATED HUMAN PLASMA VIA SPR (BIACORE) ANALYSIS	020200054_r	09 February 2015	04 December 2015

* Based on date of completion of the final report (final signature from QA on signature page), not the end of the in-life phase.

Clinical studies

Product Name: CSL627 (rVIII-SingleChain)

Study title	Study number	Date of completion*	Date of submission of final study report
International comparative field study evaluating the assay performance of rVIII-SingleChain in plasma samples at clinical hemostasis laboratories	N/A	18 September 2015	04 December 2015
Lot vs. Pharmacokinetic Comparisons for Clinical Studies CSL627_1001 and CSL627_3002	Based on protocol of CSL627_1001 & CSL627_3002	10 November 2015	04 December 2015
Population Pharmacokinetic Analysis of Recombinant Coagulation Factor VIII-SingleChain(rVIII-SingleChain) (CSL627) in Subjects with Hemophilia A	CSL627_1001 & CSL627_3002	17 November 2015	04 December 2015
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	CSL627_1001	07 May 2015	04 December 2015
A Phase III Open-label Pharmacokinetic, Efficacy and Safety Study of rVIII-SingleChain in a Pediatric Population with Severe Hemophilia A	CSL627_3002	18 August 2015	04 December 2015
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	CSL627_3001 (PTP Arm: 1 and 3)	28 November 2019	13 January 2020
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	CSL627_3001 (PUP Arm: 2)	25 June 2021	02 July 2021

* Based on final sign off date on reports