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Division / Office	OBRR/DH
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Applicant	CSL Behring
Established Name	Antihemophilic Factor (Recombinant), SingleChain
(Proposed) Trade Name	AFSTYLA
Pharmacologic Class	
Formulation(s), including Adjuvants, etc	Recombinant DNA-derived, antihemophilic factor
Dosage Form(s) and Route(s) of Administration	For Intravenous Injection, Powder and Solvent for Injection
Dosing Regimen	Single dose
Indication(s) and Intended Population(s)	The proposed indication is for use in adults and children with hemophilia A (congenital Factor VIII deficiency) for: 1) On-demand treatment and control of bleeding episodes, 2) Routine prophylaxis to prevent or reduce the

	frequency of bleeding episodes, 3) Perioperative management of bleeding.

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GLOSSARY

ABR	Annualized bleeding rate
ADA	Anti-drug antibody
AE	Adverse event
AsBR	Annualized spontaneous bleeding rate
BDDrFVIII	B domain-deleted recombinant factor VIII
CHMP	Committee for Medicinal Products for Human Use
CHO	Chinese hamster ovary
ChS	Chromogenic substrate (assay)
CI	Confidence interval
CSL627	Sponsor-assigned drug code for AFSTYLA
CSR	Clinical study report
ED	Exposure day
EMA	European Medicines Agency
FVIII	Factor VIII
GCP	Good Clinical Practice
ICH	International Conference on Harmonisation
IV	Intravenous
pdFVIII	Plasma-derived Factor VIII
PK	Pharmacokinetic(s)
PP	Per protocol
rFVIII	Recombinant coagulation factor VIII
rVIII-SingleChain	Recombinant single-chain coagulation factor VIII
SAE	Serious adverse event
SD	Standard deviation
TEAE	Treatment-emergent adverse event
WFH	World Federation of Hemophilia

1. EXECUTIVE SUMMARY

This original Biologics License Application (BLA) submission seeks marketing authorization of the recombinant Antihemophilic Factor (AFSTYLA). The product is proposed to be administered in adults and children with hemophilia A (congenital Factor VIII deficiency) for on-demand treatment and control of bleeding episodes, routine prophylaxis to prevent or reduce the frequency of bleeding episodes, and perioperative management (surgical prophylaxis).

The AFSTYLA clinical program comprises three studies: pivotal study CSL627-1001, pediatric study CSL627-3002 and on-goin g extension study CSL627-3001. This statistical review memo focuses on the efficacy analysis and safety analysis of study 1001 and 3002, as well as the interim efficacy and safety analysis of studies 3001.

Both the efficacy and safety of AFSTYLA are supported by results of study 1001, which was a phase I/III, open-label, multicenter, crossover safety, efficacy, and PK study of AFSTYLA compared to recombinant human antihemophilic factor VIII for adult and adolescent subjects. In study 1001, among 835 treated bleeding episodes from 173 subjects evaluated by the investigator, 783 (93.8%; CI: 91.0%, 95.7%) were assessed as a hemostatic success. Since the lower limit of the two-sided 95% CI of the hemostatic efficacy success rate is higher than the pre-specified threshold 70%, the study met the success criterion for the control of bleeding episodes. The annualized spontaneous bleeding rate (AsBR) of the prophylaxis group (146 subjects) is 1.6, which which is lower than that of the on-demand group (27 subjects), 19.5. The ratio of AsBR of prophylaxis group over the on-demand group is 0.08 (CI: 0.07, 0.10). The upper limit of CI is less than 0.50 and the p-value of testing the equivalence of AsBR from these two groups in two-sided is less than 0.0001. For surgical prophylaxis, 13 subjects achieved hemostatic success in all 16 surgeries.

Study 3002 was a Phase III, open-label, multicenter, uncontrolled study to assess the efficacy, safety, and PK of AFSTYLA in pediatric patients with severe hemophilia A. A total of 347 bleeding episodes from 83 subjects were treated with AFSTYLA and 96.3% were rated a success (334/347), with two-sided 95% CI (91.4%, 98.4%). The lower limit of the 95% CI was also higher than 70%.

No inhibitor occurred in study 1001 as well as study 3002 and 3001. The upper limit of 95% confidence interface of inhibitor incidence was lower than the pre-specified threshold 6.8% in all three studies ([0%, 2.1%] in study 3001, [0, 4.3%] in study 3002, and [0, 3.4%] in study 3001).

2. CLINICAL AND REGULATORY BACKGROUND

2.1 Disease or Health-Related Condition(s) Studied

Hemophilia A (coagulation factor VIII [FVIII] deficiency) is a rare and serious X-linked hereditary disorder of blood coagulation due to decreased levels of FVIII that results in

bleeding into joints, muscles or internal organs, either spontaneously or as result of accidental or surgical trauma.

In patients with hemophilia A, the primary platelet-driven hemostasis is not affected, but generation of a stable, fibrin-rich clot is defective because inadequate amounts of thrombin are generated. Affected patients suffer from both spontaneous, non-traumatic bleeding episodes as well as substantially prolonged bleeding episodes upon injury. Rarely, life-threatening bleeding may also occur.

2.2 Currently Available, Pharmacologically Unrelated Treatment(s)/Intervention(s) for the Proposed Indication(s)

The primary aim of care for patients with hemophilia A is to either control bleeding episodes as they occur (on-demand) or to prevent bleeding episodes (prophylaxis). Replacement therapy with exogenous FVIII (either plasma-derived factor FVIII [pdFVIII] or recombinant [rFVIII]) provides a temporary correction of the coagulation factor deficiency by increasing FVIII levels to arrest the bleeding episode (on-demand treatment) or to prevent bleeding (prophylaxis, with the administration interval on an individually determined basis). The aim of prophylaxis is to keep trough total FVIII activity > 1%, i.e. to reduce disease severity from severe to moderate. The therapeutic goal is to prevent as many joint bleeds as possible and thereby delay or even avoid the onset of crippling joint disease.

2.4 Previous Human Experience with the Product (Including Foreign Experience)

The proposed product, AFSTYLA, is a single-chain recombinant coagulation factor VIII produced in Chinese hamster ovary (CHO) cells. It replaces the missing coagulation factor VIII needed for effective hemostasis. Compared to full-length rFVIII, AFSTYLA is a high-purity product with improved PK properties without the need for glycopegylation or fusion to antibody fragments.

The clinical development program for AFSTYLA was developed in accordance with the European Medicines Agency (EMA) Committee for Medicinal Products for Human Use (CHMP) Guideline on Clinical Investigation of Recombinant and Human Plasma-derived Factor VIII Products (EMA, 2011) and in conjunction with guidance from the FDA and the (b) (4) This clinical program was designed to determine the PK profile, safety and efficacy of AFSTYLA in adult and pediatric subjects with hemophilia A (FVIII activity < 1%)

2.5 Summary of Pre- and Post-submission Regulatory Activity Related to the Submission

The following meetings/correspondence with statistical content occurred during the AFSTYLA development stage:

- Type B Pre-IND meeting CRMTS 7945 (May 6, 2011) for the clinical development program. Agreements included:
  - A quantitative clarification of factor infusions is acceptable to distinguish between "Good" and "Moderate" in the 4-point efficacy scale.

  - Proposed study of 104 patients, resulting in 6.77% as the upper limit of a two-sided 95% confidence interval for an inhibitor rate of 2 out of 104 is acceptable.
  - Agreed to CSLB's proposal to adapt the "Four-point scale for Efficacy Evaluation of Major Trauma or Life Threatening Bleeds" to have a similar clarification and distinguishing of parameters as presented in the Efficacy Evaluation of AFSTYLA in the prophylaxis of bleeding episodes in patients with Hemophilia A undergoing surgical procedures (e.g. not more than 20% more bleeding than would be expected in a non-factor deficient patient).
  - To discuss pediatric use with CSLB after reviewing the data from 20 adult patients.
- Type C meeting CRMTS 9127 for the ongoing clinical development program (IND 14791). FDA sent a written response and request for CMC information as well as a pediatric study on November 22, 2013.
- Pre-BLA meeting CRMTS 9559. FDA sent the written response on November 20, 2014. Agreements included:
  - FDA agreed that, theoretically, both OC and CS assays may be suitable for monitoring patients' FVIII:C levels during treatment; however, the final decision on the appropriateness of either approach can only be reached after review of the complete data set in the BLA.
  - The dataset and proposed presentation for Module 2.7.4 appear to support the overall safety profile of your product. However, final determination will be based on the complete review of the data in the BLA.
  - The trial will be considered successful if the lower limit of the 95% CI of hemostatic efficacy success rate is above 70%.
  - The dataset may be adequate to support a prophylaxis indication, and can be confirmed only after complete review of the data in the BLA.
  - The proposed dataset of 11 major surgeries in 10 unique subjects is sufficient for the surgery indication.
  - Section 2.7.4 is the appropriate location for the interim safety and PK report.
- Advice letter of March 26, 2015 requesting analyses in the BLA of overall clinical assessment of hemostatic efficacy and ABR by race as well as key safety analyses by demographic subgroups.

3. SUBMISSION QUALITY AND GOOD CLINICAL PRACTICES

3.1 Submission Quality and Completeness

This submission was adequately organized for conducting a complete statistical review without unreasonable difficulty.

5. SOURCES OF CLINICAL DATA AND OTHER INFORMATION CONSIDERED IN THE REVIEW

All data sources are included in the applicant's eCTD submission located in the FDA/CBER Electronic Document Room (EDR).

5.1 Review Strategy

The clinical development program consists of three studies:

- Study 1001: A phase I/III open-label, multicenter, crossover safety, efficacy and PK 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 (*completed*).
- Study 3002: A phase III open-label pharmacokinetic, efficacy and safety study of AFSTYLA in a pediatric population with severe hemophilia A *(completed).*
- Study 3001: Phase III open-label, multicenter, extension study (to parent Studies 1001 and 3002) to assess the safety and efficacy of recombinant coagulation Factor VIII (AFSTYLA) in subjects with severe hemophilia A (*ongoing*).

This review memo focuses on the efficacy and safety analyses of Study 1001. Studies 3001 and 3002 are also reviewed for interim efficacy and safety data. Surgery results from Study 1001 are reviewed for the perioperative management indication. The PK data is reviewed in a separate PK document provided by OBRR.

5.2 BLA/IND Documents That Serve as the Basis for the Statistical Review

This BLA was based on IND 14791. Data from the completed Study 1001 and interim PK and safety from the ongoing Study 3002 were submitted in the original BLA application. Additional pediatric PK and safety data from study 3002 were provided in the 4-month safety update (125591/0.3, September 24, 2015). An interim safety report for the ongoing Study 3001 was also provided in the 4-month safety update. A clinical study report of study 3002 was submitted under IND 14791 (IND14791/92) on Feb 3, 2016. The following documents (listed by Module number) in the BLA submission were reviewed:

- 1.6 Meetings
- 1.14 Labeling
- 2.2 Introduction
- 2.5 Clinical Overview
- 2.7 Summary of Clinical Efficacy
- 5.3.5 Protocol (CSL627-1001, CSL627-3001, CSL627-3002)
- 5.3.5 Report-body (CSL627-1001, CSL627-3001, CSL627-3002)
- 5.3.5 Sample-crf (CSL627-1001)
- 5.3.5 Statistical-methods (CSL627-1001, CSL627-3001, CSL627-3002)
- 5.3.5 Synopsis (CSL627-1001, CSL627-3001, CSL627-3002)

5.3 Table of Studies/Clinical Trials

Table 1 presents all three clinical studies of AFSTYLA.

Table 1: Overview of AFSTYLA Clinical Studies contributing to the Clinical Development Program

Study, Status	***Type of Study***	***Study Design***	***Primary objective(s) of the study***	***Number and Age of Subjects***	***Duration of Treatment***	***Location of study centers***
Study 1001 Complete	Safety, Efficacy and PK	Phase I / III, prospective multicenter, open label with surgery substudy	Characterize the PK profile of CSL-627. Demonstrate efficacy in the control of bleeding episodes. Demonstrate efficacy of a routine prophylaxis regimen over on demand regimen. Demonstrate efficacy of AFSTYLA in surgical prophylaxis. Characterize rate of inhibitor formation.	174 subjects *Surgery substudy*: 13 subjects Median (min, max) age: 31.3 (12, 64) years	Mean: 8.5 months (Actual) Median number of EDs: 64 EDs	Australia, Austria, Canada, Czech Republic, Germany, Hungary, Italy, Japan, Lebanon, Malaysia, Netherlands, Philippines, Poland, Romania, Russian Federation, South Africa, Spain, Ukraine, United Kingdom, United States
Study 3002 Complete	Safety, Efficacy and PK	Phase III, prospective multicenter, open label	Evaluate efficacy of AFSTYLA in treatment of major and minor bleeding episodes based on investigator's 4-point assessment scale	84 subjects 0 to < 6 years: 35 subjects ≥ 6 to <12 years: 49 subjects Median (min, max) age: 7.0 (1*, 11) years	≥ 50 subjects achieving 50 EDs (Planned)	Australia, Georgia, Germany, Italy, Lebanon, Malaysia, Netherlands, Poland, Thailand, Ukraine, United States
Study 3001 Ongoing	Safety, Efficacy	Phase III, prospective, multicenter, open label (extension study)	Evaluate safety of long-term use of AFSTYLA	154 subjects	≥ 200 subjects achieving ≥ 100 EDs (Planned)	Australia, Austria, Canada, Czech Republic, Germany, Hungary, Italy, Japan, Lebanon, Malaysia, Netherlands, Philippines, Poland, Romania, South Africa, Spain, Ukraine, United Kingdom, United States

*: There were two pediatric subjects aged 1 in this study.
Source: Adapted from Original BLA. Module 2.5: Clinical-overview.pdf, page 16.

6. DISCUSSION OF INDIVIDUAL STUDIES/CLINICAL TRIALS

6.1 Trial #1: CSL627-1001

This study was designed to determine the rate of FVIII inhibitors, the frequency of adverse events (AEs) and serious adverse events (SAEs) associated with the use of AFSTYLA, evaluate the PK of 50 IU/kg AFSTYLA compared to Advate, and evaluate the efficacy of AFSTYLA in subjects with severe hemophilia A.
A surgical sub-study evaluated the safety and efficacy of AFSTYLA in the treatment of bleeding during surgical procedures.

6.1.1 Objectives

The primary objectives of this study were to:

- Characterize the rate of inhibitor formation
- Characterize the PK profile of AFSTYLA
- Demonstrate efficacy in the treatment of bleeding events
- Demonstrate the efficacy of routine prophylaxis treatment over on-demand treatment
- Demonstrate the efficacy of AFSTYLA in surgical prophylaxis

The secondary objectives of this study were to:

- Characterize the safety profile of AFSTYLA
- Perform the PK comparison of AFSTYLA to Advate

6.1.2 Design Overview

This was an open-label, international, multi-center, cross-over study, which followed the recommendations of the FDA and EMA. The study consisted of three parts:

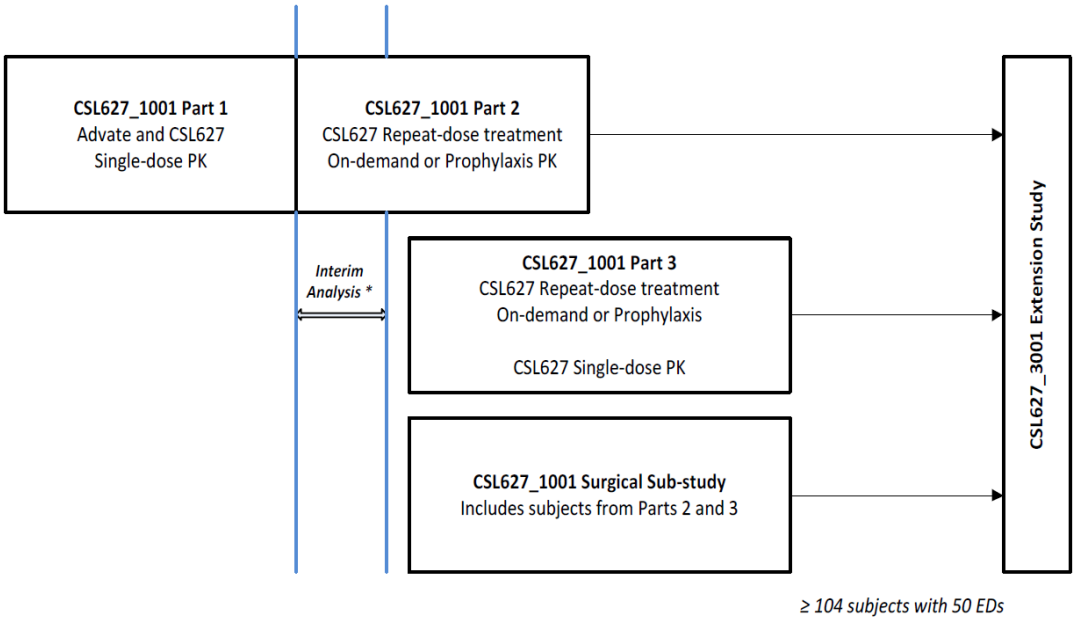
- Part 1: This part of the study conducted a single-sequence crossover PK comparison of Advate and AFSTYLA. Subjects received a single intravenous (IV) dose of Advate followed by the same dose of AFSTYLA after a 4-day wash-out period. An interim analysis of the open-label data was conducted on the PK and safety data following the completion of the last PK sample collection for the last evaluable PK subject in this part of the study. PK data from Part I confirmed that the dosing selection and schedules for Part 3 of the study (as based on World Federation of Hemophilia [WFH] guidelines) were appropriate.
- Part 2: This part of the study assessed efficacy and safety of AFSTYLA with continued dosing from Part 1. The first five subjects had to receive on-demand treatment to confirm the hemostatic potential of AFSTYLA, while the remaining subjects received either on-demand or prophylaxis treatment based on their preference and investigator discretion. It was planned that approximately 30 subjects be enrolled to achieve 26 evaluable subjects in this stage.
- Part 3: This part of the study assessed the safety and efficacy of AFSTYLA with continued dosing of new subjects, and included a repeat PK assessment for at

least 13 subjects. After PK assessment, subjects then began on-demand or prophylaxis treatment for at least 50 Exposure Days (EDs). It was planned that approximately 100 new subjects would achieve at least 104 evaluable subjects in this stage.

After enrollment commenced in Part 3, a surgical sub-study was conducted with a minimum of five subjects from either Parts 2 or 3.

Figure 1 shows the overall study design.

Figure 1: The overall study design of CSL627-1001



*The interim analysis was conducted after the last PK sample collection for the last evaluable PK subject in Part 1.
Source: Original BLA, Module 5.3.5.1: CSL627-1001/report-body.pdf, Figure 9-1, page 25.

6.1.3 Population

Subjects meeting all of the following inclusion criteria were eligible for enrolment into the study:

- Diagnosis of severe hemophilia A defined as < 1% FVIII: C documented in medical records.
- Males between ≥ 18 and ≤ 65 years of age (Parts 1 and 2).
- Males between ≥ 12 and ≤ 65 years of age (Part 3).
- Subjects who had received or were currently receiving FVIII products (plasma-derived and/or recombinant FVIII) and have had > 150 EDs with a FVIII product.
- Written informed consent for study participation had been obtained before undergoing any study specific procedures.

Subjects meeting any of the following exclusion criteria were not eligible for enrolment into the study:

- Any history of or current FVIII inhibitors
- Any first order family history of FVIII inhibitors
- Use of an Investigational Medicinal Product (IMP) within 30 days prior to the first
- AFSTYLA administration.
- Not capable of receiving treatment at home
- Administration of any cryoprecipitate, whole blood or plasma within 30 days prior to administration of AFSTYLA or reference product.
- Known hypersensitivity (allergic reaction or anaphylaxis) to any FVIII product or hamster protein.
- Any known congenital or acquired coagulation disorder other than congenital FVIII deficiency.
- Platelet count < 100,000/μL at Screening.
- Human immunodeficiency virus (HIV) positive subjects with a CD4 count < 200/mm3, in their medical history or at Screening if available results are older than 1 year. (HIV positive subjects may participate in the study and antiviral therapy is permitted, at the discretion of the investigator).
- Subjects were currently receiving IV immunomodulating agents such as immunoglobin or chronic systemic corticosteroid treatment.
- Subject with serum aspartate aminotransferase or serum alanine aminotransferase values > 5 times (x) the upper limit of normal (ULN) at Screening.
- Subjects with serum creatinine values >2 x ULN at Screening
- Subjects with serum creatinine values >2 x ULN at Screening.
- Evidence of thrombosis, including deep vein thrombosis, stroke, pulmonary embolism, myocardial infarction and arterial embolus within 3 months prior to Day 1.
- Experienced life-threatening bleeding episode or had major surgery or an orthopedic surgical procedure during the 3 months prior to Day 1.
- Demonstrated inability (eg, language problem or mental condition) or unwillingness to comply with study procedures or history of noncompliance.
- Employee at the study site, or spouse/partner or relative of the investigator or Subinvestigators.
- Re-entry of subjects previously enrolled or participating in the current study.
- Mental condition rendering the subject (or the subject's legally acceptable representative[s]) unable to understand the nature, scope and possible consequences of the study.
- Suspected inability (eg, language problems) or unwillingness to comply with study procedures.
- Mental condition rendering the subject (or subject's legally acceptable representative[s]) unable to understand the nature, scope and possible consequences of the study.
- Any condition that is likely to interfere with evaluation of the IMP or satisfactory conduct of the study.

6.1.4 Study Treatments or Agents Mandated by the Protocol

A dose each of 50 IU/kg of Advate and AFSTYLA was used for the PK assessment in Part 1. Doses during the treatment period ranged from 20 to 50 IU/Kg for rVIII-SingleChain (Part 2 and Part 3). Higher or lower doses were used at investigator discretion, based on historical dosing with previous FVIII product, bleeding phenotype, and PK data. The following are the details for each part of this study:

- In Part 1, subjects received a single IV dose of 50 IU/kg Advate on Day 1, and after a 4-day wash-out period, a single IV 50 IU/kg dose of AFSTYLA.

- In Part 2, all prophylaxis subjects were to receive AFSTYLA at a dose of 20 to 40 IU/kg body weight every second day or 20 to 50 IU/kg body weight 2 to 3 times per week, or at other doses and frequencies at the investigator's discretion. All on-demand treatment subjects were to receive AFSTYLA at a dose similar to the FVIII product used prior to enrollment for the same type of bleeding event.

- In Part 3, at least 13 new subjects were to participate in the full PK evaluation of AFSTYLA and should have received a single dose of 50 IU/kg. Repeat PK analysis, using the same strength of AFSTYLA, was performed after 3 to 6 months. After the initial PK, subjects began on-demand or prophylaxis treatment and continued treatment for at least 50 EDs or until at least 104 subjects reached 50 EDs.

- In the surgical sub-study, dosing regimens with AFSTYLA were individualized based on the type of surgery and clinical status of the subject.

6.1.6 Sites and Centers

This was a multinational study. Subjects were screened for study participation from 22 countries. One hundred seventy-five subjects were enrolled into the study at sites across 20 countries.

6.1.7 Surveillance/Monitoring

An Independent Data Monitoring Committee (IDMC) was established to monitor the safe conduct of the study and consisted of individuals external to CSL Behring who had relevant clinical trial expertise and experience in safety assessment. The IDMC charter outlined the roles and responsibilities of the committee and guided its operations. The IDMC was responsible for:

- Providing recommendations to CSL Behring regarding study conduct matters that affected safety.
- Reviewing safety data at ad hoc time points and identifying if significant safety concerns arise during the study
- Reviewing PK data and any other data that may affect subject continuation.
- Making recommendations regarding study progression.

6.1.8 Endpoints and Criteria for Study Success

The primary safety endpoint is the incidence of inhibitor formation to FVIII evaluated from the time of first dose through the end of study visit. Inhibitor formation to FVIII is defined as any detectable inhibitors (≥ 0.6 Bethesda Units [BU]/mL). Success will be achieved if the upper confidence limit for the incidence of inhibitor formation is less than the acceptable upper limit of 6.8%.

The primary efficacy endpoint for the control of bleeding episodes is the investigator's overall clinical assessment of hemostatic efficacy for treatment of bleeding episodes, based on the following four point ordinal scale:

- Excellent: Pain relief and/or improvement in signs of bleeding (i.e., swelling, tenderness, and/or increased range of motion in the case of musculoskeletal hemorrhage) within approximately 8 hours after the first infusion
- Good: Pain relief and/or improvement in signs of bleeding at approximately 8 hours after the first infusion, but requires two infusions for complete resolution
- Moderate: Probable or slight beneficial effect within approximately 8 hours after the first infusion; requires more than two infusions for complete resolution
- No response: No improvement at all or condition worsens (i.e., signs of bleeding) after the first infusion and additional hemostatic intervention is required with another FVIII product, cryoprecipitate, or plasma for complete resolution.

Success is defined as a rating of "excellent" or "good". Treatment will be considered successful if the lower limit of the 95% CI for the hemostatic success rate is above 70%.

Hemostatic efficacy was also the primary efficacy endpoint for surgical prophylaxis. The pre-specified success criterion for this endpoint is that the observed success rate should be > 70%, where success is defined as a rating of "excellent" or "good" on the same four point ordinal scale. Assessment of hemostasis during surgical procedures by the investigator was as follows:

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

hemostatic intervention required with another FVIII product, cryoprecipitate, or plasma for complete resolution.

The primary efficacy endpoint for routine prophylaxis to prevent or reduce the frequency of bleeding episodes was Annualized spontaneous bleeding rate (AsBR), which is defined for each subject as follows:

365.25*(number of spontaneous bleeding episodes) /
(observed treatment period of interest).

Only those spontaneous bleeding episodes requiring treatment were included. Data during the PK and surgical periods were excluded. The primary comparison was between the prophylaxis arm and the on-demand arm. A 50% reduction in the AsBR with prophylaxis treatment was anticipated. The test results would be claimed as statistically significant only when the results are favoring the prophylaxis group.

Secondary efficacy endpoints include:

- Annualized bleeding rate (ABR) for total bleeds, traumatic bleeds, and joint bleeds
- Proportion of infusions of AFSTYLA required to achieve hemostasis (1, 2, 3, or >3)

Other endpoints include:

- The consumption of AFSTYLA during routine prophylaxis and on-demand treatment.
- The number of bleeding episodes occurring within the intervals ≤24, >24 to ≤48, >48 to ≤72, >72 to ≤96 and >96 hours from the last prophylaxis infusion.
- The rate of treatment success for major bleeding episodes defined as a rating of "excellent" or "good" on the investigator's overall clinical assessment of hemostatic efficacy four-point scale.
- The consumption of AFSTYLA during surgical prophylaxis.
- Predicted and estimated blood loss during surgery.
- Predicted and actual transfusion requirements during surgery.
- Change in hemoglobin levels between baseline, intra-operation and post-operation.

6.1.9 Statistical Considerations & Statistical Analysis Plan

Sample size calculation

Approximately 30 subjects were planned to be enrolled into Part 1, to ensure 26 evaluable subjects for the PK comparison.

Approximately 100 additional subjects were planned to be enrolled in Part 3, combined with the 26 to 30 subjects from Parts 1 and 2, to ensure that at least 104 total subjects who received at least one dose of AFSTYLA are evaluable (they either develop an inhibitor or complete 50 EDs without developing an inhibitor). Based on a two-sided 95% exact binomial CI, an acceptable upper bound for the rate of inhibitor development is determined to be 6.8% as recommended by the FDA. It was assumed that no more than 2 subjects out of 104 would develop an inhibitor during the study. At most 2 subjects

developing an inhibitor out of 104 total subjects is sufficient to maintain an upper confidence limit within the acceptable upper bound of 6.8%.

Analysis Populations
The Safety population consists of all subjects who received at least one dose (or partial dose) of AFSTYLA during the study and was used for all safety analyses.

The Efficacy population consists of all subjects who received at least one dose of AFSTYLA as part of either routine prophylaxis treatment or on-demand treatment during the study. The Efficacy population is the primary efficacy analysis population; secondary efficacy endpoint analyses also utilized this population.

The Per-Protocol (PP) population includes all subjects in the Efficacy population who complete the study without any major protocol deviations or protocol violations that would impact the assessment of the primary efficacy endpoint. Subjects must have compliance with no less than 80% and no more than 120% of prescribed doses and actual doses within ±10% of prescribed dose. This population will be used for efficacy analyses.

The Surgical population includes all subjects enrolled in the surgical sub-study and have received at least one dose of AFSTYLA during the surgical sub-study.

Primary Safety Analysis
Please see Section 6.1.12.1.

Primary Efficacy Analyses
For hemostatic efficacy, in order to account for within-subject correlation, a generalized linear model (intercept only model) with repeated measures using generalized estimating equations and an independent correlation structure was used (b) (4)) to calculate the two-sided 95% CI about the success rate. A binomial distribution was assumed and a logit link function was used. Bleeding events were the analysis unit, clustered within subject. The following hypotheses were tested at the one-sided 0.025 level:

H_0: Proportion success $\leq 70\%$
H_a: Proportion success $> 70\%$

In addition, the following two sensitivity analyses on hemostatic efficacy were performed:

1. Missing investigator ratings counted as failure.
2. Missing investigator ratings counted as successes.

Hemostatic efficacy was also to be reported for the following subgroups:

- Region: US, Japan, Europe, and Rest of World
- Age group: 12- <18, ≥ 18 years of age
- Race; White, Asian, Black, and Others

For AsBR, the following hypotheses were tested at a two-sided 0.05 level with a Poisson regression model:

H_0: Prophylaxis AsBR = On-demand AsBR
H_a: Prophylaxis AsBR ≠ On-demand AsBR

The corresponding prophylaxis/on-demand ratio with 95% CI was planned to be presented to see if the upper limit is less than 50%.

Secondary Efficacy Analyses

The ABR for total bleeds was subject to the same analysis as that for spontaneous bleeds for prophylaxis and on-demand patients.

The ABR for traumatic and for joint bleed were summarized using descriptive statistics. No statistical inference will be performed on this data.

The number and percentage of bleeding episodes requiring 1, 2, 3 or more than 3 infusions of AFSTYLA to achieve hemostasis were summarized using frequency counts and percentages. No statistical inference was planned for this data.

Multiplicity Adjustment

Multiplicity for the one safety and two efficacy endpoints was accounted for using a hierarchical testing approach in the following order:

Testing was to begin by estimating the risk of inhibitor development. If the 97.5% CI upper bound for the risk of inhibitor development is greater than 6.8%, then the study will have failed and further testing will stop.

If the study rules out a 6.8% risk of inhibitor development, then testing would proceed to the evaluation of hemostatic efficacy for the treatment of bleeding episodes. If the lower limit of the two-sided 95% CI for the observed success rate is less than 70%, then the study will have failed on this endpoint and further testing will stop.

Otherwise, if hemostatic efficacy is demonstrated, then testing will proceed to the evaluation of AsBR. If a test of the null hypothesis of no difference between the prophylaxis and the on demand groups is not rejected at the two-sided 0.05 level, then the study will have failed on this endpoint and further testing will stop.

Interim analysis

There were no pre-defined statistical analyses for early stopping in this study.

Missing data handling

No imputation due to withdrawals or missing data was applied for analyses of efficacy or safety endpoints.

6.1.10 Study Population and Disposition

6.1.10.1 Populations Enrolled/Analyzed

Table 2 summarizes all analysis populations used in this study.

Table 2: Analysis Populations

	Number of subjects
Safety population	174
Efficacy population	173
Prophylaxis	146
On demand	27
PP population	156
PK population	
PK part 1	27
PK part 2	64
Surgical population (surgical sub study)	13

Source: Original BLA, Module 5.3.5.1: CSL627-1001/report-body.pdf, Table 11-1, page 67.

Lack of compliance with the prescribed dose or prescribed prophylaxis dosing regimen accounted for protocol deviations by 17 subjects, who were excluded from the PP population: four subjects of on-demand group and five subjects of prophylaxis group were not compliant with the prescribed dose, and eight subjects of prophylaxis group were not compliant with the prescribed prophylaxis regimen.

The Surgical population comprised 3 subjects in the on-demand group and 10 subjects in the prophylaxis group.

6.1.10.1.1 Demographics

The demographic and baseline characteristics of the Safety and Efficacy populations are summarized in Tables 3 and 4, respectively. Only male subjects were enrolled. The majority of subjects in the Efficacy population were White (72.3%).

Table 3: Demographics of Safety Population

	Total (N=174)
Age (years)	
Mean (SD)	31.3 (11.77)
Median	29.5
Min, Max	12, 64
Age group (n[%])	
≥ 12 to <18 years	14 (8.0)
≥ 18 to ≤ 65 years	160 (92.0)
Weight (kg)	
Mean (SD)	74.6 (16.99)
Median	75.0
Min, Max	27, 120
BMI (kg/m^2)	
Mean (SD)	24.3 (4.70)
Median	24.5
Min, Max	13, 39
BMI category (n[%])	
< 30 kg/m^2	156 (89.7)
≥ 30 kg/m^2	18 (10.3)
Race (n[%])	
Asian	31 (17.8)
Black of African American	14 (8.0)
White	126 (72.4)
Other	3 (1.7)
Ethnicity (n[%])	
Hispanic or Latino	12 (6.9)
Not Hispanic or Latino	161 (92.5)
Not reported	1 (0.6)
Geographical region (n[%])	
United States	22 (12.6)
Japan	10 (5.7)
Europe	86 (49.4)
Rest of the world	56 (32.2)

Source: Original BLA, Module 5.3.5.1: CSL627-1001/report-body.pdf, Table 11-2, page 68.

Table 4: Demographics of Efficacy Population

	On-Demand (N=27)	*Prophylaxis (N=146)*	*Total (N=173)*
Age (years)			
N	27	146	173
Mean (SD)	40.3 (12.40)	29.7 (10.96)	31.3 (11.77)
Median	39.0	28.0	29.0
Min, Max	23, 64	12, 58	12, 64
Age group (n[%])			
≥ 12 to <18 years	0	14 (9.6)	14 (8.1)
≥ 18 to ≤ 65 years	27 (100.0)	132 (90.4)	160 (91.9)
Weight (kg)			
Mean (SD)	78.1 (15.63)	74.0 (17.26)	74.6 (17.04)
Median	76.0	74.6	75.0
Min, Max	39, 110	27, 120	27, 120
BMI (kg/m^2)			
Mean (SD)	25.2 (4.07)	24.1 (4.82)	24.3 (4.71)
Median	25.5	24.2	24.5
Min, Max	17, 33	13, 39	13, 39
BMI category (n[%])			
< 30 kg/m^2	23 (85.2)	132 (90.4)	156 (89.6)
≥ 30 kg/m^2	4 (14.8)	14 (9.6)	18 (10.4)
Race (n[%])			
Asian	1 (3.7)	30 (20.5)	31 (17.9)
Black of African American	3 (11.1)	11 (7.5)	14 (8.1)
White	23 (85.2)	102 (69.9)	126 (72.3)
Other	0	3 (2.1)	3 (1.7)
Ethnicity (n[%])			
Hispanic or Latino	2 (7.4)	10 (6.8)	12 (6.9)
Not Hispanic or Latino	25 (92.6)	135 (92.5)	161 (92.5)
Not reported	0	1 (0.7)	1 (0.6)
Geographical region (n[%])			
United States	4 (14.8)	18 (12.3)	22 (12.7)
Japan	1 (3.7)	9 (6.2)	10 (5.8)
Europe	16 (59.3)	69 (47.3)	86 (49.1)
Rest of the world	6 (22.2)	50 (34.2)	56 (32.4)

Source: Original BLA, Module 5.3.5.1: CSL-1001/report-body.pdf, Table 11-3, page 69.

6.1.10.1.2 Medical/Behavioral Characterization of the Enrolled Population
A summary of subjects' hemophilia A history is presented in Table 5.

Table 5: Hemophilia A History; Safety population

	N=174
Spontaneous bleeding episodes in last 12 months	
N	171
Mean (SD)	21.3 (37.03)
Median	9.0
Traumatic bleeding episodes in last 12 months	
N	172
Mean (SD)	4.0 (8.17)
Median	1.0
Bleeding episodes of unknown causality in last 12 months	
N	171
Mean (SD)	1.8 (6.21)
Median	0

Source: Original BLA, Module 5.3.5.1: CSL627-1001/report-body.pdf, Table 11-6, page 72.

In the 12 months before study entry, subjects in the Safety population experienced a higher number (mean [SD]) of spontaneous bleeding episodes (21.3 [37.03]) compared to traumatic bleeding episodes (4.0 [8.17]) and bleeding episodes of unknown causality (1.8 [6.21]).

6.1.10.1.3 Subject Disposition

A total of 204 subjects from 22 countries were screened for study participation; 175 subjects from 20 countries were enrolled. A total of 174 subjects were exposed to treatment with AFSTYLA. One hundred and sixty-one of the 174 subjects (92.5%) completed the study. A total of 13 (7.5%) subjects were discontinued from the study. Eight (4.6%) subjects withdrew consent for study participation, 1 (0.6%) subject was discontinued from the study based on the physician's decision and 4 (2.3%) subjects were discontinued from the study for the following 'other' reasons: surgery of the right knee (Subject 040000-1001), subject completed the study (55 EDs) but did not reach 6 months (Subject 2760030-1002), 50 EDs were not met (Subject 8400184-1001), and subject completed Month 12 but did not have 50 EDs (Subject 8400184-1002). Tables 6 and 7 summarize the subject disposition of the Safety and Efficacy populations, respectively.

Table 6: Subject Disposition (Safety Population)

	Number of subjects (%)
Screened	204
Enrolled	175
Treated (Safety population)	174
Completed study	161 (92.5)
Discontinued from study	13 (7.5)
Reasons for discontinuation	
Withdrawal by subject	8 (4.6)
Other	4 (2.3)
Physician decision	1 (0.6)

Source: Original BLA, Module 5.3.5.1: CSL627-1001/report-body.pdf, Table 10-1, page 63.

Table 7: Subject Disposition (Efficacy Population)

	On-demand (N=27)(%)	*Prophylaxis (N=146)(%)*	*Total (N=173)(%)*
Efficacy population	27	146	173
Completed study	21 (77.8)	140 (95.9)	161 (92.5)
Discontinued from study	6 (22.2)	6 (4.1)	12 (6.9)
Reasons for discontinuation			
Withdrawal by subject	1 (3.7)	6 (4.1)	7 (4.6)
Other	4 (14.8)	0	4 (2.3)
Physician decision	1 (3.7)	0	1 (0.6)

Source: Original BLA, Module 5.3.5.1: CSL627-1001/report-body.pdf, Table 10-2, page 64.

Table 8 summarizes protocol violations that resulted in the exclusion of subjects from the Efficacy population, resulting in 156 subjects in the PP population.

Table 8: Exclusions from the Efficacy Population

	On-demand (N=27)	*Prophylaxis (N=146)*	*Total (N=173)*
Any exclusion from the Efficacy population	4 (14.8)	13 (8.9)	17 (9.8)
Reasons for exclusions from the Efficacy population			
Non-compliant to the prescribed dose	4 (14.8)	5 (3.4)	9 (5.2)
Non-compliant to the prescribed prophylaxis regimen	0	8 (3.5)	8 (4.6)

Source: Original BLA, Module 5.3.5.1: CSL627-1001/report-body.pdf, Table 10-3, page 66.

6.1.11 Efficacy Analyses

6.1.11.1 Analyses of Primary Endpoint(s)

Control of bleeding episodes

According to the pre-specified hierarchical testing algorithm (see Section 6.1.9), testing for hemostatic efficacy could proceed since the risk of inhibitor development met its success criterion (see Section 6.1.12.5).

A summary of the overall investigator's assessment of hemostatic efficacy for the Efficacy population is presented in Table 9.

Table 9: Overall Investigator's Assessment of Hemostatic Efficacy (Efficacy Population)

	On-demand (N=27)	*Prophylaxis (N=146)*	*Total (N=173)*
Number of bleeding episodes	594	278	872
Number of treated bleeding episodes	590	258	848
Efficacy evaluation by investigator	577	258	835
Excellent (n[%])	421 (71.4)	182 (70.5)	603 (71.1)
Good (n[%])	124 (21.0)	56 (21.7)	180 (21.2)
Moderate (n[%])	32 (5.4)	20 (7.8)	52 (6.1)
Poor/no response (n[%])	0	0	0
Missing (n[%])	13 (2.2)	0	13 (1.5)
Treatment success	545	238	783
Rate of treatment success (%)	94.5	92.2	93.8
95% CI for rate	(90.9, 96.7)	(86.3, 95.8)	(91.0, 95.7)

Source: Adopted from Original BLA, Module 5.3.5.1: CSL627-1001/report-body.pdf, Table 11-25, page 72.

A total of 848 bleeding episodes were treated during the study and 835 bleeding episodes were evaluated by investigator. The point estimate for the rate of treatment success was 93.8% (783 of 835 bleeding episodes), with two-sided 95% CI (91.0%, 95.7%). Since the lower limit of the two-sided 95% CI is > 70%, the success criterion was met.

The rate of treatment success was similar in the on-demand and prophylaxis groups (94.5% and 92.2%, respectively). All treated bleeding episodes were considered as minor or moderate; no major bleeding events were recorded in the study.

There were thirteen missing values among 848 bleeding episodes. These 13 missing values were excluded in the primary efficacy analysis. Two additional sensitivity analyses were conducted for missing values and both of them revealed similar results for the primary analysis (Table 10).

Table 10: Sensitivity Analyses of Hemostatic Efficacy (Efficacy Population)

	On-demand (N=27)	*Prophylaxis (N=146)*	*Total (N=173)*
Number of treated bleeding episodes	590	258	848
Missing (n[%])	13 (2.2)	0	13 (1.5)
Sensitivity analysis 1: all missing values are counted as failure	545	238	783
Number of treated bleeding episodes	590	258	848
Rate of treatment success	92.4	92.2	92.3
95% CI for rate	(87.9, 95.3)	(86.3, 95.8)	(88.9, 94.8)
Sensitivity analysis 2: all missing values are counted as success	558	238	796
Number of treated bleeding episodes	590	258	848
Rate of treatment success	94.6	92.2	93.9
95% CI for rate	(91.0, 96.8)	(86.3, 95.8)	(91.1, 95.8)

Source: Adopted from Original BLA, Module 5.3.5.1: CSL627-1001/report-body.pdf, Table 11-25, page 122.

Results from the PP population were consistent with those for the Efficacy population.

Routine prophylaxis

According to the pre-specified hierarchical testing algorithm (see Section 6.1.9), testing for AsBR could proceed since both the risk for inhibitor development (see Section 6.1.12.5) and hemostatic efficacy (see Section 6.1.11.1) met their success criteria.

The AsBR is summarized in Table 11 for routine prophylaxis and on-demand treatment. The ratio of AsBR of prophylaxis group over on-demand group is 0.08 with 95% CI (0.07, 0.10). The upper limit of the CI is less than 0.50, thus meeting the success criterion.

Table 11: Annualized Spontaneous Bleeding Rate – AFSTYLA Prophylaxis Compared with AFSTYLA On-demand (Efficacy Population)

	On-demand (N=27)	*Prophylaxis (N=146)*
Spontaneous bleeding episodes		
Mean (SD)	24.84 (33.843)	2.10 (4.764)
Median	11.73	0.00
Q1, Q3	2.8, 36.5	0.0, 2.4
Min, Max	0.0, 15.0	0.0, 40.6
Number of bleeding episode per year (95% CI)	19.5 (17.8, 21.3)	1.6 (1.3, 1.8)
p-value	<0.0001	
Prophylaxis / On-demand ratio (95% CI)	0.08 (0.07, 0.10)	

Source: Adopted from Original BLA, Module 5.3.5.1: CSL627-1001/report-body.pdf, Table 11-29, page 127.

In the prophylaxis group, 54% of 146 subjects received AFSTYLA three times weekly, 32% of subjects two times weekly, 6% of subjects every other day, and 8% of subjects received other regimens. The AsBR was comparable between subjects on a 3 times weekly regimen and those on a 2 times weekly regimen. Table 12 summarizes AsBR for the 3 times weekly regimen and the 2 times weekly regimen.

Table 12: Annualized Spontaneous Bleeding Rate – AFSTYLA Prophylaxis Three times per week vs Two times per week

	3 times per week (N=77)	*2 times per week (N=46)*
Spontaneous bleeding episodes		
Mean (SD)	2.31 (3.89)	2.38 (6.74)
Median	0.00	0.00
Q1, Q3	0.0, 3.5	0.0, 1.1
Min, Max	0.0, 18.0	0.0, 40.6
Number of bleeding episode per year (95% CI)	1.9 (1.6, 2.3)	1.3 (1.0, 1.8)
P-value of prophylaxis/on-demand	<0.0001	< 0.0001
Prophylaxis/On-demand	0.10 (0.08, 0.12)	0.07 (0.05, 0.10)

Source: Adopted from Original BLA, Module 5.3.5.1 CSL627-1001/report-body.pdf, Table 14.2.2.2.6, page 352, Table 14.2.2.2.7, page 353.

Perioperative (surgical) management

A summary of the investigator's overall clinical assessment of hemostatic efficacy for surgical prophylaxis is shown in Table 13.

Table 13: Overall Clinical Assessment of Hemostatic Efficacy during the Surgical Sub-study (Surgical Population)

Assessment	*Overall (N=13)*
Number of surgeries	16
Excellent (n[%])	15 (93.8)
Good (n[%])	1 (6.2)
Moderate (n[%])	0
Poor/No response (n[%])	0
Success (n[%])	16 (100.0)

Source: Original BLA, Module 5.3.5.1: CSL627-1001/report-body.pdf, Table 11-34, page 132.

There were 16 surgeries in 13 subjects during the study, all of which were recorded as non-emergency surgeries. The treatment success rate in the surgical prophylaxis setting was 100% which is greater than 70%; therefore the success criterion was met.

6.1.11.2 Analyses of Secondary Endpoints

Annualized Bleeding Rate
A summary of the ABR for the Efficacy population is presented in Table 14. The ABR was reduced 90% for prophylaxis subjects compared to on-demand subjects.

Table 14: Annualized Bleeding Rate –Prophylaxis Compared with On-demand (Efficacy Population)

	On-demand (N=27)	*Prophylaxis (N=146)*
Total bleeding episodes		
Mean (SD)	31.14 (35.56)	3.11 (5.05)
Median	19.64	1.14
Q1, Q3	6.2, 46.5	0.0, 4.2
Min, Max	0.0, 163.3	0.0, 40.6
Number of bleeding episode per year (95% CI)	24.9 (23.0, 27.0)	2.6 (2.3, 2.9)
p-value	<0.0001	
Prophylaxis / On-demand ratio (95% CI)	0.10 (0.09, 0.12)	

Source: Adopted from Original BLA, Module 5.3.5.1: CSL627-1001/report-body.pdf, Table 11-29, page 127.

The applicant also compared the ABR for subjects who received AFSTYLA 3 times weekly vs 2 times weekly; the results are presented in Table 15.

Table 15: Annualized Bleeding Rate – AFSTYLA Prophylaxis
Three times per week vs Two times per week

	3 times per week (N=77)	*2 times per week (N=46)*
Spontaneous bleeding episodes		
Mean (SD)	3.30 (4.31)	3.34 (6.88)
Median	1.53	0.00
Q1, Q3	0.0, 4.4	0.0, 3.3
Min, Max	0.0, 19.3	0.0, 40.6
Number of bleeding episode per year (95% CI)	2.9 (2.5, 3.4)	2.4 (1.9, 3.0)
P-value of prophylaxis/on-demand	<0.0001	< 0.0001
Prophylaxis/On-demand	0.12 (0.10, 0.14)	0.10 (0.08, 0.12)

Source: Adopted from Original BLA, Module 5.3.5.1: CSL627-1001/report-body.pdf, Table 14.2.2.2.6, page 352, Table 14.2.2.2.7, page 353.

Number of infusions

The number of injections required to achieve hemostasis in the Efficacy population is summarized in Table 16. The majority of treated bleeding episodes required one injection (81%; 686/848).

Table 16: Number of Injections Required to Achieve Hemostasis (Efficacy Population)

	On-demand (N=27)	*Prophylaxis (N=146)*	*Total (N=173)*
Number of bleeding episodes	594	278	872
Number of bleeding treated episodes	590	258	848
Number of subjects with ≥ 1 bleeding episode	26	85	111
Number of subjects with ≥ 1 treated bleeding episode	26	83	109
Number of injections required to achieve hemostasis (n [%]))			
1 injection	488 (82.7)	198 (76.7)	686 (80.9)
2 injections	71 (12.0)	36 (14.0)	107 (12.6)
3 injections	19 (3.22)	10 (3.88)	29 (3.42)
>3 injections	12 (2.03)	14 (5.43)	26 (3.07)

Source: Adapted from Original BLA, Module 5.3.5.1: CSL627-1001/report-body.pdf, Table 11-28, page 126.

6.1.11.3 Subpopulation Analyses

No subgroup analysis of sex was needed because all subjects are male.

Control of Bleeding Episodes

According to the SAP, hemostatic efficacy was also analyzed for the region (Table 17) and age (Table 18) subgroups.

Reviewer comment: I also analyzed hemostatic efficacy by race (Table 19).

Similar results were observed in the subgroup analyses for which there was adequate data. Japan in the region subgroup analyses and Asian in the race subgroup analyses have too small of sample sizes to validate any statistical conclusion. For the black subgroup, 9 of 44 episodes were missing; the hemostatic efficacy would be 88.6% with CI (73.3%, 96.8%) if the 9 missing values were excluded.

Table 17: Overall Investigator's Assessment of Hemostatic Efficacy – by Region (Efficacy Population)

Region *Bleeding type assessment*	*On-demand* *(N=27)*	*Prophylaxis* *(N=146)*	*Total* *(N=173)*
Region: United States			
Number of treated bleeding episodes	62	20	82
Treatment success	50	19	69
Rate of treatment success	80.6	95.0	84.1
95% CI for rate	(45.4, 95.4)	(70.6, 99.3)	(56.0, 95.7)
Region: Japan			
Number of treated bleeding episodes	7	22	29
Treatment success	6	20	26
Rate of treatment success	85.7	90.9	89.7
95% CI for rate	(42.1, 99.6)	(69.9, 97.8)	(74.7, 96.2)
Region: Europe			
Number of treated bleeding episodes	459	104	563
Treatment success	429	92	521
Rate of treatment success	93.5	88.5	92.5
95% CI for rate	(89.6, 96.0)	(75.5, 95.0)	(89.0, 95.0)
Region: Rest of the world			
Number of treated bleeding episodes	62	112	174
Treatment success	60	107	167
Rate of treatment success	96.8	95.5	96.0
95% CI for rate	(83.6, 99.4)	(86.4, 98.6)	(89.7, 98.5)

Source: Adapted from original BLA, Module 5.3.5.1: CSL627-1001/report-body.pdf, Table 11-26, page 123.

Table 18: Overall Investigator's Assessment of Hemostatic Efficacy – by Age (Efficacy Population)

Age Group *Bleeding type assessment*	*On-demand* *(N=27)*	*Prophylaxis* *(N=146)*	*Total* *(N=173)*
Age groups: ≥ 12 to <18 years			
Number of treated bleeding episodes	0	46	46
Treatment success	N/A	44	44
Rate of treatment success	N/A	95.7	95.7
95% CI for rate	N/A	(85.2, 98.8)	(85.2, 98.8)
Age groups: ≥18 to ≤ 65 years			
Number of treated bleeding episodes	590	212	802
Treatment success	545	194	739
Rate of treatment success	92.4	91.5	92.1
95% CI for rate	(87.8, 95.3)	(84.4, 95.6)	(88.5, 94.7)

Source: Adapted from original BLA, Module 5.3.5.1: CSL627-1001/report-body.pdf, Table 11-27, page 125.

Table 19: Overall Investigator's Assessment of Hemostatic Efficacy – by Race (Efficacy Population)

Race *Bleeding type assessment*	*On-demand (N=27)*	*Prophylaxis (N=146)*	*Total (N=173)*
White			
n	23	102	125
Number of treated bleeding episodes	539	144	683
Treatment success	508	131	639
Rate of treatment success	95.7	91.0	93.6
95% CI for rate	(93.6, 97.2)	(85.1, 95.1)	(91.5, 95.3)
Asian			
n	1	30	31
Number of treated bleeding episodes	7	82	89
Treatment success	6	75	81
Rate of treatment success	85.7	91.5	91.0
95% CI for rate	(42.1, 99.6)	(83.2, 96.5)	(83.1, 96.0)
Black or Africa American			
n	3	11	14
Number of treated bleeding episodes	44	21	65
Treatment success	31	21	52
Rate of treatment success	70.4	100	80
95% CI for rate	(54.8, 83.2)	(86.7, 100)	(68.2, 88.9)
Others			
n	0	3	3
Number of treated bleeding episodes	N/A	11	11
Treatment success	N/A	11	11
Rate of treatment success	N/A	100	100
95% CI for rate	N/A	(89.0, 95.0)	(89.0, 95.0)

Routine Prophylaxis

The subgroup analyses of AsBR and ABR by geographic region, age, and race are presented in Table 20 to Table 25. The statistical significance was observed in all regions except Japan and Asian subgroup, in which the sample size of the on-demand arm was very small.

Table 20: AsBR – prophylaxis compared with on-demand – by Region (Efficacy Population)

Region	*On-demand (N=27)*	*Prophylaxis (N=146)*
Region: United States		
n	4	18
Mean (SD)	9.70 (7.03)	0.49 (1.21)
Median	11.67	0.00
Q1, Q3	4.6, 14.9	0.0, 0.0
Min, Max	0.0, 15.5	0.0, 4.2
Bleeding episodes per year (95% CI)	7.0 (4.9, 10.01)	0.3 (0.1, 0.7)
P-value	< 0.0001	
Prophylaxis / On-demand ratio (95% CI)	0.04 (0.01, 0.10)	
Region: Japan		
n	1	9
Mean (SD)	3.55	1.83 (4.27)
Median	3.55	0.00
Q1, Q3	3.55, 3.55	0.0, 1.1
Min, Max	3.55, 3.55	0.0, 13.0
Bleeding episodes per year (95% CI)	6.2 (3.0, 13.0)	2.0 (1.2, 3.3)
P-value	< 0.3093	
Prophylaxis / On-demand ratio (95% CI)	0.56 (0.1920, 1.7011)	
Region: Europe		
n	16	69
Mean (SD)	35.49 (40.46)	1.46 (5.07)
Median	22.71	0.00
Q1, Q3	5.8, 54.7	0.0, 1.2
Min, Max	0.0, 151.0	0.0, 40.6
Bleeding episodes per year (95% CI)	27.5 (24.9, 30.4)	1.0 (0.8, 1.4)
P-value	< 0.0001	
Prophylaxis / On-demand ratio (95% CI)	0.04 (0.03, 0.058)	
Region: Rest of the world		
n	6	50
Mean (SD)	10.08 (10.80)	3.62 (4.91)
Median	5.54	1.33
Q1, Q3	2.8, 19.9	0.0, 7.4
Min, Max	0.0, 26.7	0.0, 18.0
Bleeding episodes per year (95% CI)	9.3 (6.7, 12.8)	3.4 (2.8, 4.2)
P-value	< 0.0001	
Prophylaxis / On-demand ratio (95% CI)	0.37 (0.25, 0.54)	

Source: Adapted from original BLA, Module 5.3.5.1: CSL627-1001/report-body.pdf, Table 14.2.2.3, page 355-360.

Table 21: ABR – prophylaxis compared with on-demand – by Region (Efficacy Population)

Region	*On-demand (N=27)*	*Prophylaxis (N=146)*
Region: United States		
n	4	18
Mean (SD)	17.13 (10.10)	1.73 (1.77)
Median	17.75	1.16
Q1, Q3	9.5, 24.8	0.0, 2.8
Min, Max	4.7, 28.3	0.0, 6.1
Bleeding episodes per year (95% CI)	14.0 (11.0, 18.0)	1.3 (0.8, 1.9)
P-value	< 0.0001	
Prophylaxis / On-demand ratio (95% CI)	0.09 (0.05, 0.15)	
Region: Japan		
n	1	9
Mean (SD)	6.22	2.51 (4.56)
Median	6.22	0.00
Q1, Q3	6.22, 6.22	0.0, 1.4
Min, Max	6.22, 6.22	0.0, 13.0
Bleeding episodes per year (95% CI)	6.2 (3.0, 13.0)	2.9 (1.9, 4.5)
P-value	< 0.0845	
Prophylaxis / On-demand ratio (95% CI)	0.47 (0.20, 1.11)	
Region: Europe		
n	16	69
Mean (SD)	41.59 (42.38)	2.48 (5.37)
Median	28.08	0.00
Q1, Q3	12.9, 60.3	0.0, 3.5
Min, Max	0.0, 163.3	0.0, 40.6
Bleeding episodes per year (95% CI)	32.4 (29.6, 35.5)	2.0 (1.7, 2.5)
P-value	< 0.0001	
Prophylaxis / On-demand ratio (95% CI)	0.06 (0.05, 0.08)	
Region: Rest of the world		
n	5	50
Mean (SD)	16.76 (15.705)	4.57 (5.222)
Median	14.33	2.57
Q1, Q3	2.8, 26.7	0.0, 7.7
Min, Max	2.7, 39.7	0.0, 19.3
Bleeding episodes per year (95% CI)	15.5 (12.1, 19.9)	4.5 (3.8, 5.5)
P-value	< 0.0001	
Prophylaxis / On-demand ratio (95% CI)	0.29 (0.21, 0.40)	

Source: Adapted from original BLA, Module 5.3.5.1: CSL627-1001/report-body.pdf, Table 14.2.2.3, page 355-360.

Table 22: AsBR – prophylaxis compared with on-demand – by age (Efficacy Population)

	On-demand (N=27)	*Prophylaxis (N=146)*
≥ 12 to < 18 years		
n	0	14
Mean (SD)	N/A	6.1 (10.66)
Median	N/A	2.2
Q1, Q3	N/A	1.1, 6.9
Min, Max	N/A	0, 41
Bleeding episodes per year (95% CI)	N/A	3.7 (2.6, 5.4)
P-value	N/A	
Prophylaxis / On-demand ratio (95% CI)	N/A	
≥ 18 to ≤ 65 years		
n	27	132
Mean (SD)	23.8 (33.84)	1.7 (3.45)
Median	11.7	0.0
Q1, Q3	2.8, 36.5	0.0, 1.8
Min, Max	0, 151	0, 18
Bleeding episodes per year (95% CI)	19.5 (17.8, 21.3)	1.4 (1.2, 1.6)
P-value	< 0.0001	
Prophylaxis / On-demand ratio (95% CI)	0.07 (0.06, 0.09)	

Source: Adopted from Original BLA, Module 5.3.5.1: CSL627-1001/report-body.pdf, Table 14.2.2.4, page 361-363.

Table 23: ABR – prophylaxis compared with on-demand – by age (Efficacy Population)

	On-demand (N=27)	*Prophylaxis (N=146)*
≥ 12 to < 18 years		
n	0	14
Mean (SD)	N/A	7.7 (10.34)
Median	N/A	5.3
Q1, Q3	N/A	1.1, 10.1
Min, Max	N/A	0, 41
Bleeding episodes per year (95% CI)	N/A	5.7 (4.3, 7.7)
P-value	N/A	
Prophylaxis / On-demand ratio (95% CI)	N/A	
≥ 18 to ≤ 65 years		
n	27	132
Mean (SD)	31.1 (35.56)	2.6 (3.88)
Median	19.6	1.0
Q1, Q3	6.2, 46.5	0.0, 3.8
Min, Max	0, 163	0, 19
Bleeding episodes per year (95% CI)	24.9 (23.0, 27.0)	2.3 (2.0, 2.7)
P-value	< 0.0001	
Prophylaxis / On-demand ratio (95% CI)	0.09 (0.08, 0.11)	

Source: Adopted from Original BLA, Module 5.3.5.1: CSL627-1001/report-body.pdf, Table 14.2.2.4, page 361-363.

Table 24: AsBR – prophylaxis compared with on-demand – by Race (Efficacy Population)

Race	*On-demand (N=27)*	*Prophylaxis (N=146)*
White		
n	23	102
Mean (SD)	26.55 (36.34)	1.23 (4.32)
Median	11.24	0
Q1, Q3	2.81, 37.32	0, 1.0
Min, Max	1, 151.0	0, 40.583
Bleeding episodes per year (95% CI)	20.54 (12.29, 34.25)	0.89 (0.63, 1.26)
P-value	< 0.0001	
Prophylaxis / On-demand ratio (95% CI)	0.044 (0.034, 0.056)	
Asian		
n	1	30
Mean (SD)	3.55	3.914 (4.63)
Median	3.55	2.286
Q1, Q3	3.55, 3.55	0, 7.61
Min, Max	3.55, 3.55	0, 16.02
Bleeding episodes per year (95% CI)	3.56 (1.34, 9.50)	3.06 (2.15, 5.12)
P-value	0.8915	
Prophylaxis / On-demand ratio (95% CI)	0.93 (0.339, 2.560)	
Black or Africa American		
n	3	11
Mean (SD)	18.81 (6.88)	4.24 (6.14)
Median	15.46	1.93
Q1, Q3	14.24, 26.72	0, 7.716
Min, Max	14.24, 26.73	0, 18.01
Bleeding episodes per year (95% CI)	18.17 (12.24, 26.95)	3.75 (1.59, 8.87)
P-value	< 0.0001	
Prophylaxis / On-demand ratio (95% CI)	0.21 (0.12, 0.35)	
Others		
n	0	3
Mean (SD)	N/A	5.71 (8.48)
Median	N/A	1.683
Q1, Q3	N/A	0, 15.46
Min, Max	N/A	0, 15.46
Bleeding episodes per year (95% CI)	N/A	5.61 (1.00, 31.42)
P-value	N/A	
Prophylaxis / On-demand ratio (95% CI)	N/A	

Table 25: ABR – prophylaxis compared with on-demand – by Race (Efficacy Population)

Race	*On-demand (N=27)*	*Prophylaxis (N=146)*
White		
n	23	102
Mean (SD)	33.57 (37.97)	2.32 (4.66)
Median	19.63	0.655
Q1, Q3	4.67, 50.655	0, 3.06
Min, Max	0, 163.3	0, 40.583
Bleeding episodes per year (95% CI)	26.54 (17.33, 40.63)	1.96 (1.51, 2.55)
P-value	< 0.0001	
Prophylaxis / On-demand ratio (95% CI)	0.074 (0.062, 0.089)	
Asian		
n	1	30
Mean (SD)	6.22	4.83 (4.85)
Median	6.22	3.45
Q1, Q3	6.22, 6.22	0, 8.057
Min, Max	6.22, 6.22	0, 16.02
Bleeding episodes per year (95% CI)	6.24 (2.97, 13.1)	4.32 (2.94, 6.36)
P-value	0.3512	
Prophylaxis / On-demand ratio (95% CI)	0.69 (0.32, 1.50)	
Black or Africa American		
n	3	11
Mean (SD)	20.72 (6.26)	4.65 (5.95)
Median	15.46	2.57
Q1, Q3	14.24, 26.73	0, 7.716
Min, Max	14.24, 26.73	0, 18.0
Bleeding episodes per year (95% CI)	19.64 (13.49, 28.58)	4.15 (1.91, 9.04)
P-value	< 0.0001	
Prophylaxis / On-demand ratio (95% CI)	0.21 (0.12, 0.36)	
Others		
n	0	3
Mean (SD)	N/A	7.0 (10.74)
Median	N/A	1.683
Q1, Q3	N/A	0, 19.33
Min, Max	N/A	0, 19.33
Bleeding episodes per year (95% CI)	N/A	6.86 (1.16, 40.43)
P-value	N/A	
Prophylaxis / On-demand ratio (95% CI)	N/A	

6.1.11.4 Dropouts and/or Discontinuations

The proportion of missing data was low. The applicant used all available data in the analyses and summaries of the final study report. There was no special handling for dropouts and missing data, except for the hemostatic efficacy endpoint of treatment success. Results of these two sensitivity analyses are included in section 6.11.1.1.

6.1.11.5 Exploratory and Post Hoc Analyses

Not applicable.

6.1.12 Safety Analyses

The (mean [SD]) number of EDs for subjects in the Safety population was 82.2 (61.35) EDs. A total of 120 subjects (69.0%) had ≥ 50 EDs, of whom 52 subjects (29.9%) had ≥ 100 EDs.

6.1.12.1 Methods

Descriptive statistics were used in this study. A two-sided exact Clopper-Pearson 95% CI was calculated for the incidence of inhibitors.

6.1.12.3 Deaths

There were no deaths in the study.

6.1.12.4 Nonfatal Serious Adverse Events

Seven subjects (4.0% of 174) experienced a total of 9 treatment-emergent serious adverse events (TESAEs). Eight of 9 TESAEs were considered by the investigator as unrelated to the study drug. The event of hypersensitivity of subject 6080002-1001 (in the ≥ 12 to < 18 year age group, prophylactic treatment) was considered to be severe in intensity and related to the study drug. The dose of AFSTYLA was reduced as a result of the event. The subject made a complete recovery. A summary of the incidence of Treatment-emergent Serious Adverse Events (TESAEs) in the Safety population is presented in Table 25.

Table 25: Treatment-emergent Serious Adverse Events by System Organ Class and Preferred Term (Safety Population)

	No. of subjects	*No. of events*
Number of TESAEs	7	9
Blood and lymphatic system disorders	1	2
Anaemia	1	1
Thrombocytopenia	1	1
Gastrointestinal disorders	1	1
Varices oesphageal	1	1
Immune system disorders	1	1
Hypersensitivity	1	1
Infections and infestations	1	1
Viral infection	1	1
Injury, poisoning and procedural complication	1	1
Ankle fracture	1	1
Investigations	1	1
Blood uric acid increased	1	1
Psychiatric disorders	1	1
Suicidal ideation	1	1
Respiratory, thoracic and mediastinal disorders	1	1
Tonsillar haemorrhage	1	1

Source: Original BLA, Module 5.3.5.1: CSL627-1001/report-body.pdf, Table 12-12 page 152.

6.1.12.5 Adverse Events of Special Interest (AESI)

The incidence of inhibitors among subjects in the safety analysis population was 0% (95% CI, 0 to 2.1%). The upper limit of the 95% CI of inhibitor incidence was lower than the pre-specified threshold 6.8%. According to the pre-specified hierarchical testing

approach of multiplicity in the study, since the success criterion was met for the primary safety endpoint, and further testing in the primary efficacy endpoints was conducted.

A predefined set of TEAEs, namely Thromboembolic events (TEEs) and hypersensitivity reactions, were considered to be AESIs for this study. There were no reports of TEEs and the overall proportion of subjects who experienced hypersensitivity reactions was 1.1%.

6.1.12.7 Dropouts and/or Discontinuations

There were no TEAEs leading to withdrawal from the study.

6.2 Trial #2: CSL627-3002

6.2.1 Objectives

The primary objective is to evaluate the efficacy of AFSTYLA in the treatment of major and minor bleeding episodes in pediatric population.

The secondary objectives are to:

- Evaluate the annualized bleeding rate during prophylaxis treatment
- Evaluate the annualized bleeding rate during on-demand treatment
- Evaluate the proportion of bleeding episodes requiring 1, 2, 3, or > 3 injections of AFSTYLA to achieve hemostasis
- Evaluate the consumption of AFSTYLA

Other objectives include:

- Evaluate the PK profile of AFSTYLA
- Assess the rate of inhibitor formation to AFSTYLA
- Assess the safety of AFSTYLA with regard to AEs, laboratory parameters, physical examination, and vital signs (blood pressure, heart rate, temperature, and respiratory rate)

6.2.2 Design Overview

This is an international, multicenter, open-label study to assess the efficacy, safety, and PK of AFSTYLA in pediatric patients with severe hemophilia A. Subjects were enrolled to achieve at least 50 EDs to AFSTYLA.

6.2.3 Population

Subjects who meet all of the following inclusion criteria are eligible for enrolment into the study:

- Diagnosis of severe hemophilia A defined as < 1% FVIII concentration (FVIII:C) documented in medical records
- Males < 12 years of age
- Subjects who have received > 50 EDs with a FVIII product
- Written informed parental or guardian consent and assent of minors for study participation obtained before undergoing any study specific procedures
- Prior PK data (at least incremental recovery and half-life) from previous FVIII exposure for subjects participating in the PK assessment

- Investigator believes that the subject is willing and able to adhere to all protocol requirements. Investigator believes that the subject's parent(s) or legally acceptable representative(s) is / are willing and able to adhere to all protocol requirements

Subjects who meet any of the following exclusion criteria are not eligible for enrolment into the study:

- Any history of or current FVIII inhibitors
- Any first order family (i.e., siblings) history of FVIII inhibitors
- Use of an IMP within 30 days prior to the first AFSTYLA administration
- Current participation in an investigational trial other than a non-interventional trial where no IMP is administered
- Administration of any cryoprecipitate, whole blood or plasma within 30 days prior to administration of AFSTYLA
- Known hypersensitivity (allergic reaction or anaphylaxis) to any FVIII product or hamster protein
- Any known congenital or acquired coagulation disorder other than congenital FVIII deficiency
- Platelet count < 100,000/ L at Screening
- Human immunodeficiency virus (HIV) positive subjects with a CD4 count < 200/mm^3 at Screening, if available, or medical history results of less than one year. (HIV positive subjects may participate in the study and antiviral therapy is permitted, at the discretion of the investigator)
- Currently receiving IV immunomodulating agents such as immunoglobulin or chronic systemic corticosteroid treatment
- Serum aspartate aminotransferase or serum alanine aminotransferase values > 5 times (x) the upper limit of normal at Screening
- Serum creatinine values > 2 x the upper limit of normal at Screening
- Evidence of thrombosis, including deep vein thrombosis, stroke, pulmonary embolism, myocardial infarction and arterial embolus within 3 months before Day 1
- Experienced life-threatening bleeding episode or had major surgery or an orthopedic surgical procedure during the 3 months before AFSTYLA administration
- Demonstrated or suspected inability (e.g., language problem or mental condition) of guardian / caregiver or unwillingness to comply with study procedures or history of noncompliance
- Re-entry of subjects previously enrolled
- Any condition that is likely to interfere with the evaluation of AFSTYLA, or satisfactory conduct of the study
- Participated in another interventional clinical study within 30 days before the first administration of AFSTYLA or at any time during the study
- Alcohol, drug or medication abuse within 1 year before the study
- Currently receiving a therapy not permitted during the study
- Known or suspected hypersensitivity to AFSTYLA or to any excipients of

- AFSTYLA
- Any issue that, in the opinion of the investigator, would render the subject unsuitable for participation in the study

6.2.4 Study Treatments or Agents Mandated by the Protocol

The dose selected for treatment was based on the subject's weight at the most recent visit, the discretion of the investigator, and the subject's tolerability. The investigator could review the subject's previous dose with FVIII products, available PK data from AFSTYLA, and the bleeding phenotype data. In the event of a bleeding episode, subjects were treated on-demand at a dose determined by the investigator based on the subject's previous treatment dose for a bleeding episode. The desired FVIII level for the treatment of a bleeding episode (on-demand treatment) was based on the recommendations of the World Federation of Hemophilia (WFH) with a minimum dose of 15 IU/kg.

6.2.6 Sites and Centers

A total of 88 subjects were screened for this study at 37 study sites in 19 countries. Eighty-four of the screened subjects were eligible and enrolled into the study

6.2.7 Surveillance/Monitoring

Insert text here

6.2.8 Endpoints and Criteria for Study Success

The primary endpoint is treatment success of hemostatic efficacy, defined as a rating of "excellent" or "good" on the investigator's overall clinical assessment of hemostatic efficacy for each bleeding episode based on a four point ordinal scale (excellent, good, moderate, poor/none; Table 26).

Table 26: Efficacy evaluation of bleeding episodes by the investigator

Category	*Description*
Excellent	Definite pain relief and/or improvement in signs of bleeding (i.e., swelling, tenderness, and/or increased range of motion in the case of musculoskeletal hemorrhage) within approximately 8 hours after the first AFSTYLA infusion.
Good	Definite pain relief and/or improvement in signs of bleeding at approximately 8 hours after the first AFSTYLA infusion, but requires two infusions for complete resolution.
Moderate	Probable or slight beneficial effect within approximately 8 hours after the first AFSTYLA infusion; requires more than two infusions for complete resolution.
Poor/No response	No improvement at all or condition worsens (i.e., signs of bleeding) after the first AFSTYLA infusion and additional hemostatic intervention is required with another FVIII product, cryoprecipitate, or plasma for complete resolution.

Source: Original BLA, Module 5.3.5.1: CSL627-3002/protocol-amnd-2.pdf, Table 6, page 50.

The secondary endpoints are:

- ABR (traumatic and non-traumatic) during on-demand and during prophylaxis treatment
- The occurrence of bleeding (traumatic or non-traumatic) requiring 1, 2, 3, or > 3 injections of AFSTYLA to achieve hemostasis
- The consumption of AFSTYLA, expressed as number of injections and

IU/kg per month and per year, as well as IU/kg per event for both on-demand and prophylaxis treatment

Other secondary endpoints include:

- The occurrence of inhibitor formation to AFSTYLA evaluated from the time of first dose through the End-of-Study visit as a safety parameter of AFSTYLA
- Safety measures including AEs, laboratory parameters, physical examination, and vital signs (blood pressure, heart rate, temperature, and respiratory rate) during the treatment period

6.2.9 Statistical Considerations & Statistical Analysis Plan

Sample size calculation
The determination of the sample size was based on the EMA guidelines for recombinant and human plasma-derived Factor VIII products in children < 12 years of age. This guideline requires a minimum of 25 subjects ≥ 6 years of age to < 12 years of age and 25 subjects < 6 years of age suffering from severe hemophilia A.

Approximately 75 subjects are to be enrolled to ensure that at least 25 subjects in each age cohort receive 50 EDs of AFSTYLA, as outlined in the guidance.
No formal statistical comparisons are planned in this study.

Population
The screened population will consist of all subjects who signed informed consent.

The Safety population will consist of all subjects who received at least one dose of AFSTYLA during the study.

The Efficacy population will be comprised of the subjects who participate in the efficacy portion of the study (i.e., received on-demand or routine prophylaxis treatment) and have received at least one dose of AFSTYLA.

The PP population will include all subjects in the Efficacy population who complete the study without any major protocol deviations that would impact the assessment of the primary efficacy endpoint. Subjects must have compliance with no less than 80% and no more than 120% of prescribed doses and actual doses within ±10% of prescribed dose. Bleeds not treated as per protocol will be excluded. The subjects to be excluded from the PP population will be agreed prior to database lock and all reasons for exclusion will be documented.

Efficacy analysis
All efficacy and safety data will be summarized. Continuous data will be summarized using descriptive statistics including means, SD, medians, lower and upper quartiles, minimum and maximum. Other descriptive statistics may be reported when appropriate. Categorical variables will be summarized with frequencies and percentages.

The primary aim of the analyses is to provide descriptive summaries, and in some cases point and interval estimates, of key variables or parameters. The probability of hemostatic success will be estimated along with a two-sided 95% confidence interval for bleeding events with Poisson regression model.

6.2.10 Study Population and Disposition

As of May 14, 2015, enrollment was complete and 84 subjects had been enrolled into the study. All 84 enrolled subjects were exposed to treatment with AFSTYLA and comprised the Safety Population.

6.2.10.1 Populations Enrolled/Analyzed

Table 27 summarizes the safety population and PK population.

Table 27: Subject Populations (Enrolled Population)

	0 to < 6 years	*≥ 6 to < 12 years*	*Total*
Enrolled	35	49	84
Safety Population	35	49	84
Efficacy Population	35	48	83
PP Population	31	44	75
PK Population	20	19	39

Source: IND 14791/92, Module 5.3.5.2: CSL627-3002/report-body.pdf, Table 11-1, page 69.

6.2.10.1.1 Demographics

Table 28 summarizes the safety population demographics.

Table 28: Subject Demographics (Safety Population)

	<6 years (N=35)	≥6 to < 12 years *(N=49)*	*Total (N=84)*
Age (years)			
Mean (SD)	3.5 (1.34)	8.8 (1.77)	6.6 (3.11)
Median	4.0	9.0	7.0
Min, Max	1*, 5	6, 11	1, 11
Weight (kg)			
Mean (SD)	16.62 (3.566)	35.45 (12.361)	27.60 (13.447)
Median	16.00	32.00	25.00
Min, Max	10.0, 26.2	18.7, 87.5	10.0, 87.5
BMI (kg/m^2)			
Mean (SD)	15.78 (1.715)	18.50 (4.018)	17.37 (3.517)
Median	15.63	17.60	16.80
Min, Max	12.4, 20.0	11.9, 29.6	11.9, 29.6
Race (n[%])			
Asian	9 (25.7)	13 (26.5)	22 (26.2)
White	25 (71.4)	36 (73.5)	61 (72.6)
Other	1 (2.9)	0	1 (1.2)
Ethnicity (n[%])			
Hispanic or Latino	1 (2.9)	1 (2.0)	2 (2.4)
Not Hispanic or Latino	33 (94.3)	48 (98.0)	81 (96.4)
Not reported	1 (2.9)	0	1 (1.2)

*: There were two subjects aged 1 in this study.
Source: IND 14791/92, Module 5.3.5.2: CSL627-3002/report-body.pdf, Table 11-2, page 70.

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6.2.10.1.2 Medical/Behavioral Characterization of the Enrolled Population
A summary of subjects' hemophilia A history is presented in Table 29.

Table 29: Hemophilia A History (Safety population)

	<6 years (N=35)	≥6 to < 12 years *(N=49)*	*Total (N=84)*
Spontaneous bleeding episodes in last 12 months			
n	35	48	83
Mean (SD)	3.4 (8.41)	6.4 (9.94)	5.1 (9.39)
Median	1.0	2.0	2.0
Traumatic bleeding episodes in last 12 months			
n	35	48	83
Mean (SD)	3.6 (4.93)	5.0 (7.60)	4.4 (6.61)
Median	2.0	2.5	2.0
Bleeding episodes of unknown causality in last 12 months			
n	35	49	84
Mean (SD)	0.5 (1.12)	3.7 (9.97)	2.4 (7.77)
Median	0.0	0.0	0.0

Source: BLA 125591/0.3, Module 5.3.5.1: CSL627-3002/report-body.pdf, Table 14.1.6, page 122.

6.2.10.1.3 Subject Disposition
Eighty-four of the screened subjects were eligible and enrolled into the study and all 84 subjects were exposed to treatment with AFSTYLA. Eighty-one subjects were assigned to a prophylaxis regimen, the remaining 3 subjects were assigned to on-demand regimen. Overall, 65 subjects completed the study, 19 subjects were discontinued from the study. One of the subjects who did not complete the study (subject (b) (6)) was discontinued from the study by the physician due to a series of complex social circumstances, including suspected Munchausen by proxy. Another subject (subject (b) (6) was discontinued from the study due to AE. A summary of subject disposition for the safety population is presented in Table 30.

Table 30: Subject Disposition

	0 to < 6 years	*≥ 6 to < 12 years*	*Total*
Enrolled	35	49	84
Completed study (%)	27 (77.1)	38 (77.6)	65 (77.4)
Discontinued from study (%)	8 (22.9)	11 (22.4)	19 (22.6)
Reasons for discontinuation (%)			
AEs	0	1 (2.0)	1 (1.2)
Physician decision	1 (2.9)	0	1 (1.2)
Other	7 (20.0)	10 (20.4)	17 (20.2)

Source: IND 14791/92, Module 5.3.5.2: CSL627-3002/report-body.pdf, Table 10-1, page 66.

6.2.11 Efficacy Analyses

6.2.11.1 Analyses of Primary Endpoint

Hemostatic efficacy

A summary of the overall investigator's assessment of hemostatic efficacy for the efficacy population is presented in Table 31.

Table 31: Overall Investigator's Assessment of Hemostatic Efficacy (Efficacy Population)

	On-demand (N=3)	*Prophylaxis (N=83)*	*Total (N=83)*
Number of bleeding episodes	133	256	389
Number of treated bleeding episodes	132	215	347
Efficacy evaluation by investigator			
Excellent (n[%])	132 (100.0)	164 (76.3)	296 (85.3)
Good (n[%])	0	38 (17.7)	38 (11.0)
Moderate (n[%])	0	12 (5.6)	12 (3.5)
Poor/no response (n[%])	0	1 (0.5)	1 (0.3)
Treatment success	132	202	334
Rate of treatment success (%)	100	94.0	96.3
95% CI for rate	N/A	87.8, 97.1	91.4, 98.4

Source: IND 14791/92, Module 5.3.5.2: CSL627-3002/report-body.pdf, Table 11-16, page 97.

The investigator assessment of hemostatic efficacy was "excellent" for 296 treated bleeding episodes, "good" for 38 bleeding episodes, "moderate" for 12 bleeding episodes, and "poor/no response" for 1 bleeding episode. Thus, the rate of treatment success was 96.3% (ie, 334 of 347 episodes), with a 95% CI of 91.3% to 98.4%.

6.2.11.2 Analyses of Secondary Endpoint

Annualized Bleeding Rate

In the 80 subjects on prophylaxis, the median observed ABR was 3.69 bleeding episodes per year for total bleeding episodes, and 0.00 for spontaneous bleeding episodes (Table 11-20). The calculated number of total bleeding episodes per year, based on a Poisson distribution, was 5.5 (95% CI: 4.8 to 6.3). Twenty-one of the 80 subjects (26.3%) had no bleeding episodes requiring treatment with AFSTYLA.

As expected, the observed ABRs across all bleeding types were substantially higher in the 3 subjects on the on-demand regimen (35.1, 78.6 and 86.6 total bleeding episodes per year).

Table 32 summarizes ABR for study 3002.

Table 32: Annualized Bleeding Rate – AFSTYLA Prophylaxis Compared with AFSTYLA On-demand (Efficacy Population)

	On-demand (N=3)	*Prophylaxis (N=80)*
Total bleeding episodes		
Mean (SD)	66.77 (27.70)	5.22 (5.56)
Median	78.56	3.69
Q1, Q3	35.12, 86.62	0.00, 7.20
Min, Max	35.1, 86.6	0.0, 23.7
Number of bleeding episode per year (95% CI)	71.5 (60.3, 84.80)	5.5 (4.8, 6.3)
Spontaneous bleeding episodes		
Mean (SD)	24.83 (22.19)	1.70 (2.97)
Median	31.76	0.00
Q1, Q3	0.0, 42.73	0.00, 2.20
Min, Max	0.0, 42.7	0.0, 14.0
Number of bleeding episode per year (95% CI)	28.7 (21.5, 37.0)	1.9 (1.5, 2.4)

Source: IND 14791/92, Module 5.3.5.2: CSL627-3002/report-body.pdf, Table 11-20, page 104.

6.2.11.3 Subpopulation Analyses

No subgroup analysis of sex was needed because all subjects are male.

Hemostatic efficacy

According to the SAP, hemostatic efficacy was also analyzed for the region (Table 33), age (Table 34) and race (Table 35) subgroups. Similar results were observed in the subgroup analyses for which there was adequate data.

Table 33: Overall Investigator's Assessment of Hemostatic Efficacy – by Region (Efficacy Population)

Region *Bleeding type assessment*	*On-demand* *(N=3)*	*Prophylaxis* *(N=80)*	*Total* *(N=83)*
Region: United States			
n	0	4	4
Number of treated bleeding episodes	0	10	10
Treatment success	0	9	9
Rate of treatment success	N/A	90.0	90.0
95% CI for rate	N/A	59.3, 98.2	59.3, 98.2
Region: Japan			
n	0	0	0
Number of treated bleeding episodes	0	0	0
Treatment success	0	0	0
Rate of treatment success	N/A	N/A	N/A
95% CI for rate	N/A	N/A	N/A
Region: Europe			
n	3	46	49
Number of treated bleeding episodes	132	92	224
Treatment success	132	82	214
Rate of treatment success	100.0	89.1	95.5
95% CI for rate	N/A	76.5, 95.4	86.6, 98.6
Region: Rest of the world			
n	0	30	30
Number of treated bleeding episodes	0	113	113
Treatment success	0	111	111
Rate of treatment success	N/A	98.2	98.2
95% CI for rate	N/A	94.2, 99.5	94.2, 99.5

Source: IND 14791/92, Module 5.3.5.2: CSL627-3002/report-body.pdf, Table 14.2.1.11, page 303-306.

Table 34: Overall Investigator's Assessment of Hemostatic Efficacy – by Age (Efficacy Population)

Age Group *Bleeding type assessment*	*On-demand* *(N=3)*	*Prophylaxis* *(N=80)*	*Total* *(N=83)*
Age groups: 0 to <6 years			
n	0	35	35
Number of treated bleeding episodes	0	50	50
Treatment success	0	47	47
Rate of treatment success	N/A	94.0	94.0
95% CI for rate	N/A	83.7, 97.9	83.7, 97.9
Age groups: ≥ 6 to < 12 years			
n	3	45	48
Number of treated bleeding episodes	132	165	297
Treatment success	132	155	287
Rate of treatment success	100.0	93.9	96.6
95% CI for rate	N/A	85.8, 97.5	90.6, 98.9

Source: IND 14791/92, Module 5.3.5.2: CSL627-3002/report-body.pdf, Table 14.2.1.3, page 295-296.

Table 35: Overall Investigator's Assessment of Hemostatic Efficacy – by Race (Efficacy Population)

Race *Bleeding type assessment*	*On-demand (N=3)*	*Prophylaxis (N=80)*	*Total (N=83)*
White			
n	3	58	61
Number of treated bleeding episodes	132	132	264
Treatment success	132	121	253
Rate of treatment success	100	91.7	95.8
95% CI for rate	N/A	82.2, 96.3	88.7, 98.5
Asian			
n	0	21	21
Number of treated bleeding episodes	0	81	81
Treatment success	0	79	79
Rate of treatment success	N/A	97.5	97.5
95% CI for rate	N/A	92.4, 99.2	92.4, 99.2
Black or Africa American			
n	0	0	0
Number of treated bleeding episodes	0	0	0
Treatment success	0	0	0
Rate of treatment success	N/A	N/A	N/A
95% CI for rate	N/A	N/A	N/A
Others			
n	0	1	1
Number of treated bleeding episodes	0	2	2
Treatment success	0	2	2
Rate of treatment success	N/A	100.0	100.0
95% CI for rate	N/A	N/A	N/A

Source: IND 14791/92, Module 5.3.5.2: CSL627-3002/report-body.pdf, Table 14.2.1.7, page 299-302.

6.2.11.4 Dropouts and/or Discontinuations

There was no special handling for dropouts and missing data, except for the investigator's assessment of hemostatic efficacy endpoint. However, there were no missing investigator ratings.

6.2.12 Safety Analyses

6.2.12.1 Methods

Descriptive statistics were used in this study. A two-sided exact Clopper-Pearson 95% CI was calculated for the incidence of inhibitors.

6.2.12.3 Deaths

There were no deaths in the study.

6.2.12.4 Nonfatal Serious Adverse Events

Seven subjects (0 to < 6 years age group: 3 subjects; ≥ 6 to <12 years age group: 4 subjects) experienced a total of 10 TESAEs in the study, 1 of which (immune system disorder in Subject (b) (6)) was considered by the investigator as related to administration of AFSTYLA. A summary of the incidence of TESAEs in the Safety Population by SOC and PT is presented in Table 36.

Table 36: Treatment-emergent Serious Adverse Events by System Organ Class and Preferred Term (Safety Population)

	No. of subjects (N=84)	*No. of events*
Any TEAEs	7	10
General disorders and administration site conditions	2	2
Device occlusion	1	1
Systemic inflammatory response syndrome	1	1
Injury, poisoning and procedural complications	2	2
Hand fracture	1	1
Splenic rupture	1	1
Blood and lymphatic system disorders	1	3
Anaemia	1	3
Gastrointestinal disorders	1	1
Dyspepsia	1	1
Immune system disorders	1	1
Hypersensitivity	1	1
Infections and infestations	1	1
Bacteremia	1	1

Source: Adopted from BLA 125591/0.3, Module 5.3.5.1: CSL627-3002/report-body.pdf, Table 12-6, page 77.

Two TEAEs (systemic inflammatory response syndrome in 4-year-old Subject (b) (6) and splenic rupture in 7-year-old Subject (b) (6)) were reported to be severe and were also serious; however the investigator considered both events as unrelated to AFSTYLA. I defer the medical reviewer to make the final judgment on these two TEAEs.

There were two TEAEs in one subject (Subject (b) (6)) that were considered by the investigator to be related to AFSTYLA: one event of hypersensitivity and one event of immune system disorder (low-titer inhibitor). The latter TEAE of immune system disorder (low-titer inhibitor) was initially considered by the investigator to be related to AFSTYLA and was also a TESAE. However, the low-titer inhibitor was later identified as preexisting (already present at Screening), and thus not a de-novo inhibitor developing under exposure to AFSTYLA. Consequently, causality was updated to be unrelated to AFSTYLA after May 14, 2015.

6.2.12.5 Adverse Events of Special Interest (AESI)

No subjects developed any inhibitors during exposure to AFSTYLA, including the 10 subjects with at least 50 EDs, for whom the incidence of inhibitors was 0% (95% CI, 0 to 11.6%). The incidence of inhibitors among all 84 subjects in the Safety Population was also 0% (95% CI, 0 to 4.3%).

6.2.12.6 Clinical Test Results

Not available.

6.2.12.7 Dropouts and/or Discontinuations

Not available.

6.3 Trial #3: CSL627-3001

Study CSL627-3001 is a phase III, open label, multicenter, extension study to assess the safety and efficacy of AFSTYLA in subjects with severe hemophilia A.

6.3.1 Objectives

The primary objective of this study is to evaluate the safety of long term use of AFSTYLA.

The secondary objectives of the study are:

- To measure the incidence rate of inhibitor formation to FVIII after 10 EDs and after 50 EDs
- To collect and evaluate additional efficacy information on the prophylaxis and treatment of bleeding events
- To assess the hemostatic efficacy of AFSTYLA for subjects who undergo surgery
- To characterize the safety profile of AFSTYLA

6.3.2 Design Overview

This multicenter, non-randomized, open-label, single-arm phase 3 extension study will continue to investigate the safety and efficacy on the long-term use of AFSTYLA in male subjects with severe hemophilia A (FVIII activity levels < 1%). This study was designed to evaluate the prophylaxis and on-demand treatment of bleeding episodes in at least 200 subjects who achieve at least 100 EDs. The duration of the study for an individual subject is expected to be up to 3 years. The study was designed so that subjects enroll immediately after participation in a previous AFSTYLA study (study 1001 or 3002), without interruption of their treatment with AFSTYLA. Subjects are assigned by the investigator to either a prophylaxis or on-demand treatment regimen.

A sub-study will investigate the use of AFSTYLA in surgery. Any subject requiring surgery during the course of the study could participate in the surgery sub-study.

6.3.3 Population

Subjects who meet all of the following inclusion criteria are eligible for enrolment into the study:

1. Capable of providing written informed consent and willing and able to adhere to all protocol requirements, or the subject's parent(s) or legally acceptable representative(s) capable of providing written informed consent
2. Participated in a previous CSL-sponsored AFSTYLA investigational study

Subjects who meet any of the following exclusion criteria are not eligible for enrolment into the study:

1. Currently receiving a therapy not permitted during the study, as defined in Section 7.2 of the clinical study protocol

2. Previous participation in the current study
3. Mental condition rendering the subject (or the subject's legally acceptable representative[s]) unable to understand the nature, scope and possible consequences of the study
4. Known or suspected hypersensitivity to AFSTYLA or to any excipients of AFSTYLA or CHO proteins
5. Any issue that, in the opinion of the investigator, would render the subject unsuitable for participation in the study

6.3.4 Study Treatments or Agents Mandated by the Protocol

Subjects are administered AFSTYLA as IV injections. The investigator determines the dose and dosing schedule for the subject based upon the subject's PK profile, AFSTYLA PK data, previous FVIII treatment regimen, and bleeding phenotype, if available.

6.3.6 Sites and Centers

The study is being conducted at approximately 115 study sites in the world.

6.3.7 Surveillance/Monitoring

An Independent Data and Safety Monitoring Committee (IDMC) was established to monitor the safe conduct of the study. The IDMC will:

- Be responsible for providing recommendations to CSL surrounding study conduct matters that affect safety.
- Review the safety data at ad hoc time points and identify if significant safety concerns arise during the study.
- Review pharmacokinetics data and any other data that may affect subject continuation.
- Make recommendations regarding study progression.

6.3.8 Endpoints and Criteria for Study Success

The primary outcome measure is the incidence rate of inhibitor formation to AFSTYLA over 100 EDs.

Secondary efficacy endpoints include:

- The rate of treatment success for bleeding episodes defined as a rating of "excellent" or "good" on the investigator's clinical assessment of hemostatic efficacy 4-point scale
- The annualized bleeding rate (traumatic and non-traumatic) during prophylaxis and on-demand treatment
- The proportion of bleeding episodes requiring 1, 2, 3, or > 3 infusions of AFSTYLA to achieve hemostasis
- Consumption of AFSTYLA, expressed as number of infusions and IU/kg per month and per year, as well as IU/kg per event (prophylaxis, on-demand, and surgery)
- Investigator's assessment of hemostatic efficacy of AFSTYLA for subjects who undergo surgery

Secondary safety endpoints include: inhibitor development, adverse events, laboratory exams, physical exams, and vital signs.

6.3.9 Statistical Considerations & Statistical Analysis Plan

Sample Size
No sample size calculations were performed. The target enrolment is at least 200 subjects completing at least 100 EDs each during enrolment in the CSL sponsored AFSTYLA studies.

Primary Safety Analysis
See Section 6.3.12.1.

6.3.10 Study Population and Disposition

6.3.10.1 Populations Enrolled/Analyzed

As of May 29, 2015, 154 subjects were enrolled in this study (132 subjects ≥ 12 to ≤ 65 years of age from completed study 1001 and 22 subjects 0 to < 12 years of age from study 3002). The majority of subjects (143 of 154 subjects) were assigned to the prophylaxis treatment modality; 11 subjects were assigned to the on-demand treatment modality.

Table 37: Subject Populations (Enrolled Population)

	0 to < 6 years	*≥ 6 to < 12 years*	*≥ 6 to < 12 years*	*≥ 6 to < 12 years*	*Total*
Enrolled	7	15	14	118	154
Surgical populations	0	0	0	4	4

Source: Adapted from BLA 125591/0.3, Module 5.3.5.1: CSL627-3001/report-body.pdf, Table 11-1, page 43.

6.3.10.1.1 Demographics

A summary of the demographic and baseline characteristics of the Enrolled Population overall and by age group is presented in Table 38.

Table 38: Demographic Characteristics (Enrolled Population)

	0 to < 6 years N = 7	*≥ 6 to < 12 years N=15*	*≥ 6 to < 12 years N=14*	*≥ 6 to < 12 years N=118*	*Total N=154*
Age in Study 3001 (years)					
N	7	15	14	118	154
Mean (SD)	5.4 (0.98)	10.3 (1.79)	15.9 (1.98)	32.5 (11.07)	27.6 (13.31)
Age in previous study(years)					
N	7	15	14	118	154
Mean (SD)	4.1 (1.07)	9.1 (1.71)	15.4 (2.10)	31.8 (11.08)	26.8 (13.41)
Weight (kg)					
N	7	15	14	118	154
Mean (SD)	19.76 (2.59)	36.89 (11.889)	62.09 (23.24)	76.88 (16.42)	69.05 (23.013)
BMI (kg/m^2)					
N	6	13	14	116	149
Mean (SD)	15.61 (1.70)	18.55 (4.57)	20.67 (5.00)	25.07 (4.68)	23.71 (5.32)
Race (n[%])					
Asian	3 (42.9)	7 (46.7)	6 (42.9)	20 (16.9)	36 (23.4)
Black or African American	0	0	0	12 (10.2)	12 (7.8)
White	4 (57.1)	8 (53.3)	8 (57.1)	85 (72.0)	105 (68.2)
Other	0	0	0	1 (0.8)	1 (0.6)
Ethnicity (n[%])					
Hispanic or Latino	0	1 96.7)	1 (7.1)	7 (5.9)	9 (5.8)
Not Hispanic or Latino	7 (100)	14 (93.3)	13 (92.9)	111 (94.1)	145 (94.2)
Geographical region (n[%])					
United States	0	2 (13.3)	2 (14.3)	14 (11.9)	18 (11.7)
Japan	0	0	2 (14.3)	5 (4.2)	7 (4.5)
Europe	2 (28.6)	4 (26.7)	6 (42.9)	58 (49.2)	70 (45.5)
Rest of world	5 (71.4)	9 (60.0)	4 (28.6)	41 (34.7)	59 (38.3)

Source: Adapted from BLA 125591/0.3, Module 5.3.5.1: CSL627-3001/report-body.pdf, Table 11-2, page 45.

6.3.10.1.2 Medical/Behavioral Characterization of the Enrolled Population
The medical/surgical history data were transferred from the previous pivotal studies (1001 and 3002). There was no new assessment at enrollment into study 3001.

6.3.10.1.3 Subject Disposition
A summary of subject disposition for the Enrolled Population, by age group, is presented in Table 39.

Table 39: Subject Disposition (Enrolled Population)

	0 to < 6 years	*≥ 6 to < 12 years*	*≥ 6 to < 12 years*	*≥ 6 to < 12 years*	*Total*
Enrolled	7	15	14	118	154
Completed study	0	0	0	0	0
Discontinued from study	0	0	0	3	3
Reasons for discontinuation					
AE	0	0	0	2	2
Withdrawal by subject	0	0	0	1	1

Source: Adapted from BLA 125591/0.3, Module 5.3.5.1: CSL627-3001/report-body.pdf, Table 10-1, page 42.

6.3.11 Efficacy Analyses

No efficacy analyses were included in this submission. Efficacy analyses will be performed at the end of the study and will be reported in the final study report of 3001.

6.3.12 Safety Analyses

6.3.12.1 Methods

Descriptive statistics were used in this study. A two-sided exact Clopper-Pearson 95% CI was calculated for the incidence of inhibitors.

6.3.12.3 Deaths

As of May 29, 2015, there were no deaths in the study.

6.3.12.4 Nonfatal Serious Adverse Events

Five subjects (all from study 1001) experienced a total of six SAEs in the study. None of these SAEs were considered by the investigator as related to AFSTYLA, and all SAEs were reported as resolved as of 29 May 29, 2015. One SAE (nephritis) led to discontinuation of the subject from the study.

6.3.12.5 Adverse Events of Special Interest (AESI)

No inhibitors were detected in any of the 142 subjects with inhibitor tests. The incidence of inhibitors was 0% among the 142 subjects with inhibitor tests (95% CI, 0 to 2.6%) as well as in the 107 subjects with ≥ 100 EDs (95% CI, 0 to 3.4%).

10. CONCLUSIONS

10.1 Statistical Issues and Collective Evidence

For study 1001, the hierarchical testing approach to account for multiple tests was executed. All tests met their success criteria.

For hemostatic efficacy, a total of 848 bleeding episodes were treated during study 1001 and 835 episodes were evaluated and 93.9% were rated a success (783/835), with two-sided 95% CI (91.0%, 95.7%). The pre-specified success criterion for this endpoint (that the lower limit of the two-sided 95% CI should be > 70%) was met. The rate of treatment success was similar in the on-demand and prophylaxis groups (94.5% and 92.2%, respectively). In the pediatric study 3002, a total of 347 bleeding episodes were treated with AFSTYLA and 96.3% were rated a success (334/347), with two-sided 95% CI (91.4%, 98.4%). The lower limit of the 95% CI was also higher than 70%.

Also in study 1001, the AsBR was significantly reduced for prophylaxis subjects (1.6; n=146) compared to on-demand subjects (19.5; n=27). The ratio of AsBR of prophylaxis over on-demand group is 0.08 with CI (0.07, 0.10). The upper limit of CI is lower than the pre-specified threshold 0.50. The p-value of testing the equivalence of AsBR for these two groups is less than 0.0001.

For surgical prophylaxis in study 1001, treatment was rated a success for 100% of the 16 surgeries in the 13 subjects. The pre-specified success criterion for this endpoint (i.e., that the observed success rate should be > 70%) was met.

Currently no incidence of inhibitors has been detected in any of the three studies. The 95% CI of incidence of inhibitors were (0, 2.1%) for study 1001, (0, 4.3%) for pediatric study 3002, and (0, 3.4%) for extension study 3001. The upper limit of 95% confidence interface of inhibitor incidence was lower than the pre-specified threshold 6.8% in all studies.

10.2 Conclusions and Recommendations

This applicant submitted a BLA for the recombinant Antihemophilic Factor (AFSTYLA) for the use in adults and children with hemophilia A (congenital Factor VIII deficiency) for:

- On-demand treatment and control of bleeding episodes,
- Routine prophylaxis to prevent or reduce the frequency of bleeding episodes,
- Perioperative management of bleeding.

The efficacy analyses of study 1001 and 3002 support the above three indications for adults and pediatric subjects. The safety of AFSTYLA are established by safety analysis of study 1001, safety report of pediatric study 3002, and interim safety report of extension study 3001. No statistical concerns were detected.