

**BLA Clinical Review Memorandum**

Application Type	Original Application
STN	125591/0
CBER Received Date	May 29, 2015
PDUFA Goal Date	May 28, 2016
Division / Office	DHCR/OBRR
Priority Review (Yes/No)	No
Reviewer Name(s)	Victor C. Baum
Review Completion Date / Stamped Date	
Supervisory Concurrence	
Applicant	CSL Behring Recombinant Facility AG
Established Name	Antihemophilic Factor (Recombinant), Single Chain
(Proposed) Trade Name	Afstyla
Pharmacologic Class	Antihemophilic Factor (Recombinant), Single Chain
Formulation(s), including Adjuvants, etc.	Intravenous injection
Dosage Form(s) and Route(s) of Administration	Lyophilized powder in single-dose vials containing nominally 250, 500, 1000, 2000 or 3000 international units to be reconstituted with sterile water from a pre-filled single-dose vial, Intravenous
Dosing Regimen	Required dose (IU) = body weight (kg) x desired Factor VIII rise (IU per dL or % of normal) x 0.5 (IU/kg per IU/dL)  Routine Prophylaxis: Begin at 20-50 IU/kg 2 to 3 times per week. Children may require more frequent or higher doses  Prevention of Bleeding episodes:

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	<p>Repeat injection every 12 to 24 hours to maintain required Factor VIII level</p> <p>Perioperative management: Repeat injection every 8 to 24 hours to maintain required Factor VIII level</p>
Indication(s) and Intended Population(s)	<ul style="list-style-type: none"><li>• On-demand Treatment and Control of bleeding episodes;</li><li>• Routine prophylaxis to prevent or reduce the frequency of bleeding episodes; and</li><li>• Perioperative management of bleeding</li></ul> <p>in adults and children with hemophilia A (congenital Factor VIII deficiency)</p>
Orphan Designated (Yes/No)	No

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GLOSSARY

GLOSSARY

ABR	annualized bleeding rate
AE	adverse event
ASBR	annualized spontaneous bleeding rate
AUC t	area under the curve extrapolated to last measurable point
AUC <sub>(0-∞)</sub>	area under the curve extrapolated to infinity
BE	bleeding episode(s)
BU	Bethesda units
CHO	Chinese hamster ovary
CI	confidence interval
CL	clearance
C <sub>max</sub>	maximum concentration
CS	chromogenic assay
DSUR	development safety update report
ED	exposure days
FVIII	factor VIII
FVIII:C	Factor VIII activity
IR	incremental recovery
IU	international units
MRT	mean residence time
NOAEL	no observed adverse effect level
OS	one-stage clotting assay
PAER	periodic adverse event report
pd	plasma-derived
PK	pharmacokinetic
PUP	previously untreated patient
PV	pharmacovigilance
rFVIII	recombinant factor VIII
rhFVIII	recombinant human factor VIII
rVIII-SC	this recombinant product, rVIII-SingleChain (CSL627), Afstyla
SAE	serious adverse event
SUSAR	suspected unexpected serious adverse event
t <sub>1/2</sub>	half-life
TEAE	treatment emergent adverse event
TESAE	treatment emergent serious adverse event
V <sub>ss</sub>	volume of distribution at steady state
VWF	vonWillebrand factor

## 1. Executive Summary

STN 125591 is an original biologics license application (BLA) submitted by the applicant, CSL Behring (CSL) for a recombinant factor VIII (rFVIII), Single Chain design under the trade name Afstyla. The proposed indications for use in adults and children are on-demand treatment and control of bleeding episodes (BEs), routine prophylaxis to prevent or reduce the frequency of BEs, and perioperative management of bleeding. These indications reflect the recently instituted Center for Biologics Evaluation and

Research/Office of Blood Research and Review preferred language for indications for coagulation factor labeling.

Afstyla is produced in a Chinese Hamster Ovary (CHO) cell line. The B-domain, which is not required for hemostatic activity, has been truncated and four adjacent amino acids in the  $\alpha 3$  domain have been deleted. The molecule is expressed as a single chain with a covalent bond linking the light and heavy chains. (b) (4)

(b) (4), (b) (4)  
(b) (4). CSL states that this design results in increased stability and higher binding affinity to von Willebrand factor (VWF). In turn this improves the pharmacokinetic (PK) and pharmacodynamic (PD) properties of this product compared to full-length rFVIII<sup>1</sup> by the additional protection from proteolysis afforded by VWF. CSL states that this modification could potentially allow less frequent dosing than that required with full length rFVIII, (b) (4)

(b) (4)  
(b) (4) After activation by thrombin and removal of the (b) (4) B- and  $\alpha 3$  domains, the activated rFVIII molecule has an amino acid sequence and structure identical to native activated FVIII. As a recombinant product, Afstyla also avoids potential transmission of blood borne pathogens.

Safety and efficacy data from single phase 3 clinical trials in adults (CSL627\_1001) and children (CSL627\_3002) were submitted in support of CSL Behring's proposed indications for Afstyla.

Trial CSL627\_1001 was a phase 3 trial that evaluated 174 subjects with severe hemophilia A, for a total of 14,306 exposure days (ED) and 616 spontaneous BEs requiring treatment (872 overall BEs). The data from this trial confirm the effectiveness of Afstyla to be within the expectations of a rFVIII replacement product, and exceed the pre-set efficacy criteria.

Pediatric data were reported on 84 subjects in the pediatric trial CSL627\_3002. FDA had communicated to CSL during the development of Afstyla that the preliminary pediatric data submitted would suffice to support a pediatric indication, with additional data to follow in the 4-month safety update. These preliminary pediatric PK and safety data were submitted in 125591/0.3, received September 24, 2015 with data as of May 29, 2015. The final clinical study report for CSL627\_3002 was submitted as IND 14791/93, received on February 4, 2016. In this trial subjects 0 to <12 years of age were treated with a total of 5242 ED. There were 389 BEs of which 347 required treatment with Afstyla. The data from this trial confirmed the safety and efficacy of Afstyla in the pediatric population, confirmed the superiority of prophylactic versus on-demand treatment, and confirmed that the PK characteristics of Afstyla are similar to other rFVIII replacement products.

Of the BEs reported in the adult trial CSL627\_1001, 91.9% were joint, 10.7% were muscle and 11.2% were other<sup>2</sup>. Pre-specified success criteria for treatment of BEs,

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1 Zollner S, Raquet E, Claar P, *et al.* Non-clinical pharmacokinetics and pharmacodynamics of rVIII-SingleChain, a novel recombinant single-chain factor VIII. *Thromb Res.* 2014;134:125-31.

2 Subjects could self-report a BE at more than one site, for example arm and shoulder, accounting for the total exceeding 100% (see response to information request, 125591/0.10).

routine prophylaxis, and surgical prophylaxis were all met. Success was defined as a rating score of good or excellent, with the lower bound of 95% confidence limit for treatment success >70% for treating BEs and surgical prophylaxis, and success for routine prophylaxis was defined as lower bound of 95% confidence limit >70% for annualized spontaneous bleeding rate on routine prophylaxis versus on-demand treatment.

Treatment of BEs with Afstyla in the adult trial were rated as excellent or good in 92.3% of 848 treated BEs (24 BEs did not require treatment) and 100% of 16 surgical procedures. Afstyla successfully treated 93.5% of BEs with one or two injections, and there was no reported difference if subjects had been treated with prophylaxis or on-demand treatment when the BE occurred. As with other factor VIII (FVIII) preparations, both plasma-derived and recombinant, the recommended dosing of Afstyla for on-demand treatment varies with the severity of the bleeding, and on the measured blood level of FVIII activity (FVIII:C). The treatment schedule for Afstyla (recommended starting dose for prophylaxis 20-40 IU per kg every 2 days or 20-50 IU per kg 2 to 3 times per week) is similar to other licensed FVIII products.

Routine prophylaxis resulted in 1.14 total BEs per year and no spontaneous BEs per year. There were no BEs reported in 43% of those on routine prophylaxis. The reported annualized rate of spontaneous BEs was decreased 92% from subjects' prior rates with on-demand treatment with other FVIII products. The lower limit of the 95% confidence limit for this decrement from prior rates with on-demand treatment was 88.9%, which exceeded the pre-specified success criterion.

Perioperative efficacy was evaluated in 16 major surgical procedures, defined as surgical procedure that involved anesthesia (general, spinal, epidural or regional block) or respiratory assistance. Results were assessed as excellent in 94% of surgical prophylaxis cases and good in 6% (a single case).

Afstyla showed a safety profile consistent with products of the same class and within the expected background pathology for patients with hemophilia A. No new safety concerns were identified during the review. No subject discontinued participation due to an adverse event (AE) and no cases of FVIII inhibitor or antibody to CHO protein formation were recorded in any subjects treated with Afstyla. There were no thromboembolic events or deaths reported in either clinical trial.

Data from the pediatric trial demonstrated adequate efficacy and safety in a pediatric population to support use in children. Hemostatic efficacy of treatment of BEs with Afstyla was rated as "excellent" or "good" (the defined success criterion) in 96.3% of BEs. There was no difference in subjects 0 to <6 years of age and those 6 to <12 years of age.

Results from the two available assay methodologies, the Chromogenic Substrate (ChS) and the One Stage (OS) assays are discrepant for Afstyla. The OS assay is more routinely used in the United States. CSL Behring concluded that potency assignment using the ChS assay results in the most accurate assignment of 1 unit to the hemostatic potential of FVIII in 1 mL plasma in healthy individuals. Consequently that assay is used in the supporting data for this BLA. CSL Behring proposed a conversion factor (ChS

activity = <sup>(b) (4)</sup> x OS activity). After discussion with the applicant and submission of additional information, FDA accepted this conversion factor (see Appendix).

No post-marketing studies are recommended for this product; however discrepancies between the results of the two available assay techniques, the ChS and OS assays, will require specific plans to educate the relevant populations (physicians, pharmacists, and patients).

**Recommendation:**

Based on my review of the submitted data, Afstyla is safe and effective for use in adult and pediatric patients with hemophilia A for the proposed indications.

**1.1 Demographic Information: Subgroup Demographics and Analysis Summary**

There were no statistically significant differences in either safety or efficacy attributable to race or age.

These demographic data are summarized in Tables 1 and 2.

**Exposure by Sex**

Hemophilia A occurs almost entirely in males. All subjects were male.

**Table 1: Exposure by Age**

Age Group	Total n (%)
<b>CSL627_1001</b>	
≥12 to <18 years	14 (8)
≥18 to ≤65 years	160 (92)
<b>Total</b>	<b>174</b>
<b>CSL627_3002</b>	
0 to <6 years	35
6 to <12 years	49
<b>Total</b>	<b>84</b>

**Table 2: Exposure by Race**

Race	Number of Subjects n (%)
<b>CSL627_1001</b>	
Caucasian	126 (72.4)
Asian	31 (17.8)
Black or African American	14 (8.0)
Other	3 (1.7)
<b>CSL 627_3002</b>	
Caucasian	61 (72.6)
Asian	22 (26.2)

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Black or African American	0
Other	1 (1.2)

Tables 1 and 2 adapted from: BLA Summary of Clinical Safety, Table 1-4, p. 21, and Final Study Report, CSL627\_3002, Table 11-2, page 70 of 172.

Does not include additional pediatric subjects included in the 4-month safety update, September, 2015. These are described more completely in section 6.2.

### Exposure by Ethnicity

In the adult trial there were 12 Hispanic/Latino subjects (6.9%). The remainder was not Hispanic/Latino. Ten subjects (5.8%) were Japanese. In the pediatric trial there were 2 (2.4%) subjects who were Hispanic or Latino.

## 2. Clinical and Regulatory Background

### 2.1 Disease or Health-Related Condition(s) Studied

Hemophilia A (hemophilia) is an X-linked coagulopathy in which affected individuals (almost entirely males) do not produce adequate functional FVIII to achieve satisfactory hemostasis. It is the most common of the severe inherited coagulopathies with an incidence of approximately 1 in 10,000 births (1 in 5,000 male births), with approximately 20,000 males in the United States affected.<sup>3</sup> Disease severity is classified by the level of FVIII:C: mild (5 to <40% of normal), moderate (1-5%), and severe (<1%). BEs can occur shortly after birth with circumcision or with immunizations. The most common sequelae are recurrent traumatic and spontaneous BEs, particularly in joints and muscles. Repeated hemarthroses and hematomas can produce long term disabilities. Additional sites for BEs include the central nervous system, the genitourinary and gastrointestinal tracts, the eyes, and the retroperitoneum. Bleeding from surgical trauma, even minor procedures such as tooth extraction, can be life-threatening.

Fifty years ago the average life expectancy for patients with hemophilia A was less than 20 years, with a quality of life severely limited by joint complications and intracranial hemorrhage. Prognosis has been markedly improved with the introduction of replacement therapies (refer to Section [2.3](#)). Replacement therapy with FVIII is typically initiated in children at the time of the first joint bleed, and primary prophylaxis with a rFVIII product is currently the preferred treatment for children with severe disease. Prophylaxis has been shown to prevent complications later in life and to decrease the incidence of inhibitor formation (refer to Section [2.3](#)). Delayed prophylaxis is referred to as secondary prophylaxis. Even secondary prophylaxis can reduce the frequency of BEs. The typical prophylactic regimen for FVIII is 25-40 International units (IU) per kg every other day or 3 times per week, although an intermediate dose of 15-25 IU per kg is sometimes used.

The most serious complication of treatment for hemophilia is inhibitor formation, which occurs in up to 30% of patients with severe hemophilia A.<sup>4</sup>

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3 <https://www.hemophilia.org/About-Us/Fast-Facts>

4 Gouw SC, van der Bom JG, Ljung R, *et al.* Factor VIII products and inhibitor development in severe hemophilia A. *N Engl J Med.* 2013;368:231-9.

The first generation licensed rFVIII products were produced in hamster cells and included Recombinate (Bayer; also claimed by Wyeth, approved in 1992) and Helixate FS (Bayer; approved in 1993). These products used media enriched with human or animal plasma proteins for initial cell culture and contained albumin in the final formulation. Second generation products, such as Helixate FS/Kogenate FS (Bayer/CSLBehring) and ReFacto (Wyeth), did not contain albumin in the final formulation. Third generation products such as Advate (Baxter) and Xyntha / ReFacto AF (Pfizer) do not contain any human or animal plasma proteins in the purification or final formulation.

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

Additional therapeutic options include:

- Antifibrinolytic therapy to delay clot dissolution can be used as a secondary, nonspecific, adjunctive therapy but this is not a primary treatment option. These medications such as epsilon-aminocaproic acid and tranexamic acid help preserve the hemostatic plug. They are typically used for mucocutaneous bleeding from the mouth or nose, and for dental procedures.
- Desmopressin (DDAVP) is an arginine vasopressin analogue that causes a transient rise in FVIII and VWF. It is typically used for mild hemophilia.

## **2.3 Safety and Efficacy of Pharmacologically Related Products**

Pathogen transmission, inhibitor formation and thromboembolic phenomena are the main risks when treating hemophilia patients with FVIII replacement therapy. The availability of rFVIII products reduces the risk of pathogen transmission, but not inhibitor development or the potential for thromboemboli.

Clinical management and life expectancy of patients with hemophilia A were markedly improved by the introduction of cryoprecipitate, and subsequently plasma-derived (PD) FVIII concentrates as replacement therapy. Unfortunately many patients were infected by HIV during the 1980s from PD products. The risk for transmission of blood-borne pathogens has been ameliorated by the development of recombinant products. Full-length and modified rFVIII have been produced in CHO cell lines or baby hamster kidney (BHK) cell lines. Several rFVIII products produced in human embryonic kidney (HEK) cell lines have been approved.

Additionally, there are potential risks with FVIII products, including rFVIII products, for the development of neutralizing antibodies (inhibitors) and allergic reactions to animal-based proteins remaining from the manufacturing process. The development of inhibitors decreases the efficacy of replacement therapy, increases the risk of unmanageable bleeding, and increases cost of treatment (by 3-5 fold).<sup>5,6</sup> The incidence of inhibitor

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5 Goudemand J: Hemophilia. Treatment of patients with inhibitors: cost issues. *Haemophilia* 2013;5:397-491.

6 Gringeri A, Mantovani LG, Scalone L, *et al*: Cost of care and quality of life for patients with hemophilia complicated by inhibitors: the COCIS Study Group. *Blood* 2003; 102:2358-63.

development is approximately 30% in severe disease and less in mild or moderate disease. The highest incidence is in previously untreated patients with severe disease (reported to be from 3-52%).<sup>7</sup> Inhibitor development in previously treated patients is less, reported as 0.9-4%.<sup>8,9</sup> Additional potential risk factors for inhibitor development include genetic factors such as the type of FVIII gene mutation, human leucocyte antigen (HLA) type, polymorphisms in immune regulatory regions, family history of inhibitors and ethnic background, as well as immunologic environment during early treatment, and high intensity of treatment (either peak acute treatment or high overall treatment frequency).

Afstyla is a B-domain truncated rFVIII produced in a CHO cell line. A recently approved rFVIII product, Eloctate, is B-domain deleted analogue of human FVIII covalently linked to the human immunoglobulin G<sub>1</sub> (IgG<sub>1</sub>) F<sub>C</sub> domain sequence. This modification of the B-domain results in a prolonged half-life (19.7 hours after a single dose) with levels >1% for 5 days (prophylactic dosing interval every 3-5 days, more frequently in children <6 years old).

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

Afstyla is not currently licensed for use in any country. The studies reported in this BLA represent the entire human experience.

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

CRMTS # 7708 (December 7, 2010) – Agreement between FDA and CSL that OS and ChS assays should be performed in a central laboratory and final assessment of the labeling will be made after finalization of the clinical studies.

CRMTS # 7945 (June 2, 2011) – Clarified definitions of ordinal efficacy scales.

CRMTS # 9127 (November 22, 2013) – CSL's proposal to support an indication for routine prophylaxis by comparison with on-demand regimen in the confirmatory trial CSL627\_1001 was accepted by FDA. Data from 15 pediatric subjects from all representative age groups may be adequate to support a pediatric indication.

CRMTS # 9559 (November 20, 2014) - FDA agreed to CSL's proposal to submit an interim PK and safety report for Study CSL627\_3002 in the BLA containing PK data on 10 previously treated pediatric subjects <12 years of age, and an updated interim PK and safety report in the 4-month safety update containing PK data on an additional 10 subjects < 12 years of age to meet FDA's request for PK data on at least 20 pediatric subjects "preferably equally distributed between ages 0 to <6 years and ≥6 to 12 years in addition to the available adolescent data" considered necessary for the pediatric

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7 Franchini M, Tagliaferri A, Mengoli C, *et al.*: Cumulative inhibitor incidence in previously untreated patients with severe hemophilia A treated with plasma-derived versus recombinant factor VIII concentrates: a critical systematic review. *Crit Rev Oncol Hematol* 2012; 81: 82-93.

8 Peerlinck K, Hermans C: Epidemiology of inhibitor formation with recombinant factor VIII replacement therapy. *Haemophilia* 2006; 12: 579-90.

9 Coppola A, Tagliaferri A, Franchini M: Searching for the role of primary prophylaxis in preventing inhibitor development in hemophilia A. *J Thromb Haemost* 2012; 10:1954-60.

indication. Additionally, FDA agreed that theoretically, both OS and ChS assays may be suitable for monitoring FVIII during treatment. The final decision could only be made after review of the complete data set in the BLA. Also, treatment efficacy as lower limit of 95% confidence limit >70% was established.

**Reviewer Note: An Interim PK and Safety Report for 39 pediatric subjects (20 subjects < 6 years and 19 subjects ≥6 to <12 years) was submitted on September 24, 2015. The final study report for this trial was received on February 4, 2016, reporting on a total of 84 pediatric subjects. The data and assessments in this review include the data in the final study report.**

CSL applied for orphan designation on January 30, 2015, (Application 15-4719). FDA's Office of Orphan Products Development responded on April 9, 2015, stating that orphan designation was unable to be granted because it was determined that Afstyla is the same drug as other antihemophilic factor drugs that are approved for use for the same indications, and a plausible hypothesis for clinical superiority had not been provided.

CRMTS #9649 (February 26, 2015) - Comparison of the two available FVIII activity assays, OS and ChS. CSL concluded that potency assignment using the ChS assay results in the most accurate assignment of 1 unit to the hemostatic potential of FVIII in 1 mL plasma in healthy individuals. The ChS assay is used in the supporting data for this BLA.

In support of a request by FDA (CRMTS #9649) that CSL provide a summary of the number of laboratories in the United States that use the OS versus the ChS assay, CSL responded (in the 4 month safety update, section 5.3.1.4, received September 24, 2015) that responses to a survey (email and telephone follow up) of the 142 U.S. hemophilia treatment centers had a 60% response rate. Of the 85 responders 70 (93%) have the OS assay available in house and 23 (27%) have or are working on establishing the ChS assay in house. As additional 53 centers (62%) have access to the ChS assay by an external laboratory. Only 17 (20%) do not have access to the ChS assay or that using an external laboratory would require excessive time.

Also in response to a request by FDA, CSL reported the results of a field trial comparing the ChS and OS assays in the BLA application, section 5.3.1.4. (b) (4) laboratories (of (b) (4) requested) completed data entry (13 from the United States). Laboratories were supplied with spiked samples of (b) (4) for both Afstyla and a (b) (4), to be assayed in multiple aliquots [(b) (4) the results from the ChS and OS assays]. The results showed a relatively (b) (4) relationship between values obtained by ChS or OS assays, with a suggested conversion factor of ChS activity = (b) (4) x OS activity.

A consultative report regarding the potency labeling for Afstyla was solicited from a Special Government Employee (Dr. Donna Di Michele, M.D. [NHLBI]). Dr. Di Michele agreed that the submitted data supported the applicant's proposal to assign potency based on the ChS assay. Dr. Di Michele confirmed the need for communication to physicians and other health care professionals. Dr. Di Michele felt that listing both potencies on the package insert would be confusing, and that giving the means to interpret that data (i.e. the conversion factor) would be better.

Additional graphs were submitted to support this conversion factor, in response to an FDA Information Request (of February 9, 2016). The issue of an appropriate conversion factor was discussed at the External Late Cycle Meeting with CSL on February 18, 2016. It was agreed that a conversion factor of (b) (4) was appropriate.

Also at the late cycle meeting discussions were held about appropriate communications strategies to communicate these assay differences and the clinical implications. CSL offered suggestions and additional discussions are ongoing.

## 2.6 Other Relevant Background Information

There have been no cases describing dosing errors based on the assay type used for optional monitoring of FVIII levels reported from the Afstyla clinical development program.

Protocol Amendment 1 for Trial CSL627\_3002: (May 21, 2013) extended the duration of study participation to allow for ≥50 ED and additional clarifications and minor modifications.

Protocol Amendment 2 for Trial 627\_3001: (March 28, 2014) minor changes and update for an extension trial CSL627\_3001.

## 3. SUBMISSION QUALITY AND GOOD CLINICAL PRACTICES

### 3.1 Submission Quality and Completeness

The submission was adequately organized and integrated to accommodate the conduct of a complete clinical review without unreasonable difficulty. It was submitted electronically and formatted as an electronic Common Technical Document (eCTD) according to FDA guidance for electronic submission. This submission consisted of the five modules in the common technical document structure.

### 3.2 Compliance With Good Clinical Practices And Submission Integrity

The studies supporting this submission were conducted in compliance with good clinical practices, including informed consent, site-specific issues, and in accordance with acceptable ethical standards. The following international sites were inspected by FDA Bioresearch Monitoring (BIMO). All sites participated in Trial627\_1001.

Site Number	Study Site	Location	Enrolled Subjects	FDA Form 483 Issued	Classification
7100001	Charlotte Maxeke Johannesburg Academic Hospital	Johannesburg, South Africa	14	No	NAI
6160014	Samodzielny	Warsaw,	11	Yes	VAI

	Publiczny Kliniczny	Poland			
6080001	Perpetual Succour Hospital	Cebu, Philippines	8	No	NAI

NAI = No Action Indicated; VAI = Voluntary Action Indicated

### Applicant-identified protocol deviations

In Trial627\_1001, 17 protocol deviations resulted in exclusion of subjects from the Per-protocol Population (four in the on-demand group and 13 in the prophylaxis group). These were all for non-compliance with the prescribed dose or the prophylaxis regimen. In Trial CSL627\_3002 17 subjects had a total of 20 major protocol violations. Of these only one resulted in exclusion from the efficacy population. Subject (b) (6), a 10 year old Asian male, due to a laboratory screening error was reported as pre-existing inhibitor negative when in fact he was positive (3.46 BU/mL). Eight subjects (four in each of the two age groups) in the efficacy population were determined to be non-compliant and were removed from the Per-protocol Population. One subject was enrolled with less than a 30 day period between the last FVIII product and the first dose of Afstyla. This subject continued in the trial and was included in both the efficacy and Per-protocol Populations.

### 3.3 Financial Disclosures

Covered clinical study (name and/or number): CSL627_1001		
Was a list of clinical investigators provided:	Yes <input checked="" type="checkbox"/>	No <input type="checkbox"/> (Request list from applicant)
Total number of investigators identified: <u>196</u>		
Number of investigators who are sponsor employees (including both full-time and part-time employees): <u>1</u>		
Number of investigators with disclosable financial interests/arrangements (Form FDA 3455): <u>4</u>		
If there are investigators with disclosable financial interests/arrangements, identify the number of investigators with interests/arrangements in each category (as defined in 21 CFR 54.2(a), (b), (c) and (f)):		
Compensation to the investigator for conducting the study where the value could be influenced by the outcome of the study: <u>0</u>		
Significant payments of other sorts: <u>4</u>		
Proprietary interest in the product tested held by investigator: <u>0</u>		
Significant equity interest held by investigator in sponsor of covered study: <u>0</u>		
Is an attachment provided with details of the disclosable financial interests/arrangements:	Yes <input checked="" type="checkbox"/>	No <input type="checkbox"/> (Request details from applicant)

Is a description of the steps taken to minimize potential bias provided:	Yes <input checked="" type="checkbox"/>	No <input type="checkbox"/> (Request information from applicant)
Number of investigators with certification of due diligence (Form FDA 3454, box 3) <u>0</u>		
Is an attachment provided with the reason:	Yes <input type="checkbox"/>	No <input type="checkbox"/> (Request explanation from applicant)
Covered clinical study (name and/or number): CSL627_3002		
Was a list of clinical investigators provided:	Yes <input checked="" type="checkbox"/>	No <input type="checkbox"/> (Request list from applicant)
Total number of investigators identified: <u>109</u>		
Number of investigators who are applicant employees (including both full-time and part-time employees): <u>0</u>		
Number of investigators with disclosable financial interests/arrangements (Form FDA 3455): <u>3</u>		
<p>If there are investigators with disclosable financial interests/arrangements, identify the number of investigators with interests/arrangements in each category (as defined in 21 CFR 54.2(a), (b), (c) and (f)):</p> <p>Compensation to the investigator for conducting the study where the value could be influenced by the outcome of the study: <u>0</u></p> <p>Significant payments of other sorts: <u>3</u></p> <p>Proprietary interest in the product tested held by investigator: <u>0</u></p> <p>Significant equity interest held by investigator in applicant of covered study: <u>0</u></p>		
Is an attachment provided with details of the disclosable financial interests/arrangements:	Yes <input checked="" type="checkbox"/>	No <input type="checkbox"/> (Request details from applicant)
Is a description of the steps taken to minimize potential bias provided:	Yes <input checked="" type="checkbox"/>	No <input type="checkbox"/> (Request information from applicant)
Number of investigators with certification of due diligence (Form FDA 3454, box 3) <u>0</u>		
Is an attachment provided with the reason:	Yes <input type="checkbox"/>	No <input type="checkbox"/> (Request explanation from applicant)

Covered clinical study (name and/or number): CSL627_3002		
Was a list of clinical investigators provided:	Yes <input checked="" type="checkbox"/>	No <input type="checkbox"/> (Request list from applicant)
Total number of investigators identified: <u>109</u>		
Number of investigators who are applicant employees (including both full-time and part-time employees): <u>0</u>		
Number of investigators with disclosable financial interests/arrangements (Form FDA		

3455): <u>3</u>		
If there are investigators with disclosable financial interests/arrangements, identify the number of investigators with interests/arrangements in each category (as defined in 21 CFR 54.2(a), (b), (c) and (f)):  Compensation to the investigator for conducting the study where the value could be influenced by the outcome of the study: <u>0</u> Significant payments of other sorts: <u>3</u> Proprietary interest in the product tested held by investigator: <u>0</u> Significant equity interest held by investigator in applicant of covered study: <u>0</u>		
Is an attachment provided with details of the disclosable financial interests/arrangements:	Yes <input checked="" type="checkbox"/>	No <input type="checkbox"/> (Request details from applicant)
Is a description of the steps taken to minimize potential bias provided:	Yes <input checked="" type="checkbox"/>	No <input type="checkbox"/> (Request information from applicant)
Number of investigators with certification of due diligence (Form FDA 3454, box 3) <u>0</u>		
Is an attachment provided with the reason:	Yes <input type="checkbox"/>	No <input type="checkbox"/> (Request explanation from applicant)

#### 4. SIGNIFICANT EFFICACY/SAFETY ISSUES RELATED TO OTHER REVIEW DISCIPLINES

##### 4.1 Chemistry, Manufacturing, and Controls

Afstyla is a rFVIII produced in CHO cells. The B-domain of the full-length FVIII has been truncated and four amino acids of the adjacent a3 domain removed. Afstyla is expressed as a single chain FVIII molecule with the heavy and light chains covalently linked. Afstyla is provided as a sterile lyophilized powder to be reconstituted with sterile water. The lyophilized powder is supplied in single-use vials containing five fill sized (250, 500, 1000, 2000 or 3000 IU) and four dosage strengths (100, 200, 400 and 600 IU/mL). The actual FVIII potency (units) for each manufactured lot is indicated on the vial label. CSL reports that Afstyla does not contain any novel excipients, or excipients of animal or human origin.

##### 4.2 Assay Validation

Validations of the assays were submitted in section 4.2.2.1 of the BLA and are described also in section 2.3.S.2.5. Minor concerns were raised by the CMC reviewer as reported in the minutes of the Late-Cycle meeting (submission 125591/0.26, Section 1.6.3). These will not impact approval of Afstyla.

### 4.3 Nonclinical Pharmacology/Toxicology

Pharmacodynamic studies were conducted in rat, (b) (4) monkey and FVIII deficient mouse. Repeat-dose studies were conducted in rats and (b) (4) monkeys. In studies in rats and (b) (4) monkeys Afstyla showed a concentration-dependent effect on thrombin generation, a correction of thromboelastography abnormalities in hemophiliac mice, and an improved activated partial thromboplastin time equivalent to that of a licensed FVIII comparator. Afstyla had equivalent effects on hemostasis in hemophiliac mice as did four comparator FVIII products. Afstyla was at least as potent as these other products when dosed according to ChS FVIII activity, and more potent when dosed according to clotting FVIII activity. Repeat-dose studies in rates did not show any neurobehavioural or histologic abnormalities. Repeat-dose studies in monkeys and dogs at doses up to 1550 IU/kg did not show treatment-related clinical signs. The nonclinical studies provided supporting evidence for the safe use of Afstyla in clinical trials, and justified the doses selected for evaluation in those trials.

### 4.4 Clinical Pharmacology

Evaluation of clinical pharmacology of Afstyla in subjects with hemophilia A was part of both clinical trials.

#### 4.4.1 Mechanism of Action

Afstyla contains the active substance, human rFVIII. As such, it temporarily restores the inadequate levels of FVIII found in hemophilia A patients, and allows for adequate hemostasis. Upon activation of the clotting cascade, FVIII is converted to activated FVIII, and acts as a cofactor for activated factor IX, thus accelerating the conversion of factor X to activated factor X on phospholipid surfaces. Activated factor X ultimately converts prothrombin to thrombin and leads to the formation of a fibrin clot.

#### 4.4.2 Human Pharmacodynamics (PD)

The pharmacodynamic effects of Afstyla are the same as those of endogenous coagulation FVIII. Afstyla binds to VWF similarly to that of native FVIII.

#### 4.4.3 Human Pharmacokinetics (PK)

The PK profiles for Afstyla from the adult and pediatric trials are shown in Tables 3 and 4.

**Table 3**  
**PK data in adults (from Trial CSL627\_1001)**

Parameter, unit	ChS (N=26)	OS (N=26)
Cmax (IU/dL)	114 (14.7)	55.5 (13.9)
IR (IU/dL)(IU/kg)	2.27 (14.7)	1.08 (15.5)
AUC <sub>(0-last)</sub> (IU*h/dL)	2030 (27.8)	1260 (28.6)
AUC <sub>(0-∞)</sub> (IU*h/dL)	2130 (29.8)	1340 (33.2)
T <sub>1/2</sub> (h)	14.7 (25.4)	15.5 (31.9)
CL (mL/h/kg)	2.55 (28.9)	4.13 (31.6)
Vss (mL/kg)	49.3 (13.5)	88.8 (14.0)

MRT (h)	17.3 (26.5)	23.3 (31.9)
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Data are Mean (coefficient of variation)

Adapted from Clinical Study Report Trial CSL627\_1001: Section 11.4.1.2.1, Table 11-13, page 108 of 196

**Table 4**  
**PK data in children (from Trial CSL627\_3002)**

Parameter, unit	Mean (CV%)			
	0 to < 6 years (N = 19)		> 6 to < 12 years (N = 19)	
	ChS	OS	ChS	OS
C <sub>max</sub> , IU/dL	80.2 (21.2)	45.0 (81.8)	83.5 (19.5)	42.3 (20.1)
IR, (IU/dL)/(IU/kg)	1.61 (21.4)	0.893 (82.8)	1.66 (19.7)	0.841 (20.3)
AUC <sub>t</sub> , IU*h/dL	1020 (28.4)	564 (44.7)	1090 (26.4)	635 (32.3)
AUC <sub>inf</sub> , IU*h/dL	1090 (31.4)	632 (59.3)	1170 (26.3)	683 (33.2)
t <sub>1/2</sub> , h	10.5 (28.6)	11.1 (48.8)	10.2 (19.4)	10.3 (26.6)
CL, mL/h/kg	5.01 (30.3)	9.73 (45.4)	4.63 (29.5)	8.44 (42.4)
V <sub>ss</sub> , mL/kg	70.8 (12.1)	134 (27.5)	67.1 (22.3)	121 (21.7)
MRT, h	12.6 (24.1)	12.5 (31.2)	12.3 (16.8)	12.8 (17.5)

Abbreviations: AUC<sub>t</sub>, area under the activity/concentration curve from time point zero to the last quantifiable time point; AUC<sub>inf</sub>, area under the activity / concentration curve from zero extrapolated to infinity; ChS, chromogenic substrate (assay); CL, total plasma clearance; CV, coefficient of variation; C<sub>max</sub>, maximum observed concentration/activity; IR, incremental recovery; IU, international units; MRT, mean residence time; N, total number of subjects; OS, one-stage clotting (assay); t<sub>1/2</sub>, half-life; V<sub>ss</sub>, volume of distribution at steady-state.

Data are Mean (coefficient of variation)

Source: Final Study Report, CSL627\_3002, Table 11-12, page 91 of 172

**Reviewer Note: The PK data show the discrepancy between the ChS and OS assays that are being addressed. In addition, the clearance in younger children is higher than in older children and adults. This is typical of FVIII replacement products, and the extent of this difference varies somewhat from product to product.**

#### 4.5 Statistical

Statistical analyses were based on the methods outlined in version 2 of the Statistical Analysis Plan.

#### 4.6 Pharmacovigilance

The proposed pharmacovigilance plan is shown in Table 5.

**TABLE 5**  
**Detailed Action Plan for Safety Observations/Signals**

Concern	Action Plan	Milestones
Hypersensitivity and Anaphylactic Reactions	Routine pharmacovigilance including specific follow up questionnaire	4-month safety update
	CSL627_3002 Phase III in previously treated children	DSUR/PAERs
	CSL627_3001 extension study	SUSARs
Non-Inhibitory Anti-Drug Antibodies	Routine pharmacovigilance	4-month safety update
	CSL627_3002 Phase III in previously treated children	DSUR/PAERs
	CSL627_3001 extension study	SUSARs
Development of Inhibitors	Routine pharmacovigilance including specific follow up questionnaire	4-month safety update
	CSL627-3002 Phase III in previously treated children	DSUR/PAERs
	CSL627_3001 extension study	SUSARs
Errors based on Assay type (ChS vs OS)	Routine PV including additional follow up	4-month safety update
	CSL627_3002 Phase III in previously treated children	DSUR/PAERs
	CSL627_3001 extension study	SUSARs
Development of anti-CHO antibodies	Routine PV	4-month safety update
	CSL627_3002 Phase III in previously treated children	DSUR/PAERs
	CSL627_3001 extension study	SUSARs
Inhibitor formation in PUPs	Routine PV including additional follow up and specific follow up questionnaire	4-month safety update
	CSL627_3001 extension study (to include PUP study arm)	DSUR/PAERs
		SUSARs
Pregnancy and Lactation	Routine PV including additional follow up and pregnancy follow up questionnaire	4-month safety update
		DSUR/PAERs
Geriatric Patients	Routine PV including additional follow up	4-month safety update
		DSUR/PAERs
		SUSARs

Adapted from BLA Risk Management Plan, Section 1.16, tables 21 through 28

**Reviewer Comment: The applicant’s proposed Trial CSL627\_3001, an extension of Trial CSL627\_1001, is a phase 3 trial that will investigate the safety of long term Afstyla (≥100 ED, 200 subjects). The primary outcome will be inhibitor formation to FVIII. This proposed pharmacovigilance plan is acceptable. However, in addition CSL will supply a detailed description of the communication plan to educate health care providers and consumers about the discrepancy between the ChS and OS FVIII:C assays.**

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

### 5.1 Review Strategy

Final data from CSL627\_1001 and CSL627\_3002 were reviewed as were prior communications with the sponsor.

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

- 1.2 Cover Letter
- 1.3.3 Debarment Certification
- 1.3.4 Financial Disclosure
- 1.6 Meetings
- 1.9.2 Request for Deferral of Pediatric Studies
- 1.12 Other Correspondence
- 1.14.1 Draft Labeling
- 1.16 Risk Management Plans
- 2.2 Introduction
- 2.4 Nonclinical Overview
- 2.5 Clinical Overview
- 4 Nonclinical Study Reports

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## 5 Clinical Study Reports

### 5.3 Table of Studies/Clinical Trials

Protocol	Type	Design	# Subjects	Primary Endpoint	Status
CSL627_1001	PK, efficacy, safety	Pivotal, prospective, multicenter, crossover, phase 1/3	175 adults and adolescents	PK vs. comparator, Prevention, Prophylaxis, Surgical	Completed
CSL627_3002	PK, efficacy, safety	Prospective, multicenter, multinational, phase 3	84 pediatric	PK efficacy, safety	Completed

### 5.4 Consultations

#### 5.4.1 Advisory Committee Meeting (if applicable)

An advisory committee meeting was waived by OBRR.

#### 5.4.2 External Consults/Collaborations

There were no external consults/collaborations needed during this review.

### 5.5 Literature Reviewed (if applicable)

Not applicable.

## 6. DISCUSSION OF INDIVIDUAL STUDIES/CLINICAL TRIALS

### 6.1 Trial #1

“A Phase I/III Open-label, Multicenter, Crossover Safety, Efficacy and Pharmacokinetic Study of Recombinant Coagulation Factor VIII (rFVIII) Compared to Recombinant Human Antihaemophilic Factor VIII (rFVIII; INN: octocog alfa) in Subjects with Hemophilia A, and a Repeat PK, Safety and Efficacy Study”

#### 6.1.1 Objectives (Primary, Secondary, etc)

##### Primary

- Characterize PK profile of Afstyla
- Demonstrate efficacy in prevention and treatment of BEs
- Demonstrate efficacy of routine prophylaxis treatment over on-demand treatment
- Characterize the rate of inhibitor formation
- Surgical substudy:
  - Demonstrate the efficacy of Afstyla in surgical prophylaxis

##### Secondary

- Characterize the safety profile of Afstyla
- Perform the PK comparison of Afstyla to a comparator rFVIII

### 6.1.2 Design Overview

All subjects were males  $\geq 18$  years of age (Parts 1 and 2) or 12 to 65 years (Part 3) with severe hemophilia A (FVIII:C  $< 1\%$ ), previously treated with FVIII.

Three Parts:

**Part 1:** This was a single-sequence crossover PK comparison of Afstyla with a comparator licensed rFVIII product. After an interim analysis of PK and safety data at the completion of this part, the PK data were used to confirm the dosing selection and schedules for Part 3.

**Part 2:** This part assessed efficacy and safety of Afstyla with continued dosing in subjects from Part 1. The first five subjects received on-demand treatment to confirm efficacy. The remaining subjects received either on-demand or prophylaxis, based on subject preference (often related to prior treatment regimen) and investigator discretion.

**Part 3:** This part assessed safety and efficacy with continued dosing in new subjects, including a repeat PK assessment in 13 subjects. Subjects received on-demand or prophylactic treatment for  $\geq 50$  ED.

**Surgical sub-study (perioperative prophylaxis):** This was conducted with at least five subjects from either Parts 2 or 3. Dosing regimens were individualized based on the type of surgery and the clinical status of the subject.

All subjects completing Part 3 were eligible to continue in an ongoing extension trial (Trial CSL627\_3001) to evaluate long term efficacy and safety.

Compliance was defined by:

Prophylaxis: Subject received 80-120% of scheduled doses

Prophylaxis or on-demand:  $\geq 80\%$  of treatment doses within  $\pm 10\%$  of the prescribed dose

### 6.1.3 Population

Inclusion criteria

- $> 150$  ED prior exposure to FVIII (PD or recombinant)
- Severe hemophilia A (FVIII:C  $< 1\%$ )
- Ages 18 to 65 (parts 1 and 2) or 12 to 65 (part 3)

Major exclusion criteria

- FVIII inhibitors (in subject or first order family member)
- Unable to receive treatment at home
- Known hypersensitivity to FVIII or hamster protein
- Coagulation disorder other than congenital FVIII deficiency
- Human immunodeficiency virus (HIV) with CD4 count  $< 200$  per  $\text{mm}^3$
- Currently receiving intravenous immunomodulatory agents
- Elevated liver enzymes  $> 5$  times upper limit of normal
- Serum creatinine  $> 2$  times upper limits of normal
- Evidence of thromboembolic disease within 3 months
- Life threatening BE or major surgery within 3 months

6.1.4 Study Treatments or Agents Mandated by the Protocol

**Part 1:** 50 IU/kg of comparator as a single intravenous injection with measurements for PK up to 72 hours. After a delay to attain a washout of  $\geq 4$  days, subjects received 50 IU/kg Afstyla

**Reviewer Comment: This was a single sequence trial; therefore, all subjects received drug in this order. The order was not randomized.**

**Part 2:** On-demand: Afstyla at a dose of the FVIII product used prior to enrolment for the same type of BE, continued until 50 ED or until  $\geq 104$  subjects reached 50 ED.

Prophylaxis: Recommended starting dose 20-40 IU per kg Afstyla every 2 days or 20-50 IU per kg 2 to 3 times per week. However, dosing was at the investigator's discretion, taking into account the subject's treatment schedule prior to enrolment. The dose could be adjusted as necessary (e.g., 2 or more BEs over a 2 week period). See Table 6 for dosing suggestions for treatment of BEs.

**Part 3:** PK as in Part 1 and treatment as in Part 2.

**Perioperative prophylaxis:**

Treatment was individualized, based on the type of surgical procedure and the clinical status of the subject, to achieve and maintain FVIII:C at a level recommended by the World Federation of Hemophilia . See Table 7 for approximate dosing suggestions.

**Table 6**  
**Dosing for Control and Prevention of BEs**

Type of Bleeding Episode	Factor VIII Activity Level Required (% or IU/dL)	Frequency of Doses (hours)
<b>Minor</b> Uncomplicated hemarthrosis, minor muscle bleeding or oral bleeding	20-40	Repeat injection every 12-24 hours until the bleeding is resolved.
<b>Moderate</b> Muscle bleeding (except iliopsoas), hemarthrosis, or mild trauma	30-60	Repeat injection every 12-24 hours until the bleeding is resolved.
<b>Major/Life-threatening</b> Limb threatening hemorrhage, deep muscle bleeding (including iliopsoas), intracranial and retropharyngeal bleeding, fractures or head trauma	60-100	Repeat injection every 8-24 hours until bleed is resolved.

Source: Afstyla BLA, 125591/0.25 Section 1.14.1.3draft label, Table 1

**Table 7**

**Dosing for Perioperative Management**

Type of Surgery	Factor VIII Activity Level Required (% or IU/dL)	Frequency of Doses (hours) / Duration of Therapy (days)
<b>Minor</b> (including tooth extraction)	30-60	Repeat injection every 24 hours for at least 1 day, until healing is achieved.
<b>Major</b> (intracranial, intra-abdominal, intrathoracic, or joint-replacement)	80-100	Repeat injection every 8-24 hours until adequate wound healing, then continue therapy for at least another 7 days to maintain a Factor VIII activity of 30-60% (IU/dL).

Major surgery was defined as a surgical procedure that involved anesthesia (general, spinal, epidural or regional block) or respiratory assistance (including but not limited to orthopedic and cardiac surgery).  
Source: Afstyla BLA, 125591/0.25 Section 1.14.1.3draft label, Table 2

**6.1.5 Directions for Use**

Afstyla is supplied for single use, with dosing as per section 6.1.4.

**6.1.6 Sites and Centers**

Australia (2), Austria (2), Canada (1), Czech Republic (1), Germany (6), Hungary (1), Italy (4), Japan (8), Lebanon (1), Malaysia (1), Netherlands (1), Philippines (2), Poland (3), Romania (1), Russia (2), South Africa (2), Spain (4), Ukraine (3), United Kingdom (1), United States (6).

**6.1.7 Surveillance/Monitoring**

Efficacy and safety data (including inhibitor data) were monitored by an Independent Data Monitoring Committee composed of recognized experts in the field of hemophilia clinical care who were not actively recruiting subjects.

**Assessments**

Part 1: Subjects were observed for AEs, abnormal laboratory values and development of inhibitors until 4 days after the dose of Afstyla

Part 2: Routine clinical evaluations and evaluations for FVIII inhibitors, anti-CHO proteins and anti-Afstyla antibodies, AEs (diary), and investigator assessment of efficacy were made weekly through month 6 and every 3 months for months 9 to 24.

Part 3 (on-demand and prophylaxis): Routine evaluations and evaluations for serum chemistries, FVIII inhibitors, anti-CHO proteins and anti-Afstyla antibodies, AEs (diary), and investigator evaluation of efficacy were made weekly through month 6 and every 3 months for months 9 to 24.

**6.1.8 Endpoints and Criteria for Study Success**

As established in CRMTS #9559, trial success was defined *a priori* as exceeding a lower limit of the 95% confidence limit of 70% for treatment success. Individual subject

treatment success was defined as an assessment of excellent or good in hemostatic effect.

**Routine prophylaxis:**

Primary endpoint:

- Annualized spontaneous bleeding rate (ASBR)

Secondary endpoints:

- Annualized bleeding rate (ABR)
- Number of injections of Afstyla to achieve hemostasis
- Consumption of Afstyla
- Number of BEs over time

Others:

- ABR and ASBR between subjects on prophylaxis treatment and on-demand treatment within Trial CSL627\_1001
- Comparison of ABR/ASBR between subjects on prophylaxis and those subjects' historical experience of ABR/ASBR
- Comparisons of ABR and ASBR between the different prophylaxis regimens

**On-demand:**

Efficacy was evaluated by the investigator on an ordinal scale using the following criteria (Table 8).

**Table 8**  
**Efficacy Rating Scale**

Excellent	Definite pain relief and/or improvement in signs of bleeding (ie, swelling, tenderness, and/or increased range of motion in the case of musculoskeletal hemorrhage) within approximately 8 h after the first rVIII-SingleChain injection.
Good	Definite pain relief and/or improvement in signs of bleeding at approximately 8 h after the first rVIII-SingleChain injection, but requires 2 injections for complete resolution.
Moderate	Probable or slight beneficial effect within approximately 8 h after the first rVIII-SingleChain injection; requires more than 2 injections for complete resolution.
Poor/No response	No improvement at all or condition worsens (ie, signs of bleeding) after the first rVIII-SingleChain injection and additional hemostatic intervention is required with another FVIII product, cryoprecipitate, or plasma for complete resolution.

Source: BLA Clinical Study Report Trial CSL627\_1001, 9.5.1.3, page 42 of 196  
rVIII-SingleChain = Afstyla

Efficacy for major trauma or life-threatening BE was evaluated by the investigator using the scale in Table 9.

**Table 9**  
**Rating Scale for Major Trauma or Life-threatening bleeding**

Excellent	Hemostasis clinically not significantly different from (eg, achieved hemostasis comparable to that expected for a similar bleed in a non-factor deficient patient) and estimated blood loss is not more than 20% higher than the estimated predicted blood loss for the type of injury or problem
Good	Normal or mildly abnormal hemostasis in terms of quantity and/or quality (eg, Slight oozing, prolonged time to hemostasis with somewhat increased bleeding compared to a non-factor deficient patient ) or estimated blood loss is greater than 20% but less than or equal to 30% higher than the estimated predicted blood loss for this type of injury or problem
Moderate	Moderately abnormal hemostasis in terms of quantity and/or quality (eg, 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 (eg, severe hemorrhage that is difficult to control) and/or additional hemostatic intervention required with other FVIII product, cryoprecipitate, or plasma more than expected for the type of injury or problem

Source: BLA Clinical Study Report Trial CSL\_627\_1001 9.5.1.3, page 43 of 196

**Reviewer Comment: The ability to clinically differentiate 20% versus 30% of estimated projected blood loss is questionable, however the criterion for successful treatment includes both excellent and good ratings, so this would not affect the outcome.**

#### **Surgical prophylaxis**

Efficacy was evaluated by the anesthesiologist and/or surgeon on an ordinal scale using the following criteria (Table 10).

**Table 10**  
**Efficacy Measures, Surgical Prophylaxis**

Excellent	Hemostasis clinically not significantly different from normal (eg, 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 (eg, 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 greater than 20% but less than or equal to 30% higher than the predicted

blood loss for intended surgery.

Moderate	Moderately abnormal hemostasis in terms of quantity and/or quality (eg, 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 (eg, severe hemorrhage that is difficult to control) and/or additional hemostatic intervention required with another FVIII product, cryoprecipitate, or plasma for complete resolution.

Source: BLA Clinical Study Report Trial CSL627\_1001, 9.5.1.3, page 44 of 196

#### 6.1.9 Statistical Considerations & Statistical Analysis Plan

Subjects who discontinued participation and did not have an inhibitor were replaced to ensure eventually at least 104 subjects would be evaluated for development of inhibitors. Subjects who discontinued but who had developed inhibitors were not replaced.

#### 6.1.10 Study Population and Disposition

##### 6.1.10.1 Populations Enrolled/Analyzed

The following populations were defined:

- Screened population
  - All subjects who provided written consent
- Enrolled population
  - All subjects who were not screen failures and were enrolled
- Safety population
  - All subjects who received at least one dose (or partial dose) of Afstyla
- Efficacy population
  - All subjects who received at least one dose of Afstyla as part of either routine prophylaxis or on-demand treatment
- PK population
  - Subjects who received one dose of 50 IU/kg Afstyla and for whom a sufficient number of analyzable PK samples were obtained to permit evaluation of the PK profile. Subjects with a major protocol violation were excluded.
- Per-protocol Population
  - All subjects in the Efficacy population who completed the trial without any major protocol violations that would have impacted the assessment of the primary efficacy endpoint. Compliance with 80 to 120% of prescribed doses (prophylaxis regimen) and  $\geq 80\%$  of actual dose within  $\pm 10\%$  of the prescribed dose (prophylaxis and on-demand regimens)
- Surgical population
  - All subjects enrolled in the surgical sub-study who received at least one dose of Afstyla during the surgical sub-study

6.1.10.1.1 Demographics  
(Refers to percentage of treated subjects)

**Table 11**  
**Demographics**

Parameter	Number of subjects* (%)
<b>Age:</b>	
12 to <18 years	14 (8%)
18-65 years	160 (92%)
<b>Race:</b>	
Caucasian	126 (72%)
Asian	31 (17%)
Black or African American	14 (8%)
Other	3 (2%)
<b>Ethnicity:</b>	
Hispanic/Latino	12 (7%)
Japanese	10 (6%)
Not reported	1 (0.6%)

\*All subjects were male

6.1.10.1.2 Medical/Behavioral Characterization of the Enrolled Population

71% of subjects had a notable prior medical history and 91% of subjects had a current medical problem. These were all related to the effects of chronic hemophilia. Sixty-eight percent currently had a musculoskeletal problem (50% hemophiliac arthropathy). Thirty-one percent had hepatitis, most commonly hepatitis C (31%).

6.1.10.1.3 Subject Disposition

93% of subjects completed the study. No subjects withdrew due to a treatment emergent adverse event (TEAE). Thirteen subjects withdrew from the trial. Discontinued subjects are described in more detail in section [6.1.12.6](#).

A flow chart is shown in Table 12.

**Table 12**  
**Subject Disposition**

	Number (%) of subjects
Screened	204
Enrolled	175
Treated (Safety population)	174 (100)
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: BLA Clinical Study Report Trial CSL627\_1001, 9.5.1.3, page 63 of 196.

### Safety Population

161 of the 174 treated subjects (92.5%) completed the trial. Reasons for withdrawal were:

- 8 (4.6%) withdrew consent
- 1 (0.6%) withdrew based on physician's decision
- 4 (2.3%) other
  - Surgery of the right knee (Subject 040000-1001)
  - Completed study but did not reach 6 months (Subject 2760030-1002)
  - 50 ED not met (Subjects 8400184-1001 and 8400184-1002))

### Efficacy Population

An overview of the Efficacy Population is shown in Table 13. One subject in the safety population was excluded from the Efficacy population. Subject 2760030-1005 completed the PK assessment of Part 1 but withdrew consent prior to beginning Part 2.

**Table 13**  
**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 (93.1)
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 (4.0)
Other	4 (14.8)	0	4 (2.3)
Physician decision	1 (3.7)	0	1 (0.6)

Source: BLA Clinical Study Report Trial CSL627\_1001, table 14.1.2.2, page 215

## 6.1.11 Efficacy Analyses

### 6.1.11.1 Analyses of Primary Endpoint(s)

#### **PK**

PK was assessed in 27 subjects (with comparator) in Part 1 (to 72 hours) and in 64 subjects in Part 2 (to 96 hours). Compared to the comparator, a licensed rFVIII, AUC was higher, clearance (CL) lower and half-life ( $t_{1/2}$ ) longer for Afstyla (see Table 17, below)..

The PK parameters in Part 2 were similar after initial and repeat injections (at 3 to 6 months) (Table 14).

**TABLE 14**  
**CHS assay. Subjects dosed at 50 IU/kg**  
**Initial and Repeat PK Parameters**

Parameter, unit	Initial PK (n = 64) <sup>a</sup>	Repeat PK (n = 30) <sup>a</sup>
IR <sup>b</sup> , (IU/dL)/(IU/kg)	1.85 (21.8)	1.99 (17.7)
C <sub>max</sub> <sup>b</sup> , IU/dL	99.9 (19.9)	108 (17.2)
AUC <sub>t</sub> , IU*h/dL	1780 (34.5)	1830 (33.7)
AUC <sub>inf</sub> , IU*h/dL	1830 (34.9)	1880 (34.5)
CL, mL/h/kg	3.15 (38.2)	3.05 (36.0)
V <sub>ss</sub> , mL/kg	59.5 (23.9)	53.1 (16.4)
t <sub>1/2</sub> , h	14.1 (27.1)	12.9 (29.4)
MRT, h	20.3 (26.4)	18.9 (28.5)

IR, incremental recovery; C<sub>max</sub>, maximum concentration; AUC, area under the curve; CL, clearance; V<sub>ss</sub>, volume of distribution at steady state, t<sub>1/2</sub>, half-life; MRT, mean residence time

<sup>a</sup> Repeat PK not available for all subjects

<sup>b</sup> IR and C<sub>max</sub> corrected for FVIII activity before dosing. All others uncorrected

Source: BLA Module 2.7.2, Table 2-5, page 28 of 52.

### Control of BEs

There were 616 spontaneous BEs requiring treatment. Of these 92% were joint, 11% were muscle and 11% were other. Overall there were 872 BEs, of which 848 required treatment. Treatment success (investigator rating of “excellent” or “good”) was 92.3% (783 of 848 BE). By report this is at the upper range of success rates reported for other rFVIII products. 81% of BEs were controlled with 1 injection, 12.6% required two and 3.4% required three. A summary table from the efficacy population is presented in Table 15.

**Table 15**  
**Investigator's Assessment of Hemostatic Efficacy**

Bleeding type assessment	On-demand (N=27)	Prophylaxis (N=146)	Overall (N=173)
<b>Total</b>			
Number of bleeding episodes	594	278	872
Number of treated bleeding episodes	590	258	848
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	0	0	0
Missing	13 (2.2)	0	13 (1.5)
Treatment success (a)	545 (92.4)	238 (92.2)	783 (92.3)
Rate of treatment success	92.4	92.2	92.3
95% CI for rate	(87.8, 95.3)	(86.3, 95.8)	(88.9, 94.8)
Treatment success (b)	545 (94.5)	238 (92.2)	783 (93.8)
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)
Treatment success (c)	558 (94.6)	238 (92.2)	796 (93.9)
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)

Success = rating of excellent or good (see Section 6.1.8 for rating scale definition). Treatment success (a) = missing data counted as treatment failure, (b) all missing data excluded, (c) missing data counted as treatment success.

Source: BLA Clinical Study Report Trial CSL627\_1001, Table 11-25, Section 14.2.1.1, 9.5.1.3, page 122 of 196

The success rate was similar for BEs occurring during on-demand and prophylactic treatments. Both exclusion of missing data and counting missing data as treatment success demonstrated similar results as the primary analysis, and results from the Per-Protocol Population were similar to the Efficacy Population. When data were analyzed by age, the hemostatic efficacy was consistent with that reported for the overall population. When assessed by geographical region (United States n=84 [82 treated], Japan n=35 [29 treated], Europe n= 566 [563 treated], Rest of World n=187 [174 treated]) the investigators' assessments of hemostatic efficacy were similar (Range 81 to 100%; the region reporting 81% had 18% missing data).

**Reviewer Comment: With a lower limit of the 95% CI of 89%, the a priori success rate (lower limit of 95% CI ≥70%) was met. This success rate is similar to that reported for B-domain deleted rFVIII<sup>10,11</sup>**

10 Recht M, Nemes L, Matysiak M, *et al*: Clinical evaluation of moroctocog alfa (AF-CC), a new generation of B-domain deleted recombinant factor VIII (BDDrFVIII) for treatment of haemophilia A: demonstration of safety, efficacy, and pharmacokinetic equivalence to full length recombinant factor VIII. *Haemophilia* 2009;15:869-80.

11 Mahlangu J, Powell JS, Ragni, *et al*. Phase 3 study of recombinant factor VIII Fc fusion protein in severe hemophilia A. *Blood* 2014;123:317-25.

### **Routine prophylaxis**

Fifty-four percent of subjects received Afstyla 3 times per week and 32% received it 2 times per week.

Observed median total ABR: median 1.14, mean 3.11 BEs per year (95% CI 2.3 to 2.9)

Observed median ASBR: median 0, mean 2.1 BEs per year (95% CI 1.3 to 1.8)

Forty-three percent of subjects receiving routine prophylaxis had no BE. Results were independent of treatment frequency.

Based on a Poisson model, routine prophylaxis decreased the ASBR by 92% ( $P < 0.0001$ ) and 90% for ABR, compared to historical on-demand treatment (historical control: median 11.7, 95% CI 14.9 to 17.8 for ASBR; and 14.49 and 17.0 to 20.1 for all ABR).

Data for the Per-protocol Population were similar to the Efficacy Population.

**Reviewer Comment: These ABRs are lower than that reported for other FVIII products.**<sup>6,12,13,14</sup>

### **Surgical Prophylaxis**

Of 16 total surgical procedures, surgical hemostasis was rated as “excellent” in 94% (15 of 16) procedures and “good” in 1.

**Reviewer Comment: The treatment success rate was therefore 100%, meeting the a priori success criterion for this endpoint of >70%.**

The median use of Afstyla was 56.1 IU/kg (range 40 to 106) preoperatively, 41.3 IU/kg (range 22 to 50) intraoperatively and 255 IU/kg (range 89 to 436) during postoperative hours 0 to 72. The types of surgery, and the expected factor requirements, differed significantly, from circumcision to total joint replacement.

### **Primary Safety Endpoint**

The primary safety endpoint was the rate of inhibitor formation (defined as  $\geq 0.6$  BU/mL) measured at screening, every month for 6 months and then every 3 months to end of study.

- Inhibitors were not detected in any subjects, including the 120 subjects with  $\geq 50$  ED

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12 Kessler C, Oldenburg J, Ettingshausen CE, *et al*: Spotlight on the human factor: building a foundation for the future of haemophilia A management: report from a symposium on human recombinant FVIII at the World Federation of Hemophilia World Congress, Melbourne, Australia on 12 May 2014. *Haemophilia* 2015;21 Suppl 1:1-12.

13 Kavakli K, Yang R, Rusen L, *et al*: Prophylaxis vs. on-demand treatment with BAY 81-8973, a full-length plasma protein-free recombinant factor VIII product: results from a randomized trial (LEOPOLD II). *J Thromb Haemost* 2015;13:360-9.

14 Lentz SR, Misgav M, Ozelo M, *et al*: Results from a large multinational clinical trial (guardianTM1) using prophylactic treatment with turoctocog alfa in adolescent and adult patients with severe haemophilia A: safety and efficacy. *Haemophilia* 2013;19:691-7.

- Eight subjects had non-inhibitory anti-drug antibodies at study entry; six of these were negative at end of study
- Four subjects developed non-inhibitory anti-drug antibodies during the study; two of these remained positive at end of study
- No subjects had anti-CHO antibodies at any time point

**Reviewer Comment: The a priori success criterion for inhibitor formation was upper bound for the 95% confidence limit of <6.8%. Since no inhibitors were detected in any subjects the criterion for success was met. The reported incidence of non-inhibitor antibodies does not exceed that reported in the literature for similar products.**

#### 6.1.11.2 Analyses of Secondary Endpoints

##### **Number of Afstyla injections required to achieve hemostasis**

The number of Afstyla injections required to achieve hemostasis is shown in Table 16. One or two injections were adequate to achieve hemostasis in 93.5% of the 848 treated BEs. Results were similar for the on-demand and prophylaxis groups.

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

	On-demand (N=27)	Prophylaxis (N=146)	Overall (N=173)
Number of bleeding episodes	594	278	872
Number of bleeding treated episodes	590	258	848
Number of subjects with $\geq 1$ bleeding episode	26	85	111
Number of subjects with $\geq 1$ 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 BLA Clinical Study Report Trial CSL627\_1001, Table 11-28, Section 9.5.1.3, page 126 of 196

##### **Routine prophylaxis to prevent or reduce ABRs**

Routine prophylaxis decreased the ABR by 90% compared to on-demand treatment. Data for the Per-protocol Population were similar to the Efficacy Population. In each geographic region, ABR was lower in subjects receiving prophylactic treatments as compared to those receiving on-demand treatments.

See Table 16 for comparison data of prophylaxis versus on-demand treatment.

##### **PK of Afstyla versus comparator rFVIII**

The comparison of Afstyla with a comparator rFVIII is shown in Table 17. Subjects received 50 IU per kg of either product.

**Table 17**  
**PK Comparison of Afstyla and Comparator rFVIII**

	<b>Comparator</b>	<b>Afstyla</b>
<b>C<sub>max</sub> (IU/dL)</b>	118 (14.8)	114 (14.7)
<b>IR (IU/dL)/(IU/kg)</b>	2.35 (15.0)	2.27 (14.7)
<b>AUC<sub>(0-last)</sub> (IU*<b>h</b>/dL)</b>	1510 (32.9)	2030 (27.8)
<b>AUC<sub>(0-INF)</sub> (IU*<b>h</b>/dL)</b>	1580 (34.6)	2130 (29.8)
<b>T<sub>1/2</sub> (h)</b>	13.4 (33.0)	14.7 (25.4)
<b>CL (mL/h/kg)</b>	3.58 (37.1)	2.55 (28.9)
<b>V<sub>ss</sub> (mL/kg)</b>	56.2 (18.8)	51.0 (15.9)

Data are expressed as Mean (Coefficient of variation).

Source: BLA Clinical Study Report Trial CSL627\_1001, Table 11-15, Section 9.5.1.3, page 110 of 196

C<sub>max</sub> and IR were similar. AUC was higher for Afstyla than for the comparator. Clearance was lower for Afstyla and the t<sub>1/2</sub> somewhat longer.

There were no PK differences in subjects receiving Afstyla in strengths of 250 versus 3000 IU/mL.

#### 6.1.11.3 Subpopulation Analyses

Investigator's assessments of hemostatic efficacy were similar independent of geographic location. Initial and PK differences were comparable between subjects 12 to <18 years and 18 to ≤65 years.

#### 6.1.11.4 Dropouts and/or Discontinuations

No major protocol violations led to the exclusion of any subject from the per-protocol analysis.

Four subjects (15%) were excluded from the on-demand group and 13 (9%) from the prophylaxis group (see [section 6.1.10.1.3](#)). Analysis imputing all missing or excluded data as either all success or all failure produced similar results to those of the primary analysis (see [Table 15](#) above).

### 6.1.11.5 Exploratory and Post Hoc Analyses

### 6.1.12 Safety Analyses

Of the 174 subjects in the safety population, 121(69.5%) experienced a total of 325 AEs, and 113 (64.9%) experienced a total of 292 TEAEs, in 14,592 injections and 14,306 ED. No subject withdrew due to an AE.

#### 6.1.12.1 Methods

The incidence of FVIII inhibitor development was the primary safety objective in the clinical studies. In addition, Afstyla was tested for altered immunogenic potential by testing for the presence of non-inhibitory anti-drug antibodies, and antibodies against CHO host cell proteins. Further safety assessments were based on AE reporting, with a focus on hypersensitivity and thromboembolic events (i.e., AEs of special interest [AESI]), and the assessment of local tolerability, laboratory safety (biochemistry and hematology), vital signs, and physical examinations.

#### 6.1.12.2 Overview of Adverse Events

One hundred thirteen subjects experienced a total of 292 TEAEs in 14,592 injections and 14,306 ED. Thirteen subjects (7.5%) developed 19 TEAEs considered related to study drug. These are summarized in Table 18.

**Table 18**  
**TEAEs Assessed by the Investigator as Related by System Organ Class and Preferred Term**

System organ class Preferred term	No. (%) of subjects (N = 174)	No. of events
<b>Related TEAEs</b>	13 (7.5)	19
<b>General disorders and administration site conditions</b>	4 (2.3)	5
Chills	1 (0.6)	2
Feeling hot	1 (0.6)	1
Injection site pain	1 (0.6)	1
Pyrexia	1 (0.6)	1
<b>Nervous system disorders</b>	3 (1.7)	3
Dizziness	2 (1.1)	2
Paraesthesia	1 (0.6)	1
<b>Skin and subcutaneous tissue disorders</b>	3 (1.7)	3
Erythema	1 (0.6)	1
Pruritus	1 (0.6)	1
Rash	1 (0.6)	1
<b>Immune system disorders</b>	2 (1.1)	3
Hypersensitivity	2 (1.1)	3
<b>Musculoskeletal and connective tissue disorders</b>	1 (0.6)	4
Arthralgia	1 (0.6)	3
Joint range of motion decreased	1 (0.6)	1
<b>Investigations</b>	1 (0.6)	1
Drug specific antibody present <sup>a</sup>	1 (0.6)	1

<sup>a</sup> Presence of an anti-drug antibody reported in error by investigator as TEAE. Events during surgical period excluded.

Source: Summary of Clinical Safety Table 2-4, page 33 of 54. Data from Study 1001 CSR, Table 14.3.2.5

No TEAEs led to the subject's withdrawal from the trial. Seven subjects (4.0%) reported nine treatment emergent serious AEs (TESAEs), one of which was considered related to the study drug (see [6.1.12.4](#)). No subject withdrew due to an AE.

The most commonly reported AEs were nasopharyngitis, arthralgia and headache. TEAEs occurring in  $\geq 2\%$  of subjects are shown in Table 19.

**Table 19**  
**TEAEs occurring in  $\geq 2\%$  of Subjects, by Decreasing Frequency of Preferred Term**

Preferred term	No. (%) of subjects (N = 174)	No. of events
<b>Number of subjects with TEAEs</b>	113 (64.9)	292
Nasopharyngitis	18 (10.3)	22
Arthralgia	17 (9.8)	19
Headache	12 (6.9)	13
Rash	7 (4.0)	8
Toothache	6 (3.4)	8
Upper respiratory tract infection	6 (3.4)	6
Back pain	5 (2.9)	6
Cough	5 (2.9)	6
Hypertension	5 (2.9)	5
Dizziness	4 (2.3)	5
Pyrexia	4 (2.3)	5
Influenza	4 (2.3)	4

Source: BLA Summary of Clinical Safety, Table 2-2, page 31 of 54. Data from Trial 1001 CSR, Table 14.3.2.10

Most injections (99.3%) were locally well tolerated. Slight to moderate reactions were reported in 0.7% of subjects and none had severe reactions.

AEs in surgical procedures: 15 AEs were reported in 13 subjects. AEs reported during the perioperative period were typical of events associated with surgery, with or without hemophilia, and none were considered related to Afstyla. Procedural pain was the most common (5) followed by nausea (2). Only one AE was considered serious (wound infection).

### 6.1.12.3 Deaths

There were no deaths reported.

#### 6.1.12.4 Nonfatal Serious Adverse Events

Seven subjects experienced a total of nine TESAEs. A single TESAE was considered related to the drug. A male subject (6080002-1001) in the 12 to ≤18 year group receiving prophylactic treatment developed evidence of hypersensitivity reaction that was assessed as being related to Afstyla.

**Subject 6080002-1001** was a 17 year old Asian male who developed pruritis, fever, erythema, headache, dyspnea, chest discomfort and rash. He had a history including hypersensitivity to cryoprecipitate, local hypersensitivity to a brand of adhesive dressing, and extrinsic asthma. This subject received 43 IU/kg of Afstyla as part of the prophylaxis treatment group. Approximately 2.5 hours after his last injection of Afstyla he developed severe pruritis, erythema of the hands and feet, chest pressure with dyspnea and severe headache. Upon admission to the emergency room there was no wheezing or stridor and he had good air entry. He was treated in the emergency room with steroids and antihistamines, and the episode resolved within approximately 17.5 hours after onset. He was discharged on the day of the event with a 5-day tapering course of steroids. He remained on Afstyla and tolerated it well thereafter without sequelae, and with no change in dose or treatment schedule. However, he did receive premedication prior to subsequent dosing.

Additional SAEs were (N=1 for all) assessed as not related to rFVIII-SC. All were Caucasian, non-Hispanic/Latino males:

<b><u>Subject# (age years)</u></b>	<b><u>SAE</u></b>	<b><u>Intensity</u></b>
2760066-1003 (36)	Tonsillar hemorrhage	Moderate
3800022-1002 (32)	Anemia	Severe
3800022-1002 (32)	Thrombocytopenia	Severe
6160014-1009 (53)	Elevated uric acid	Mild
6160014-1009 (53)	Esophageal varices	Mild
6420030-1002 (50)	Viral infection	Moderate
8400184-1006 (17)	Suicidal ideation	Severe
8400204-1001 (23)	Ankle fracture	Severe

**Reviewer Comment: This reviewer agrees with the assessment of these AEs as not related and the AE of Subject 6080002-1001 as related to Afstyla.**

#### 6.1.12.5 Adverse Events of Special Interest (AESI)

Predefined Treatment Emergent AESIs were thromboembolic events and hypersensitivity reactions.

There were no thromboembolic events were reported. One subject developed a hypersensitivity reaction and is described above.

There were 14 reports of possible hypersensitivity reactions (1.1%). Upon review, 11 were excluded for mild and nonspecific signs (e.g. cough and sneezing), leaving four:

- **Subject 6080001-1002**, a 32 year old Asian male with 2 related non-serious TEAEs of hypersensitivity. The dose of study drug was unchanged for both events. The subject was advised to take one tablet of cetirizine at night prior to the treatment with Afstyla, and after the second event, he was advised to remain in the clinic for observation for 1 hour after Afstyla injection. The subject recovered from both events.
- **Subject 6080001-1003**, a 23 year old Asian male with one related non-serious TEAE of erythema. The dose of Afstyla was unchanged, no other treatment was given. The subject recovered.
- **Subject 8400154-1004**, a 21 year old Caucasian male with one related non-serious TEAE of bilateral hand rash. Afstyla infusion was interrupted due to this event, but no other action was taken, and the subject was recovering at the time of reporting. It was reported that this bilateral hand rash was possibly related to a new job that required the use of latex gloves.

These three TEAEs could not be ruled out as hypersensitivity reactions, but none were deemed anaphylaxis. The symptoms were mild pruritis or rash.

**Reviewer Comment: Symptoms of mild allergic reactions are nonspecific. This reviewer agrees with the assessment that the 11 excluded subjects did not have allergic reactions. I also agree that these three reactions do not represent anaphylaxis.**

#### 6.1.12.6 Clinical Test Results

No patterns of clinically significant laboratory abnormalities (i.e., value outside the range of normal with a normal value at baseline) were reported.

#### 6.1.12.7 Dropouts and/or Discontinuations

Thirteen subjects prematurely discontinued participation in the trial. Eight (4.6%) withdrew consent, 1 (0.6%) was withdrawn by their physician and 4 (2.3%) for other reasons (knee surgery, completed >50 ED but not 6 months, did not reach 50 ED [2 subjects]). No subjects discontinued due to AEs, lack of efficacy, loss to follow up or protocol violations.

In response to an information request (December 4, 2015), CSL responded that subjects could withdraw consent at any time without providing a reason, as indicated on the Informed Consent form. CSL reviewed data on subjects for whom the reason for discontinuation was "withdrawal by subject". In the case report form (CRF) options for subjects who did not complete the trial included AE, death, lack of efficacy, loss to follow up, physician decision, protocol violation, study termination by sponsor, withdrawal by subject or other.

Specific information about the reason for withdrawal for the eight subjects who withdrew consent was requested. None of the above reasons for discontinuing were selected by

the investigator. However a review by CSL showed that two of the eight subjects developed an AE during the trial:

- **Subject 2760030-1001**, a 54 year old Caucasian, non-Hispanic/Latino male-developed pain at the injection site that occurred approximately 2.5 months prior to discontinuation. The AE was assessed as related, resolved the same day, and the subject continued participation.
- **Subject 8400154-1004**, a 21 year old Caucasian, non-Hispanic/Latino male – a bilateral hand rash occurred approximately 2 months prior to discontinuation. This may have been related to a new job that required the use of latex gloves. The rash cleared with topical steroid use. Shortly after use of Afstyla was temporarily paused the subject withdrew consent due to personal reasons prior to a planned re-challenge.
- **Subject 8400184-1003**, a 25 year old Caucasian non-Hispanic/Latino male was discontinued by physician decision. The investigator determined that the subject was non-compliant with study procedures (completing the e-diary).

#### 6.1.13 Study Summary and Conclusions

PK:

With a dose of 50 IU/kg the  $t_{1/2}$  of Afstyla was longer than a comparator rFVIII and the  $AUC_{inf}$  greater with a similar peak FVIII activity (Table 17). The estimated time to 1% FVIII activity of Afstyla was approximately 5.5 days. The PK profile in adolescents ( $\geq 12$  to  $< 18$  years) was similar to that in adults. PK parameters were stable with time and repeat measures.

**Reviewer Comment: Although the PK parameters indicate a somewhat longer half-life than some other products, this difference does not appear substantial enough to alter the treatment interval in a meaningful way.**

Efficacy:

- On-demand treatment and control: Treatment success was rated as excellent or good in 92.3% of BE, exceeding the a priori success rate.
- Routine Prophylaxis: Routine prophylaxis decreased the ASBR by 92% and the ABR by 90%, exceeding the a priori success criterion.
- Perioperative management: Surgical hemostasis rates were rated excellent in 94% and good in a single case, exceeding the a priori success criterion.

Safety:

No inhibitors were detected in any subjects, exceeding the a priori bound for inhibitor development. There were no deaths. Seven subjects experienced a total of nine SAEs. A single SAE (hypersensitivity) was assessed as related to the product.

**Reviewer Comment: In this trial Afstyla appeared to be safe and effective for the proposed indications.**

## 6.2 Trial #2

“A Phase III Open-label Pharmacokinetic, Efficacy and Safety Study of rVIII-SingleChain in a Pediatric Population with Severe Hemophilia A”

### 6.2.1 Objectives (Primary, Secondary, etc)

#### Primary

Evaluate the efficacy of Afstyla in treatment of major and minor bleeding episodes based on the investigator’s 4-point assessment scale

#### Secondary

To evaluate the ABR during prophylaxis treatment

To evaluate the ABR during on-demand treatment

To evaluate the proportion of BEs requiring 1,2,3, or >3 injections of Afstyla to achieve hemostasis

To evaluate the consumption of Afstyla

To evaluate the PK profile of Afstyla

To assess the rate of inhibitor formation to Afstyla

To assess the safety of Afstyla with regard to AEs, laboratory parameters, physical assessment and vital signs (blood pressure, heart rate, temperature and respiratory rate)

**Reviewer Comment: Interim PK and safety data were submitted in the 4-month safety update, September 24, 2015. This fulfilled the applicant’s agreement with FDA (CRMTS # 9559, Pre-BLA meeting, November 20, 2014) to submit an interim PK and safety report for 10 previously treated pediatric subjects <12 years of age in the BLA (to be followed by an updated interim PK and safety report in the 4-month safety update containing PK data on an additional 10 subjects < 12 years of age). The data on these 20 subjects was preferably to be equally distributed between ages 0 to <6 years and ≥6 to 12 years in addition to the adolescent data. The final clinical study report for CSL627\_3002 was submitted as IND 14791/93, received on February 4, 2016, and those data are included in this review.**

### 6.2.2 Design Overview

This trial was initiated after the Independent Data Monitoring Committee reviewed PK data from 20 subjects with 50 ED in Trial CSL627\_1001 (Trial #1, above).

This trial was an open-label, international, phase 3 study to investigate the PK, efficacy and safety of Afstyla for prophylaxis, prevention and treatment of BEs in pediatric subjects <12 years old who have had >50 ED with a FVIII product before enrollment.

### 6.2.3 Population

Planned enrollment was for 75 subjects, to provide 50 evaluable subjects: 25 subjects 6 to < 12 years and 25 subjects < 6 years old. At least 24 subjects (12 subjects < 6 years and 12 subjects 6 to <12 years) would participate in the PK part of the trial.

Eighty-four subjects were enrolled; 35 subjects 0 to < 6 years of age and 49 subjects 6 to < 12 years of age. Thirty-nine subjects were enrolled in the PK arm (20 subjects 0 to < 6 years of age and 19 subjects 6 to < 12 years of age). Subjects were equivalently distributed by race and ethnicity between the two age groups. Only three subjects were in the on-demand treatment group; the remainder were treated prophylactically.

#### Major Inclusion Criteria

- Severe hemophilia (FVIII:C<1%)
- Males < 12 years old
- Prior history of >50 ED with a FVIII product

#### Major Exclusion Criteria

- FVIII inhibitors (in subject or first order family member)
- Unable to receive treatment at home
- Known hypersensitivity to FVIII or hamster protein
- Coagulation disorder other than congenital FVIII deficiency
- Human immunodeficiency virus (HIV) with CD4 count <200 per mm<sup>3</sup>
- Currently receiving intravenous immunomodulatory agents
- Elevated liver enzymes > 5 times upper limit of normal
- Serum creatinine > 2 times upper limits of normal
- Evidence of thromboembolic disease within 3 months
- Life threatening BE or major surgery within 3 months

### 6.2.4 Study Treatments or Agents Mandated by the Protocol

#### **PK**

The PK data were derived using a dose of 50 IU/kg Afstyla ( $\pm$  10%) with samples taken at baseline and at 1,5,10, 24 and 48 hours after dosing.

#### **Prophylaxis and on-demand treatment**

Subjects could be assigned to either an on-demand or a prophylaxis regimen, based on investigator/family preference. Doses and dosing intervals, and changes in these, were made at the discretion of the local investigator.

### 6.2.4 Study Treatments or Agents Mandated by the Protocol

#### **PK**

The PK data were derived using a dose of 50 IU/kg Afstyla ( $\pm$  10%) with samples taken at baseline and at 1,5,10, 24 and 48 hours after dosing.

#### **Prophylaxis and on-demand treatment**

Subjects could be assigned to either an on-demand or a prophylaxis regimen, based on investigator/family preference. Doses and dosing intervals, and changes in these, were made at the discretion of the local investigator.

### 6.2.5 Directions for Use

PK: Single dose. All subjects received a single dose of 50 IU/kg Afstyla.

Prophylaxis and on-demand treatment: The doses selected for treatment of bleeding episodes and prophylaxis were based on the subject's weight at the most recent visit and at the discretion of the investigator. The investigator could review the subject's previous dose with FVIII products, available PK data with Afstyla, and the bleeding phenotype data. 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), 2012.

### 6.2.6 Sites and Centers

Australia (3), Austria (3), France (7), Georgia (5), Germany (5), Italy (1), Lebanon (6), Malaysia (4), Netherlands (6), Philippines (8), Poland (2), Portugal (2), Romania (1), Spain (2), Switzerland (1), Thailand (10), Turkey (8), Ukraine (6), United States (4)

### 6.2.7 Surveillance/Monitoring

Subjects were assessed in the clinic every 28 days until month 6, and then every 3 months until 50 ED is achieved. After 50 ED there was a final visit at end of study. These visits included history, clinical chemistry and hematology laboratory tests, and physical examination.

### 6.2.8 Endpoints and Criteria for Study Success

#### **Primary**

Evaluate the efficacy of Afstyla in the treatment of major and minor BEs based on the investigator's 4-point assessment scale ([Table 8](#)). Success based on a rating of excellent or good.

#### **Secondary**

Evaluate ABR during prophylaxis treatment  
Evaluate ABR during on-demand treatment  
Evaluate the proportion of BEs requiring 1,2,3, or >3 injections of Afstyla  
Evaluate the consumption of Afstyla  
Evaluate the PK profile  
Assess the rate of inhibitor formation (measured after 10 to 15 and 50-75 days)  
Assess the safety of Afstyla

### 6.2.9 Statistical Considerations & Statistical Analysis Plan

Continuous variables were summarized in terms of the mean, standard deviation, median, and minimum and maximum. Other descriptive statistics (e.g., quartiles, coefficient of variation) were reported when appropriate. Categorical variables were summarized using frequency counts and percentages. There were no *a priori* statistical hypotheses or predefined success criteria. There were no plans to produce p values. Two-sided 95% confidence intervals (CIs) were provided for select parameters.

## 6.2.10 Study Population and Disposition

### 6.2.10.1 Populations Enrolled/Analyzed

Safety Population: All 84 subjects who received at least one dose of Afstyla

**PK Population:** All subjects in the PK group who received Afstyla. It excluded subjects with a major protocol violation or who received FVIII for treatment of a BE during the PK period, unless there was a period for adequate washout (N=84); 39 subjects (20 subjects <6 years old, 19 subjects 6 to <12 years old). A single subject (4 years old) received 56.4 IU per kg, higher than the allowed deviance of 50 IU per kg  $\pm$  10%. PK parameters were presented for all PK subjects both including and excluding this subject.

**Efficacy Population:** All subjects who received at least 1 dose of Afstyla as part of either a routine prophylaxis or on-demand regimen during the trial (N=83). **Subject (b) (6)**, a 10 year old Asian male, was identified with a pre-existing inhibitor to FVIII, based on reexamination of the screening sample that had initially been reported as negative due to laboratory process error (true value 3.46 BU). The subject continued in the study, but was excluded from the efficacy population.

**Per-protocol Population:** All subjects in the efficacy population who completed the study without any major protocol deviations or protocol violations that would have impacted the assessment of the primary efficacy endpoint (N=75). Eight subjects, all in the efficacy group of the prophylaxis treatment arm, were excluded due to noncompliance with the prescribed dose or regimen.

In the safety population, by the end of the trial 65/84 subjects (77%) had reached  $\geq$ 50 ED (77.6% and 77.1% for each age group), eight of whom (9.5%) had reached  $\geq$ 100 ED (all in the 6 to <12 year age group).

#### 6.2.10.1.1 Demographics

The demographics of the safety population are shown in Table 20.

**Table 20**  
**Safety Population Demographics**

Parameter	# Subjects <6 years	# Subjects 6 to <12 years
<b>Age</b>		
	35	49
<b>Race</b>		
Asian	9 (25.7%)	13 (26.5%)
Caucasian	25 (71.4%)	15 (73.5%)
Other	1(2.9%)	0
<b>Ethnicity</b>		
Hispanic/Latino	1(2.9%)	1

		(2.0%)
Not Hispanic/Latino	33 (94.3%)	48 (98.0%)
Not reported	1 (2.9%)	0
<b>Geographical Region</b>		
Australia	1	2
Austria	1	2
Georgia	2	3
Germany	2	3
Italy	1	0
Lebanon	2	4
Malaysia	0	4
Netherlands	3	3
Poland	1	1
Portugal	0	2
Romania	1	0
Spain	0	2
Switzerland	0	1
Thailand	5	5
Turkey	3	5
Ukraine	2	4
United States	2	2

The demographic characteristics of the PK population were similar, except all PK subjects were Caucasian.

#### 6.2.10.1.2 Medical/Behavioral Characterization of the Enrolled Population

The active and past medical histories are as expected for a pediatric population with this condition. The most commonly reported conditions were surgical and medical procedures, and musculoskeletal and connective tissue disorders, such as hemophilia-related hemarthroses and its sequelae, upper respiratory infections, and orthopedic procedures secondary to hemarthroses.

#### 6.2.10.1.3 Subject Disposition

Overall there were 84 subjects. One subject discontinued for an AE.

#### 6.2.11 Efficacy Analyses

##### 6.2.11.1 Analyses of Primary Endpoint(s)

##### **Efficacy in treating BE**

Assessment of all BEs was based on the investigator's 4-point scale, Table 20.

**Table 21**  
**Efficacy Evaluation of BEs by Investigator**

Excellent	Definite pain relief and/or improvement in signs of bleeding (ie, swelling, tenderness, and/or increased range of motion in the case of musculoskeletal hemorrhage) within approximately 8 h after the first rVIII-SingleChain injection.
Good	Definite pain relief and/or improvement in signs of bleeding at approximately 8 h after the first rVIII-SingleChain injection, but requires 2 injections for complete resolution.
Moderate	Probable or slight beneficial effect within approximately 8 h after the first rVIII-SingleChain injection; requires more than 2 injections for complete resolution.
Poor / No response	No improvement at all or condition worsens (ie, signs of bleeding) after the first rVIII-SingleChain injection and additional hemostatic intervention is required with another FVIII product, cryoprecipitate, or plasma for complete resolution.

FVIII, factor VIII; rVIII Single Chain, Afstyla  
Source: Final Study Report, CSL627\_3002, Table 9-5, page 40 of 172.

In the event of major or life threatening BEs, investigator's used the following scale (Table 22).

**Table 22**  
**Efficacy Evaluation for Major Trauma or Life Threatening BEs**

Excellent	Hemostasis clinically not significantly different from (eg, achieved hemostasis comparable to that expected for a similar bleed in a non-factor deficient subject) and estimated blood loss is not more than 20% higher than the estimated predicted blood loss for the type of injury or problem
Good	Normal or mildly abnormal hemostasis in terms of quantity and / or quality (eg, slight oozing, prolonged time to hemostasis with somewhat increased bleeding compared to a non-factor deficient subject) or estimated blood loss is greater than 20% but less than or equal to 30% higher than the estimated predicted blood loss for this type of injury or problem
Moderate	Moderately abnormal hemostasis in terms of quantity and / or quality (eg, 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 (eg, severe hemorrhage that is difficult to control) and/or additional hemostatic intervention required with other FVIII product, cryoprecipitate, or plasma more than expected for the type of injury or problem

Abbreviations: FVIII, factor VIII.  
Source: Final Study Report, CSL627\_3002, Table 9-6, page 40 of 172.

There was a total of 389 BEs in 83 subjects in the Efficacy Population, of which 347 BEs in 62 subjects required treatment with Afstyla. The number of treated BEs was higher in the on-demand regimen than in the prophylaxis regimen (132 BEs in 3 subjects versus 215 BEs in 59 subjects). Of the 347 treated BEs, 346 were categorized as minor/moderate. The single major/life threatening BE was major, but not life threatening. This was a spontaneous hip joint BE that required treatment with two Afstyla injections and the hemostatic efficiency was rated as "good".

The investigator assessment of hemostatic efficacy was "excellent" for 296 treated BE, "good" for 38, "moderate" for 12 and "poor/no response" for a single BE. Thus the treatment success was 96.3% (334/347) with a 95% CI of 91.3% to 98.4%. These results, with several sensitivity analyses, are shown in Table 23. The rate of treatment success was similar in the two age groups (94% and 96.6%).

**Table 23**  
**Treatment Success**

<b>Bleeding type assessment</b>	<b>On-demand regimen (N = 3)</b>	<b>Prophylaxis regimen (N = 80)</b>	<b>Overall (N = 83)</b>
Number of bleeding episodes	133	256	389
Number of treated bleeding episodes	132	215	347
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	0	1 (0.5)	1 (0.3)
Treatment success (a)	132	202	334
Rate of treatment success	100.0	94.0	96.3
95% CI for rate	N/A	[87.8, 97.1]	[91.3, 98.4]
Treatment success (b)	132	202	334
Rate of treatment success	100.0	94.0	96.3
95% CI for rate	N/A	[87.8, 97.1]	[91.3, 98.4]
Treatment success (c)	132	202	334
Rate of treatment success	100.0	94.0	96.3
95% CI for rate	N/A	[87.8, 97.1]	[91.3, 98.4]

Abbreviations: CI, confidence interval; N, total number of subjects (overall or within a given regimen); n, number of subjects within a given criterion; N/A, not applicable

Notes:

[1] Treatment success is defined as a rating of excellent or good. (a) Primary analysis: missing counted as treatment failure; (b) Sensitivity analysis: all missing excluded. (c) Sensitivity analysis: missing counted as treatment success.

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

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

[4] Percentages are based on the number of treated bleeding episodes.

Source: Final Study Report, CSL627\_3002, Table 11-16, page 98 of 172.

**Efficacy Analysis by Subgroup**

**BMI**

No subjects had BMI > 30 kg/m<sup>2</sup> and no analysis was done for these subgroups.

**Race**

Analysis by race is shown in Table 24.

**Table 24**  
**Analysis by Race**

	<b>On-Demand (N=3)</b>	<b>Prophylaxis (N=58)</b>	<b>Total (N=61)</b>
Race			
Caucasian			
# Treated BEs	132	132	264
Excellent	132 (100%)	97 (73.5%)	229 (86.7%)

Good	0	24 (18.8%)	24 (9.1%)
Moderate	0	10 (7.6%)	10 (3.8%)
Poor/No Response	0	1 (0.8%)	1 (0.4%)
Success (a)	132	121	253
Success Rate	100	91.7	95.8
95% CI for Rate	N/A	(82.2, 96.3)	(88.7, 98.5)
Success (b)	132	121	253
Success Rate	100	91.7	95.8
95% CI for Rate	N/A	(82.2, 96.3)	(88.7, 98.5)
Success (c)	132	121	253
Success Rate	100	91.7	95.8
95% CI for Rate	N/A	(82.2, 96.3)	(88.7, 98.5)
Asian			
# Treated BEs	0	81	81
Excellent	0	66 (81.5%)	66 (81.5%)
Good	0	13 (16%)	13 (16%)
Moderate	0	2 (2.5%)	2 (2.5%)
Poor/No Response	0	0	0
Success (a)	0	79	79
Success Rate	N/A	97.5	97.5
95% CI for Rate	N/A	(92.4, 99.2)	(92.4, 99.2)
Success (b)	0	79	79
Success Rate	N/A	97.5	97.5
95% CI for Rate	N/A	(92.4, 99.2)	(92.4, 99.2)
Success (c)	0	79	79
Success Rate	N/A	97.5	97.5
95% CI for Rate	N/A	(92.4, 99.2)	(92.4, 99.2)
Other			
# Treated BEs	0	2	2
Excellent	0	1 (50%)	1 (50%)
Good	0	1 (50%)	1 (50%)
Moderate	0	0	0
Poor/No Response	0	0	0
Success (a)	0	2	2
Success Rate	N/A	100	100
95% CI for Rate	N/A	N/A	N/A
Success (b)	0	2	2
Success Rate	N/A	100	100
95% CI for Rate	N/A	N/A	N/A

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Success (c)	0	2	2
Success Rate	N/A	100	100
95% CI for Rate	N/A	N/A	N/A

[a] Primary analysis: missing counted as failure

[b] Sensitivity analysis: all missing excluded

[c] Sensitivity analysis: missing counted as success

Modified from Final Study Report, CSL627\_3002, Tables 14.2.1.7, 14.2.1.9 and 14.2.1.10.

### Geographic Distribution

There were no differences among the geographic areas with respect to hemostatic efficacy.

### 6.2.11.2 Analyses of Secondary Endpoints

#### **ABR during prophylaxis**

The median observed ABR was 3.7 BEs/year (total) and 0 BEs/year (spontaneous). Twenty-one of the 80 subjects (26.3%) had no BEs requiring treatment. Data from the Per-protocol Population were similar to those for the Efficacy Population.

The median observed ABR was 2.3 with three times/week dosing and 4.37 with twice weekly dosing, and the percentage of subjects with no BEs was higher in the three times/week group (37.5% versus 15%).

#### **ABR during on-demand treatment**

In the three subjects in the on-demand treatment group, the observed ABR was substantially higher (35.1, 78.6 and 86.6 for the three subjects).

**Reviewer Note: The very small numbers of subjects in the on-demand treatment group precludes meaningful statistical analysis, but the magnitude of differences is noteworthy.**

#### **Evaluate factor consumption**

Overall one or two injections of Afstyla was sufficient to obtain hemostasis in 332/347 treated BEs (95.7%). Seven BEs in four subjects required >3 injections. Data from the Per-protocol Population were similar to those from the Efficacy Population and the number of BEs requiring one or two injections was similar for both age groups (94% and 96%). The overall dosing per BE was 33.5 IU/kg/injection/BE in the 0 to <6 year old group and 26.8 IU/kg/injection/BE in the 6 to <12 year old group.

Despite the protocol allowance for higher doses in less frequent dosing regimens, doses per injection were not higher in the twice weekly than in the three times/week regimens. Annual doses were 4,117 versus 5,469 IU/kg/subject per year, respectively (resulting in a 25% lower overall consumption in the twice weekly regimen). Because subjects in the prophylaxis group had fewer treatments for BEs, the total consumption of Afstyla was not substantially higher in the prophylaxis group versus the on-demand group. There were no age-related differences in Afstyla consumption.

The three subjects on the on-demand regimen received 5.1, 7.58, and 7.7 Afstyla injections per month.

**PK**

PK data are shown in Table 25 below. These data exclude the single subject who received a dose in excess of the maximum.

**Table 25**  
**Descriptive PK Statistics for subjects Dosed at 50 IU/kg**  
Mean (CV%)

Parameter, unit	0 to < 6 years (N = 19)		> 6 to < 12 years (N = 19)	
	ChS	OS	ChS	OS
$C_{max}$ , IU/dL	80.2 (21.2)	45.0 (81.8)	83.5 (19.5)	42.3 (20.1)
IR, (IU/dL)/(IU/kg)	1.61 (21.4)	0.893 (82.8)	1.66 (19.7)	0.841 (20.3)
AUC <sub>t</sub> , IU*h/dL	1020 (28.4)	564 (44.7)	1090 (26.4)	635 (32.3)
AUC <sub>inf</sub> , IU*h/dL	1090 (31.4)	632 (59.3)	1170 (26.3)	683 (33.2)
t <sub>1/2</sub> , h	10.5 (28.6)	11.1 (48.8)	10.2 (19.4)	10.3 (26.6)
CL, mL/h/kg	5.01 (30.3)	9.73 (45.4)	4.63 (29.5)	8.44 (42.4)
V <sub>ss</sub> , mL/kg	70.8 (12.1)	134 (27.5)	67.1 (22.3)	121 (21.7)
MRT, h	12.6 (24.1)	12.5 (31.2)	12.3 (16.8)	12.8 (17.5)

Abbreviations: AUC<sub>t</sub>, area under the activity/concentration curve from time point zero to the last quantifiable time point; AUC<sub>inf</sub>, area under the activity / concentration curve from zero extrapolated to infinity; ChS, chromogenic substrate (assay); CL, total plasma clearance; CV, coefficient of variation; C<sub>max</sub>, maximum observed concentration/activity; IR, incremental recovery; IU, international units; MRT, mean residence time; N, total number of subjects; OS, one-stage clotting (assay); t<sub>1/2</sub>, half-life; V<sub>ss</sub>, volume of distribution at steady-state.

Source: Final Study Report, CSL627\_3002, Table 11-12, page 91 of 172.

Mean PK parameters were similar in both pediatric age group cohorts by both the OS and ChS assays. At the last sampling time (48 hr) 3/6 of the younger subjects and 7/7 of the older subjects had FVIII:C >1% (mean levels 2.59% and 2.69%). Because FVIII should peak at the end of administration and in this pediatric population with limited blood sampling the first PK measurement was taken at 1 hour, the observed C<sub>max</sub> and IR values would be underreported.

**Reviewer Comment: Consistent with the known differences in the two assay methodologies, FVIII activity levels determined by the OS assay were approximately 45% lower than those determined by the ChS assay. This is consistent with the results of the adult trial, CSL627\_1001. As is typical for this class of products, clearance (CL) was higher and half-life (t<sub>1/2</sub>) was shorter in the pediatric versus the adolescent and adult population (in trial CSL627\_1001), and clearance was slightly higher in the younger subjects, also as expected for FVIII products.**

**The ratio of adult: children <6 years old for clearance was 5.01:2.55, or 1.96:1. This is higher than is generally observed with FVIII products. The draft label includes the statement “More frequent or higher doses may be required in children <12 years of age to account for the higher clearance in this age group”. FDA has not previously required specific PK-based dosing recommendations for FVIII products, even for those with a ration of >1.5:1.**

## Safety

### 6.2.11.3 Subpopulation Analyses

There were no clinically relevant differences in the incidence of TEAEs, TESAEs, and AESIs by race or age. Because there were no subjects with BMI  $\geq 30\text{kg/m}^2$  no subgroup analysis could be made by BMI.

### 6.2.11.4 Dropouts and/or Discontinuations

A single subject withdrew for an AE in the preliminary submitted safety information. This was due to complex social issues, including Munchausen by proxy. However, there was no AE listed in the database or the clinical report form. This was updated in the 4-month Safety Update Report as “physician decision”.

In the updated pediatric PK and safety information there was a single subject with a TEAE that led to withdrawal from the trial. **Subject (b) (6)**, a 10 year old in the prophylaxis arm developed hip arthralgia of moderate intensity. A bleed was excluded by MRI. The subject was withdrawn from the trial 21 days later, and the event was assessed as non-serious and not related.

**Reviewer Comment: This reviewer agrees with these assessments.**

### 6.2.11.5 Exploratory and Post Hoc Analyses

None

### 6.2.12 Safety Analyses

#### 6.2.12.1 Methods

AEs were coded by MedDRA 16.1.

Safety was assessed based on the following:

- FVIII inhibitors<sup>15</sup>
- Non-inhibitory anti-drug antibodies (ADAs), and antibodies against CHO host cell proteins<sup>2</sup>
- AEs
- Laboratory safety parameters (serum chemistry and hematology) and treatment-emergent abnormal laboratory values
- Physical examination
- Vital signs (sitting or supine blood pressure, heart rate, temperature, respiratory rate), clinically significant vital signs
- Local tolerability at the injection site (subject/caregiver and investigator assessments)

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15 FVIII inhibitors were tested for at screening, after 10 to 15 EDs, after 50 to 75 EDs and at the end-of study visit. Any samples were tested locally with a duplicate tested at the central laboratory. A sample was considered positive for inhibitor if the central laboratory sample was  $\geq 0.6$  Bethesda units (BU)/mL. Low titer inhibitors had a titer of  $\leq 5$  BU/mL.

### 6.2.12.2 Overview of Adverse Events

#### Tolerability:

Assessments of tolerability were assessed as “none” (i.e. no reaction) in 99.3% (3,337 of 3,362) of the assessments. Subjects reported assessments as moderate or less in intensity in 25 (0.74%). Two subjects experienced a single severe local reaction. One reaction was in the skin above the infusion port and one on the [ears](#).

An overview of AEs is shown in Table 26.

**Table 26**  
**Summary of Adverse Events – Safety Population**

	Total (N = 84)	
	No. (%) of subjects	No. of events
<b>AEs</b>	55 (65.5)	124
<b>TEAEs</b>	50 (59.5)	113
<b>TEAEs leading to study withdrawal</b>	1 (1.2)	1
<b>TEAE severity</b>		
Mild	40 (47.6)	85
Moderate	18 (21.4)	26
Severe	2 (2.4)	2
<b>TEAE related to study drug</b>	1 (1.2)	2
<b>TEAE outcome</b>		
Death related to AE	0	0
Not recovered / not resolved	4 (4.8)	7
Recovered / Resolved	46 (54.8)	97
Recovered / Resolved with sequelae	0	0
Recovering / Resolving	9 (10.7)	9
<b>SAEs</b>	7 (8.3)	10
<b>TESAEs</b>	7 (8.3)	10
<b>TESAEs related to study drug</b>	1 (1.2)	1

Source CSL627\_3002, BLA 125591/0.3 Table 12-2 (Submitted September, 2015), page 70 of 101

Common AEs listed by System Organ Class (SOC) and Preferred Term (Safety Population) are shown in Table 27.

**Table 27**  
**TEAEs occurring in ≥2% of Subjects in the Safety Population by SOC and Preferred Term**

System organ class Preferred term	Total (N = 84) No. (%) of subjects	No. of events
<b>Any TEAEs</b>	<b>50 (59.6)</b>	<b>113</b>
<b>Infections and infestations</b>	<b>31 (36.9)</b>	<b>41</b>
Nasopharyngitis	11 (13.1)	12
Rhinitis	6 (7.1)	6
Device related infection	2 (2.4)	2
Skin infection	2 (2.4)	2
Upper respiratory tract infection	2 (2.4)	2
<b>Musculoskeletal and connective tissue disorders</b>	<b>12 (4.3)</b>	<b>13</b>
Arthralgia	4 (4.8)	4
Pain in extremity	4 (4.8)	4
Musculoskeletal pain	2 (2.4)	2
<b>Injury, poisoning and procedural complications</b>	<b>10 (11.9)</b>	<b>12</b>
Contusion	2 (2.4)	3
Laceration	2 (2.4)	2
<b>Respiratory, thoracic and mediastinal disorders</b>	<b>8 (9.5)</b>	<b>13</b>
Cough	4 (4.8)	7
Oropharyngeal pain	2 (2.4)	2
<b>General disorders and administration site conditions</b>	<b>6 (7.1)</b>	<b>6</b>
Pyrexia	3 (3.6)	3
<b>Nervous system disorders</b>	<b>5 (6.0)</b>	<b>8</b>
Headache	4 (4.8)	6
<b>Blood and lymphatic system disorders</b>	<b>4 (4.8)</b>	<b>6</b>
Anaemia	3 (3.6)	5
<b>Gastrointestinal disorders</b>	<b>4 (4.8)</b>	<b>5</b>
Vomiting	2 (2.4)	2
<b>Ear and labyrinth disorders</b>	<b>2 (2.4)</b>	<b>2</b>
Ear pain	2 (2.4)	2

N = Number of subjects.

Source CSL627\_3002, BLA 125591/0.3 Table 12-3 (Submitted September, 2015), page 72 of 101

Fifty subjects experienced a total of 113 TEAEs. All but two were mild or moderate. There were two severe TEAEs. **Subject (b) (6)**, a 4 year old Asian, developed a systemic inflammatory response syndrome and **Subject (b) (6)**, a 7 year old Caucasian, developed a splenic rupture. Both were considered unrelated to Afstyla.

There were 10 TESAEs experienced by 7 subjects. Two TESAEs, in a single subject, **Subject (b) (6)**, 10 year old Asian, were considered by the investigator as related to Afstyla (hypersensitivity, mild, and immune system disorder, low-titer inhibitor, mild in severity).

**Reviewer Comment: The latter TESAE was updated to a preexisting inhibitor after originally being reported as a TESAE (see following).**

### TESAEs

Nine subjects developed 11 TESAEs. All were in the prophylaxis treatment arm.

- **Subject (b) (6)** : An 8 year old Caucasian male lacerated several fingers with a knife and required surgical repair.
- **Subject (b) (6)** : Device occlusion in a 6 year old Caucasian male in the prophylaxis arm. A Port-a-Cath® developed an intramural thrombus 5 weeks into treatment. This device had been in situ for 3 years. This was not considered a thrombotic event as “the complication was restricted to the administration device and was not associated with any intravascular thrombus formation” (4-month PK and Safety Update, page 88/101).

**Reviewer Comment: The TEAE in Subject (b) (6) was not considered a thromboembolic event as it was an isolated device occlusion. However, this reviewer disagrees. This device had been in place for several years and developed a thrombosis during treatment with Afstyla. In addition, this event is listed as a TEAE of special interest (“Embolitic and thrombotic events, device occlusion”) in Table 12-8 of the 4-month PK and Safety Update. This reviewer would assess this event as thromboembolic and possibly related.**

- **Subject (b) (6)** : Anemia in a 1 year old Caucasian male in the prophylaxis arm. Diagnosed as Munchausen syndrome by proxy (three reports of TESAE of anemia).
- **Subject (b) (6)** : Dyspepsia in a 2 year old Asian male subject in the prophylaxis arm. Abdominal pain and vomiting 12 days after beginning treatment. Admitted to the hospital. Symptoms resolved with *nil per os* for 4 to 6 hours and intravenous fluids. Discharged in 2 days.
- **Subject (b) (6)** : Bacteremia and development of inhibitor (2 SAEs) in a 10 year old Asian male in the prophylaxis arm. This subject developed bacteremia after a dose of Afstyla was injected through a peripheral intravenous catheter that had been in place for several days. The bacteremia resolved with antibiotics. In retrospect, due to a laboratory processing error, this subject’s screening sample had been reported as negative when it was in fact positive for a preexisting inhibitor (3.46 BU/mL). By 4 months into treatment the inhibitor titer was negative (0.55 BU/mL) despite ongoing doses of Afstyla.
- **Subject (b) (6)** : Pneumonia in a 4 year old Caucasian male
- **Subject (b) (6)** : Systemic inflammatory response syndrome in a 4 year old Asian male in the prophylaxis arm. Parents flushed residual study medication through catheter with unsterile saline. He received multiple subsequent doses of Afstyla without problems.

- **Subject (b) (6)** : Hand fracture in a 6 year old Asian male in the prophylaxis arm. Unrelated to product.
- **Subject (b) (6)** : Splenic rupture in a 7 year old Caucasian male in the prophylaxis arm. Snowmobile accident with splenic laceration. He was treated emergently with another FVIII product (allowed by protocol) and then Afstyla. A splenectomy was not required.

**Reviewer Note: Reviewer Comment: All were considered by the applicant as unrelated to Afstyla. This reviewer agrees that these TESAEs were unrelated to the investigational product with one exception, the device occlusion.**

#### 6.2.12.3 Deaths

There were no deaths reported.

#### 6.2.12.4 Nonfatal Serious Adverse Events

**Subject (b) (6)** : A 4 year old Asian male, enrolled in the prophylaxis arm developed systemic inflammatory response syndrome (high fever and shivering) very shortly after the subject's parents flushed the catheter with unsterile saline.

**Subject (b) (6)** This 1 year old Caucasian male had several hospital admissions for anemia, eventually diagnosed as Munchausen syndrome by proxy, and he was withdrawn from the trial.

#### 6.2.12.5 Adverse Events of Special Interest (AESI)

TEAEs of special interest were identified as

- Thromboembolic events (TEEs)
- Hypersensitivity
- Anaphylactic reactions

Medical events of special interest were defined as:

- Minor surgery
- Hospital admission for <24 hours for events not considered AEs
- Overdose (any AE related to Afstyla dose double or higher than prescribed)
- Inhibitor identified by local laboratory
- Hypersensitivity reactions
- Thrombotic events

No inhibitor formation during exposure to Afstyla was observed, including the 64 subjects with  $\geq 50$  ED.

Ten subjects had non-inhibitory antibody on enrollment; 10 subjects developed non-inhibitor antibodies during the trial. Of these 10 subjects, 3 had a negative result at end-of-study and 7 had a positive result. None developed any related symptoms. There was no apparent age relationship.

No subject had or developed antibodies to CHO host cell proteins.

Thirteen subjects developed 19 events suggestive of a hypersensitivity reaction. All but one were considered unrelated to the study drug by the investigators and the adjudicators. Symptoms in additional subjects (cough and exacerbation of asthma) were not considered to be associated with hypersensitivity reactions, but rather associated with the common cold.

**Subject (b) (6)** : a 9 year old Asian male experienced a single event of hypersensitivity considered mild. It was controlled with steroids and antihistamines, and the dose of Afstyla was not altered.

**Subject (b) (6)** : a 6 year old Caucasian male developed a thromboembolic event, the catheter thrombosis described above.

#### 6.2.12.6 Clinical Test Results

The mean changes from baseline across all hematology measures were small; no more than two subjects at any visit had treatment-emergent abnormal values. Six subjects had TEAEs of anemia, none of which were considered related to Afstyla by the investigator. In five of these the TEAEs were non-serious and mild or moderate in severity. All but one resolved. **Subject (b) (6)**, described above, had reports of three TESAEs of anemia, and was diagnosed as Munchausen by proxy. No subject developed treatment-emergent abnormal biochemistry values.

#### 6.2.12.7 Dropouts and/or Discontinuations

Seventeen subjects had a total of 20 major protocol violations. Of these only one resulted in exclusion from the Efficacy Population. **Subject (b) (6)** a 10 year old Asian male, due to a laboratory screening error, had the screening simple reported as negative for pre-existing inhibitor when in fact it was positive (3.46 BU/mL). This subject was continued in the trial (prophylaxis arm) but was removed from the efficacy population.

In addition, eight subjects (four in each age group) in the Efficacy Population were determined to be non-compliant and were removed from the Per-protocol Population

**Subject (b) (6)**, a 1 year old Caucasian male, was discontinued, for non-Afstyla related Munchausen syndrome by proxy and one subject, **Subject (b) (6)**, a 10 year old Caucasian, for hip arthralgia, also not related to Afstyla. There was no impact on the trial of these discontinued subjects.

#### 6.2.13 Study Summary and Conclusions

As expected, the trial showed a shorter mean  $t_{1/2}$  and greater mean CL compared to adolescents and adults (Trial CSL627\_1001). Compared to the adult trial, some difference in IR could in part be related by the later first sampling time in the children due to limitations in blood sampling volumes. Sixteen of 20 subjects in the younger age

group and 16/19 subjects in the older age group had FVIII:C >1% at the last sampling point (48 hours). Over 80% had FVIII:C levels >1% at 48 hours (median 3.78 and 3.43 IU/dL in the younger and older groups, respectively). Prophylactic treatment was shown to be efficacious and superior to on-demand treatment (although there were only three subjects in the on-demand group). The safety profile is consistent with the safety observations in adolescents and adults in Trial CSL627\_1001.

**Reviewer Comment: It is noted that no previously untreated subjects were included in this trial. The risk of inhibitor formation will be lower in subjects previously treated than in previously untreated subjects, particularly since those who might be at higher risk would have already developed inhibitors and would have been excluded from the trial. A trial of previously untreated patients, including children, is planned.**

**The applicant's suggestion that PK differences in children versus adults is due to differences in sampling time is possible, but there are known PK differences for this class of drug, and the older children had intermediate values despite similar sampling regimens. Given the PK differences in the adult versus the pediatric data (CL in children 0-6 years of age 5.01 versus 2.55 in adults [ratio 1.96]) a different dosing range may be required in younger children. This has not been required for FVIII products but is currently being considered by the Agency when pediatric and adult PK is substantially disparate.**

## 7. INTEGRATED OVERVIEW OF EFFICACY

### 7.1 Indication #1

Control and prevention of bleeding episodes

#### 7.1.1 Methods of Integration

Both phase 3 trials present data to support efficacy for this proposed indication.

#### 7.1.2 Demographics and Baseline Characteristics

Trial subjects were all male, predominantly Caucasian (approximately 72% in both trials). There were 14 subjects 12 to <18 years of age in the adult trial CSL627\_1001. All adolescents in the adult trial were enrolled in the prophylaxis group (Indication #2).

#### 7.1.3 Subject Disposition

No subjects discontinued the adult trial due to an AE. Several subjects were removed from the efficacy or per-protocol populations in the pediatric trial, but there was no impact on the trial of these discontinued subjects.

#### 7.1.4 Analysis of Primary Endpoint(s)

Treatment success (investigator rating of excellent or good) in the adult study was documented in 92% (783 of 848) BEs in the combined on-demand and prophylaxis regimens. The lower limit of the 95% CI of 88.9% exceeded the pre-specified success criterion of >70%. Treatment was similar for the on-demand and prophylaxis groups (92.4% and 92.2%, respectively). Imputing missing data as either all excluded or as all failures produced similar results (93.8 and 92.3%, respectively).

Breakthrough BEs in subjects on the prophylaxis regime were treated with 1 additional injection in 76% and 2 injections in 14% of events. In the pediatric trial, treatment success using the same criterion was 96.3% (334 of 347) with a 95% CI of 91.3% to 98.4%. There were no missing efficacy assessments in this trial and treatment success was similar for both age groups (94% and 96.6%).

#### 7.1.5 Analysis of Secondary Endpoint(s)

All secondary endpoints were met for both trials.

#### 7.1.6 Other Endpoints

Additional endpoints for the pediatric trial were PK profile, occurrence of inhibitor formation and safety measures. The PK profile was discussed in section [6.2.11.2](#). There was no inhibitor formation observed and the safety profile was acceptable.

#### 7.1.7 Subpopulations

There were no differences in the results based on age, race or geographic origin in either trial.

#### 7.1.8 Persistence of Efficacy

Subjects in the adult trial were followed for 24 months. In a surrogate for effect, a subset of 13 subjects had repeat PK measures at 3 to 6 months that showed equivalent responses to those at the beginning of the study. In simulations from the population PK model, it is estimated that with treatment of 20 IU per kg twice weekly (on days 0 and 3) the FVIII:C level would be maintained >1% in approximately 61% of subjects. At a dose of 50 IU per kg twice weekly approximately 90% would have a FVIII:C level >1% and 73% would have a FVIII level >1% on Day 7. In the pediatric trial at the last sampling time (48 hr) 3/6 of the younger subjects and 7/7 of the older subjects had FVIII:C >1%.

#### 7.1.9 Product-Product Interactions

Not applicable

#### 7.1.10 Additional Efficacy Issues/Analyses

None

#### 7.1.11 Efficacy Conclusions

This product has demonstrated adequate efficacy in treating BEs in both pediatric and adult populations.

### 7.2 Indication #2

Routine prophylaxis to prevent or reduce the frequency of BEs

#### 7.2.1 Methods of Integration

Both trials present data to support this proposed indication.

#### 7.2.2 Demographics and Baseline Characteristics

See section [7.1.2](#)

#### 7.2.3 Subject Disposition

See [7.1.3](#)

#### 7.2.4 Analysis of Primary Endpoint(s)

##### **Annualized Bleeding Rate**

In the adult trial the median ABR was 1.1 BEs per year and 43.2% of subjects had no BEs. In the pediatric trial the ABR was somewhat higher, at 3.7 BEs per year (compared to 35.1, 78.6 and 86.6 for the three subjects in the on-demand treatment group), and 26.3% had no BEs requiring treatment.

**Reviewer comment: Children would be expected to have a somewhat higher incidence of traumatic BEs than adults.**

##### **Annualized Spontaneous Bleeding Rate**

The median ASBR was 0 BEs per year for both adults and children.

The ABR and ASBR did not differ between subjects on a twice-weekly or a three times/week prophylactic schedule in the adult trial, however the median ABR was higher in children treated twice weekly than three times/week (4.4 versus 2.3).

In the adult trial both ABR and ASBR were lower in subjects receiving prophylactic compared to on-demand treatment. Based on a Poisson model, this represented a reduction of  $\geq 90\%$  with prophylaxis compared to on-demand treatment. The ABR and ASBR in the prophylaxis group were also lower than historical controls of on-demand use in a prior CSL VWF/FVIII product (Biostate).

#### 7.2.5 Analysis of Secondary Endpoint(s)

Secondary endpoints for this indication are reported only in trial [CSL627 1001](#). All secondary endpoints were met.

#### 7.2.6 Other Endpoints

None

#### 7.2.7 Subpopulations

There were no differences in the results based on age, race or geographic origin for either trial.

#### 7.2.8 Persistence of Efficacy

In the adult trial, the PK profile did not change with continued use.

#### 7.2.9 Product-Product Interactions

Not applicable

#### 7.2.10 Additional Efficacy Issues/Analyses

None

#### 7.2.11 Efficacy Conclusions

Afstyla was effective when used prophylactically in both children and adults. Efficacy when used prophylactically exceeded that when given for on-demand treatment.

### **7.3 Indication #3**

Perioperative management

#### 7.3.1 Methods of Integration

The applicant included a single completed phase 1/3 trial (Trial CSL627\_1001) to support efficacy in this proposed indication. Trials CSL627\_3002 (pediatric study) did not include subjects having surgery.

#### 7.3.2 Demographics and Baseline Characteristics

In Trial CSL627\_1001 15 subjects underwent 16 major surgical procedures.

#### 7.3.3 Subject Disposition

No subjects discontinued the trial due to an AE.

#### 7.3.4 Analysis of Primary Endpoint(s)

Surgical hemostasis was rated as excellent in 15 (94%) of the procedures and good in one (6%).

#### 7.3.5 Analysis of Secondary Endpoint(s)

Secondary endpoints for this indication are reported only in trial [CSL627 1001](#). All secondary endpoints were met.

#### 7.3.6 Other Endpoints

None

#### 7.3.7 Subpopulations

The number of subjects in the surgical population was too small to make valid inferences or conclusions.

#### 7.3.8 Persistence of Efficacy

Use of Afstyla decreased with time postoperatively: median of 3.5 IU/kg/h for hours 1 to  $\leq 72$ , 2.7 IU/kg/h for hours 0 to  $\leq 168$  and 2.0 IU/Kg/h for hours 0 to  $\leq 336$  postoperatively.

#### 7.3.9 Product-Product Interactions

None

#### 7.3.10 Additional Efficacy Issues/Analyses

None

#### 7.3.11 Efficacy Conclusions

Afstylo demonstrated adequate efficacy in surgical prophylaxis.

### 8. INTEGRATED OVERVIEW OF SAFETY

#### 8.1 Safety Assessment Methods

Safety was assessed by: the nature and incidence of AEs; the development of antibodies against Afstylo and CHO proteins; the development of inhibitors; vital signs; the development of treatment-emergent abnormal laboratory values; changes in physical examination; clinical signs of thrombosis; and local tolerability. AEs were solicited at each visit by non-leading questioning. Subjects (or their families) in both trials recorded assessments of local tolerability in an electronic diary.

## 8.2 Safety Database

The Safety Populations (N=174, adults and N=84, children) included all subjects who received at least one dose of Afstyla.

### 8.2.1 Studies/Clinical Trials Used to Evaluate Safety

Safety data were derived from both trials.

### 8.2.2 Overall Exposure, Demographics of Pooled Safety Populations

One hundred and seventy-four subjects (12 to  $\leq 65$  years of age) are included in the safety database from Trial CSL627\_1001 and 84 pediatric subjects from Trial CSL627\_3002. One hundred and twenty adult subjects achieved  $\geq 50$  ED and 54 subjects reached  $\geq 100$  ED in Trial CSL627\_1001. In Trial CSL627\_3002, 65 pediatric subjects achieved  $\geq 50$  ED, eight of whom (all 6 to  $< 12$  years of age) achieved  $\geq 100$ .

### 8.2.3 Categorization of Adverse Events

All serious and non-serious AEs were coded according to the Medical Dictionary for Regulatory Activities (MedDRA v16.1).

## 8.3 Caveats Introduced by Pooling of Data Across Studies/Clinical Trials

None

## 8.4 Safety Results

### 8.4.1 Deaths

There were no deaths reported in either trial.

### 8.4.2 Nonfatal Serious Adverse Events

Of 10 SAEs reported in Trial CSL627\_1001 only 1 SAE was judged by the investigator to be related to Afstyla. This was an event of hypersensitivity controlled with steroids and antihistamines. The subject remained on Afstyla and tolerated it well thereafter. There were two SAEs reported in the pediatric trial (systemic inflammatory response syndrome due to non-sterile flush of a catheter, and Munchausen by proxy), both were unrelated to Afstyla.

### 8.4.3 Study Dropouts/Discontinuations

There were no dropouts due to TEAEs. There were 17 dropouts from Trial CSL627\_1001 (all for minor protocol violations) and two from Trial CSL627\_3002 (one for Munchausen syndrome by proxy and one for arthralgia). These dropouts did not affect the efficacy or safety conclusions of the trials.

#### 8.4.4 Common Adverse Events

The three most common TEAEs reported in Trial CSL627\_1001 were nasopharyngitis, arthralgia and headache. The most common TEAEs reported in Trial CSL627\_3002 were rhinitis, arthralgia, pain in an extremity, cough, contusion, nasopharyngitis, and headache. AEs were reported in 13 surgical subjects. The most common AEs reported for surgical subjects in Trial CSL627\_1001 were procedural pain (5/13 subjects) and nausea (2/13 subjects). The most commonly reported AEs in CSL627\_3002 were nasopharyngitis, arthralgia and headache.

#### 8.4.5 Clinical Test Results

Neither trial identified any patterns of clinically significant laboratory, vital signs or physical examination findings.

#### 8.4.6 Systemic Adverse Events

None

#### 8.4.7 Local Reactogenicity

In Trial CSL627\_1001, 99.3% of 13,580 injections were reported with no reactions, 0.7% with very slight to moderate reactions, and none with severe reactions. In Trial CSL627\_3002, 99.3% (3,337 of 3,362) assessments of tolerability were reported with no reaction. Subjects in CSL627\_3002 reported assessments as moderate or less in intensity in 25 (0.74%) assessments. Two subjects experienced a single severe local reaction. One reaction was in the skin above the infusion port and one on the ears.

#### 8.4.8 Adverse Events of Special Interest

**Thromboembolic events:** No thromboembolic events were reported in trial CSL627\_1001. There was a single event of intraluminal thrombosis of a long term indwelling venous catheter in trial CSL627\_3002 that this reviewer assesses as possibly related.

**Inhibitor formation:** Inhibitor formation was not detected in any subject in either trial including those subjects with  $\geq 50$  ED.

**Immunogenic events:** Of eight subjects in trial CSL627\_1001 who had non-inhibitory anti-drug antibodies present at baseline, seven remained positive until the end of the trial. Four subjects developed non-inhibitory IgG and/or IgM antibodies during the trial. Two of these became negative by the end of the trial. No subject in this trial had or developed anti-CHO antibodies.

In Trial CSL627\_3002 10 subjects had non-inhibitory antibody on enrollment and 10 subjects developed non-inhibitor antibodies during the trial. Of these 10 that developed antibodies during the trial, 3 had a negative result at end-of-study and 7 had a positive result. None developed any related symptoms.

No subject in either trial had or developed antibodies to CHO host cell proteins.

**Hypersensitivity reactions:** A single serious hypersensitivity reaction was reported in Trial CSL627\_1001 (see [6.1.12.4](#)). In addition two additional cases of non-serious hypersensitivity reactions were reported. These two were mild, controlled with antihistamines and did not recur with continued administration of Afstyla (without antihistamines).

In Trial CSL627\_3002, seven subjects developed events suggestive of a hypersensitivity reaction. All but one were considered unrelated to the study drug by the investigators and the adjudicators. A single subject experienced a single event of hypersensitivity 2 days after the first dose of Afstyla that was considered mild. Treatment with Afstyla continued and there was no recurrence.

## 8.5 Additional Safety Evaluations

### 8.5.1 Dose Dependency for Adverse Events

AEs were not dose-related.

### 8.5.2 Time Dependency for Adverse Events

AEs were not related to duration of treatment.

### 8.5.3 Product-Demographic Interactions

There was no relationship of efficacy or safety to age, race, ethnicity or geographic origin.

### 8.5.4 Product-Disease Interactions

None

### 8.5.5 Product-Product Interactions

Not applicable

### 8.5.6 Human Carcinogenicity

There was no indication of carcinogenicity reported.

### 8.5.7 Overdose, Drug Abuse Potential, Withdrawal, and Rebound

Not applicable

### 8.5.8 Immunogenicity (Safety)

See [8.4.8](#)

### 8.5.9 Person-to-Person Transmission, Shedding

Not applicable

## 8.6 Safety Conclusions

The safety profile of Afstyla is acceptable. Afstyla showed an AE/SAE profile consistent with products of the same class and within the expected background pathology for patients with hemophilia A. The subject retention rate was high in both trials. No subject in either trial discontinued due to a TEAE. There was no reported inhibitor formation or any deaths in either clinical trial. There was a single thrombotic event possibly related to Afstyla in Trial CSL627\_3002.

## 9. ADDITIONAL CLINICAL ISSUES

None

### 9.1 Special Populations

No clinically important differences in the safety profile of Afstyla were observed when data were analyzed by age. Subjects >65 years of age were not studied.

**Reviewer Comment: The findings in these trials showed the expected differences in PK variables of children versus adults. Although that might imply a different dosing schedule in pediatric patients, inter-individual variability in rFVIII PK is equally important. A recent publication of rFVIII PK in children and adults showed a 5-fold variation in weight-adjusted CL and a 4-fold variation in  $t_{1/2}$ .<sup>16</sup> The biological variance exceeded the PK variance due to known factors such as weight or age. However, with the difference in CL, consideration could be given to a dose modification in young children (0 to <6 years). This has not previously been required of similar products, an appropriate statement in the labeling has sufficed.**

#### 9.1.1 Human Reproduction and Pregnancy Data

Hemophilia A occurs almost exclusively in males. No females were included in any of the trials.

#### 9.1.2 Use During Lactation

Not applicable

#### 9.1.3 Pediatric Use and PREA Considerations

As a new drug, PREA was triggered. The Pediatric Review Committee (PeRC) agreed with the Division's recommendation that the pediatric data submitted in this BLA is adequate for approval for children (CRMTS #9559).

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16 Bentorp E, Spotts G, Patrone L, *et al*: Advancing personalized care in hemophilia A: ten years' experience with advanced category antihemophilic factor using a plasma/albumin-free method. *Biologics: Targets and Therapy* 2014;8:115-27.

#### 9.1.4 Immunocompromised Patients

This product has not been specifically evaluated in immunocompromised patients.

#### 9.1.5 Geriatric Use

Subjects >65 years of age were not studied.

### **9.2 Aspect(s) of the Clinical Evaluation Not Previously Covered**

Both Trials CSL627\_1001 and CSL627\_3002 enrolled only previously treated subjects. Previously treated subjects are known to have a lower incidence of development of inhibitors. Previously untreated subjects will be addressed in upcoming evaluations.

## 10. CONCLUSIONS

Afstyla is safe and effective for the proposed indications. Based on my review of the submitted data, this product appears safe and efficacious in children and adults with hemophilia A. An approval is recommended for the proposed indications.

## 11. RISK-BENEFIT CONSIDERATIONS AND RECOMMENDATIONS

### **11.1 Risk-Benefit Considerations**

#### **Table 28. Benefit-Risk Considerations**

Decision Factor	Evidence and Uncertainties	Conclusions and Reasons
<b>Analysis of Condition</b>	<ul style="list-style-type: none"> <li>• Hemophilia A is a hereditary bleeding disorder characterized by recurrent and potentially life threatening bleeding. If left untreated, bleeds can lead to chronic arthropathy, muscular atrophy and deformities.</li> <li>• Treatment of bleeds may delay these complications, but does not prevent it.</li> <li>• Primary prophylaxis with regular FVIII injections initiated at an early age is becoming the standard of care</li> </ul>	<ul style="list-style-type: none"> <li>• Hemophilia A is a hereditary, life-threatening disease</li> <li>• Hemophilia A can have a debilitating impact on physical and psychosocial well being</li> </ul>
<b>Clinical Benefit</b>	<p>The results from two phase 3 trials (one adult and one pediatric) were submitted. All subjects had severe hemophilia A and had been previously treated with a factor VIII replacement product. Efficacy was demonstrated for the treatment of acute bleeds, perioperative management (in adults), and routine prophylaxis. No new safety concerns were identified.</p>	<p>The evidence for clinical benefit is compelling</p>
<b>Risk</b>	<ul style="list-style-type: none"> <li>• The most substantial risks of treatment with Afstyla are thromboembolic events, allergic reactions and development of FVIII inhibitors. No, inhibitors or significant allergic reactions were noted during the trials. Only a single possible thrombotic event was noted. However, the study may have been underpowered to adequately identify these potential risks.</li> <li>• Only two single, transient, serious adverse events were found to be attributable to Afstyla.</li> <li>• No other safety signals were apparent</li> </ul>	<ul style="list-style-type: none"> <li>• All evidence indicates that Afstyla is well tolerated and safe.</li> </ul>
<b>Risk Management</b>	<ul style="list-style-type: none"> <li>• The most substantial risks of treatment with Afstyla are thromboembolic events, allergic reactions and development of FVIII inhibitors.</li> <li>• No other safety signals were apparent.</li> </ul>	<ul style="list-style-type: none"> <li>• If Afstyla were approved, routine measures, such as the package insert and the current pharmacovigilance plan would be adequate to manage the risks, in addition to a comprehensive communication plan discussing disparate results in the two assay methodologies.</li> </ul>

## 11.2 Risk-Benefit Summary and Assessment

**Benefits:** The efficacy of Afstyla has been established for on-demand treatment and control of BEs, perioperative management of BEs, and routine prophylaxis in clinical studies in adults and in children.

**Risks:** Although no subjects developed neutralizing antibodies to FVIII in the clinical trials, the potential for developing inhibitors is discussed in the Warnings and Precautions section of the Package Insert. Both Trials CSL627\_1001 and CSL627\_3002 enrolled only previously treated subjects. Previously untreated subjects, those at highest risk to develop inhibitors, were not included in these trials. Thromboembolic events are a potential risk for this class of drug and were listed as an AESI in trial CSL627\_1001. No clearly related thromboembolic events were reported in either trial.

There is a substantial discrepancy between results reported by the two available assays of FVIII activity, the ChS and OS assays. A conversion factor, deemed appropriate by FDA, is clearly indicated in the label. Communication with relevant healthcare practitioners will also be needed.

### **11.3 Discussion of Regulatory Options**

The identification and characterization of risk factors for inhibitor formation require an improved understanding of how patient-specific and treatment-related factors work together to influence inhibitory antibody production. Pre-market studies are limited in their ability to identify risk factors because most studies are underpowered and are limited to only previously treated patients who do not have a history of inhibitor formation. The larger hemophilia community that will be exposed to the product after licensure, including minimally treated and previously untreated patients as well as patients undergoing surgery and/or switching regimens, are often not included in pre-market studies. Large prospective post-marketing surveillance studies that include the patient population at large and designed to actively monitor and evaluate the risk factors for inhibitors are important for further characterization of the risk of inhibitor formation. The submitted Pharmacovigilance Plan is sufficient to address these important potential risks.

At the external late-cycle meeting with CSL the need for a specific communication program was conveyed by FDA and CSL will provide this.

### **11.4 Recommendations on Regulatory Actions**

This clinical reviewer recommends approval of this BLA. Efficacy and safety clinical data for Afstyla were found adequate to make a favorable benefit/risk determination and to support approval for the proposed indications of:

- Control and prevention of bleeding episodes,
- Perioperative management (surgical prophylaxis),
- Routine prophylaxis to prevent or reduce the frequency of bleeding episodes.

### **11.5 Labeling Review and Recommendations**

Please see the product label review memo. In response to an Information Request, CSL provided a draft label on February 29, 2016 (amendment 25) updating the label with the final data from the pediatric trial, CSL627\_3002.

### 11.6 Recommendations on Postmarketing Actions

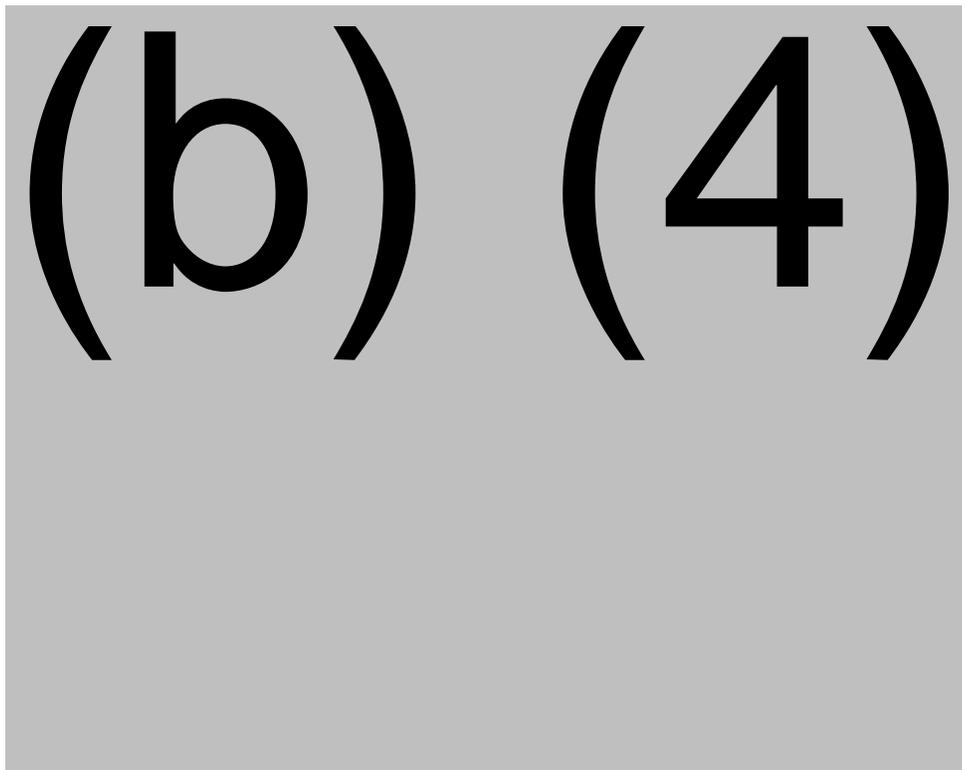
The proposed postmarketing pharmacovigilance studies (4.6) are deemed adequate. In addition, the CSL will undertake a specific communication plan to inform health care providers how to manage patients in light of the discrepancy in the two available FVIII assays.

INSERT FIRST APPENDIX HEADING HERE

#### APPENDIX. SUPPORT FOR A CONVERSION FACTOR OF (b) (4)

CSL submitted materials supporting a conversion factor of (b) (4) to bring results by the OS assay in alignment with the ChS assay. These included the results of a field trial, assessing the reliability of local laboratories versus the central laboratory (BLA section 5.3.1.4). Additional data were submitted in response to an FDA information request (BLA 125591/0.22, February 17, 2016).

In the following graph potential conversion factors of (b) (4) 2.0 are applied. Although there is some dispersion in the data points, a factor of (b) (4) seems appropriate and better than 2.0. In addition, comparison is made with Advate. (b) (4) product, (b) (4) might be expected to have less variance with the two methods.



The two following graphs show the results when the conversion factor of (b) (4) is applied to the data from Parts 1 and 3 of trial CSL627\_1001 (above) and CSL627\_3002 (below).

(b) (4)

CSL reports that no cases describing dosing errors based on the assay type used for treatment monitoring of FVIII levels have been reported from the Afstyla clinical development program. However, since no FVIII activity measurements were required per protocol, the significance of this statement is unclear.

Additional data are available in BLA 126691/0.22.

**\*\*\*Do Not Change Anything Below This Line\*\*\***

