



**Department of Health and Human Services
Food and Drug Administration
Center for Biologics Evaluation and Research**

MEMORANDUM

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To: Alexey Khrenov
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Subject: Pharmacovigilance Plan Review

Sponsor: CSL Behring

Product: Afstyla (Antihemophilic Factor (Recombinant), Single Chain)

Proposed Indication: Treatment and prophylaxis of patients with hemophilia A (Congenital Factor VIII deficiency) in adults and children

Submission: Original BLA 125591/0

Submission Date: May 29, 2015

Action Due Date: May 28, 2016

1.0 INTRODUCTION

Hemophilia A is a congenital deficiency of Factor VIII (FVIII), inherited as an X-linked recessive trait in approximately 1 in 5,000 males [1]. Deficiency of this clotting factor causes episodes of prolonged or spontaneous bleeding, following or in the absence of trauma. Common symptoms of this condition include excessive bleeds from superficial abrasions and shallow lacerations as well as intraarticular, intramuscular, and intracranial bleeds. Mild hemophiliacs (5-25% of normal concentration of active clotting factor) have few to no bleeding episodes in the absence of serious trauma and can often be managed with desmopressin; most mild and moderate hemophiliacs (1-5% of normal concentration of clotting factor) can be treated as needed during bleeding episodes (BE). Severe hemophiliacs (<1% of normal concentration of clotting factor) require regular supplementation with exogenous FVIII (usually every 2-3 days) as well as additional prophylactic doses prior to surgical procedures and after trauma [2].

1.1 Product Description

Recombinant factor VIII single-chain (rVIII-SingleChain; proposed proprietary name: Afstyla) is produced in Chinese hamster ovary (CHO) cells as a construct where the B-domain occurring in wild type full-length Factor VIII has been truncated and 4 amino acids of the adjacent acidic a3 domain were removed. Afstyla is expressed as a novel single-chain FVIII molecule with covalent linkage between heavy and light chains; thereby keeping the molecule in the single chain form. The sponsor suggests that this process results in increased stability and increased von Willebrand Factor (VWF) affinity. The sponsor further proposes that given that VWF binds FVIII and protects the molecule from early proteolysis, these properties contribute to an improved pharmacokinetic (PK) profile, thus improving hemophilia A treatment by allowing less frequent dosing than required with full length recombinant FVIII products. If approved, Afstyla will be the first single chain rFVIII product for the treatment of hemophilia A.

Afstyla is purified by a controlled multi-step process including two dedicated virus reduction steps. No human or animal derived proteins are used in the purification or formulation processes. The final drug product is provided as a preservative-free, sterile, non-pyrogenic, lyophilized powder to be reconstituted with water for intravenous injection. The product is available in single-use vials containing 250, 500, 1000, 2000 or 3000 IU of drug (b) (4)

The sponsor proposes that the product be indicated in adults and children with hemophilia A for the following purposes:

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

The dosing algorithm for control and prevention of bleeding episodes is outlined in the table below (adapted from Pharmacovigilance plan, p 9):

Table 1: Dosing for Control and Prevention of Bleeding Episodes

Type of bleeding episode	FVIII level required (% or IU/dL)	Frequency of doses (hours)
Early hemarthrosis, muscle bleeding or oral bleeding	20 - 40	Repeat injection every 12-24 hours until the bleeding is resolved.
More extensive hemarthrosis, muscle bleeding or hematoma	30 - 60	Repeat injection every 12-24 hours until the bleeding is resolved.
Life-threatening hemorrhages	60 - 100	Repeat injection every 8-24 hours until the bleed is resolved.

The dosing algorithm for perioperative management is outlined in the table below (adapted from Pharmacovigilance plan, p 10):

Table 2: Target FVIII Activity Levels for Perioperative Management

Type of bleeding episode	FVIII activity level required (% or IU/mL)	Frequency of doses (hours) / Duration of therapy (days)
Minor (including tooth extraction)	30-60	Repeat injection every 24 hours for at least 1 day, until healing is achieved.
Major	80-100	Repeat injection every 8-24 hours until adequate wound healing, then continue therapy for at least another 7 days to maintain a FVIII activity of 30-60% (IU/dL).

For routine prophylaxis, the recommended starting regimen is 20 to 50 IU/kg of Afstyla administered 2 to 3 times weekly. The regimen is intended to be adjusted based on patient response.

1.2 Pertinent Regulatory Information

Afstyla is not yet marketed anywhere in the world.

1.3 Objectives

The purpose of this review is to identify potential safety issues that may need to be addressed through postmarketing safety surveillance or studies should the product be approved. Available safety-related data for Afstyla, including data derived from 3 clinical studies, was assessed. The Pharmacovigilance Plan (PVP) included in the Risk Management Plan submitted by the sponsor was also evaluated. Materials assessed as part of this safety review are listed below.

Table 3: Materials Reviewed

Source	Document Type	Document
CSL-Behring, 125591/0	Study Report	Complete study report for CSL627_1001, BLA section 5.3.5.1
CSL-Behring, 125591/0	Safety Report	Interim safety report for ongoing study CSL627_3001, BLA section 5.3.5.2
CSL-Behring, 125591/0	Safety Report	Interim safety report for ongoing study CSL627_3002, BLA section 5.3.5.2
CSL-Behring, 125591/0	Other	Clinical Overview, BLA section 2.5
CSL-Behring, 125591/0	Other	Introduction, BLA section 2.2.2
CSL-Behring, 125591/0	Other	Risk Management Plan, BLA section 1.16
CSL-Behring, 125591/0	Other	Clinical Safety Summary, BLA section 2.7.4
CSL-Behring, 125591/0	Product Label	Proposed Labeling Information, BLA section 1.14
CSL-Behring, 125591/0	Other	Sponsor response in 17 February 2016 submission (for FDA Information Request dated 09 February 2016)

2.0 PHARMACOVIGILANCE PLAN REVIEW: CLINICAL SAFETY DATABASE

The sponsor submitted data from 3 clinical studies in support of the application: one completed pivotal study and two ongoing studies.

Table 4: Subjects Enrolled in Pre-licensure Studies of Afstyla

Protocol ID	CSL627_1001 (complete)	CSL627_3002 (ongoing)	CSL627_3001 (ongoing)
Study Description	Evaluation of PK, safety, efficacy, and dose-tolerability of Afstyla in previously treated patients	PK, efficacy, and safety study of Afstyla in children	Extension study to evaluate long-term safety of Afstyla in subjects previously enrolled in study 1001 or 3002
Subjects	174	84	154
0<6 yrs	0	35	7
≥6-<12 yrs	0	49	15
≥12 yrs	174	0	132

All subjects were males with Hemophilia A, with FVIII activity <1% (severe), who were previously treated with FVIII supplementation, with no history of FVIII inhibitors or history of hypersensitivity to FVIII product or hamster protein. A total of 258 unique subjects received at least one dose of Afstyla (all subjects in CSL627_3001 were derived from studies CSL627_1001 and 3002). For protocol CSL627_3002, data from all visits occurring on or before the visit cut-off date of 14 May 2015 are available for evaluation. For protocol CSL627_3001, data from all visits occurring on or before 29 May 2015 are available for evaluation.

2.1 Safety data from CSL627_1001

The design and key results from the CSL627_1001 pivotal trial are summarized below.

Table 5: Summary of Pivotal trial CSL627_1001

Study Title:	A Phase I/III Open-label, Multicenter, Crossover Safety, Efficacy and Pharmacokinetic Study of recombinant Coagulation Factor VIII (rFVIII) Compared to Recombinant Human Antihemophilic Factor VIII (rFVIII; INN: octocog alfa) in Subjects with Hemophilia A, and a Repeat PK, Safety and Efficacy Study	
Study Design:	<p><u>Part 1 – PK evaluation/crossover study with octocog alfa (Advate):</u> Recruited subjects received a single infusion of Advate at 50 IU/kg body weight and then crossed over to receive a single infusion of Afstyla at 50 IU/kg body weight over a 72 hour period for PK comparison. Results were used to establish dosing regimens for subjects in ensuing parts of the trial.</p> <p><u>Part 2 – On demand or prophylaxis treatment safety/efficacy evaluation:</u> Recruited subjects from Part 1 were allocated to receive either on demand or prophylactic treatment with Afstyla for 50 exposure days (EDs)/6 months. The first 5 subjects continuing from Part 1 participated in a substudy and received on demand treatment to characterize the dose most efficacious for treatment of bleeding events; subsequent subjects received Afstyla for efficacy/safety evaluation when used either on demand or as prophylaxis. Subjects from this part were also eligible for enrollment into the surgical substudy of Part 3.</p> <p><u>Part 3 – Safety/Efficacy/PK evaluation:</u> New subjects were enrolled and received on demand or prophylactic treatment based on their regimens prior to enrollment. Dosing was determined based on standard treatment guidelines in addition to previously established PK information from Part 1, and subjects were treated for at least 50 EDs/6 months. Subjects undergoing surgical procedures were enrolled (along with appropriate subjects from Part 2) into a surgical substudy.</p>	
Eligibility criteria:	Males with severe hemophilia A (FVIII:C <1%) previously treated with FVIII supplementation, with no history of FVIII inhibitors or history of hypersensitivity to FVIII product or hamster protein. Subjects in Parts 1/2 were required to be age 18-65 years; subjects in Part 3 were eligible if they were 12-65 years of age. 174 subjects enrolled.	
Study Duration:	15-Feb-2012 to 12-Dec-2014	
Study Status:	Complete (achieved predefined safety endpoint of ≥104 subjects with at least 50 EDs)	
Objectives:	<ul style="list-style-type: none"> ○ To demonstrate the efficacy of Afstyla in the prevention and treatment of bleeding events, surgical prophylaxis, and in use as routine prophylaxis over on-demand treatment ○ To characterize the PK profile of Afstyla and compare this profile to that of octocog alfa (Advate) ○ To characterize the safety profile of Afstyla, including rate of inhibitor formation 	
Safety related endpoints:	Adverse events (AE) including serious adverse events (SAE), antibodies against CHO proteins, FVIII inhibitors (≥0.6 Bethesda Units [BU], vital signs, thromboembolic events, and local tolerability. Laboratory parameters were assessed at screening, prior to dosing, at month 1-6 visits, and every 3 months until end-of-study visit; local tolerability was documented by both investigators and by subjects in an eDiary.	
Safety Population Demographics:	Total (n):	174
	Age (years):	
	Mean	31.3
	Range	12-64
	Race:	
	White	126 (72.4%)
	Black/AfAm	14 (8.0%)
	Asian	31 (17.8%)
Other	3 (1.7%)	
Key Study Results Relevant to Safety:	8 subjects withdrew from the study before completion. No withdrawals were documented as due to AE or death. No deaths occurred during the study. 9 SAEs occurred during the study, including 1 that was attributed to the product.	

2.1.2 Safety-related Data from CSL627_1001

Local tolerability: Local reactions at infusion site were assessed by both investigator and subject. The severity of the reaction at 13,580 individual infusion sites (subjects could have multiple infusion sites during the same infusion event) were assessed by subject 30 minutes after infusion as “none,” “very slight,” “slight,” “moderate,” or “severe.” 13,573 (99.9%) of all reactions were assessed as “none,” “very slight,” or “slight” by subjects. Seven reactions were assessed as “moderate,” and zero reactions were assessed as “severe.” Investigators assessed the infusion site demonstrating the most severe reaction during 553 infusion events; 552 (99.8%) such sites were assessed as “none” and one site (0.2%) was assessed as “very slight.”

Systemic adverse events: The most common clinical adverse experiences (incidence >5%) were nasopharyngitis (18 subjects/10.3%), arthralgia (17 subjects/9.8%), and headache (12 subjects/6.9%). Three subjects experienced non-serious hypersensitivity reactions that required no change in treatment; one additional subject experienced a serious hypersensitivity reaction, described below.

Serious adverse events (SAEs): 7 subjects reported 9 SAEs: anemia, thrombocytopenia, esophageal varices, hypersensitivity, viral infection (described as “moderate severity, resolved after eight days), ankle fracture, blood uric acid increased, suicidal ideation, and tonsillar hemorrhage. The episode of hypersensitivity was the only SAE attributed to the product and involved a 17 year-old Asian male who experienced pruritus, erythema of the upper extremities, headache and chest pressure 2.5 hours following his fifth prophylactic infusion. The reaction resolved after the subject was treated with steroids and an antihistamine. The subsequent infusion was given at a reduced dose and with a concomitant antihistamine without incident, and the subject continued in the study.

Of note, no thromboembolic events (TEEs) were documented during the trial.

Development of inhibitors and new antibodies: No subjects developed inhibitors during the study.

Information regarding development of non-inhibitory anti-drug antibodies (ADAs) is summarized in the table below.

Table 6: Overall Summary of Non-inhibitory ADAs (Safety Population, N=174)

	No. (%) of subjects
Positive any time during the study	12 (6.9)
Positive at baseline	8 (4.6)
Positive at baseline and positive at any time post-baseline	8 (4.6)
Positive at baseline and positive at End-of-Study	6 (3.4)
Negative at baseline and positive at any time post-baseline	4 (2.3)
Negative at baseline and positive at End-of-Study	2 (1.1)

Four subjects developed ADAs during the study, including two who continued to test positive for ADAs at the end of the study. Neither of these subjects experienced any SAEs during the trial.

No subjects developed antibodies to CHO host cell proteins during the trial.

Deaths and Discontinuations: No deaths were reported. Thirteen subjects (7.5%) discontinued the study before completion of the trial, including eight who voluntarily withdrew from the study, one that was discontinued by physician decision due to protocol violation and four that were discontinued due to ‘other’ reasons: surgery of the right knee (Subject 040000-1001), subject completed the study (55 EDs) but did not reach 6 months (Subject 2760030-1002), 50 EDs were not met (Subject 8400184-1001), and subject completed month 12 but did not have 50 EDs (Subject 8400184-1002). Subjects who voluntarily withdrew were not asked to provide a reason for withdrawal. Of the eight subjects that voluntarily withdrew, six had no documented AEs; the AEs experienced by the remaining two subjects were non-serious.

2.2 Safety data from CSL627_3002 (pediatric study)

The design and key results from the CSL627_3002 ongoing pivotal clinical trial are summarized in the table below.

Table 7: Summary of Clinical trial CSL627_3002

Study Title:	A Phase III Open-label Pharmacokinetic, Efficacy and Safety Study of rVIII-SingleChain in a Pediatric Population with Severe Hemophilia A		
Study Design:	Multicenter, non-randomized, open-label, single-arm, phase III study. <u>Part 1 – PK evaluation:</u> 39 subjects received 50 IU/kg body weight of Afstyla with blood samples taken pre-dose and then 1, 10, 24, and 48 hours after dosing for PK assessment. <u>Part 2 – Safety/Efficacy evaluation:</u> Subjects from Part 1 as well as 45 newly enrolled subjects received on demand or prophylactic treatment based on the investigator and subject/caregivers determination of the best treatment in the interest of the subject. Prophylactic dosing was determined by subject’s previous dose with a prior FVIII, available PK data from Afstyla, and the bleeding phenotype data of the subject. On demand dosing was determined by the investigator and was based on the subject’s previous FVIII dosing for bleeding episodes.		
Eligibility criteria:	Males <12 years of age with severe hemophilia A (FVII:C <1%) previously treated with FVIII supplementation for at least 50 EDs, with no personal or family history of FVIII inhibitors or history of hypersensitivity to FVIII product or hamster protein		
Study Duration:	26-Mar-2014 until complete follow up information (50 EDs) is available for at least 50 subjects		
Study Status:	Ongoing. Enrollment complete (84 subjects).		
Objectives:	<ul style="list-style-type: none"> ○ To demonstrate the efficacy of Afstyla in the prevention and treatment of bleeding events, surgical prophylaxis, and in use as routine prophylaxis over on-demand treatment ○ To characterize the PK profile of Afstyla ○ To characterize the safety profile Afstyla, including rate of inhibitor formation 		
Safety related endpoints:	Adverse events (AE) including serious adverse events (SAE), antibodies against CHO proteins, FVIII inhibitors (≥ 0.6 Bethesda Units [BU]), vital signs, thromboembolic events, and local tolerability. Laboratory parameters were assessed at screening, after 10 to 15 EDs, and after 50 to 75 EDs. Local tolerability was documented by both investigators and by subjects in an eDiary.		
Safety Population Demographics:		0 to <6 years old	≥ 6 years to <12 years old
	Number of subjects (N=84)	35	49
	Mean Age (years)	3.5	8.8
	Range (years)	1-5	6-11

	Race		
	White	25 (71.4%)	36 (73.5%)
	Asian	9 (25.7%)	13 (26.5)
	Other	1 (2.9%)	0
Study Results:	Complete follow up data is available for 5 subjects in the 0 to <6 year old group (“younger” group) and 13 subjects in the ≥6 years to >12 year old group (“older” group); partial follow up data was assessed for all other subjects. 1 subject in each age group discontinued the study; the subject in the older group was documented to have withdrawn due to a non-treatment associated AE. 9 SAEs occurred during the study. No deaths occurred during the study.		

2.2.2 Safety-related Data from CSL627_3002

Local tolerability: Local reactions at infusion site were assessed by both investigator and subject/subject caregiver. The severity of the reaction at 3,362 individual infusion sites (subjects could have multiple infusion sites during the same infusion event) was assessed one hour after infusion by the subject/subject caregiver as “none,” “very slight,” “slight,” “moderate,” or “severe.” 3,351 (99.7%) of all reactions were assessed as “none,” “very slight,” or “slight” by subjects. 11 reactions (0.3%) were assessed as “moderate.” Investigators assessed erythema at the infusion site demonstrating the most severe reaction during 193 infusion events as “none,” “very slight,” “well-defined,” “moderate to severe,” and “severe.” 191 (99%) of such sites were assessed as “none” and two sites (1%) were assessed as “well-defined.”

Systemic adverse events: The most common clinical adverse experiences (incidence > 5%) were nasopharyngitis (11 subjects/13.1%), and arthralgia (6 subjects/7.1%). One subject experienced a non-serious hypersensitivity reaction that was attributed to the product but required no change in treatment; one additional subject experienced the AE of “erythematous rash” which could not be ruled out as potentially related to a hypersensitivity reaction.

Serious adverse events: 7 subjects reported 9 SAEs: device occlusion, hand fracture, splenic rupture, anemia (3 events), dyspepsia, bacteremia and systemic inflammatory response syndrome (SIRS). The device occlusion occurred within a port-a-cath, not intravenously, and was determined not to be a TEE. The events of hand fracture and splenic rupture occurred in the context of accidents. The three events of anemia occurred in a single subject as a result of three episodes of melena; this subject was ultimately discontinued from the study in light of information that local authorities were investigating the subject’s family for possible Munchausen’s by proxy syndrome. The subject that experienced “dyspepsia” also reported nausea and vomiting consistent with gastroenteritis; symptoms resolved with IV hydration. The AE of “bacteremia” was documented on 08 April 2015; the subject experienced fever and chills after a dose of Afstyla was injected through a heparin-locked peripheral vascular catheter that had been in place for several days. The peripheral vascular catheter was subsequently removed and he was treated with antibiotics. The subject recovered from the bacteremia on 20 April 2015. The AE “SIRS” occurred in a subject who had received on-demand treatment dose of Afstyla at home on 17 August 2014. The subject’s parents flushed the infusion line with unsterile saline that had been drawn from a bottle that had been open for several days; saline from this bottle had previously been used to irrigate dressings that had been applied to the (b) (6) of the subject’s (b) (6). Within 30 minutes the subject developed high fevers and chills and

subsequently became tachycardic and hypotensive. The illness resolved following treatment with antibiotics. No SAEs were attributed to Afstyla by investigator and, with the exception of the discontinued subject, treatment regimens were not altered in any subject.

Of note, no thromboembolic events were documented during the trial.

Development of inhibitors and new antibodies: No subjects developed inhibitors during the study.

Six subjects developed non-inhibitory ADAs at some point during the study. Of these six subjects, three subjects have completed the study; two subjects were negative for ADAs at the End-of-study visit and one remained positive. None of the subjects, who were positive for ADAs, were assessed by investigators to have experienced AEs attributable to the ADA.

No subjects developed antibodies to CHO host cell proteins during the trial.

Deaths and Discontinuations: No deaths were reported. Two subjects have thus far discontinued the study before completion of the trial: one subject discontinued due to persistent non-serious hip arthralgia that was determined by MRI to be unrelated to a bleed, and the aforementioned subject that experienced three episodes of anemia.

2.3 Safety data from CSL627_3001(extension study)

The design and key results from the CSL627_3001 clinical trial are summarized in the table below.

Table 8: Summary of Clinical trial CSL627_3001

Study Title:	A Phase III Open Label, Multicenter, Extension Study to Assess the Safety and Efficacy of Recombinant Coagulation Factor VIII (rVIII-SingleChain, CSL627) in Subjects with Severe Hemophilia A
Study Design:	Multicenter, non-randomized, open-label, single-arm, phase III long term follow up extension study for subjects previously enrolled in CSL627_1001 and CSL627_3002. Subjects from either study who achieved ≥ 50 EDs became eligible to be rolled into this extension study. Additionally, once the target number of subjects with at least 50 EDs had been achieved in the previous pivotal studies, all remaining subjects still in the pivotal studies were/will be permitted to begin participation in Study 3001 regardless of the EDs achieved in the pivotal study.
Eligibility criteria:	Subjects previously enrolled in CSL627_1001 or CSL627_3002 with < 100 EDs at the start of Study 3001 were rolled into this extension study to continue treatment. This study also plans to enroll previously untreated patients (PUPs) in the future.
Study Duration:	13-OCT-2014 until complete follow up information (100 EDs) is available for at least 200 subjects
Study Status:	Ongoing
Objectives:	<p>Efficacy:</p> <ul style="list-style-type: none"> ○ To continue to collect efficacy information on Afstyla during use for prophylaxis, management of acute bleeding events, and during surgical procedures <p>Safety:</p> <ul style="list-style-type: none"> ○ To characterize long-term safety profile of Afstyla, particularly with regards to inhibitor formation
Safety related endpoints:	Adverse events (AE) including serious adverse events (SAE), antibodies against CHO proteins, FVIII inhibitors (≥ 0.6 Bethesda Units [BU]), vital signs, thromboembolic events, and local

	tolerability. Subjects are to return to the clinic for assessments every 3 months (\pm 7 days) until at least 100 EDs. Laboratory parameters were assessed were collected at the closest visit after 10, 50, and 100 EDs. Local tolerability was documented by subjects/caregivers in an eDiary.				
Study Population Demographics:		0 to <6 years old	\geq 6 years to <12 years old	\geq 12 years to <18 years old	\geq 18 years to <65 years old
	Number of subjects (N=154)	7	15	14	118
	Mean Age (years)	5.4	10.3	15.9	32.5
	Age range (years)	4-7	7-13	12-18	18-65
	Race				
	White	4 (57.1%)	8 (53.3)	8 (57.1)	105 (68.2)
	Black	0	0	0	12 (10.2)
	Asian	3 (42.9%)	7 (46.7)	6 (42.9)	20 (16.9)
Other	0	0	0	1 (0.6)	
Study Results:	154 subjects from the pivotal trials have rolled into this extension study as of data cut-off. Complete follow up data is available for 132 subjects \geq 12 to \leq 65 years of age from CSL627_1001 and 22 subjects 0 to < 12 years of age from CSL627_3002; partial follow up data was assessed for all other subjects. To date, there have been no deaths and none of the 6 SAEs documented to date have been attributed to the product. Two subjects in the oldest age group have discontinued, including one subject due to product-attributable non-serious AE.				

2.3.2 Safety-related Data from CSL627_3001

Local tolerability: Local reactions at infusion site were assessed by subject/subject caregiver. The severity of the reaction at 8,587 individual infusion sites (subjects could have multiple infusion sites during the same infusion event) was assessed one hour after infusion by the subject as “none,” “very slight,” “slight,” “moderate,” or “severe.” All 8,587 reactions (100%) were assessed as “none,” “very slight,” or “slight” by subjects.

Systemic adverse events: The most common clinical adverse experiences (incidence >2%) were nasopharyngitis (8 subjects/5.2%), and upper respiratory tract infection (4 subjects/2.6%). One subject, a 55 year-old male originally enrolled in CSL627_1001, experienced a non-serious hypersensitivity reaction (details of reaction were not provided) that was attributed to the product after 65 EDs. The AE resolved within 24 hours but the subject was discontinued from the study after a positive rechallenge. One additional subject experienced the AE of “rash/rash pruritic” which could not be ruled out as potentially related to a hypersensitivity reaction.

Serious adverse events: Five subjects have reported 6 SAEs: appendicitis, pneumonia, laceration, road traffic accident, musculoskeletal stiffness, and nephritis. Of note, “musculoskeletal stiffness” occurred following “road traffic accident” in the same subject. “Nephritis” was diagnosed in a 20 year-old male enrolled from CSL627_1001 with history of asthma and syringomyelia; the subject had no documented history of renal disease and serum creatinine level on 30 January 2015 was 0.62. On 27 February 2015 the subject was hospitalized with abdominal

pain and diagnosed with right-sided nephritis; he was treated with antibiotics until 12 March 2015 and illness resolved completely. The subject continued to receive scheduled prophylactic doses of the product throughout the hospitalization. The investigator did not attribute this AE to the product, but discontinued the subject from the study following discharge nonetheless.

Development of inhibitors and new antibodies: No subjects have developed inhibitors, non-inhibitory ADAs, or antibodies to CHO host cell proteins during the study.

Deaths and Discontinuations: No deaths were reported. Two subjects described above have thus far discontinued the study before completion of the trial: one due to non-serious hypersensitivity, and one due to nephritis.

3.0 PHARMACOVIGILANCE PLAN (PVP)

The sponsor’s identified safety concerns and PVP are summarized in the tables below.

Table 9: Summary of Safety Concerns

[adapted from tables 13-17 in pharmacovigilance plan, p 26-31 and from CSL-Behring’s response in 17 February 2016 submission (for FDA Information Request dated 09 February 2016)]

		Nature of Risk
Important identified risks	Hypersensitivity and anaphylactic reactions	Hypersensitivity and anaphylactic reactions are rare but well known adverse reactions to FVIII products.
Important potential risks	Clinical impact of non-inhibitory ADAs	In common with all therapeutic proteins, there is potential for immunogenicity in patients exposed to treatment with Afstyla. Health risks are unknown.
	Development of inhibitors	Inhibitors may bind to the functional epitopes of coagulation factors, resulting in the neutralization of activity or promotion of clearance from the blood. Loss of efficacy and inadequate hemostasis may occur.
	Development of antibodies against CHO host cell proteins	Process impurities such as host cell proteins are a known risk for biological products. Although the severity and nature of this risk are unknown at this point in time, the CHO genome contains many proteins that are substantially dissimilar to the human genome from the T-cell epitope standpoint, and thus inherently pose some risk of triggering anti-self immune responses
	Clinical impact of discrepant potency assay measurements of FVIII activity	A discrepancy between the results of the one-stage (OS) and chromogenic substrate (ChS) assays was observed during development, such that FVIII activity levels determined by the OS assay were approximately 45% lower than those determined by the ChS assay. CSL has proposed that FVIII activity monitoring be performed using ChS but indicated that a consistent conversion factor can be used by clinicians who wish to use the OS assay; clinicians unaware of this discrepancy using the OS assay may underestimate FVIII activity, potentially leading to inadvertent overdosing and possible increased risk of thrombogenicity. (Of note, the OS assay is more widely used in the U.S.)

Missing information	Experience of inhibitor formation in PUPs* Experience in pregnancy/lactation/labor and delivery Experience in geriatric subjects	These were underrepresented populations in the Clinical Safety Database and there is limited information regarding the use of Afstyla in these patients.
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*PUPs= previously untreated patients

Table 10: Pharmacovigilance plan for Afstyla

Safety Concern	Planned Action(s)
Hypersensitivity and anaphylactic reactions	<ul style="list-style-type: none"> - Product label to include a contraindication for individuals with known life-threatening hypersensitivity to recombinant FVIII products or their excipients, including hamster protein. The warnings and precautions section of the product label will also include a warning of the possibility of allergic reactions and a recommendation regarding hypersensitivity. - Routine PV including additional follow-up and specific follow-up questionnaire. - CSL627_3002 Phase III in previously treated children. - CSL627_3001 extension study.
Development of inhibitors to FVIII products	<ul style="list-style-type: none"> - Proposed product labeling states that “patients should be monitored for the development of neutralizing antibodies (inhibitors) by appropriate clinical observations and laboratory tests.” - Routine PV including additional follow-up and specific follow-up questionnaire. - CSL627_3002 Phase III in previously treated children. - CSL627_3001 extension study.
Development of antibodies against CHO host cell proteins Clinical impact of non-inhibitory ADAs	<ul style="list-style-type: none"> - Routine PV including additional follow-up and specific follow-up questionnaire. - CSL627_3002 Phase III in previously treated children. - CSL627_3001 extension study.
Clinical impact of discrepant potency assay measurements of FVIII activity	<ul style="list-style-type: none"> - Proposed product labeling states in WARNINGS AND PRECAUTIONS that “there is a consistent and predictable difference in FVIII activity measurements between the 2 assay formats... ChS assay results most accurately reflect the clinical hemostatic potential... If the OS assay is used, interpret results taking into account that OS assay results are approximately 45% lower than those of the ChS assay (i.e., the OS results can be aligned to ChS assay results by multiplying the OS result by ^{(b) (4)}.” - Additional communication on assays, directed at clinicians involved with product dosing, including hematologists and pathologists.
Experience of inhibitor formation in PUPs	<ul style="list-style-type: none"> - Routine PV including additional follow-up and specific follow-up questionnaire. - CSL627_3001 extension study (planned enrollment of PUPs in this study)
Experience in pregnancy/lactation/labor and delivery Experience in geriatric subjects	<ul style="list-style-type: none"> - Routine PV including additional follow-up with Pregnancy follow-up questionnaire.

Routine pharmacovigilance is described by the sponsor as standard practices of collection of reports of suspected adverse reactions (including spontaneous reports, reports from clinical

studies); preparation of reports for regulatory authorities (e.g., individual case safety reports, PSURs), and maintenance of continuous monitoring of the safety profile of the approved product (including signal detection and evaluation, updating of labeling, and liaison with regulatory authorities).

In addition to routine pharmacovigilance and the proposed labeling pertinent to identified risks, the sponsor plans to complete two ongoing clinical trials: CSL627_3002 pediatric study and CSL627_3001 extension study. The study design and endpoints for CSL627_3002 have been previously described. In order to obtain safety information on the use of the product in PUPs, the sponsor has proposed modifications to the protocol for CSL627_3001 which will allow for enrollment and follow-up of PUPs. The sponsor has indicated that complete details about these modifications will be included along with the next interim CSR.

The sponsor estimates that study CSL627_3002 will be completed shortly following licensure. CSL627_3001 is estimated to be completed with submission of final CSR in 2020.

Finally, the sponsor has proposed a multi-faceted communication plan designed to educate hematologists and pathologists about the need to use a conversion factor if using the OS assay to monitor FVIII activity (described below in section 4.3).

4.0 INTEGRATED RISK ASSESSMENT

4.1 Limitations of the Clinical Safety Database

A total of 258 unique patients have been evaluated in studies reviewed in support of this original BLA 125591 for licensure of Afstyla, and all are male hemophiliacs, reflecting the rarity of the disease in females. Thus, although experience regarding use of this product in females is limited, the database reflects the preponderance of the population in which the product will be used.

71 of these 258 patients (27.5%) were non-Caucasian. Black subjects were notably absent from the pediatric safety population. It is important to note that non-Caucasian race may be a risk factor for the development of inhibitors [3], and the somewhat narrow range of ethnic diversity represented in the clinical safety database poses limitations in assessment of the risk profile in the indicated total treatment population.

Finally, the clinical development program for Afstyla included no PUPs. The lack of safety data about PUPs is a significant gap in understanding the safety profile of the product in the indicated population, specifically with regards to the potential for development of inhibitors. It may be that by requiring enrolled subjects to have a history of previous FVIII treatment while demonstrating no history of inhibitors, the subject population in the clinical trials was systematically restricted to individuals inherently at decreased risk of developing inhibitors. Additionally, it has been suggested that recombinant FVIII product use in PUPs is associated with a higher degree of inhibitor development when compared to the use of plasma derived FVIII in PUPs [4], highlighting the continued need for safety data regarding inhibitor development in PUPs.

4.2 Assessment of safety data and PVP

The sponsor identified several safety concerns potentially associated with use of the product, including hypersensitivity/anaphylaxis, development of inhibitors to FVIII product (particularly in PUPs) as well as non-inhibitory ADAs, development of antibodies to hamster proteins, and insufficient safety information on special populations, including females (specifically those who are pregnant, lactating, or delivering) and geriatric patients. As previously noted, non-Caucasians may also represent an additional special population in which the safety of the product was insufficiently evaluated.

Review of the clinical safety database identified no other substantial safety concerns. Infusion site reactions were rare and mild when they were noted. SAEs occurred infrequently and were usually readily discerned to be unlikely to be attributed to the product. There were no apparent patterns/clustering of AEs with regards to involved organ system. Notably, no TEEs were documented. Thus, available safety data for the product was largely reassuring.

Anaphylaxis/hypersensitivity

Six of 258 (0.02%) unique patients developed hypersensitivity reactions or symptoms that could not be ruled out as related to hypersensitivity. No patients developed anaphylaxis, but one of the cases of hypersensitivity reaction was determined to be serious. While there are no population-based estimates in the literature for occurrence of hypersensitivity AEs in patients receiving exogenous FVIII, documented cases have been published [5]. These reactions are a known risk associated with this class of blood product. The fact that most incidents of hypersensitivity were mild is reassuring. The proposed label warnings and routine pharmacovigilance as well as additional collection of relevant safety data from the ongoing studies are adequate measures to monitor this risk.

Development of FVIII Inhibitors

The development of inhibitors to exogenous FVIII products is likely part of the natural history of hemophilia A [3,6]. Development of inhibitors represents a significant challenge to individuals with Hemophilia A, as these antibodies inactivate the procoagulant activity of FVIII and inhibit patients' response to replacement therapy [3].

To date, no subjects in these clinical trials have developed inhibitors during the clinical follow-up periods. However, all study subjects in the clinical safety database are previously treated patients (PTPs). There is currently no experience with the use of this product in PUPs and information about the use of the product in this particular population will not be available until the planned postlicensure inclusion of the PUPs study arm to CSL627_3001, should the product be licensed. This strategy is consistent with recommendations from the European Medicines Agency (EMA) and the International Society on Thrombosis and Hemostasis (ISTH) regarding the use of PTPs. PTPs, by virtue of not having developed an inhibitor, are generally considered to be tolerant of factor VIII and therefore at a relatively low risk for inhibitor development. The EMA recommends that PTPs are a reasonable cohort in which to determine whether new products are highly immunogenic, and that determination of high immunogenicity potential is sufficient for prelicensure studies [7]. Additionally, because of the rarity of PUPs and the fact

that PUPs have a certain risk – but not clearly defined – of inhibitor formation, the ISTH recommends that PUPs should be reserved for studies of the natural history of inhibitor development [8]. Thus, with no available safety information about use of Afstyla in PUPs at this time, it is not possible to determine the true risk of inhibitor development in the complete indicated population.

Additionally, as previously noted, most of the safety data is from non-Caucasians. The additional information on non-Caucasian subjects that will be made available from completing ongoing clinical trials, as well as information derived from the modifications to CSL627_3001 that include a new arm involving PUPs, will be critical for closing the current gaps in the ability to assess these risks.

Development of non-inhibitory ADAs and antibodies to hamster proteins

As described in Table 8, use of this product may induce immunogenicity in the form of both non-inhibitory ADAs and novel antibodies to hamster proteins. The level of risk associated with these theoretical AEs is unknown. Additionally, the fact that no subjects to date have developed either of these AEs may suggest that these AEs would rarely manifest, although exclusive use of PTPs in the clinical trials likely restricted study patients to individuals inherently less prone to immunogenicity. Acquiring additional data from ongoing trials, the proposed label inclusions, and routine pharmacovigilance are likely sufficient to monitor risks associated with these AEs.

Special populations

As previously noted, the preponderance of the safety data is derived from male subjects. This is expected given the natural demographics for the disease [1]. Additionally, although the life expectancy of hemophiliacs is increasing due to improved treatments and increased viral screening of transfused blood products, the proportion of severe hemophiliacs who are aged 65 years and older remains small [9]. The small numbers of non- males and geriatric patients with Hemophilia A renders observational studies specifically in these special populations both prohibitively impractical and of relatively low utility. Routine pharmacovigilance is adequate to monitor risks in these special populations.

4.3 Clinical impact of discrepant potency assays for laboratory monitoring of FVIII activity

The physician's determination of Afstyla dosing may be based on the clinical monitoring of the patient's plasma FVIII activity, which is measured by either a chromogenic assay or a one-stage clotting assay. The significant potency difference between the chromogenic and one-stage assays, if interpreted incorrectly, may lead to incorrect dose administration in real-world clinical practice. The one-stage assay is used more widely in the U.S. Underdosing would lead to lack of efficacy and poor management of bleeding episodes, while overdosing may increase the risk of thrombogenicity. Available literature suggests that thrombotic events in the setting of FVIII supplementation are rare, potentially reflecting the fact that the disease mitigates any risk that might be incurred due to administering exogenous FVIII [10]. However, a theoretical risk should be considered.

In an Information Request response (dated February 17, 2016), the sponsor proposed strategies to accomplish the necessary communication for education of hematologists and pathologists regarding FVIII assays (Table 11). The proposed communication plan was discussed by the multidisciplinary BLA review team and FDA comments were provided to the sponsor regarding potential avenues of clinician education that would be acceptable.

Table 11: Sponsor proposed communication plan regarding assays to measure factor VIII activity

Target Audience: HTC (Hemophilia Treatment Center) Hematologists Non-HTC Hematologists	FDA Comments
Communication points <ul style="list-style-type: none"> • rVIII-SingleChain is approved by FDA for treatment of Hemophilia A • For FVIII activity monitoring, both OS and ChS assays are acceptable • ChS assay is preferred for accuracy, request this assay if available at your lab • When interpreting test results: <ul style="list-style-type: none"> ○ Confirm which assay was used (OS or ChS) ○ If ChS assay, use reported factor levels ○ If OS assay, multiply factor level results by ^{(b) (4)} 	
Communication methods <ul style="list-style-type: none"> • Scientific communication <ul style="list-style-type: none"> ○ Publications in scientific journals ○ Education at professional society meetings, e.g., American Society of Hematology, Hemostasis & Thrombosis Research Society (handouts and discussions at CSLB promotional and Medical booths) ○ Outreach by CSLB Medical experts ○ Peer-to-peer education (rVIII-SingleChain speaker programs) • Sales Force communication <ul style="list-style-type: none"> ○ Training and education for CSLB sales representatives ○ Audience-appropriate handouts/communications • Additional actions <ul style="list-style-type: none"> ○ Dedicated section of www.ProductName.com website ○ Key word optimization to allow for search engines to find rVIII- SingleChain laboratory monitoring test information ○ Medical Information phone line available: 1-800-504-5434 	<ul style="list-style-type: none"> - Acceptable - Acceptable - Acceptable if consistent with the approved product label/medical experts may provide other information in response to unsolicited requests - Acceptable if consistent with promotional/ advertising regulations - Acceptable - Acceptable if consistent with promotional/advertising regulations - Acceptable - Acceptable - Acceptable

FDA plans to continue ongoing discussions with the sponsor regarding acceptability of the proposed actions and overall optimization of the communication plan. In addition to the above components, FDA suggested other communication strategies to enhance awareness of healthcare providers regarding the potency assays:

- a. Creation of webinar with case studies this is consistent with the approved product label
- b. Creation of a laboratory monitoring Instruction For Use (IFU) document accompanying the package insert
- c. Outreach to pharmacy/medical informatics to include flagging of electronic physician orders or laboratory orders to display warning
- d. Dear Healthcare Provider letters
- e. Outreach to medical centers and their healthcare facility formularies
- f. Use of focus groups to evaluate the usefulness of the educational materials

FDA also plans to discuss other labeling strategies in future labeling meetings with the sponsor. This would include the addition of a boxed warning on monitoring laboratory tests and the need to use a conversion factor to align the results of the one-stage assay with those of the chromogenic substrate assay. Positioning this important monitoring information in a boxed warning would ensure its ubiquitous presentation in prescribing tools and in promotional materials.

Finally, FDA asked that the sponsor include communication plan activities regarding the potency assay discrepancy in future versions of the pharmacovigilance plan.

5.0 RECOMMENDATIONS

At this time, OBE/DE agrees with the proposed pharmacovigilance activities and postmarketing studies proposed by the sponsor in BLA 125591/0.

- A. Routine pharmacovigilance, which includes reporting of postmarketing adverse experiences to FDA in accordance with 21 CFR 600.80.
- B. Distribution reports should be provided to FDA in accordance with 21 CFR 600.81.
- C. Communication strategies (in addition to labeling) for management of the potential risk of dosing error due to discrepancy in assays to monitor plasma FVIII activity in patients treated with Afstyla. The communication plan is currently under discussion with the sponsor; agreed upon strategies should also be included in future versions of the pharmacovigilance plan.
- D. While we defer to OBRR on the two ongoing clinical studies [CSL627-3001 (extension study) and CSL627_3002 (pediatric study)], continuation of these studies in the postmarketing period will be useful in collecting additional safety data in underrepresented populations in the Clinical Safety Database such as previously untreated patients (PUPs) and on its long-term safety profile. The sponsor should provide the protocol for the proposed modifications of CSL627-3001 to include PUPs as well as timelines for expected safety analyses. The

sponsor should provide planned dates for completion of CSL627_3002 and submission of the final study report.

At this time, the available safety data do not substantiate a need for a postmarketing requirement (PMR) study with safety as a primary endpoint, or a Risk Evaluation and Mitigation Strategy (REMS).

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