PAS 125591 Recombinant Coagulation Factor VIII (rVIII-Single Chain)

FROM: Karl Kasamon, M.D., Medical Officer, BHB, OTP, CBER

THROUGH: Prasad Mathew MD, Brach Chief, BHB, OTP, CBER

SUBJECT: STN 125591 Labeling Supplement

PRODUCT: Recombinant Coagulation Factor VIII (rVIII-Single Chain)

SPONSOR: CSL Behring Recombinant Facility AG

STUDY TITLE: CSL627_3001: a Phase 3 Open-Label, Multicenter, *Extension Study* to Assess the Safety and Efficacy of Recombinant Coagulation Factor VIII (rVIII-Single Chain, CSL627) in Subjects with Severe Hemophilia A.

Introduction

Afstyla is an antihemophilic factor (Recombinant), single chain (rVIII-Single Chain), approved on 25 May 2016 for the indications for use in adults and children with hemophilia A (congenital Factor VIII deficiency) for:

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

Behring has submitted a safety supplement in support of the proposed labeling changes to expand the clinical indication to previously untreated patients (PUPs).

Executive Summary:

This submission is a safety review labeling supplement for antihemophilic factor (Recombinant), single chain (rVIII single chain) licensed in 2016 for the treatment of adults and children with hemophilia A for on demand treatment and control of bleeding episodes, routine prophylaxis to reduce frequency of bleeding episodes, and perioperative management of bleeding. The Applicant submitted data from Arm 2 (PUPs) of study CSL627_3001 in support of the proposal to add information about treatment of PUPs to the package insert. The Agency has already evaluated efficacy data with initial approval of AFSTYLA for previously treated patients (PTPs) from study CSL627_3001 arms 1 and 3, and review of efficacy data for this PAS labeling supplement is unnecessary given no mechanism for a differential response to AFSTYLA

by PTPs (in original indication), vs. PUPs (evaluated in the current study data). Due to potential for the development of inhibitory antibodies against AFSTYLA (factor inhibitor) in PUPs, a review of safety data was performed.

Study CSL627_3001 was a multicenter, nonrandomized, open-label, multiple-arm extension study, closed 19 January 2021. It was designed to satisfy EMA 2011 guidelines stipulating a population size of 50 exposed for 50 EDs, which were abandoned in 2018. Thus, during the conduct of the study, an amendment was issued that decreased the planned population size to the final PUP population of 24.

Data from the PUP cohort 2 of Study CSL627_3001 indicate that 12 of 24 subjects who started treatment (50%) developed an inhibitor to Factor VIII. Six of these (25%) had peak inhibitor values in the high titer range, and six (25%) were low. The protocol primary safety endpoint was the incidence of high titer inhibitor (≥ 5BU) in subjects reaching ≥ 50EDs. Of the 24 treated subjects, 21 reached 50 EDs, and 6 of these had high titer inhibitors. The overall median EDs until initial inhibitor development was 10 EDs (range: 4 to 23). Of 12 subjects with inhibitors, 11 subjects have remained in the trial; 9 experienced successful eradication of the inhibitor. The median (range) EDs to inhibitor eradication was 37.00 (16.0 to 194.0). The median (range) time to inhibitor eradication was 14.29 (7.7 to 64.4) weeks. Two subjects with high titer inhibitors remained inhibitor positive: one subject was withdrawn from the immune tolerance induction (ITI) substudy after approximately 12 months, another subject completed the ITI substudy after approximately 24 months.

Study CSL627_3001; Arm 2 (PUPs)

Primary Objective(s)
• To characterize the safety with respect to inhibitor development in PUPs.
• To evaluate efficacy of on-demand and prophylaxis treatment of rVIII-Single Chain in PUPs.
Secondary Objective(s)
• To further characterize the safety profile of rVIII-Single Chain with respect to inhibitor development.
• To characterize the safety profile of rVIII-Single Chain with respect to antibodies against rVIII-Single Chain and antibodies to Chinese hamster ovary (CHO) proteins.
• To collect and evaluate the number of rVIII-Single Chain injections required for the treatment of bleeding episodes.
• To characterize consumption of rVIII-Single Chain in prophylaxis, on-demand treatment, and surgery.
• To assess the hemostatic efficacy of rVIII-Single Chain for PUPs who undergo surgery,
using the 4-point efficacy evaluation of surgical treatment scale.
• To assess the occurrence of clinically significant abnormalities in vital signs after rVIII-Single Chain administration.

Overall Study Design and Plan: Description
Multicenter, open-label, phase 3 extension study to investigate the safety and efficacy of rVIII-SingleChain in PUPs with severe hemophilia A for prophylaxis and on-demand treatment of bleeding episodes in subjects who achieved at least 75 EDs. A surgical substudy (open to subjects from all study arms) investigated the use of rVIII-SingleChain in surgery. In addition, an ITI substudy was conducted for those subjects who developed an inhibitor during treatment with rVIII-SingleChain.

Eligible subjects were males diagnosed with severe hemophilia A (FVIII activity levels < 1%), and in Arm 2 were PUPs who had not participated in any clinical study with rVIII-SingleChain and had no other prior exposure to any FVIII product.

Exposure:
The mean (SD) number of EDs for the overall 24 subjects was 245.5 (161.56). A total of 21 subjects (87.5%) attained > 50 EDs. The mean (SD) dose administered per injection was 53.3 IU/kg (26.34). Twenty-four subjects were enrolled and exposed to rVIII-Single Chain, and 12 subjects (50%) tested positive for inhibitors. Of these, 6 subjects (25%) had a peak inhibitor value in the high-titer range, and 6 subjects (25%) had a peak inhibitor value in the low-titer range.
The overall median ED for initial inhibitor development was 10 EDs (range 4 to 23 EDs). Of the 12 inhibitor-positive subjects, 1 subject was withdrawn from the study because of protocol requirement as a result of high inhibitor titer at diagnosis (8.50 BU/mL); following this the CSP was amended to allow subjects diagnosed with inhibitor to continue participation in the study and enroll into the ITI sub study. Of the remaining 11 inhibitor-positive subjects; 9 subjects had inhibitor eradication by end of study, 1 subject was withdrawn after entering the ITI sub study (physician's decision), and 1 subject had inhibitor-positive status at the end of study.

Adverse Events
All subjects in the PUP Safety Population, experienced at least 1 TEAE. A total of 320 TEAEs were reported, the majority of which were mild (208) or moderate (93) in intensity. Seventeen TEAEs were severe. The outcome of the majority of TEAEs was recorded as resolved (292); notably, 1 nonserious TEAE of Upper Respiratory Tract Infection had an outcome of resolved with sequelae in 1 subject with 6 episodes of this TEAE. The details of sequalae were not reported and 2 subsequent episodes were reported as resolved. Twelve subjects reported 17 TEAEs related to rVIII-SingleChain. Ten subjects (41.7%) experienced 15 TEAEs of special interest that were unrelated to rVIII-Single Chain.
Fourteen subjects (58.3%) experienced a total of 21 TESAEs; 1 related TE SAE (Inhibiting Antibodies Positive) resulted in study drug withdrawal. Ten TESAEs were considered as severe, and 7 TESAEs were moderate. The outcome of the majority of TESAEs was recorded as resolved (16). No deaths or TE SAEs of special interest were reported during the study. The most frequently reported AEs are tabulated below:

Table 1. Most Common TEAEs per System Organ Class

Body System Organ Class	Number of Subjects	(%)
Infections and infestations	22	(91.7%)
General disorders and administration site conditions	16	(66.7%)
Investigations	12	(50.0%)
Injury, poisoning and procedural complications	9	(37.5%)
Gastrointestinal disorders	8	(33.3%)
Musculoskeletal and connective tissue disorders	8	(33.3%)
Respiratory, thoracic and mediastinal disorders	8	(33.3%)
Skin and subcutaneous tissue disorders	7	(29.2%)
Blood and lymphatic system disorders	6	(25.0%)

Source: reviewer calculation from ADAE dataset

Of the TEAEs reported in ≥ 10% of subjects in the overall PUP Safety Population, the most commonly reported TEAEs were Pyrexia (44 TEAEs) in 15 subjects, Upper respiratory Tract Infection (18) in 7 subjects, Nasopharyngitis (15) in 9 subjects, and PTs summarized as Inhibitor Development (14 TEAEs; Inhibiting Antibodies Positive [7], Anti-factor VIII Antibody Positive [6], and Factor VIII Inhibition [1]) in 13 subjects). This is tabulated:

Table 2. TEAEs by SOC and PT Reported in ≥ 10% of PUPs. Safety Population; N=24)

Body system organ class	**Preferred term**	**Subjects N=24**	**%**
Blood and lymphatic system disorders	Iron deficiency anemia	3	12.5%
Gastrointestinal disorders	Diarrhea	5	20.8%
	Vomiting	3	12.5%
General disorders and administration site conditions	Pyrexia	15	62.5%
Infections and infestations	Bronchitis	3	12.5%
	Conjunctivitis	3	12.5%
	Ear infection	5	20.8%
	Influenza	4	16.7%
	Nasopharyngitis	9	37.5%
	Otitis media	4	16.7%
	Rhinitis	6	25%
	Tonsillitis	5	20.8%
	Upper respiratory tract infection	7	29.2%
Infections and infestations	Varicella	6	25%
Injury, poisoning and procedural complications	Fall	4	16.7%
Investigations	Anti factor VIII antibody positive	6	25%
	Inhibiting antibodies positive	6	25%
Respiratory, thoracic and mediastinal disorders	Cough	6	25%
Skin and subcutaneous tissue disorders	Eczema	3	12.5%
	Rash	3	12.5%

Source: calculated by reviewer from ADAE dataset

Fourteen subjects (58.3%) experienced 21 TESAEs, of which 13 TESAEs were related to rVIII-Single Chain. The most commonly reported TESAEs were PTs summarized as Inhibitor Development (12 TESAEs in 12 subjects [50%] which were all considered as related; A TESAE of Hemorrhage in an inhibitor positive subject was considered as related as well. A TESAE of Fall was reported in 2 subjects (8.3%), both were considered as unrelated. All the other TESAEs were reported in 1 subject each.

TEAEs that were considered related to IP by the investigator/sponsor included: One case of fatigue, one case of pyrexia, one case of hemorrhage (biceps muscle), as well as the factor inhibitors described in the section below. The muscle hemorrhage was an SAE reported in a one year old who required hospitalization, and it resolved after treatment with Novo7®. The subject ((b) (6)) who developed the pyrexia considered related (severity mild) had this AE start on Day 556 whereas the anti FVIII antibody positive AE started on day 541, this AE was mild.

IR was sent to clarify whether these AEs attributed to IP per the sponsor's investigator constituted adverse drug reactions for the purpose of labeling. While the sponsor confirmed that the investigator did ascribe the events to the IP, the sponsor rejected this conclusion.

Reviewer comment: The Agency ultimately determined that the utility of including these events in ADR reporting in USPI was not very informative, especially when attribution of AEs by investigator was rejected by sponsor.

Inhibitor Formation

Twenty-four subjects were enrolled and exposed to rVIII-Single Chain during the study, and 12 subjects (50.0%) tested positive for inhibitors. Of these, 6 subjects (25.0%) had a peak inhibitor value in the high-titer range of ≥ 5BU.
The overall median ED for initial inhibitor development was 10 EDs (range 4 to 23 EDs). Median ED for initial inhibitor development in high titer subjects was 9.0 ED (range 4 to 23 EDs) and in low titer subjects was 10 EDs (range 5 to 23 EDs)

Of the 24 treated subjects, three discontinued prior to 50 EDs, and 21 reached 50 EDs; of these, had high titer inhibitors. One subject developed inhibitor on Day5 and discontinued the study.

Of the 12 inhibitor-positive subjects, 1 subject was withdrawn from the study because of protocol requirement as a result of high inhibitor titer at diagnosis (8.50 BU/mL); following this the CSP was amended to allow subjects diagnosed with inhibitor to continue participation in the study and enroll into the ITI substudy. Of the remaining 11 inhibitor-positive subjects; 9 subjects had inhibitor eradication by EOS, 1 subject was withdrawn after entering the ITI substudy (physician's decision), and 1 subject had inhibitor-positive status at EOS.

Time to inhibitor eradication was defined as the time between start of the first ITI dose (ie, first dose adjusted to treat the inhibitor, as defined by the investigator) to the complete response (ie, a confirmed inhibitor titer < 0.6 BU/mL at 2 consecutive visits, analyzed at the central laboratory).
Eleven subjects were treated for their inhibitor with ITI. Of these, 9 subjects had low-titer inhibitors and 2 had high-titer inhibitors at the time they began treatment for their inhibitor. In the end, 6 peak low-titer inhibitor subjects and 5 peak high-titer inhibitor subjects were treated for their inhibitor.
Nine of 11 subjects (81.8%) achieved inhibitor eradication with rVIII-Single Chain. The median (range) EDs to inhibitor eradication was 37 (16 to 194). The median (range) time to inhibitor eradication was 14.3 (8 to 64) weeks. Six peak low-titer subjects and 3 peak high-titer subjects achieved inhibitor eradication.
Six of the 11 subjects received ITI treatment with rVIII-Single Chain in the ITI substudy. Of these, 5 subjects received low-dose (50 IU/kg 3 times weekly) and 1 subject received a high-dose (200 IU/kg daily [may be split into 2 doses of 100 IU/kg daily]) ITI regimen with rVIII-Single Chain.

Recommendations
Overall, the safety signal in PUPs is similar to that on PTPs, except inhibitor formation, as would be expected. While the incidence of total inhibitors to FVIII and high titer inhibitor reported herein appeared higher that what has been noted in other, comparable products, this may be due to chance, considering the small numbers of subject treated. Ultimately this can be adequately communicated in the USPI.

Labeling: Negotiation with applicant has been completed, this included clinical team IRs, and an IR from statistics.

Conclusion:
50% of the PUPs were reported to have developed an inhibitor. The PUP study findings will be incorporated into the USPI.