Amsterdam, 16 December 2021
EMA/CHMP/753870/2021
Committee for Medicinal Products for Human Use (CHMP)

Assessment Report for paediatric studies submitted in accordance with article 46 of regulation (EC) No 1901/2006, as amended

Elocta

International non-proprietary name: efmoroctocog alfa

Procedure no.: EMA/H/C/003964/P46/007

Note

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

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1. Introduction

On 26 February 2021, the MAH submitted a clinical study report from a completed paediatric study on Elocta, in accordance with Article 46 of Regulation (EC) No1901/2006, as amended.

An expert overview has also been provided.

2. Scientific discussion

2.1. Information on the development program

The MAH stated that study "Sobi.Elocta-003 (ReITIrate)" is a stand-alone study.

2.2. Information on the pharmaceutical formulation used in the study

Investigational medicinal product rFVIIIFc was provided as a powder and solvent for solution for injection.

Each pack of rFVIIIFc contained 1 powder vial, 3 mL solvent in pre-filled syringe, 1 vial adapter, 1 infusion set, 2 alcohol swabs, 2 plasters and 1 gauze pad.

Powder: The active substance was efmoroctocog alfa (recombinant coagulation factor VIII, Fc fusion protein). Each vial of rFVIIIFc contained nominally 250, 500, 1000, 2000 or 3000 IU efmoroctocog alfa.

The other ingredients were sucrose, sodium chloride, L-Histidine, calcium chloride dihydrate, polysorbate 20, sodium hydroxide and hydrochloric acid.

Solvent:

Investigational medicinal product was dispensed in accordance with national requirements 3 mL water for injections. Home delivery of investigational medicinal product could be offered in compliance with national requirements.

2.3. Clinical aspects

2.3.1. Introduction

The MAH submitted a final report for:

Sobi.Elocta-003 (ReITIrate)

Title: A Non-Controlled, Open-Label, Multicenter, Study of Immune Tolerance Induction Performed with rFVIIIFc within a Timeframe of 60 Weeks in Severe Hemophilia A Patients with Inhibitors who have Failed Previous Immune Tolerance Induction Therapies

2.3.2. Clinical study

Clinical study number and title

Sobi.Elocta-003 (ReITIrate) is an open-label, single-arm, interventional multi-center phase 4 study of ITI treatment performed with rFVIIIFc within a timeframe of 60 weeks in severe hemophilia A patients with inhibitors, who have failed previous ITI therapies.

Description

Study centers:
The study was initiated in total of 18 sites, of those, 11 sites in North America and Europe recruited and treated patients

Studied period:
Study Initiation Date: October 17, 2017
Study Completion Date: August 31, 2020

Type of study: Phase IV

Methods

Objectives

Primary objective:
To describe the outcome of ITI treatment performed with rFVIIIFc within a timeframe of 60 weeks in patients who failed previous attempts at tolerization including use of immunosuppressants.

Secondary objectives:

- Time to tolerization (i.e. ITI success) of ITI performed with rFVIIIFc within a timeframe of 60 weeks in patients who failed previous attempts at tolerization including use of immunosuppressants.
- The relapse rate over a 48-week period following successful ITI performed with rFVIIIFc.
- Intercurrent bleeding during ITI and during the 48-week period after successful ITI performed with rFVIIIFc.

- Safety and tolerability of rFVIIIFc when used for ITI.
- Impact of ITI treatment with rFVIIIFc on health economy.
- Adherence of rFVIIIFc when used for ITI.

Exploratory objective

- Mechanism of ITI in patients undergoing ITI performed with rFVIIIFc.

Exploratory objective and results will be reported in a separate report.

Study design

This was an open-label, single-arm, interventional multi-center study designed to explore ITI treatment performed with rFVIIIFc within a timeframe of 60 weeks in patients with severe hemophilia A, who have failed previous attempts at tolerization including use of immunosuppressants.

The patient should have undergone at least one failed ITI treatment attempt with the following characteristics:

- A minimum FVIII dose equivalent to the low dose arm of the International ITI study (50 IU/kg, 3 times/week).
- A minimum ITI treatment period of 33 months.
- An ITI treatment shorter than 33 months if no downward trend of at least 20 % in the inhibitor titer in any 6-month period after the initial 3 months of the ITI treatment indicating a stagnation in the tolerization attempt.

The use of immunosuppressant drugs without the combination of the above was not sufficient.

The study consisted of 4 periods: a screening period, an ITI treatment period, a tapering period and a follow-up period.

Screening period

During the 4 to 6 weeks screening period, patients were to continue with their current treatment regimen in accordance with the local standard of care. Patients who met all inclusion and no exclusion criteria were enrolled into the study.

ITI period

The first dose of rFVIIIFc was administered at the Baseline visit and the ITI treatment was to continue until ITI success was declared or for a maximum of 60 weeks. The ITI regimen consisted of daily administration of rFVIIIFc 200IU/kg per day, which could be given as once daily injections or divided into two injection injections per day at the discretion of the investigator.

ITI outcome was assessed on an ongoing basis. Patients could achieve 1 of 4 outcomes:

- ITI success.
- Partial success (defined as achieving negative inhibitor titer and one of the pharmacokinetic parameters of ITI success: IR >66 % OR elimination half- life ≥7 hours).
- Treatment failure (defined as fulfilling one of the following 3 criteria: no downward trend of at least 20 % in the inhibitor titer in any 6-month after the initial 3 months of ITI treatment; presence of a

sustained positive inhibitor (≥0.6 BU/mL) after 60 weeks of ITI; or negative inhibitor titer without either achieving IR >66 % of expected IR or elimination half-life t½z ≥7 hours after 60 weeks of ITI).

- Not determinable due to withdrawal during the ITI period.

ITI success was defined as achieving the following criteria (in order 1, 2 and 3) simultaneously within 60 weeks:

1. Negative inhibitor titer (<0.6 BU/mL) at 2 consecutive visits.
2. Calculated IR >66 % of the expected IR at 2 consecutive visits.
3. Elimination half-life (t½) ≥7 hours.

Only the patients who achieved ITI success within 60 weeks were to continue into the tapering period.

Tapering period

During the tapering period the dose was to be reduced with the aim to reach prophylactic dose after a total of 16 weeks. The dose and regimen were adjusted by the investigator in accordance with local practice and investigator judgment. During the tapering period patients were monitored for relapse.

Relapse was defined as the occurrence of the following (with or without clinical signs or symptoms) after complete ITI success:

- A positive inhibitor (≥0.6 BU using the Nijmegen assay) on 2 consecutive assessments, performed within 2-4 weeks

AND

- An IR ≤66% of t e expected IR on 2 consecutive assessments, performed within 2-4 weeks.

Follow-up period

After completion of the tapering period, patients were to enter the follow-up period. During the follow-up period, patients were to be treated prophylactically for up to 32 weeks with dose and frequency prescribed by the investigator, and according to the label and clinical response of the patient, for 32 weeks. If the tapering period was prolonged, the follow-up period was to be shortened accordingly, but could not be less than 24 weeks.

Overall, the study covered a Screening period (4-6 weeks), ITI-period (32-60 weeks), Tapering period (16 weeks), follow-up period (24-32 weeks), and 2 weeks of safety follow-up – an more than 2 years period.

Study population /Sample size

A total of 16 patients with hemophilia A were enrolled in this study.

Patient Characteristics:

- Male patients of any age diagnosed with severe hemophilia A
- Previously treated with any plasma-derived or recombinant conventional or extended half-life FVIII
- Diagnosed with high titer inhibitors (historical peak ≥5 BU/mL according to medical records)
- Inhibitor titer ≥0.6 BU at screening
- Documented failed previous ITI attempt(s)

Treatments

For Europe and Canada, the investigational medicinal product rFVIIIFc was provided as a powder and solvent for solution for injection. In the US, commercially available ELOCTATE® in different vial strengths, with auxiliary labeling for clinical trial use, was used as rFVIIIFc supply.

Dosages were adapted to the respective study-period:

ITI period: 200 IU/kg/day which could be given as once daily doses, or divided in two doses per day.

Tapering period: The dose and regimen was adjusted by the investigator in accordance with local practice and investigator judgment.

Follow-up period: Prophylactic dose decided by the investigator according to the label and clinical response of the patient.

No reference therapy was defined due to the non-controlled study-design.

Outcomes/endpoints

The primary endpoint of the study was ITI success, defined as achieving all 3 of the following criteria simultaneously:

- Negative titer for inhibitor (<0.6 BU/mL by the Nijmegen-modified Bethesda assay) at 2 consecutive visits.
- FVIII IR >66 % of the expected IR at 2 consecutive visits.
- FVIII elimination half-life (t½) ≥7 hours.

Secondary and exploratory endpoints are identical with the respective objectives

Statistical Methods

Descriptive statistics were used to summarize the outcomes in the study and no inferential statistics were performed. Time to ITI success (time to negative inhibitor titer, time to IR >66 % of the expected IR and time to elimination half- life (t½) ≥7 hours) was analyzed using Kaplan-Maier method. The proportion of patients achieving ITI success and partial ITI success was calculated. The number of bleeds and the annualized bleeding rate for the ITI period were summarized descriptively. For each of the tapering and follow-up periods the annualized bleeding rate was summarized descriptively. Safety

data was presented descriptively across the entire study as well as by each period. Consumption was calculated for the entire study as well as for each of the periods separately.

Results

Recruitment/ Number analysed

Of the 16 patients enrolled in this study, 9 patients completed the ITI period, 2 patients entered the tapering period, one patient entered the tapering period without achieving ITI success due to site error and subsequently stopped the study, and 1 patient entered the follow-up period.

Of the 16 patients included in this study, the majority were enrolled in Europe 12 (75 %). The most frequently reported race was White (93.8%), followed by Black or African American (6.3 %).

There was only 1 adult patient. The median (min:max) age of the patients was 7.5 (3:46) years old. This patients had an average weight of 35.5 (20.2) kg, height of 136.8 (21.8) cm, and BMI of 18.1 (4.1) kg/m^2.

Baseline data

At baseline, 9 patients had pre-ITI inhibitor titers >10 BU/mL; 4 patients had historical peak inhibitor titers >200 BU/ between diagnosis of inhibitor and start of ITI.

The patient achieving ITI success presented with a historical peak inhibitor titer of 8.4 BU, and <5 years between diagnosis and start of ITI treatment.

All patients had at least 1 ITI attempt prior to study start; 10 patients had 1 ITI attempt, 4 patients 2, and 2 patients had 3 ITI attempt prior to study start.

Exposure

A median (min:max) of 62586.7 (24226.7: 89724.2) IU/kg was consumed during ITI period. Daily dose was a median of 193 IU/kg, with 193 (ITI period), 83 (Tapering period), 62 (Fup period), respectively.

Efficacy results

1 patient achieved ITI success. For this patient ITI success was achieved in 46 weeks. The patient did not experience any relapse.

2 patients were considered having partial success as final outcome. Those patients achieved partial ITI success at week 30 and 56.

6 patients had ITI failure as defined by the protocol and 7 patients were not determinable due to early withdrawal during the ITI period.

4 patients achieved confirmed negative inhibitor titer by the end of the study (at week 11, 18, 20 and 60).

3 patients had IR >66 % of expected IR (at week 30, 30.1 and 56, respectively).

2 patients reported terminal half-life t½ ≥ 7 hours (at week 46 and 59).

During the entire ITI treatment period, bleedings occurred 146 times in 12 patients; of those, 58 bleedings were traumatic, and 86 bleedings were spontaneous (information for 2 bleedings is missing). The median (min:max) annualized bleeding rate was 4.70 (0.00: 45.66) bleedings/year. The patient achieving ITI success had an annualized bleeding rate of 5.07 bleeding/year during the follow-up period.

Relevant concomitant medication

All 16 patients used concomitant medications; 143 different concomitant medications were used during this study. During the ITI period, the mean (SD) yearly consumption per kg of FEIBA and NOVOSEVEN was 9770.2 (11460.8) IU/kg/year and 54.3 (107.3) mg/kg/year, respectively. No bypassing agent was consumed during either the tapering period or the follow-up period.

Safety results

Overall, 188 TEAEs (18 serious and 170 non-serious) were reported across all 16 patients during this study.

18 treatment emergent SAEs were reported in 7 patients. Of these, 14 serious TEAE were observed during ITI period (1 severe, 12 moderate and 1 mild) and 4 during tapering period (all 4 moderate).

There were 2 reported SAE of thrombosis during the ITI period (brachiocephalic vein thrombosis and vena cava thrombosis during ITI period), both events occurred in the same patient and were considered as possible related to ITI treatment by the investigator; in addition there was 1 reported SAE of thrombosis during tapering period which was considered as not related to ITI treatment by the investigator. All 3 events were considered of moderate intensity.

There were no deaths during the study. A total of 3 SAE (infection Hickman catheter, bleeding in right thigh, and right ankle bleeding) in 2 patients led to withdrawal.

2.3.3. Discussion on clinical aspects

This ITI-study in poor-prognosis patients was thoroughly designed and covered an overall study period of more than 2 years which is considered to be adequate for this kind of long-term-intervention.

Overall, the study covered a screening period (4-6 weeks), ITI-period (32-60 weeks), tapering period (16 weeks), follow-up period (24-32 weeks), and 2 weeks of safety follow-up covering a more than 2 years period.

Of the 16 patients enrolled in this study, 9 patients completed the ITI period, 2 patients entered the tapering period, one patient entered the tapering period without achieving ITI success, and 1 patient entered the follow-up period. Only 1 "low-risk" patient (maximum inhibitor titer <10 BU) achieved ITI-success. However, the overall outcome is considered to reflect a realistic outcome in poor-prognosis patients.

Regarding safety, the reported thrombotic events raise attention with respect to the applied high dose, the extended half-life of the medicinal product, and the possible co-administration of bypassing agents.

From the narratives, the serious index-cases are reiterated, here:

A teenager with 2 thrombotic events (brachiocephalic vein thrombosis and vena cava thrombosis), potential device-infection during ITI and concomitant use of bypassing agent was reported. Both events were considered related with the study medication by the investigator. The sponsor judged the events to be unrelated. An additional jugular vein occlusion was judged to be unrelated with the study medication.

A child was reported during the tapering period with a non-occlusive thrombus in the right brachial/axillary vein. This event was assessed as non-related with the study medication and attributed to the venous catheter.

In addition, a further device related serious thrombotic event was reported. The case report concerns a child who experienced Port-catheter-thrombus during treatment. The patient received bypassing agents, including FEIBA. The event was assessed as not related to rFVIIIFc by the investigator.

Judgment of causal relationship of such thromboses as not-related is not shared with respect to the applied high dose, the extended half-life of the medicinal product, and the possible co-administration of bypassing agents. Re-evaluation is requested (Q).

In summary, 3 serious case-reports of thromboses, covering at least 5 thrombotic events, raise attention. Narratives have been provided. Causal relationship with the study medication should be re-assessed (Q): High-dose FVIII, amended half-life of this rFVIIIFc, and co-medication with bypassing agents are considered to at least contribute to the exceptional thrombus formation.

Further, non-serious AEs have not been provided in the submission. Listings and respective evaluation for thrombotic events is missing and should be amended (Q).

3. Rapporteur's overall conclusion and recommendation

Results of this ITI-study in poor-prognosis patients is considered to reflect a realistic outcome of ITI-attempts – followed for an adequate time-frame of about 2 years. Only 1 "low-risk" patient (maximum inhibitor titer <10 BU) achieved ITI-success.

Regarding safety, 3 case-reports of thromboses, covering at least 5 thrombotic events, are considered to be of interest. Number of these patients is striking (3 patients out of 9 patients in the ITI-population). Causal relationship with the study medication should be re-assessed as high-dose FVIII and amended half-life of this rFVIIIFc are considered to at least contribute to the exceptional thrombus formation (Q).

One additional thrombotic event should be amended for the first case-report in the Clinical Overview for completeness (Q).

Non-serious AE-documentation should be amended. Evaluation regarding thrombotic events is requested (Q).

Amendment of the SmPC should be discussed, respectively (Q).

☒ Not fulfilled:

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

4. Additional clarification requested

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

Safety: Thrombotic events

(1) High-dose FVIII of 200 IU/kg daily, amended half-life of this rFVIIIFc, and interaction with bypassing agents are considered to at least contribute to thrombus formation. Exclusion of a causal relationship is therefore considered to be not adequate, in general.
Consequently, re-assessment of causal relationship of all thrombotic events is requested with consecutive update of the data-base.

(2) The event "Jugular vein thrombosis" should be amended in the clinical overview within the respective case-report and all consecutive summarisations.

(3) Non-serious AEs have not been provided in the submission. Listings and respective evaluation of thrombotic events are requested.

(4) The MAH is asked to discuss the risk of thrombotic events for high-dose administration Elocta alone or in relation with bypassing agents, and respective reflection in the SmPC.

(5) A Line listing of all the studies included in the development program should be submitted (refer to Annex).

The timetable is a 30 day response timetable.

5. MAH responses to Request for supplementary information

Safety: Thrombotic events

Question 1

High-dose FVIII of 200 IU/kg daily, amended half-life of this rFVIIIFc, and interaction with bypassing agents are considered to at least contribute to thrombus formation. Exclusion of a causal relationship is therefore considered to be not adequate, in general.
Consequently, re-assessment of causal relationship of all thrombotic events is requested with consecutive update of the data-base.

MAH's responses

Two studies ((LPS16473 (997HA402) verITI 8 and ReITIrate (Sobi.Elocta-003)) involved ITI rFVIIIFc therapy (200 IU/kg/day) in patients with hemophilia A.The objective of both studies was to evaluate patients with severe hemophilia A and high-titer inhibitors to rFVIIIFc undergoing first ITI treatment (verITI-8) or after failed previous ITI therapies (ReITIrate). In the 16 patients enrolled in the verITI-8 study, no thrombotic events were reported. In the 16 patients enrolled in the ReITIrate study, four SAEs of thrombosis were reported in three patients.

Brief summaries of these SAEs are presented below:

- There were 2 reported SAEs of thrombosis during the ITI period (brachiocephalic vein thrombosis and vena cava thrombosis, both events occurred in the same patient concurrently and were considered as possibly related to ITI treatment by the investigator.

This case involves a teenager who had a Port-a-Cath placed in the left internal jugular vein with the tip terminating in the lower brachiocephalic vein. At approximately nine months after first dose of rFVIIIFc in the study, the patient presented to the hospital with complaints of dizziness, headache, and malaise, and developed neck swelling after administered with 200 IU/kg rFVIIIFc and FEIBA. The patient was subsequently hospitalized and received treatment with paracetamol and vancomycin for Staphylococcal infection. One day after infection the patient was diagnosed with a non-occlusive thrombus within the left brachiocephalic vein and superior vena cava (PT brachiocephalic vein thrombosis and vena cava thrombosis), confirmed by MRI. It was also observed that the right jugular vein was occluded. An ultrasound doppler showed extremely sluggish flow in the right subclavian and brachiocephalic veins with dominant flow into veins coming from the distended right external jugular vein.

The following day the patient's central line was removed, and FEIBA was stopped as a corrective action.

The patient was prohibited to use FEIBA in the absence of any further life-threatening bleeds. Patient recovered and therapy with rFVIIIFc was continued as planned. Blood culture was positive for S. epidermis (PT Staphylococcal infection).

Except for the infection mentioned above, the patient's medical history included several previous episodes of vascular device infections and the patient also experienced device related sepsis (catheter blood stream related infection) during the study period prior to these thrombotic events (TEs) as described in the SAE narrative.

The patient's inhibitor titer was 1 BU/mL and the patient's factor VIII activity level was very low during the TE events period, e.g <0.01 IU/ml pre dose and 0.06 IU/mL post dose.

The MAH's comment:

The patient's factor VIII activity level was low during the TE events period which indicates no correlation between the events and high factor VIII activity level.

Patient continued study drug treatment without similar events observed which indicates a negative rechallenge outcome.

The concurrent SAEs of brachiocephalic vein thrombosis and vena cava thrombosis were assessed as not related to the study drug. Multiple confounding factors including indwelling central venous catheters, infections and concomitant use of bypassing agents likely contributed to the events.

This case was included in a previous signal evaluation for thromboembolic events and described in PSUR 11.

- There was 1 reported SAE of thrombosis during tapering period which was considered as not related to ITI treatment by the investigator.

The case report involves a child patient who experienced vascular device infections on several occasions. The patient also received FEIBA for preventive or prophylactic use during rFVIIIFc treatment. The patient presented 15 months after commencing rFVIIIFc on the study with pyrexia, sore throat, cough and headache. The patient was found to have a peripherally inserted central catheter (PICC) line related infection with gram positive cocci (B. cereus). Following removal of PICC line (tip culture showed growth of Staph. epidermidis and Staph. aureus), the patient was diagnosed with a non-occlusive thrombus (PT Thrombosis) in the right brachial/ axillary vein just above the puncture site on the medial surface of the arm, by ultrasound doppler. No thrombus was seen elsewhere and no treatment was given. The event of non-occlusive thrombosis (PT Thrombosis) was assessed as not related to rFVIIIFc by the investigator and no action was taken with the study drug as a result of the event of thrombosis.

At a previously reported SAE of device related infection, there had been a concurrent reported non-serious AE of moderate jugular vein occlusion (from Day 163 to unspecified date in 2019) which were assessed as not related to the study drug by the investigator.

The MAH's comment:

The patient had low factor VIII activity level in general during study treatment period and the patient's treatment was not discontinued due to the TEs.

The event of a non-occlusive thrombus in the right brachial/ axillary vein occurred just above the puncture site on the medial surface of the arm, which indicate that this event could be device related. The MAH agrees with investigator's causality assessment that the event was not related to rFVIIIFc treatment. Multiple confounding factors including indwelling central venous catheters, repeated line infections and concomitant use of bypassing agents likely contribute to the events.

This case was included in the signal evaluation and has been described in the PSUR 10.

- In addition, one SAE of device related thrombosis event (Port catheter thrombus) during treatment.

A child undergoing ITI had a port catheter thrombus which was assessed as not related to rFVIIIFc by the Investigator.

Patient's medical history included mutiple central venous catheterizations, device related infections and catheter associated sepsis. The patient received bypassing agents during study treatment period. On Day 89 of the study rFVIIIFc treatment, the patient visited the clinic to check his port catheter (has not been rinsed for several days). The injection was possible only under pressure. It was confirmed by fluoroscopy that the patient had port tip thrombosis, and it was decided to remove the line. The pre-operative sonography of the carotid arteries showed no other abnormalities, apart from the known thrombus. The event resolved and no changes were made to the study drug due to the event. The event is considered as serious due to hospitalization.
During events period, the patient's inhibitor titer was 8.95 BU/mL and the factor VIII activity level was low i.e. <1%.

The MAH's comment:

The patient's factor VIII activity level was very low during the TE events period which suggests no correlation between the events and high factor VIII activity level. The patient continued the study drug treatment without similar events observed which indicatesa negative rechallenge.

The AE of port catheter thrombus (device related thrombosis) was considered as not related to the study drug. Multiple confounding factors including indwelling central venous catheters, repeated line infections and concomitant use of bypassing agents could contribute to the events.

This case was included in the signal evaluation of thromboembolic evens and has been described in PSURs 8 and 9.

Discussion and conclusion

'Serious vascular thromboembolic events" have been included as an important potential risk in the EU RMP since the time of the marketing authorization.

Signal evaluations for "Vascular thromboembolic events" (VTEs) have been thoroughly performed. Following evaluations in 2017 (PSUR 7) and 2018 (PSUR 8), the signal was refuted. On both evaluations of VTEs, the cause of thromboembolic events in the identified case reports was assessed as multifactorial and the conclusion of the signal evaluation was that there was no sufficient evidence at that time to support a causal relationship between vascular thromboembolic events and exposure to rFVIIIFc. In July 2019, additional case reports of potential vascular thromboembolic events were identified during routine safety surveillance and there was a decision to re-open the signal. Following initial signal assessment in September 2019 the consensus was that the etiology of the reported events was multi-factorial, with an overall unclear causal relationship to rFVIIIFc. It was decided to keep the signal open to be able to also take the final data from Study 997HA306 into consideration. The signal evaluation was therefore completed and closed in February 2020 after availability of final data from Study 997HA306. Therefore, it is confirmed by EMA that signal evaluation was done for vascular thromboembolic events in 2018, 2019 and 2020. All signals have been closed.

All 4 TEs, including one device related TE in 3 patients reported in the ReITIrate study were considered of moderate intensity and occurred in patients with preexisting confounding factors that likely contributed to the thrombotic events including history of multiple prior catheter infections, indwelling central venous catheters (Ref 1-2), and concomitant use of bypassing agents. All 3 patients had low factor VIII activity levels during events which indicate no correlation between high-dose rFVIIIFc of 200 IU/kg daily and the risk of a thrombotic event in this ITI study population. All 3 patients continued treatment with study drug indicating a negative rechallenge which further supports our conclusion that these TEs were not causally related to rFVIIIFc.

In conclusion, all the cases mentioned above have been reviewed in previous PSURs (2017- 2020) and included in the previous signal evaluation, causality conclusion has been agreed with EMA during the evaluation. There is no new information from the ReITIrate (Sobi.Elocta-003) study report that could change the previous causality assessment of the reported TEs.

The current SmPC includes warning statements regarding catheter site thrombosis and cardiovascular events in patients at risk. "Device related thrombosis" has been included via the variation procedure EMEA/H/C/003964/II/0039 in 4.8. of the SmPC. No further changes to the SmPC 4.8 are proposed by the MAH. "Serious vascular thromboembolic events" are defined as an important potential risk in the updated EU RMP. It is also agreed and supported by EMA during the renewal procedure (EMEA/H/C/003964/R/0036). The proposed routine risk minimisation measures are sufficient to minimise the risks of the product in the proposed indication(s).Vascular thromboembolic events will be further closely monitored and evaluated by routine pharmacovigilance.

Assessment of the MAH's responses

The question aimed at the judgment of causal relationship of the described thromboses as "not-related" in the light of the applied high doses, the extended half-life of the medicinal product, and the co-administration of bypassing agents.

The MAH described respective four thromboembolic events in three patients on Elocta and Bypassing agents in a setting with central venous catheters, in detail. Further, regulatory actions and decisions on the issue within PSURs and signal evaluation have been reported. In the end it was decided that the reported thromboses were attributed to a multi-factorial affection caused by venous catheter (CVC) complications and concomitant use of bypassing agents. Measured low factor VIII activities are employed for supporting "no causal relationship with use of Elocta".

The medicinal context, however, still supports the suspicion, that very-high-dose Elocta is one contributing factor in this multifactorial event. Recorded low factor VIII activities do not contradict this suspicion as the high FVIII-doses are applied very distinctly into the CVC at the growing thrombus. Further, concomitant use of Bypassing agents suggests that an additive effect is at least possible – again not excluding a causal relationship with Elocta. Judgement regarding relevance of each contributing factor remains to be challenging.

Consequently, the judgment of no causal relationship of the described thrombus formations with the application of high-dose Elocta remains open. On the other hand, the MAH refers to recent and ongoing Pharmacovigilance activities and decisions which is accepted for the time being.

Conclusion:

Pharmacovigilance activities have been implemented to follow thromboses and thrombo-embolic events for further assessment. This is accepted for the time being. Point is solved.

Question 2

The event "Jugular vein thrombosis" should be amended in the clinical overview within the respective case-report and all consecutive summarisations.

MAH's responses

There is no AE coded as "Jugular vein thrombosis" in this study. There is however a non serious event coded as "Jugular vein occlusion" and included in the AE listing table in the CSR. This non-serious

event for the patient was concurrently reported when the patient experienced an episode of device related infections. No action was taken with study drug due to the event. The information was described in the SAE case report narrative above. The moderate jugular vein occlusion was assessed as not related to the study drug by the investigator. See also information in response to Q1 and details in the SAE narrative.

The second jugular vein occlusion is mentioned in the CSR narrative which described left brachiocephalic vein thrombosis and left vena cava thrombosis. The report mentioned a concomitant right jugular vein occlusion diagnosed by ultrasound as described above which had not been coded as a separate AE. See also details in response to Q1 above.

In conclusion, jugular vein occlusions were described in two patients with one event included in the non-serious AE table in the CSR. Both events were described in the narratives as they occurred concurrently with reported SAEs. Both the investigator and MAH consider that these events are not related to study drug.

Assessment of the MAH's responses

Two independent events of "jugular vein occlusion" have been described, regarding two different patients. The latter was not coded as a separate AE and is not reflected in the non-serious AE-table, respectively. However, this event is considered not to be covered by e.g. "Left brachiocephalic vein thrombosis" and "left vena cava thrombosis" (Q).

Conclusion:

Point remains open (Q)

Question 3

Non-serious AEs have not been provided in the submission. Listings and respective evaluation of thrombotic events are requested.

MAH's responses

Non-serious AEs are provided in the All AEs listing (16.2.7 which includes the non-serious event of jugular vein occulusion, detailed in response to Q2

Assessment of the MAH's responses

The MAH's response is noted. However, a clarification request in July 2021 specified, that a "separate listing and thorough evaluation of all non-serious thrombotic events irrespective of causality assessment" was expected. Such listing has not been submitted, and should be amended. Further, respective clarification request reads: "If additional serious thrombotic events – irrespective of causality – have been recorded, such cases should be listed and evaluated, in addition (Q).

Conclusion:

Point remains open (Q)

Question 4

The MAH is asked to discuss the risk of thrombotic events for high-dose administration Elocta alone or in relation with bypassing agents, and respective reflection in the SmPC.

MAH's responses

There have been two studies (verITI-8 and ReITIrate) of ITI rFVIIIFc therapy (200 IU/kg/day) in patients with hemophilia A. The objective of both studies was to evaluate patients with severe hemophilia A and high-titer inhibitors to rFVIIIFc undergoing first ITI treatment (verITI-8) or after failed previous ITI therapies (ReITIrate). In the 16 patients enrolled in the verITI-8 study, no thrombotic events were reported. In the 16 patients enrolled in the ReITIrate study, four SAEs of thrombosis were reported in three patients. Each of these three patients had concomitant and alternative factors that likely contributed to the TEs including multiple central line infections, repeated line revisions and concomitant use of bypassing agents. All these patients had low factor VIII activity levels at the time of the events, and therefore a relationship between high dose rFVIIIFc and thrombotic events can not be concluded. None of the patients discontinued the study drug due to TEs, and there was no recurrence of similar events in these patients.

Serious vascular thromboembolic events in patients with risk factors for thromboembolism are included as an important potential risk in the current EU RMP. The description of the risk of TEs and device related thrombotic events in the current SmPC 4.4 and 4.8 is considered sufficient.

The MAH will continue to evaluate the risk of thrombotic events in the ITI patient population, through routine pharmacovigilance.

For details please also see the response to Q1.

Assessment of the MAH's responses

The MAH mainly refer to verITI-8 with similar dosage of Elocta. This study in 16 patients did not identify risk of thromboembolic events with high-dose Elocta. However, this study highly differs with regard to the patient population and underlying risk factors. This study is not subject to the procedure, and will be assessed, in a separate procedure.

Serious vascular thromboembolic events in patients with risk factors for thromboembolism are included as an important potential risk in the current EU RMP. Referring to the conclusions regarding Q1, these activities are considered to be adequate, for the time being.

Conclusion:

Point is solved.

Question 5

A Line listing of all the studies included in the development program should be submitted (refer to Annex).

MAH's responses

Please find the line listing of all the studies included in the development program.

For your reference, study Elocta.Sobi-003 (ReITIrate) – subject of the current EMA procedure – is not a part of the development program.

Assessment of the MAH's responses

Listing has been provided (refer to Annex)**.**

Conclusion:

Point is solved.

6. Rapporteur's overall conclusion on the responses and recommendation

Results of this ITI-study in 16 poor-prognosis patients is considered to reflect a realistic outcome of ITI-attempts – followed for an adequate time-frame of about 2 years. Only 1 "low-risk" patient (maximum inhibitor titer <10 BU) achieved ITI-success.

Regarding safety, extraordinary thrombosis-reports raise attention. As central venous catheters and additional Bypassing agents facilitate such pathology, the contributing role of high-dose Elocta cannot be finally elucidated.

However, respective Pharmacovigilance activities are ongoing.

Two minor issues remain open (refer to section 7).

☒ Not fulfilled

Based on the data submitted, the MAH should provide additional clarifications as part of this procedure. (see section "2nd Additional clarification requested")

7. 2nd Additional clarification requested / 2nd RSI

Q1 (From Q2)

Two independent events of "jugular vein occlusion" have been described, regarding two different patients. The MAH is asked to confirm, that ("right") "jugular vein occlusion" has been coded as a separate AEs for each of the patients.

Q2 (from Q3)

The MAH's is asked to supplement a separate listing and thorough evaluation of all non-serious thrombotic events irrespective of causality assessment. Further, if additional serious thrombotic events – irrespective of causality – have been recorded, such cases should be listed and evaluated, in addition.

The timetable is a 30 day response timetable.

8. MAH responses to 2nd Request for supplementary information

Question 1 (From Q2)

Two independent events of "jugular vein occlusion" have been described, regarding two different patients. The MAH is asked to confirm, that ("right") "jugular vein occlusion" has been coded as a separate AEs for each of the patients.

Summary of MAH's responses

The MAH confirmed that the event for the 1st patient has been coded as a separate AE.

The event of "jugular vein occlusion" in the 2nd patient was not reported as a separate AE by the investigator during the study.

This was justified by the fact, that an ultrasound doppler showed flow in the right subclavian and brachiocephalic veins with dominant flow into veins coming from the distended right external jugular vein. The investigator did not consider this observation as a separate event to the reported thrombotic events and did not report jugular vein occlusion separately.

Recommendation of coding the right jugular vein occlusion in the patient as a separate AE, however, would require opening of the locked clinical study database. For data integrity reasons unlocking a clinical study database is only done under very special circumstances, which is not applicable, respectively. Internal SOP-227-336 has been outlined.

The MAH considers the event as not having a significant impact of the statistical outcome of the analysis or affecting the safety profile of the investigational product. The event information is described in the SAE narrative.

Assessment of the MAH's responses

The MAH submitted their SOP *Data Management procedures for eCRF studies performed in-house*. Further, the MAH justifies their approach for not coding the event of "jugular vein occlusion" in one of two affected patients. It is understood that the overall statistical impact on the study-outcome might not be significantly changed by one additional AE on the analysis. On the other hand, the medicinal impact is considered to be high, as the described AE is extraordinary and surprising even in the given clinical context.

Overall, the justification is taken.

Conclusion: Issue is solved.

Question 2 (from Q3)

The MAH's is asked to supplement a separate listing and thorough evaluation of all non-serious thrombotic events irrespective of causality assessment. Further, if additional serious thrombotic events – irrespective of causality – have been recorded, such cases should be listed and evaluated, in addition.

MAH's response

The table below summarizes all non/serious thrombotic events observed in this study.

Vascular disorders SOC	ITI Period (n=16)	Tapering period (n=2)	Follow up period (n=1)	Overall (n=16)
Jugular vein occlusion	2*	0	0	2*

* Two events of "jugular vein occlusion" in two different patients.

Both events have been described in the CSR narratives and have been discussed in detail in the previous responses.

Assessment of the MAH's responses

It is assumed that the term "non/serious" refers to the non-serious AE jugular-vein-occlusion in patient as respective event in patient has not been categorized. It is further assumed that no additional non-serious or serious thrombotic events have been documented or observed as no respective comment is available.

Regarding the previously discussed extraordinary safety-profile in this specific study there is nothing more to add.

Conclusion: Issue is solved.

9. Rapporteur's overall conclusion on the responses to 2nd RSI and recommendation

Results of this ITI-study in poor-prognosis patients are considered to reflect a realistic outcome of ITI-attempts – followed for an adequate time-frame of about 2 years: Only 1 out of overall 16 patients achieved ITI-success. This patient was a "low-risk" patient with a maximum inhibitor titer below 10 BU.

Regarding safety, 3 case-reports of thromboses, covering at least 5 thrombotic events, raise attention. Number of these patients is striking (3 out of 9 patients in the ITI-population). Further, extent and localisation of the thromboses are considered to be extraordinary. Although central venous catheters and additional bypassing agents facilitate such pathology, a contributing role of high-dose Elocta is at least possible, based on the available data.

Pharmacovigilance activities regarding thrombotic events are ongoing. Thorough documentation and complete and consistent documentation is recommended, therein.

☒ **Fulfilled,** no further action required

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

LINE LISTING OF ALL THE STUDIES INCLUDED IN THE DEVELOPMENT PROGRAM

Non clinical studies

Product Name: Elocta Active substance: efmoroctocog alfa

Study title	Study number	Date of completion	Date of submission of final study report
Kinetics of Thrombin Activation of FVIIIFc, Nonprocessed FVIIIFc, and BDD FVIII by SDS-PAGE	R-FR8-009	2009-05-22	2014-10-10
Protein C Inactivation of FVIIIFc, Nonprocessed FVIIIFc, and BDD	R-FR8-010	2009-05-29	2014-10-10
Biochemical In Vitro Assays for the Characterization of FVIIIFc, Nonprocessed FVIIIFc, and BDD FVIII	R-FR8-017	2009-06-02	2014-10-10
Pharmacodynamics and Pharmacokinetics of FVIIIFc and ReFacto in Hemophilia A Dogs	N-FR8-003	2009-07-23	2014-10-10
Single Dose Pharmacokinetics of rFVIIIFc and Immunogenicity after Repeat Dosing in Rats	N-FR8-004	2009-08-31	2014-10-10
Immunogenicity of rFVIIIFc and ReFacto® in FVIII- Deficient Mice	R-FR8-015	2009-09-02	2014-10-10
Pharmacodynamics of Factor VIII-Fc and ReFacto® in Factor VIII-deficient Mice by Whole Blood Clotting Time (WBCT) and Chromogenic Activity	R-FR8-014	2009-09-09	2014-10-10
Pharmacodynamics and WBCT after administration of a single dose IV of nonprocessed FVIIIFc in FVIII-deficient animals (Studies SYN829 and SYN826)	R-FR8-016	2009-09-09	2014-10-10
Pharmacokinetics and Pharmacodynamics of rFVIIIFc and Xyntha (BDD-rFVIII) in Cynomolgus Monkeys in a Crossover Design Study	N-FR8-006	2009-09-09	2014-10-10

Pilot Repeat Dose Study of rFVIIIFc in Cynomolgus Monkeys	N-FR8-001	2009-09-09	2014-10-10
Binding of FVIIIFc to FcRn: Biacore analysis	R-FR8-011	2009-09-23	2014-10-10
Four-Week IV Dose Toxicity and PK Study of FVIIIFc in Rats Followed by a 4-Week Recovery Period	CN53610	2010-03-06	2014-10-10
Four-Week IV Dose Toxicity and PK Study of FVIIIFc in Cynomolgus Monkeys Followed by a 4-Week Recovery Period	CN53056	2010-03-31	2014-10-10
Comparability of the Efficacy of rFVIIIFc Liquid Drug Product and Lyophilized Drug Product in FVIII-Deficient Mice by Whole Blood Rotational Thromboelastomy in vitro and ex vivo	N-FR8-010- R1	2010-06-04	2014-10-10
Comparability of Pharmacokinetics of rFVIIIFc Liquid Drug Product and Lyophilized Drug Product after a single IV dose in FVIII deficient Mice	N-FR8-009- R1	2010-06-04	2014-10-10
Pharmacokinetic Analysis of rFVIIIFc Liquid Drug Product and rFVIIIFc Lyophilized Drug Product Administered as a Single Intravenous Dose in Cynomolgus Monkeys (Syntonix Study N-FR8-007/Battelle Study N110489)	N-FR8-007- R2	2010-06-04	2014-10-10
Pharmacokinetics Comparison of Intravenous rFVIIIFc with Xyntha in FcRn Knock-out (KO), Normal (C57BL/6), hFcRn Transgenic (Tg32B) and FVIII-deficient (HemA) Mice	R-FR8-018	2010-06-24	2014-10-10
Acute Efficacy of rFVIIIFc Lyophilized Drug Product in the Tail Clip Bleeding Model of Hemophilia A Mice	R-FR8-019-R1	2010-06-27	2014-10-10
Four-Week IV Dose Toxicity and PK Study of FVIIIFc Lyophilized DP in Cynomolgus Monkeys Followed by a 4- Week Recovery Period	N110486	2010-10-08	2014-10-10
FVIIIFc Prophylactic Efficacy in Hemophilia A Mouse Tail Vein Transection Model	R-FR8-022-R1	2011-08-08	2014-10-10
Comparability Prolonged Efficacy (ex vivo ROTEM) of rFVIIIFc (VLA5 versus RVS2 DP) Study in Hemophilia A Mice	N-FR8-013	2012-03-22	2014-10-10

Comparability Pharmacokinetics Study of rFVIIIFc (VLA5 versus RVS2 DP) by Chromogenic Activity Assay in Hemophilia A Mice	N-FR8-011	2012-03-22	2014-10-10
Comparability Acute Efficacy Study of rFVIIIFc (VLA5 versus RVS2 DP) in the Tail Clip Bleeding Model of Hemophilia A Mice	N-FR8-012	2012-04-19	2014-10-10
Single Dose Tolerance of rFVIIIFc Clotting Factor in Cynomolgus Monkeys	N-FR8-005	2012-06-21	2014-10-10
Comparability Immunogenicity Study of rFVIIIFc (VLA5 versus RVS2 DP) in Hemophilia A Mice by FVIII Total Antibody ELISA	N-FR8-018	2012-06-21	2014-10-10
In Vivo Efficacy of Nonprocessed (Single Chain) rFVIIIFc in the Tail Vein Transection Bleeding Model in Hemophilia A Mice	R-FR8-023-R1	2012-08-27	2014-10-10
Biodistribution of 125I-labeled rFVIIIFc by Quantitative Whole Body Autoradiography (QWBA) in HemA Mice in the Presence and Absence of VWF	R-FR8-027	2012-08-31	2014-10-10
SPR Analysis of the Affinity for VWF of rFVIIIFc DS, SC rFVIIIFc, and BDD-rFVIII	R-FR8-028	2012-10-03	2014-10-10
Evaluation of Single Chain rFVIIIFc activity by One Stage (aPTT) Assay, Automated Chromogenic Substrate Assay and Thrombin Generation Assay	R-FR8-024-R2	2012-10-10	2014-10-10
Susceptibility of rFVIII Variants to Thrombin-mediated Release from VWF	R-FR8-029	2012-10-11	2014-10-10
Placental Transfer of rFVIIIFc in Pregnant Female Factor VIII Deficient (HemA) Mice	R-FR8-041	2014-09-18	2014-10-10
Comparability Pharmacokinetics Study of rFVIIIFc (RVS2 3000 IU/vial, BIIB031 3000 IU/vial, and BIIB031 3000 IU/DCS) by Chromogenic Activity Assay in Hemophilia A Mice	N-FR8-019	2012-08-28	2016-07-28
Comparability Prolonged Efficacy (ex vivo ROTEM) of rFVIIIFc (RVS2 3000 IU/vial, BIIB031 3000 IU/vial and BIIB031 3000 IU/DCS) Study in Hemophilia A Mice	N-FR8-020	2012-08-28	2016-07-28

Comparability Immunogenicity Study of rFVIIIFc (RVS2 3000 IU/vial, BIIB031 3000 IU/vial, and BIIB031 3000 IU/DCS) in Hemophilia A Mice by FVIII Total Antibody ELISA	N-FR8-021	2012-08-28	2016-07-28
Comparison of rFVIIIFc drug substance (DS) produced in 15000 L (15K) and 2000 L (2K) bioreactors by thrombin activation and APC inactivation analysis	R-FR8-025	2012-08-17	2016-07-28

Clinical studies

Product Name: Elocta Active substance: efmoroctocog alfa

Study title	Study number	Date of completion	Date of submission of final study report
A Phase I/IIa, Open-Label, Crossover, Dose-Escalation, and Multi-Center Study to Determine the Safety, Tolerability, and Pharmacokinetics of a Single Intravenous Injection of rFVIIIFc in Previously Treated Patients with Severe Hemophilia A	998HA101	2010-07-06	2014-10-10
A-LONG: An Open-label, Multicenter Evaluation of the Safety, Pharmacokinetics, and Efficacy of Recombinant Factor VIII Fc Fusion Protein (rFVIIIFc) in the Prevention and Treatment of Bleeding in Previously Treated Subjects With Severe Hemophilia A	997HA301	2012-08-06	2014-10-10
Kids A-LONG: An Open-Label, Multicenter Evaluation of Safety, Pharmacokinetics, and Efficacy of Recombinant Coagulation Factor VIII Fc Fusion Protein, BIIB031, in the Prevention and Treatment of Bleeding Episodes in Pediatric Subjects With Hemophilia A	8HA02PED	2013-12-05	2014-10-10
A Randomized, Open-Label, Crossover Study to Evaluate the Pharmacokinetics of 2 Vial Strengths of Recombinant Factor VIII Fc Fusion Protein (rFVIIIFc; BIIB031) in Previously Treated Subjects With Severe Hemophilia A	997HA307	2015-05-20	2016-11-30

A Randomized, Open-Label Study to Evaluate the Pharmacokinetics and Safety of Recombinant Factor VIII Fc Fusion Protein (rFVIIIFc; BIIB031) Manufactured at 15K Scale and at Different Vial Strengths in Previously Treated Subjects With Severe Hemophilia A	997HA309	2017-04-03	2018-01-12
ASPIRE: An Open-Label, Multicenter Evaluation of the Long-Term Safety and Efficacy of Recombinant Human Coagulation Factor VIII Fusion Protein (rFVIIIFc) in the Prevention and Treatment of Bleeding Episodes in Previously Treated Subjects With Hemophilia A	8HA01EXT	2017-10-18	2018-04-16
PUP A-LONG: An Open-Label, Multicenter Evaluation of the Safety and Efficacy of Recombinant Coagulation Factor VIII Fc Fusion Protein (rFVIIIFc; BIIB031) in the Prevention and Treatment of Bleeding in Previously Untreated Patients With Severe Hemophilia A	997HA306	2019-10-23	2020-03-16