20 September 2018
EMA/CHMP/697649/2018
Committee for Medicinal Products for Human Use (CHMP)

Assessment report

ELOCTA

International non-proprietary name: efmoroctocog alfa

Procedure No. EMEA/H/C/003964/X/0021

Note

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

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List of abbreviations

15K	15 000 L (i.e. the bioreactor volume for the manufacturing of the drug substance used to produce 15K drug product)
2K	2000 L (i.e. the bioreactor volume for the manufacturing of the drug substance used to produce 2K drug product)
ADA	Anti-drug antibody
AE	Adverse event
aPTT	Activated partial thromboplastin time
AS	active substance
AUCinf	Area under the concentration-time curve from time zero to infinity
BDD	B-domain deleted
BDD	B-domain deleted
BMI	Body Mass Index
CI	Confidence interval
CL	Clearance
Cmax	Maximum observed concentration
CSR	Clinical study report
DP	Drug Product
DS	Drug Substance
ED	Exposure day
Fc	immunoglobulin Fc part
Fc	subdomain of IgG immunoglobulin
FP	finished product
FVIII	Coagulation factor VIII
GMP	Good Manufacturing Practice
HEK cells	Human embryonic kidney cells
i.v.	Intravenous
IgG	immunoglobulin G
IgG1	immunoglobulin G1
IgG1	Immunoglobulin G1
INN	international non-proprietary name

INN	International non-proprietary name
IR	Incremental recovery
IU	International unit
IU	international unit
kDa	Kilodalton
MA	Marketing authorisation
MRT	Mean residence time
Ph. Eur.	European Pharmacopoeia
Ph.Eur.	European Pharmacopoeia
PK	Pharmacokinetic
PK1	Pharmacokinetic assessment 1, with 2K rFVIIIFc
PK2	Pharmacokinetic assessment 2, with 15K rFVIIIFc
PK3	Pharmacokinetic assessment 3, with 15K rFVIIIFc
PV	process validation
PV	Process validation
PVR	process validation run
rFVIII	recombinant Factor VIII
rFVIII	Recombinant Factor VIII
rFVIIIFc	recombinant coagulation factor VIII, Fc fusion protein
rFVIIIFc	Recombinant factor VIII Fc fusion protein
SAE	Serious Adverse Event
SE	Standard error
SWFI	Sterilised water for injections
t1/2	Terminal half-life
TEAE	Treatment-emergent adverse event
Vss	Volume of distribution at steady state

1. Background information on the procedure

1.1. Submission of the dossier

Swedish Orphan Biovitrum AB (publ) submitted on 12 January 2018 an extension of the marketing authorisation to introduce new strengths of 4000 IU, 5000 IU and 6000 IU primarily enabling prophylactic dosing in adult patients.

The legal basis for this application refers to:

Article 19 of Commission Regulation (EC) No 1234/2008 and Annex I of Regulation (EC) No 1234/2008, (2) point (c) - Extensions of marketing authorisations

Information on Paediatric requirements

Not applicable

Information relating to orphan market exclusivity

Not applicable

Similarity

Pursuant to Article 8 of Regulation (EC) No. 141/2000 and Article 3 of Commission Regulation (EC) No 847/2000, the MAH did not submit a critical report addressing the possible similarity with authorised orphan medicinal products because there is no authorised orphan medicinal product for a condition related to the proposed indication.

Scientific Advice

The MAH did not seek scientific advice at the CHMP.

1.2. Steps taken for the assessment of the product

The Rapporteur and Co-Rapporteur appointed by the CHMP were:

Rapporteur: Jan Mueller-Berghaus Co-Rapporteur: N/A

The application was received by the EMA on	12 January 2018
The procedure started on	1 February 2018
The Rapporteur's first Assessment Report was circulated to all CHMP members on	23 April 2018
The CHMP agreed on the consolidated List of Questions to be sent to the applicant during the meeting on	31 May 2018

The MAH submitted the responses to the CHMP consolidated List of Questions on	6 July 2018
The Rapporteurs circulated the Joint Assessment Report on the responses to the List of Questions to all CHMP members on	27 August 2018
The CHMP, in the light of the overall data submitted and the scientific discussion within the Committee, issued a positive opinion for granting an extension to the marketing authorisation for ELOCTA on	20 September 2018

2. Scientific discussion

2.1. Problem statement

With this extension application, the company applied for the introduction of three new strengths of Elocta, i.e. 4000 IU, 5000 IU and 6000 IU in addition to the existing strengths (250/ 500/ 750/ 1000/ 1500/ 2000/ 3000 IU, MA numbers: EU/1/15/1046/001-007).

The extension application is primarily based on quality data. Following no changes in dose, the clinical part of the submitted dossier only contains a PK study that shows comparable PK properties over the full range of vial strengths. No pre-clinical documentation is deemed necessary.

Elocta is indicated for the treatment and prophylaxis of bleeding in patients with haemophilia A (congenital factor VIII deficiency). Elocta can be used for all age groups.

2.1.1. Disease or condition

Haemophilia A is a rare and serious, X-linked, recessive bleeding disorder that predominantly affects males and is characterized by a deficiency of FVIII. In patients with haemophilia A, the primary platelet-driven hemostasis is not affected, but generation of a stable, fibrin-rich clot is defective because inadequate amounts of thrombin are generated. Affected patients suffer from both spontaneous, non-traumatic bleeding episodes as well as substantially prolonged bleeding episodes upon injury. Rarely, life-threatening bleeding may also occur. Patients exhibit variable clinical phenotypes depending on the extent of residual activity (%) of the deficient FVIII that is used to classify the disease severity (WFH, 2012):

- <1% FVIII activity: severe haemophilia A
- 1% to 5% FVIII activity: moderate haemophilia A
- 5% to 40% FVIII activity: mild haemophilia A

Patients with severe haemophilia A bleed spontaneously into joints and muscles, which often results in permanent, disabling joint damage.

2.1.2. Epidemiology

The overall reported number of haemophilia A patients estimated in the 2013 survey by the World Federation of Haemophilia (WFH) included 107 countries with a total population of 6,461,067,861 and

identified 140,313 people with haemophilia A (2.2 per 100,000 individuals). There are currently approximately 30,000 patients in the EU with a mean prevalence of approximately 0.6 patients per 10,000.

Haemophilia A is inherited as an X-linked recessive trait and the main risk factors are therefore family history and a carrier mother. Approximately 30% of patients have no family history of the disease; their disease is presumably caused by new mutations.

2.1.3. Biologic features, aetiology and pathogenesis

The factor VIII/von Willebrand factor complex consists of two molecules (factor VIII and von Willebrand factor) with different physiological functions. When infused into a haemophiliac patient, factor VIII binds to von Willebrand factor in the patient's circulation. Activated factor VIII acts as a cofactor for activated factor IX, accelerating the conversion of factor X to activated factor X. Activated factor X converts prothrombin into thrombin. Thrombin then converts fibrinogen into fibrin and a clot can be formed.

2.1.4. Clinical presentation, diagnosis

Haemophilia A manifests as profuse bleeding into the joints and muscles or internal organs, either spontaneously or as the result of accidental or surgical trauma. Recurrent joint bleeding can lead to chronic arthropathy, pain, and loss of function (Bolton-Maggs and Pasi, 2003). The majority of bleeding occurs internally into joints, most commonly hinged joints such as the ankles, knees, and elbows. Serious bleeds also occur in muscles, especially in deep compartments such as the iliopsoas, calf and forearm, and in the mucous membranes in the mouth, gums, nose, and genitourinary tract. Less frequently, life threatening bleeds can occur in or around vital areas or organs such as the gastrointestinal system or enclosed areas like the intracranial or intracerebral spaces. The approximate frequencies of bleeds at the different sites are: 70 to 80% in joints (haemarthrosis), 10 to 20% in muscle, 5 to 10% in the central nervous system, and < 5% for bleeds at all other sites (Srivastava et al., 2013).

2.1.5. Management

Standard treatment for haemophilia A patients is the replacement of the missing protein by infusion of exogenous FVIII concentrates (as plasma-derived FVIII [pdFVIII] or recombinant FVIII [rFVIII] concentrates). Treatment regimens are either on-demand therapy (given when a bleed occurs) or prophylaxis (which consists of regular infusion of FVIII given every 2 to 3 days to prevent bleeding). In the short term, prophylaxis can prevent spontaneous bleeding and in the long term, prophylaxis can prevent bleeding into joints that will eventually lead to debilitating arthropathy.

Prior to the introduction of clotting factor concentrates in the 1960s, the prognosis for haemophilia A patients was poor, average life expectancy being 15 to 25 years. Major advances in the safety of clotting factor products, including the availability of rFVIII concentrates, the availability of comprehensive haemophilia A treatment centres, the institution of routine prophylaxis, the introduction of home treatment, as well as the active roles that patients take in self-advocacy, have enabled patients with haemophilia A to lead a "close to normal" life.

About the product

rFVIIIFc is a recombinant fusion protein composed of a single molecule of human B-domain deleted Factor VIII fused to the Fc domain of human immunoglobulin G1 (IgG1).

The rFVIIIFc drug product is a sterile lyophilized powder for solution for injection for intravenous administration. It is supplied in aseptically filled single use vials in multiple nominal strengths from 250 to 6000 IU/vial. Prior to lyophilization, the nominal fill volume of all rFVIIIFc drug product strengths is 2 mL. The composition prior to lyophilization is the same for all dosage strengths; only the quantity of rFVIIIFc active ingredient varies. The lyophilized powder is reconstituted with nominal 3 mL sterilised water for injections (SWFI) supplied in a sterile prefilled syringe.

The rFVIIIFc drug product vial and pre-filled diluent (SWFI) syringe are packaged in a product pack with a plunger rod, a vial adaptor for reconstitution, an infusion set, alcohol swabs, plasters and gauze pad.

Type of Application and aspects on development

This is an application for a change of an existing marketing authorization leading to an extension as referred to in ANNEX 1 of Regulation (EC) No. 1234, 2008 - Addition of a new strength.

2.2. Quality aspects

2.2.1. Introduction

Elocta is a coagulation factor VIII Fc (rFVIIIFc, INN efmoroctocog alfa), a recombinant fusion protein comprising B-domain deleted (BDD) human FVIII covalently linked to the Fc domain of human immunoglobulin G1 (IgG1).

This is an extension application for the MA for Elocta to include three more vial strengths of 4000 IU, 5000 IU and 6000 IU. The production of vials of higher strengths, comprises a larger amount of active substance (AS) solution filled into each vial whilst maintaining the excipient content in line with the existing EU approved strengths of this product. The recommended prophylactic dosing of 50 IU/kg body weight of Elocta does not change.

Data for these additional strengths (4000, 5000 and 6000 IU/vial) with the same formulation and using the same manufacturing process were already included and had been assessed during variation EMEA/H/C/003964/II/012/G submission. They served as supportive data for the establishment of the additional production site.

Therefore, with respect to the quality assessment of the additional strengths 4000 IU, 5000 IU, 6000 IU, in some sections of the report below, reference is made to the final AR of variation II/012/G.

The finished product (FP) is presented as a powder and solvent for solution for injection containing in total, 10 different strengths ranging from 250 IU/vial to 6000 IU/vial (250, 500, 750, 1000, 1500, 2000, 3000, 4000, 5000, 6000 IU/vial).

Other ingredients are: sucrose, sodium chloride, L-Histidine, calcium chloride dihydrate, polysorbate 20, sodium hydroxide (for pH adjustment), hydrochloric acid (for pH adjustment) and water.

The product is available in a package containing: powder in a type 1 glass vial with a latex-free chlorobutyl rubber stopper, 3 mL solvent in a type 1 glass pre-filled syringe with a latex-free bromobutyl rubber plunger stopper, a plunger rod, a sterile vial adapter for reconstitution, a sterile infusion set, two alcohol swabs, two plasters and one gauze pad. All device components included in the final package are CE marked.

2.2.2. Active Substance

General information

rFVIIIFc is produced in stably transfected HEK293 cells. rFVIIIFc is a fully recombinant fusion protein consisting of a single molecule of B-domain deleted human coagulation factor VIII (FVIII) fused to the Fc domain of human immunoglobulin G1 (IgG1) with no intervening linker sequence.

The AS of Elocta, efmoroctocog alfa, is a recombinant human coagulation factor VIII, Fc fusion protein (rFVIIIFc) comprising B-domain deleted (BDD) human FVIII covalently linked to the Fc domain of human immunoglobulin G1(IgG1). It has been developed as a long-acting version of recombinant FVIII (rFVIII).

Manufacture, characterisation and process controls

With this Line Extension there are no changes to the currently approved manufacture, process controls and characterisation of the AS.

Specification

With this Line Extension there are no changes to the currently approved specification, analytical procedures, reference standards and container closure of the AS.

Stability

The currently approved stability of the AS remains unchanged.

2.2.3. Finished Medicinal Product

Description of the product and pharmaceutical development

The composition of Elocta 4000, 5000 and 6000 IU/vial is presented in **Table 1** below. The excipient content remains unchanged from the existing strengths.

Table 1 Composition of Elocta 4000, 5000 and 6000 IU/vial

Ingredient	Function
rFVIIIFc	Active
Histidine	Buffer
Sodium chloride	Stabilizer, solubilizer
Calcium chloride, dihydrate	Stabilizer
Sucrose	Lyoprotectant, stabilizer
Polysorbate 80	Stabilizer
WFI	Solvent
Hydrochloric acid	pH adjustment
Sodium hydroxide	pH adjustment

The rFVIIIFc FP is a sterile, lyophilized powder for solution for injection intended for intravenous administration, manufactured using AS from the approved process in the approved sites. It is supplied in aseptically filled single use vials in ten nominal strengths (250, 500, 750, 1000, 1500, 2000, 3000, 4000, 5000 and 6000 IU/vial).

All excipients are well known pharmaceutical ingredients and their quality is compliant with Ph. Eur standards. There are no novel excipients used in the FP formulation.

The recommended prophylactic dosing of 50 IU/kg body weight of Elocta does not change however, the new 6000 IU strength has been studied in clinical studies.

Pharmaceutical development

The initial FP development included strengths up to 3000 IU/vial. Three new strengths (4000, 5000 and 6000 IU/vial) have now been developed. The product quality of the higher strengths was confirmed by FP technical runs, comparability testing and GMP manufacturing.

The FP manufacturing process has been sequentially developed to produce the different nominal strengths, and to achieve process consistency independent of the final strength.

Due to commercial needs a subsequent, alternative manufacturing site was identified to allow for transfer of the commercial process and introduction of additional strengths of 4000, 5000 and 6000 IU/vial. FP transfer to the new site has been approved II/012/G). Assessment of the FP processes for rFVIIIFc at both sites revealed that all the major unit operations remain the same. The main difference between the two processes is the size of the lyophilizer and the introduction of additional higher strength FP. Accordingly, these changes resulted in the need for further technical evaluation in technical runs. As part of the comparability protocol, strategies were planned to compare 250 and 3000 FP manufactured at both sites.

The acceptance criteria applied to the technical runs at the new site was guided by ranges established for the existing commercial process at the existing site. Qualification data for a suitable number of lots were also submitted.

Manufacture of the product and process controls

There are no changes to the approved manufacturers with this line extension submission.

Description of manufacturing process and process controls

There are no changes to the manufacturing process description with this submission. Relevant data on the manufacturing process had already been submitted and were approved during variation II/012/G.

The batch formula is amended for the 4000, 5000 and 6000 IU/vial strengths. Regarding the controls of critical steps and intermediates there are no changes to this section. It was demonstrated during variation II/012/G that the process is controlled with comparable stringency at both production sites. Mostly, identical acceptance limits and hold times are specified. These are based on validation studies and media fill runs have been conducted for each site separately.

No new validation documents are submitted with this line extension submission. During variation II/012/G the applicant provided data from 9 process validation (PV) runs. The PV approach also covered the lower and upper freeze drier load capacity in a matrix approach; also process-challenging conditions were applied. The bracketing and matrix approach was considered in line with process validation guidance and acceptable. The PV data demonstrated that the process is under good control, meeting pre-defined acceptance limits for all process controls and quality attributes analysed during the process. In conclusion, the manufacturing process has been validated for all dosage sizes from 250 to 6000 IU/vial in line with process validation guidance documents.

Product specification

The product specification is updated and includes the protein concentration and the FVIII: chromogenic activity acceptance ranges for the additional strengths. The section 'Justification of Specifications' is amended accordingly. The release limits for the new strengths (potency) are the same as for the approved strengths. The finished product specification includes appropriate tests for identity, purity and potency.

Analytical methods

There are no changes to analytical procedures in this line extension.

Batch analysis

Batch release results of 11 lots of FP including the process validation run (PVR) lots were already presented during variation II/012/G. All lots met the release specification valid at the time of manufacture. No new batch release data are included in this line extension application.

Reference materials

There is no update of this section. The currently approved reference standards are also used at the new site.

Container closure system

The rFVIIIFc FP is provided in multiple nominal strengths. All strengths use the same container closure system for all product contact packaging components. The rFVIIIFc FP is lyophilized in a USP/Ph. Eur. Type I glass vial. The 10mL vial is closed with a 20 mm chlorobutyl rubber stopper. After the lyophilization process is complete, the stoppered vials are sealed with 20 mm aluminum seals with a polypropylene flip-off cap, of various colors, dependent on vial strength.

Stability of the product

The proposed shelf life for the FP is 48 months (4 years) when stored at 2-8 °C. During the shelf-life, the product is proposed to be stored at room temperature (up to 30°C) for a single period not exceeding 6 months. After storage at room temperature, the product may not be returned to the refrigerator.

In line with ICH Q 5C, a bracketing approach has been applied to study the stability of FP manufactured at the new site. The same release testing parameters as established for FP from the existing site are applied, which included stability indicating parameters. The process validation run (PVR) batches were monitored on stability. See **Table 2** below.

Table 2 New site PVR lots for stability

Strength (IU/vial)	**250**	**3000**	**4000**	**5000**	**6000**
Number of PVR /Stability Lots	3	1	1	1	3

All PVR batches were enrolled on stability. All formulations, fill volumes and container closure systems are the same across all strengths (250 to 6000 IU/vial) except for the quantity of protein filled in the vial to meet the target potency claim.

The stability data acquired to date include forty-eight (48) month data for lyophilized rFVIIIFc FP for the 250 to 3000 IU/vial strengths when stored at 2 to 8°C. Within the 48-month period, storage of up to 6 months at room temperature (not to exceed 30°C) was evaluated. The stability for the new site PVR lots indicate that there is highly similar stability behaviour over all dosage sizes, including the higher strengths. Stability of the new strengths (4000, 5000 and 6000 IU/vial) is supported by the comparability evaluated between the FP manufacturing process development at the two production sites and comparable stability profiles presented. This includes comparable stability profiles through at least 12 months at 5±3°C, through 12 months at 30±2°C/75±5% RH, and through 6 months at 40±2°C/75±5% RH. Accordingly a shelf life of 48 month for the 4000 to 6000 IU/vial strengths is accepted.

In line with ICH Q5C, photo-stability studies were performed which indicated that the lyophilised product is light sensitive, requiring proper storage of the product in its outer carton. In-use stability of the reconstituted rFVIIIFc FP has been assessed. The results demonstrate that reconstituted rFVIIIFc FP (250 to 3000 IU/vial) is stable at ambient temperature (30 ± 2°C/75 ± 5% relative humidity) for up to 6 hours in the FP vial, the glass diluent syringe, or the polypropylene pooling syringe. These studies are suitable to support the in-use stability of the new strengths.

The post-approval stability protocol includes lots of all strengths manufactured at the new site. In use stability will be tested for one 250 IU and one 6000 IU lot aged 42 month at 5°C, then moved to 30°C for a further 6 months. In conclusion, the proposed shelf life for the FP of 48 months (4 years) when stored at 2-8 °C is accepted. During the shelf-life, the product may be stored at room temperature (up to 30°C) for a single period not exceeding 6 months. After storage at room temperature, the product may not be returned to the refrigerator.

Adventitious agents

The manufacture of the AS has not been changed for the line extension. No material of direct animal origin was used as a FP excipient.

2.2.4. Discussion on chemical, pharmaceutical and biological aspects

The FP is manufactured at two sites using highly similar processes that have been validated independently and operate reproducibly within established parameters, leading to a product that meets preset quality attributes. The process at the new site has been validated for all strengths, including the new strengths. An adequate set of parameters has been established based on a risk analysis to control the quality of the FP. Based on available stability data, the currently approved shelf life of the FP of 48 month at 5°C with up to 6 months at room temperature (up to 30°C) can also be accepted for FP lots of the new strengths manufactured at the new site.

In conclusion, from a quality point of view the new strengths of 4000 IU/vial, 5000 IU/vial and 6000 IU/vial can be approved,

2.2.5. Conclusions on the chemical, pharmaceutical and biological aspects

The quality of this product is considered to be acceptable when used in accordance with the conditions defined in the SmPC. Physicochemical and biological aspects relevant to the uniform clinical performance of the product have been investigated and are controlled in a satisfactory way.

2.3. Non-clinical aspects

No non-clinical data were submitted with this application.

2.4. Clinical aspects

2.4.1. Introduction

This is an application for an extension of the MA for Elocta (recombinant coagulation factor VIII Fc fusion protein, rFVIIIFc) to include three more vial strengths, i.e. 4000 IU, 5000 IU and 6000 IU.

To support this line extension results from one clinical study are presented.

GCP

The Clinical trials were performed in accordance with GCP as claimed by the MAH

The MAH has provided a statement to the effect that clinical trials conducted outside the community were carried out in accordance with the ethical standards of Directive 2001/20/EC.

One PK study has been performed: study 997HA309

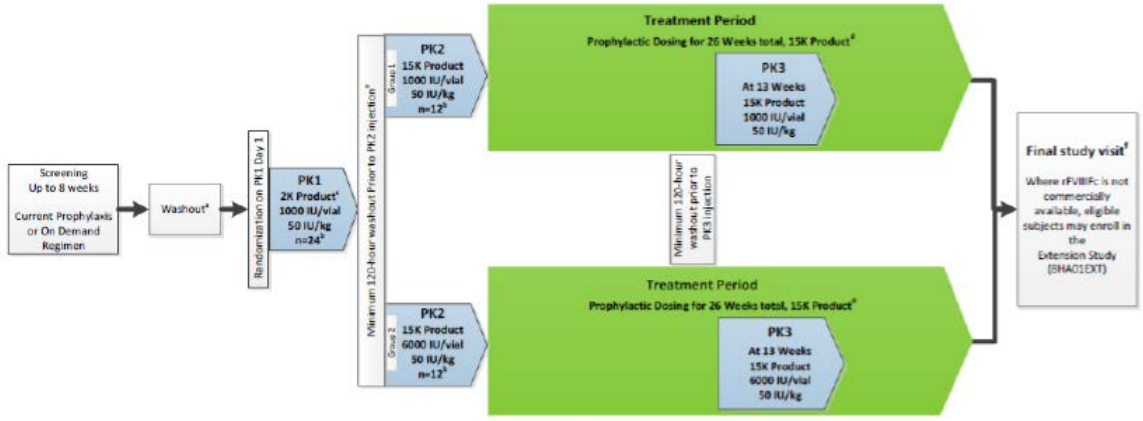
2.5. Clinical efficacy

2.5.1. Main study

Study 997HA309

Methods

Figure 1



Abbreviations: 2K=rFVIIIFc produced at 2000 L scale; 15K=rFVIIIFc produced at 15,000 L scale; PK=Pharmacokinetic sampling period
[a]Minimum of 96 hours of washout for a short-acting FVIII product, or 120 hours of washout for a long-acting FVIII product.
[b]Approximately N=24 subjects may be enrolled in order to complete the study as described in Section 7.5.
[c]If more than 2 bleeds occur during the PK1 assessment period, it will not be rescheduled. The subject may continue on the study in the treatment period.
[d]See Section 10.1.2, for dosing regimens and Section 4.2 for time windows.
[e]The 120-hour washout period for PK2 may begin at the time of the PK1 injection and include the period when the patient is undergoing the PK1 assessment if no additional treatments are needed for bleeds before the PK2 assessment.
[f]There will be a follow up phone call 7 ± 7 days after the last dose of rFVIIIFc during the treatment period unless the subject has already enrolled into the extension study, Study BHA01EXT, by that time.

Study Participants

Study participants were male patients with severe haemophilia A, defined as <1 IU/dL (<1%) endogenous FVIII as determined by one-stage clotting assay from the central laboratory at Screening. Patients were to be ≥ 12 years old at the time of informed consent, and weighing at least 40 kg. Patients were to be previously treated subjects, defined as having at least 150 documented prior EDs to any recombinant and/or plasma-derived FVIII and/or cryoprecipitate products at Day 1. Patients were not eligible in case they do have a history of a positive inhibitor test or clinical signs of decreased response to FVIII administrations. Further, patients were not enrolled in case they had measurable inhibitor activity using the Nijmegen-modified Bethesda assay (≥ 0.6 BU/mL was considered positive) at screening.

Treatments

The PK assessments were performed following a single dose of rFVIIIFc, as follows:

PK1: 2K rFVIIIFc, 1000 IU/vial, 50 IU/kg

- PK2 and PK3:
  - Group 1 received 15K rFVIIIFc, 1000 IU/vial, 50 IU/kg for both assessments.
  - Group 2 received 15K rFVIIIFc, 6000 IU/vial, 50 IU/kg for both assessments.

After completing the PK2 assessment, all subjects (whether or not evaluable for PK) began receiving treatment with 15K rFVIIIFc exclusively **(see Figure 1)**. Subjects received prophylactic dosing. The specific choice of regimen for any given subject and any subsequent dose adjustments was based on the subject's response and was at the Investigator's discretion.

Recommended starting dosing regimens included the following:

- A prophylactic regimen at a starting dose of 50 IU/kg of rFVIIIFc given every 3 to 5 days. Fur-ther dose and interval adjustments were based on individual clinical response per Investiga-tor's discretion. Dosing could be adjusted in the range of 25 to 65 IU/kg at 3- to 5-day inter-vals.
- A prophylactic regimen of 65 IU/kg administered every 7 days was considered for appropriate subjects who were selected based on the opinion of the Investigator.

Subjects were allowed to switch from 1 regimen to another if approved by the Investigator and were allowed to use any of the several available vial strengths.

Objectives

Primary Objectives

The primary objective of the study was to compare the PK of rFVIIIFc manufactured at the current scale of 2000 L (2K) to the PK of rFVIIIFc manufactured at the 15,000 L (15K) scale in previously treated subjects with severe haemophilia A.

Secondary Objectives

Secondary objectives were as follows:

- To characterise the PK of 15K rFVIIIFc at the 15K baseline and after 13 weeks of treatment
- To characterise the PK of 15K rFVIIIFc at 1000 and 6000 IU/vial strengths
- To evaluate the safety of 15K rFVIIIFc

Outcomes/endpoints

Primary:

The primary endpoint comprised of the following PK parameters for PK assessment 1 (PK1) with rFVIIIFc manufactured at 2K scale and for PK assessment 2 (PK2) with rFVIIIFc manufactured at 15K scale, including:

- area under the concentration-time curve from time zero to infinity (AUCinf)
- IR

as estimated from the FVIII activity data, measured by the aPTT clotting assay.

Secondary:

The secondary endpoints included the following:

- PK parameters, including but not be limited to AUCinf, IR, Cmax, t½, CL, volume of distribution at steady state (Vss), and mean residence time (MRT). PK was assessed using the aPTT clot-ting assay and the two-stage chromogenic assay.
  - PK parameters were assessed for the following
- 15K rFVIIIFc at the 15K baseline (i.e., at PK2) and after 13 weeks of treatment (at PK assessment 3, with 15K rFVIIIFc [PK3])
- 15K rFVIIIFc at 1000 and 6000 IU/vial strengths
- 2K rFVIIIFc (at PK1) and 15K rFVIIIFc (at PK2) (except AUCinf and IR, which are includ-ed in the primary endpoint)
- Development of inhibitors as measured by the Nijmegen-modified Bethesda assay
- Evaluation of AEs and SAEs

Sample size

A total of 24 male subjects were enrolled and included in the All-Enrolled Analysis Set; of these 23 subjects completed the study. One subject in the 15K 6000 IU/vial cohort was discontinued before the PK2 assessment due to reason marked other (the subject was unable to complete the washout period due to breakthrough bleeding).

Patient group who received at least 1 dose of rFVIIIFc (2K) comprised of 24 subjects. Patient group who received at least 1 dose of 15K rFVIIIFc comprised of 23 subjects: 11 subjects in the 15K 1000 IU/vial and 12 subjects in the 15K 6000 IU/vial cohort.

Randomisation

Subjects were randomized on Day 1 of PK1 via the Interactive Voice/Web Response System (IXRS) in a 1:1 ratio to receive either 1000 IU/kg or 6000 IU/kg of 15K rFVIIIFc (a single IV injection of 50 IU/kg) in the subsequent PK2 and PK3 assessments.

Blinding (masking)

Not applicable.

Statistical methods

PK analysis was based on the PK analysis set, which included all eligible subjects who received at least 1 dose of rFVIIIFc and had sufficient PK data points to calculate all PK parameters for a given injection in at least 1 of the 2 assays for any of the PK assessments.

Noncompartmental analysis was implemented in all subjects with sufficient data to estimate at least 1 PK parameter and was conducted for FVIII activity data from both the one-stage clotting and two-stage chromogenic assays. Noncompartmental analysis was performed on FVIII activity vs. time data

that were obtained following the i.v. infusion and adjusted for baseline and residual activity from prior therapy.

Descriptive statistics were presented for all PK parameters. Only completed subjects and evaluable PK profiles were included in the summary.

Results

Participant flow

A total of 24 male subjects were enrolled and of these 23 subjects completed the study. One subject in the 15K 6000 IU/vial cohort was discontinued before the PK2 assessment due to reason marked other (the subject was unable to complete the washout period due to breakthrough bleeding).

Patients who received at least 1 dose of rFVIIIFc (2K) comprised of 24 subjects. Patients who received at least 1 dose of 15K rFVIIIFc comprised of 23 subjects: 11 subjects in the 15K 1000 IU/vial and 12 subjects in the 15K 6000 IU/vial cohort.

Recruitment

Conduct of the study

A washout period with no FVIII treatment was required prior to each injection of rFVIIIFc for all PK assessments (96 hours for short-acting products or 120 hours for long-acting products).

PK sampling occurred predose and at 7 timepoints postinjection: 0.5 hour (±5 minutes); 1 hour and 6 hours (±10 minutes); and 24, 48, 72, and 96 hours (±60 minutes).

Baseline data

All subjects were male. The median overall age was 30 years (range: 13 to 62 years). The majority of subjects were in the 18 to 64 years of age category (n=22). The median weight was 75.95 kg (range: 45.4 to 129.0 kg), and the median BMI was 25.29 kg/m2 (range: 17.5 to 39.6 kg/m2). Race was not reported for 70.8% of subjects owing to local confidentiality requirements. Of the remaining subjects, 16.7% were white, 8.3% were black or African American, and 4.2% were Asian. The majority of subjects (70.8%) did not report ethnicity due to local confidentiality regulations. The main geographic area represented was Other (Australia and New Zealand) (70.8%).

Numbers analysed

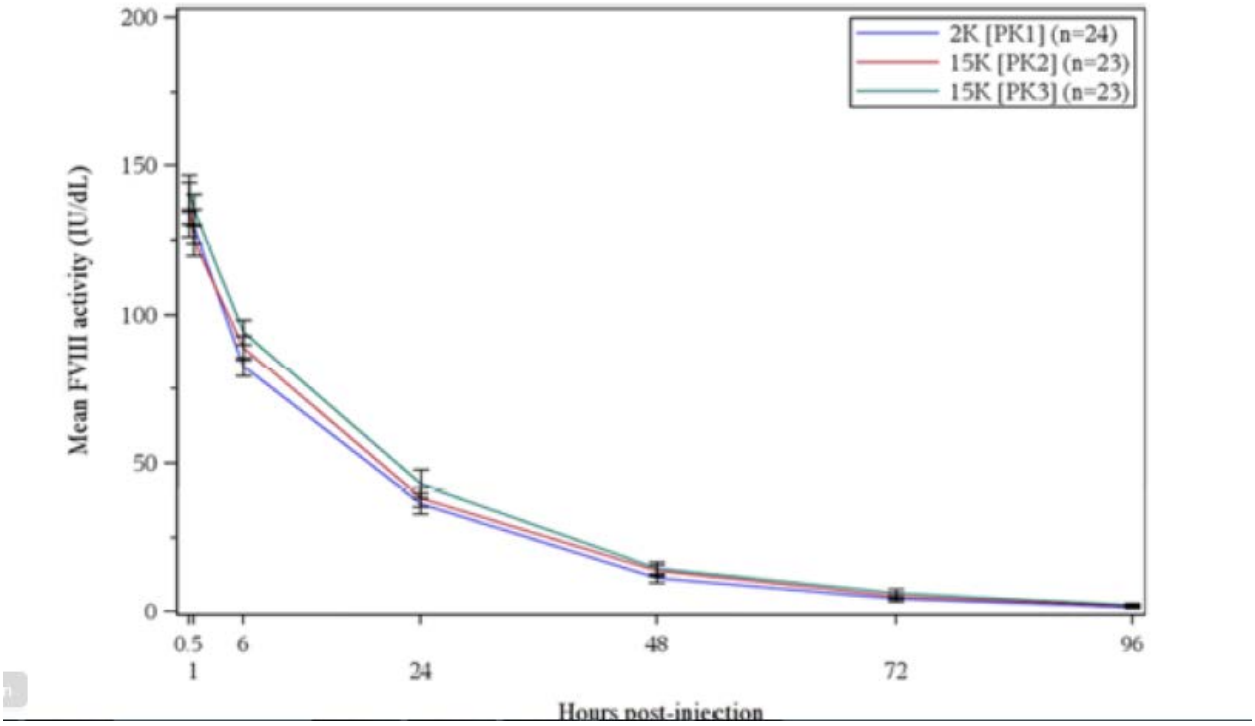
Outcomes and estimation

Primary endpoint

Pharmacokinetic characteristics across rFVIIIFc manufacturing scales: 2K (PK1) and 15K (PK2)

Concordance was high between the PK parameters for the drug product administered from the 2 manufacturing scales, and the PK profiles for the 15K and 2K manufacturing scales were comparable with considerable overlap of the SE bars **(see Figure 2)**.

Figure 2: Mean (±SE) FVIII activity over time following rFVIIIFc dosing by pharmacokinetic assessments and manufacturing scales; one-stage clotting assay (linear scale) (Pharmacokinetic analysis set)



The ratios of adjusted geometric mean of the 15K relative to the 2K manufacturing scale were close to 1 suggesting similar PK, with estimates of 1.08 (90 % CI: 0.93, 1.24) and 1.01 (90 % CI: 0.87, 1.16) for the primary parameters AUCinf and IR, respectively **(Table 3)**. These CIs fell within the range of 0.68 to 1.46, and thus met the predefined measure of comparability as specified in the study protocol and SAP.

Table 3

Table 3.3-1: Comparison of 15K (PK2) and 2K (PK1) rFVIIIFc for primary pharmacokinetic parameters: noncompartmental methods; one-stage clotting assay (Pharmacokinetic analysis set)

PK parameters	n[a]	Adjusted geometric mean for 15K (PK2) 1000 and 6000 IU/Vial (90 % CI)		Adjusted geometric mean for 2K (PK1) 1000 IU/Vial (90 % CI)		Ratio of adjusted geometric mean (90 % CI)	
AUC_{inf} (IU·h/dL)	24	2425.8	(2084.2, 2823.4)	2255.6	(1886.2, 2697.4)	1.08	(0.93, 1.24)
IR (IU/dL per IU/kg)	24	2.700	(2.458, 2.964)	2.684	(2.364, 3.049)	1.01	(0.87, 1.16)

Overall, the PK profile displayed a two-compartmental behavior with a rapid distribution phase for the first 6 hours, followed by slower elimination of FVIII activity over the remainder of the profile.

A sensitivity analysis was performed for the subjects who had evaluable AUCinf and IR for both PK1 and PK2 assessments. The results of the sensitivity analysis supported the primary analysis results, with almost identical estimates.

The PK conclusions from the one-stage clotting assay were supported by the results from the two-stage chromogenic assay.

Secondary endpoints

The secondary PK parameters (Cmax, t1/2, CL, Vss, and MRT) showed similar results to the primary parameters. The time-related parameters, t1/2 and MRT, showed a high level of consistency between the 2 manufacturing scales with the ratio of the adjusted geometric mean of 1.00 with narrow 90 % CI. The geometric mean ratios for the CL and Vss estimates were also well within the prespecified CI limit.

Pharmacokinetic characteristics across 15K rFVIIIFc at baseline (PK2) and after 13 weeks of treatment (PK3)

Overall, the key PK parameters were comparable across 15K rFVIIIFc at baseline (PK2) and after 13 weeks of treatment (PK3) for the individual 1000 and 6000 IU as well as the combined 1000/6000 IU vial strengths.

For the 1000 and 6000 IU combined results, the geometric mean estimate for AUCinf for the PK2 assessment was 2448.6 IU·h/dL (95 % CI: 2089.0, 2870.1), compared with 2697.8 IU·h/dL (95 % CI: 2295.1, 3171.0) for PK3, and the geometric mean estimate for IR was 2.693 (95 % CI: 2.429, 2.986) and 2.804 IU/dL per IU/kg (95 % CI: 2.588, 3.038) for PK2 and PK3, respectively. The 2 parameters were comparable, given the considerable overlap in the 95 % CIs.

Similarly, the geometric means estimates for the time-related parameters, t½ and MRT, and the CL and Vss were also comparable between PK2 and PK3.

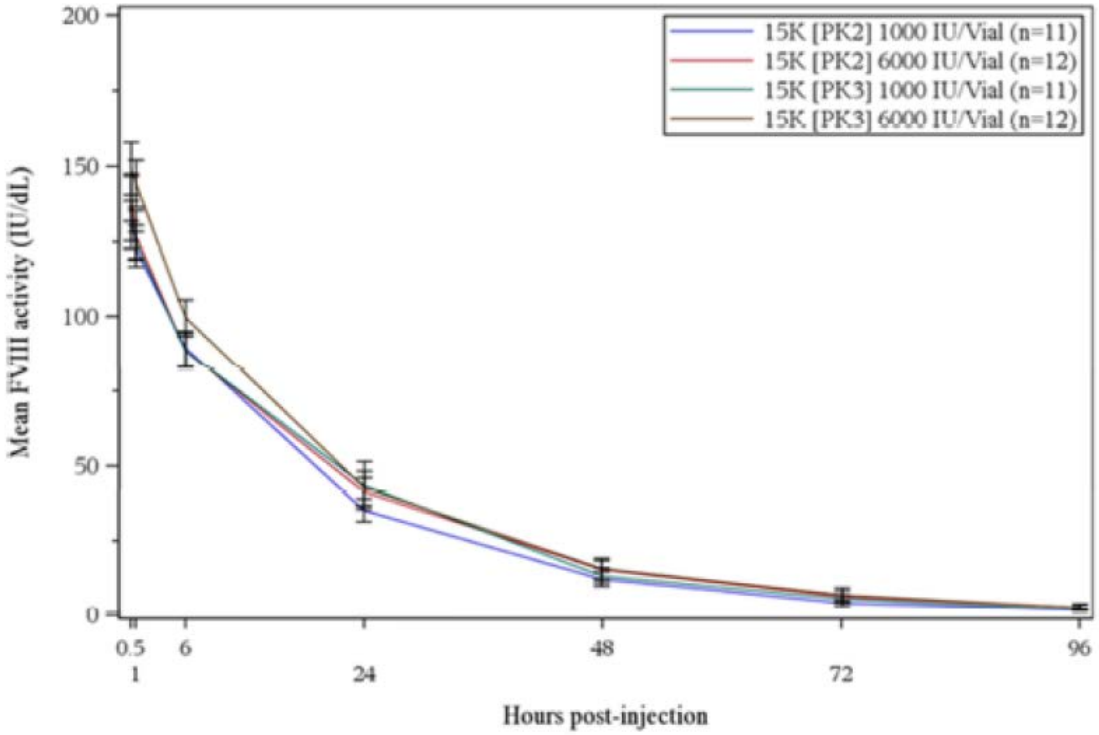
Similar trends were observed for the PK2 vs. PK3 assessments at the individual 1000 and 6000 IU vial strengths with comparable mean PK estimates and overlapping CIs between the baseline and repeat PK assessments.

The individual and combined results confirm that the PK profile is stable over 13 weeks of treatment, with the time course of activity consistent with and predictable from the first dose activity profile.

Pharmacokinetic characteristics across 15K rFVIIIFc vial strengths

Overall, the kinetics of rFVIIIFc across 15K rFVIIIFc vial strengths (1000 and 6000 IU/vial) were consistent, and the 2 strengths showed comparable PK profiles that were consistent with the typical profiles displayed by the product **(see Figure 3 below)**.

Figure 3: Mean (±SE) FVIII activity over time following 15K rFVIIIFc dosing by pharmaco-kinetic assessments and vial strengths; one-stage clotting assay (linear scale) (Pharmaco-kinetic analysis set)



For the PK2 assessment, the geometric mean estimate for AUCinf for the 1000 IU vial strength was 2356.8 IU·h/dL (95 % CI: 1950.4, 2847.9), compared with 2535.8 IU·h/dL (95 % CI: 1915.6, 3356.8) for the 6000 IU vial strength, and the geometric mean estimate for IR was 2.614 (95 % CI: 2.186, 3.126) and 2.768 IU/dL per IU/kg (95 % CI: 2.408, 3.181) for the 1000 and 6000 IU strengths, respectively. The 2 parameters were comparable, given the considerable overlap in the 95 % CIs.

The geometric means estimates for the time-related parameters, t½ and MRT, as well as CL and Vss were also similar between the 1000 and 6000 IU vial strengths.

The PK3 assessment also showed similar results across the 1000 and 6000 IU vial strengths with comparable parameter estimates and a high level of overlap in the 95 % CI.

2.5.2. Discussion on clinical efficacy

In order to support the applied line extension the MAH presented data from one PK study in which low versus high concentrated product has been compared but also 2K versus upscaled 15K product. Furthermore, PK of 15K product at baseline was compared to PK after 13 weeks of treatment.

In brief, the PK parameters across the 15K rFVIIIFc 1000 and 6000 IU vial strengths were similar. Furthermore, PK parameters across 15K rFVIIIFc at baseline (PK2) and after 13 weeks of treatment (PK3) confirm a similar time course of activity. In terms of overall comparison of 2K versus 15K material the presented data show comparable PK profiles.

Overall, the data are considered adequate to support the requested line extension. However, there was one issue identified to be addressed prior to final conclusion, i.e. a PK sub-analysis of patients who received 2K 1000 IU/vial product and then the 15k 1000 IU/vial. Subsequently the applicant provided

this sub-analysis. In brief, it was agreed that the results are consistent with the analyses on the total population. Thus, no difference between 2K and 15k material is detected.

2.5.3. Conclusions on the clinical efficacy

Overall, the data are considered adequate to support the requested line extension.

2.6. Clinical safety

Patient exposure

The Safety Analysis Set included 24 subjects who received at least 1 dose of rFVIIIFc (2K or 15K). Among the 23 subjects exposed to 15K rFVIIIFc, 23 subjects (100%) received rFVIIIFc during the study for at least 13 weeks and 15 subjects (65.2%) received rFVIIIFc during the study for at least 26 weeks.

Adverse events

During 15K rFVIIIFc treatment, 23 subjects received at least 1 dose of 15K rFVIIIFc, of which, 10 subjects (43.5%) experienced a total of 17 TEAEs. One subject experienced an AE that was considered by the Investigator as related to 15K rFVIIIFc treatment (PT: increase in alanine aminotransferase [ALT]).

During the 2K rFVIIIFc treatment, 24 subjects received at least 1 dose of 2K rFVIIIFc, of which, 3 subjects (12.5%) experienced a total of 4 TEAEs. One subject experienced an AE that was considered by the Investigator as related to 2K rFVIIIFc treatment (PT: altered taste).

Serious adverse event / deaths / other significant events

There were no deaths reported in the study. There were no TESAEs in this study. One subject experienced an AE of head injury that was considered severe; otherwise, all AEs during the study were mild or moderate.

Laboratory findings

Overall, no unusual pattern was observed in the shifts in laboratory data from baseline to values outside normal range in the noted hematology or chemistry parameters. No abnormalities reached potentially clinically significant elevated values and no AEs were reported for these subjects.

Immunological events

All 24 subjects in the Safety Analysis Set had inhibitor testing performed. No subjects developed a positive inhibitor to FVIII during the study.

Two of 24 subjects tested positive for anti-rFVIIIFc prior to receiving the first dose of rFVIIIFc in this study. Neither subject had been previously exposed to rFVIIIFc. One of these subjects had no subsequent positive measurements. The other subject who was positive for anti-rFVIIIFc prior to

treatment also had positive tests at PK1 and PK2 assessments but was negative at the PK3 assessment and final study visit. One subject tested positive for anti-rFVIIIFc at the PK3 assessment, and was negative for all other assessments and negative at the final study visit.

Discontinuation due to adverse events

No subject discontinued treatment or withdrew from the study due to an AE.

2.6.1. Discussion on clinical safety

From the safety database all the adverse reactions reported in clinical trials and post-marketing have been included in the Summary of Product Characteristics.

The safety profile of rFVIIIFc was assessed in 23 subjects who received 15K rFVIIIFc and 24 subjects who received 2K rFVIIIFc. While 2K rFVIIIFc was applied only once, i.e. for the PK, the exposure to 15K rFVIIIFc occurred over a period of up to 32 weeks (median 26 weeks).
The results showed that rFVIIIFc was well tolerated. No positive inhibitors to rFVIIIFc were detected in any subject. There were no deaths reported during the study. No subject discontinued treatment or withdrew from the study due to an AE. No subject presented a TESAE in this study.
For 15K rFVIIIFc, the most common TEAE reported was headache (3 subjects); all other TEAEs during treatment were experienced by no more than 1 subject. Most AEs observed in the study were assessed as mild or moderate by the Investigator. There were no unique safety concerns identified for the 15K rFVIIIFc manufacturing scale.
The relevance of the single adverse event of PT alanine aminotransferase increased (which was judged as possibly related by the investigator) has been discussed with the applicant. The subject concerned has a history of transient ALT elevations combined with a medical history of iron deficiency anemia, chronic hemophilic arthropathy and muscle wasting. In consequence, it was agreed to the applicant that there is not enough evidence to support a causal association between the ALT increase and treatment with Elocta.

2.6.2. Conclusions on the clinical safety

In conclusion, overall application of Elocta was well tolerated and revealed no serious safety concerns.

2.7. Risk Management Plan

No new risks have been identified for Elocta 4000 IU, 5000 IU and 6000 IU applied for in this line extension application.

Therefore, no revised RMP was provided as part of this application. The RMP version 2.0 remains the last authorised version.

2.8. Pharmacovigilance

Pharmacovigilance system

The CHMP considered that the pharmacovigilance system summary submitted by the MAH fulfils the requirements of Article 8(3) of Directive 2001/83/EC.

Periodic Safety Update Reports submission requirements

The requirements for submission of periodic safety update reports for this medicinal product are set out in the list of Union reference dates (EURD list) provided for under Article 107c(7) of Directive 2001/83/EC and any subsequent updates published on the European medicines web-portal.

2.9. Product information

2.9.1. User consultation

No full user consultation with target patient groups on the package leaflet has been performed on the basis of a bridging report making reference to Elocta. The bridging report submitted by the MAH has been found acceptable.

2.9.2. Additional monitoring

Pursuant to Article 23(1) of Regulation No (EU) 726/2004, Elocta (efmoroctocog alfa) is included in the additional monitoring list as it contains a new active substance.

Therefore the summary of product characteristics and the package leaflet includes a statement that this medicinal product is subject to additional monitoring and that this will allow quick identification of new safety information. The statement is preceded by an inverted equilateral black triangle.

3. Benefit-Risk Balance

3.1. Therapeutic Context

3.1.1. Disease or condition

Haemophilia A is a rare and serious, X-linked, recessive bleeding disorder that predominantly affects males and is characterized by a deficiency of FVIII. In patients with haemophilia A, the primary platelet-driven hemostasis is not affected, but generation of a stable, fibrin-rich clot is defective because inadequate amounts of thrombin are generated. Affected patients suffer from both spontaneous, non-traumatic bleeding episodes as well as substantially prolonged bleeding episodes upon injury.

3.1.2. Available therapies and unmet medical need

Standard treatment for haemophilia A patients is the replacement of the missing protein by infusion of exogenous FVIII concentrates (as plasma-derived FVIII [pdFVIII] or recombinant FVIII [rFVIII] concentrates). Treatment regimens are either on-demand therapy (given when a bleed occurs) or prophylaxis (which consists of regular infusion of FVIII given every 2 to 3 days to prevent bleeding). In the short term, prophylaxis can prevent spontaneous bleeding and in the long term, prophylaxis can prevent bleeding into joints that will eventually lead to debilitating arthropathy.

Prior to the introduction of clotting factor concentrates in the 1960s, the prognosis for haemophilia A patients was poor, average life expectancy being 15 to 25 years. Major advances in the safety of clotting factor products, including the availability of rFVIII concentrates, the availability of comprehensive haemophilia A treatment centres, the institution of routine prophylaxis, the introduction of home treatment, as well as the active roles that patients take in self-advocacy, have enabled patients with haemophilia A to lead a “close to normal” life.

3.1.3. Main clinical studies

This line extension intends to include three additional vial strengths (i.e. 4000 IU, 5000 IU and 6000 IU).

To support this application results from one PK clinical study (study 997HA309) are presented which was designed: (1) to investigate the pharmacokinetic (PK) profile of rFVIIIFc manufactured at the 15,000 L (15K) scale relative to the PK of rFVIIIFc manufactured at the current scale (2000 L; 2K), (2) to characterise the PK of 15K rFVIIIFc in 6000 international unit (IU) vials (the highest vial strength) versus the lower, 1000 IU vial strength, and (3) to provide 26 weeks of safety data on 15K rFVIIIFc.

3.2. Favourable effects

The PK parameters across the 1000 IU and 6000 IU vial strengths were similar. Furthermore, PK parameters across 15K rFVIIIFc at baseline (PK2) and after 13 weeks of treatment (PK3) confirm a similar time course of activity. In terms of comparison of 2K versus 15K material the presented data show comparable PK profiles.

Overall, the PK data are considered adequate to support the requested line extension.

3.3. Uncertainties and limitations about favourable effects

Not applicable.

3.4. Unfavourable effects

The safety profile of rFVIIIFc was assessed in 23 subjects who received 15K rFVIIIFc and 24 subjects who received 2K rFVIIIFc. While 2K rFVIIIFc was applied only once, i.e. for the PK, the exposure to 15K rFVIIIFc occurred over a period of up to 32 weeks (median 26 weeks).

The results showed that rFVIIIFc was well tolerated. No positive inhibitors to FVIII were detected in any subject. There were no deaths reported during the study. No subject discontinued treatment or withdrew from the study due to an AE. No subject presented a TESAE in this study.

3.5. Uncertainties and limitations about unfavourable effects

Not applicable.

3.6. Benefit-risk assessment and discussion

3.6.1. Importance of favourable and unfavourable effects

The PK parameters across the 1000 IU and 6000 IU vial strengths were similar. The results showed that rFVIIIFc was well tolerated.

3.6.2. Balance of benefits and risks

The overall benefit risk assessment for Elocta remains positive.

3.6.3. Additional considerations on the benefit-risk balance

Not applicable.

3.7. Conclusions

The overall B/R of Elocta is positive.

4. Recommendations

Outcome

Based on the CHMP review of data on quality, safety and efficacy, the CHMP considers by consensus that the benefit-risk balance of, Elocta 4000 IU, 5000 IU and 6000 IU new strengths is favourable in the following indication:

“Treatment and prophylaxis of bleeding in patients with haemophilia A (congenital factor VIII deficiency).
Elocta can be used for all age groups.”

The CHMP therefore recommends the extension(s) of the marketing authorisation for Elocta subject to the following conditions:

Conditions or restrictions regarding supply and use

Medicinal product subject to restricted medical prescription (see Annex I: Summary of Product Characteristics, section 4.2).

Conditions and requirements of the marketing authorisation

Periodic Safety Update Reports

The requirements for submission of periodic safety update reports for this medicinal product are set out in the list of Union reference dates (EURD list) provided for under Article 107c(7) of Directive 2001/83/EC and any subsequent updates published on the European medicines web-portal.

Conditions or restrictions with regard to the safe and effective use of the medicinal product

Risk Management Plan (RMP)

The MAH shall perform the required pharmacovigilance activities and interventions detailed in the agreed RMP presented in Module 1.8.2 of the marketing authorisation and any agreed subsequent updates of the RMP.

An updated RMP should be submitted:

- At the request of the European Medicines Agency;
- Whenever the risk management system is modified, especially as the result of new information being received that may lead to a significant change to the benefit/risk profile or as the result of an important (pharmacovigilance or risk minimisation) milestone being reached.

Conditions or restrictions with regard to the safe and effective use of the medicinal product to be implemented by the Member States.

Not applicable.