19 May 2022
EMA/CHMP/577398/2022
Committee for Medicinal Products for Human Use (CHMP)

Assessment report

Cevenfacta

International non-proprietary name: eptacog beta (activated)

Procedure No. EMEA/H/C/005655/0000

Note

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

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Administrative information

Name of the medicinal product:	Cevenfacta
Applicant:	Laboratoire français du Fractionnement et des Biotechnologies Tour W 102 Terrasse Boieldieu, 19ème Étage 92800 Puteaux France
Active substance:	Eptacog beta (activated)
International Non-proprietary Name:	eptacog beta (activated)
Pharmaco-therapeutic group (ATC Code):	vitamin k and other hemostatics, blood coagulation factors (B02BD08)
Therapeutic indication(s):	CEVENFACTA is indicated in adults and adolescents (12 years of age and older) for the treatment of bleeding episodes and for the prevention of bleeding in those undergoing surgery or invasive procedures in the following patient groups: • in patients with congenital haemophilia with high-responding inhibitors to coagulation factors VIII or IX (i.e. ≥5 Bethesda Units (BU)); • in patients with congenital haemophilia with low titre inhibitors (BU <5), but expected to have a high anamnestic response to factor VIII or factor IX administration or expected to be refractory to increased dosing of FVIII or FIX.
Pharmaceutical form:	Powder and solvent for solution for injection
Strengths:	1 mg (45 KIU), 2 mg (90 KIU) and 5 mg (225 KIU)
Route of administration:	Intravenous use
Packaging:	powder: vial (glass); solvent: pre-filled syringe (glass)
Package size(s):	1 vial + 1 pre-filled syringe + 1 vial adapter

	+ 1 plunger rod

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List of abbreviations

ADA	Anti-drug antibody(ies)
ADR	Adverse drug reaction
AE	Adverse event
aPCC	Activated prothrombin complex concentrate
aPTT	Activated Partial Thromboplastin Time
AUC	Area under concentration-time curve;
$AUC_{0\text{-last}}$	AUC from time 0 to the last measurable concentration
$AUC_{0\text{-inf}}$	AUC from time 0 to infinity
BHK	Baby hamster kidney (cells)
BLA	Biologics License Application
BMI	Body mass index
BSA	Body surface area
BU	Bethesda unit
C_0	Concentration at time 0
CHMP	Committee for Medicinal Products for Human Use
CI	Confidence interval
CL	Clearance
Cmax	Maximum plasma concentration
CSR	Clinical study report
CV	Coefficient of variation
DIC	Disseminated intravascular coagulation
DMC	Data Monitoring Committee
DNA	Deoxyribonucleic acid
ε	random error associated to individual subjects
E_{50}	concentration at half the maximum response
ECLA	Electrochemiluminescent assay
ED	Exposure day
EMA	European Medicines Agency
E_{max}	Maximum response
EPCR	Endothelial protein C receptor
ER	Exposure-response
ETP	Endogenous thrombin potential
EU	European Union
F (IX, VIII)	Factors
F1+2	Prothrombin fragments 1 and 2
FDA	Food and Drug Administration

FIBTEM	Fibrin-based extrinsically activated test with tissue factor and the platelet
FVII	Coagulation factor VII
FVIIa	Activated coagulation factor FVII
FX	Coagulation factor X
GEE	Generalised Estimating Equations
GLMM	Generalised linear mixed-effect model
G.M.	Geometric mean
ICH	International Council on Harmonization
Ig	Immunoglobulin
IR	Incremental recovery
ISTH	International Society of Thrombosis and Haemostasis
ITI	Immune tolerance induction
IV	Intravenous(ly)
KDa	KiloDalton
LR769	™ (Coagulation Factor VIIa [Recombinant])
MCF	Maximum clot firmness
MedDRA	Medical dictionary for regulatory activities
Max	Maximum
Min	Minimum
MRT	Mean residence time
NA	Not applicable
NC	Not calculated
NCA	Non-compartmental analysis
OPC	Objective performance criterion
PD	Pharmacodynamic(s)
PDCO	Paediatric Committee
PIP	Paediatric investigation plan
PK	Pharmacokinetic(s)
PKER	PK population exposure-response
PT	Preferred term
PT	Prothrombin Time
Q	Inter-compartmental clearance
rFVIIa	Recombinant activated human coagulation factor VII (NovoSeven®)
rhFVIIa	Activated recombinant human coagulation factor VII (LR769)
rTF	Recombinant tissue factor
RMP	Risk Management Plan or rabbit milk protein
ROTEM	Rotational thromboelastography
SAE	Serious adverse event

SAP	Statistical analysis plan
SD	Standard deviation
SmPC	Summary of the product characteristics
SOC	System Organ Class
t1/2	Terminal half-life
TAAE	Treatment-associated adverse event
TAT	Thrombin-antithrombin complex
TEAE	Treatment-emergent adverse event
TF	Tissue factor
TGA	Thrombin generation assays
TGT	Thrombin generation time
TGTp	thrombin generation test with added platelets
US	United States
VAS	Visual analog scale
Vc	volume of distribution of the central compartment using compartmental
Vd	volume of distribution determined using NCA
Vp	volume of distribution of the peripheral compartment using
V1/Vc	Volume of distribution in the central compartment
V2/Vp	Volume of distribution in the peripheral compartment

1. Background information on the procedure

1.1. Submission of the dossier

The applicant Laboratoire Francais du Fractionnement et des Biotechnologies submitted on 28 January 2021 an application for marketing authorisation to the European Medicines Agency (EMA) for Cevenfacta, through the centralised procedure falling within the Article 3(1) and point 1 of Annex of Regulation (EC) No 726/2004.

The applicant applied for the following indication: This medicinal product is indicated for the treatment of bleeding episodes and for the prevention of bleeding in those patients undergoing surgery or invasive procedures, in children and adults congenital haemophilia A or B patients with:

- High-response inhibitors to coagulation factors VIII or IX (i.e. ≥ 5 Bethesda Units (BU)), including those expected to have a high anamnestic response to factor VIII or factor IX administration;
- Low-response inhibitors (BU<5) but expected to be refractory to increased dosing of FVIII or FIX.

1.2. Legal basis, dossier content

The legal basis for this application refers to:

Article 8.3 of Directive 2001/83/EC - complete and independent application

The application submitted is composed of administrative information, complete quality data, non-clinical and clinical data based on applicants' own tests and studies and/or bibliographic literature substituting/supporting certain tests or studies.

1.3. Information on Paediatric requirements

Pursuant to Article 7 of Regulation (EC) No 1901/2006, the application included an EMA Decision(s) P/0214/2017 on the agreement of a paediatric investigation plan (PIP) and on the granting of a class waiver.

At the time of submission of the application, the PIP P/0214/2017 *w*as completed.

The PDCO issued an opinion on compliance for the PIP EMEA-C-001203-PIP02-14-M02.

1.4. Information relating to orphan market exclusivity

1.4.1. Similarity

Pursuant to Article 8 of Regulation (EC) No. 141/2000 and Article 3 of Commission Regulation (EC) No 847/2000, the applicant did submit a critical report addressing the possible similarity with authorised orphan medicinal products.

It is considered that Cevenfacta is not similar to Alprolix and Idelvion within the meaning of Article 3 of Commission Regulation (EC) No. 847/200.

1.5. Applicant's request for consideration

1.5.1. New active substance status

The applicant requested the active substance eptacog beta (activated) contained in the above medicinal product to be considered as a new active substance in comparison to eptacog alfa (activated) previously authorised in the European Union as NovoSeven, as the applicant claimed that eptacog beta (activated) differs significantly in properties with regard to safety and/or efficacy from the already authorised active substance.

However, based on the review of the available data the active substance eptacog beta (activated) contained in the medicinal product Cevenfacta is not to be qualified as a new active substance in comparison to the known eptacog alfa (activated) previously authorised in the European Union as NovoSeven as it is not demonstrated that it differs significantly in properties with regard to safety and efficacy from the previously authorised substance.

1.6. Scientific advice

The applicant received the following scientific advice on the development relevant for the indication subject to the present application:

Date	**Reference**	**SAWP co-ordinators**
23 June 2011	EMEA/H/SA/2123/1/2011/III	Alexandre Moreau and Thomas Lang
22 May 2014	EMEA/H/SA/2123/1/FU/1/2014/III	Jan Mueller-Berghaus and Thomas Lang
25 January 2018	EMEA/H/SA/2123/1/FU/2/2017/I	Jens Reinhardt and Sheila Killalea

The scientific advice pertained to the following quality, non-clinical, and clinical aspects:

- The phenotypic and genotypic stability test plan and the plan for annual genotypic assessment of the production colony after the stability study is completed. The collection and pooling strategy of milk ("source material") for production of the "starting material" to enter downstream processing. Obtaining the source material from various facilities but from the same line to be used to produce supplies of finished product. The plan/tools set to validate the purification process. The comparability testing plan and the acceptance criteria on drug substance and drug product. The overall stability programme. The control strategy developed for Rabbit Milk Proteins. The process validation plan to demonstrate that the process is capable to consistently produce drug substance with defined quality characteristics. The viral validation plan. The testing method and specifications for visible particles of the finished product.
- The proposed toxicological programme and the immunological safety profile to support MAA.
- Strategy for dose selection. Design of the proposed phase 2/3 studies, including populations, non-controlled (historical controls), the number of patients treated during the clinical development including the number of paediatric and adult patients for PK assessment, primary and secondary endpoints.

1.7. Steps taken for the assessment of the product

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

Rapporteur: Andrea Laslop Co-Rapporteur: Alexandre Moreau

The application was received by the EMA on	28 January 2021
The procedure started on	25 February 2021
The CHMP Rapporteur's first Assessment Report was circulated to all CHMP and PRAC members on	17 May 2021
The CHMP Co-Rapporteur's first Assessment Report was circulated to all CHMP and PRAC members on	20 May 2021
The PRAC Rapporteur's first Assessment Report was circulated to all PRAC and CHMP members on	31 May 2021
The CHMP agreed on the consolidated List of Questions to be sent to the applicant during the meeting on	24 June 2021
The applicant submitted the responses to the CHMP consolidated List of Questions on	20 January 2022
The CHMP Rapporteurs circulated the CHMP and PRAC Rapporteurs Joint Assessment Report on the responses to the List of Questions to all CHMP and PRAC members on	1 March 2022
The PRAC agreed on the PRAC Assessment Overview and Advice to CHMP during the meeting on	10 March 2022
The CHMP agreed on a list of outstanding issues in writing to be sent to the applicant on	24 March 2022
The applicant submitted the responses to the CHMP List of Outstanding Issues on	15 April 2022
The CHMP Rapporteurs circulated the CHMP and PRAC Rapporteurs Joint Assessment Report on the responses to the List of Outstanding Issues to all CHMP and PRAC members on	4 May 2022
The CHMP, in the light of the overall data submitted and the scientific discussion within the Committee, issued a positive opinion for granting a marketing authorisation to Cevenfacta on	19 May 2022

2. Scientific discussion

2.1. Problem statement

2.1.1. Disease or condition

Haemophilia is an X-linked congenital bleeding disorder due to a deficiency of FVIII (haemophilia A) or FIX (haemophilia B) which results from mutations of the respective clotting factor genes leading to either reduced production or a defective form of coagulation factor. Virtually only males are affected with the congenital form of haemophilia as both the FVIII and FIX genes are located on the X chromosome. However, in rare cases females may also have symptoms of disease, usually due to the preferential inactivation of one of the X chromosomes.

The most severe complication of treatment with exogenous factor concentrate is the development of antibodies to the factor concentrate, often of a neutralising form, which are referred to as inhibitors (Kempton, 2009). Treatment of these patients with factor concentrates will be less effective when high titres of inhibitors are present based on the established Bethesda assay to measure FVIII or FIX inhibitors (Bethesda Units [BU]) (Miller, 2018).

The CHMP has agreed with the following indication: Cevenfacta is indicated in adults and adolescents (12 years of age and older) for the treatment of bleeding episodes and for the prevention of bleeding in those undergoing surgery or invasive procedures in the following patient groups:

- in patients with congenital haemophilia with high-responding inhibitors to coagulation factors VIII or IX (i.e. ≥5 Bethesda Units (BU));
- in patients with congenital haemophilia with low titre-response inhibitors (BU <5), but expected to have a high anamnestic response to factor VIII or factor IX administration or expected to be refractory to increased dosing of FVIII or FIX.

2.1.2. Epidemiology

The prevalence of haemophilia A is approximately 1:7500 and of haemophilia B is 1:30000 males (Ljung, 2018). Depending on the concentration of FVIII or FIX, the disorders are classified as severe (<0.01 U/mL), moderate (0.01–0.05 U/mL), or mild (0.05–0.40 U/mL). The severe form is usually diagnosed during the first year of life due to abnormal subcutaneous hematoma after minimal trauma, or spontaneous hematomas. The typical joints affected are the ankles, knees, and elbows resulting in chronic arthropathy with significant deformities in the long term if untreated. In the pre-clotting factor concentrate era, death in both conditions was primarily due to intracranial haemorrhage or other life-threatening bleeds and patients rarely survived beyond 10 years.

2.1.3. Clinical presentation and diagnosis

Clinical presentation: Haemophilia A and B are classified as 'severe', 'moderate' or 'mild' according to endogenous FVIII or IX plasma activity level and factor levels are generally correlated to the severity of bleeding:

- Severe haemophilia: FVIII activity <1% - patients experience bleeding into joints or muscles often without any apparent reason (spontaneous bleeding).

- Moderate haemophilia: FVIII activity 1 to <5% - patients experience occasional spontaneous bleeding and prolonged bleeding with minor trauma or surgery.

- Mild haemophilia: FVIII activity 5 to <40% - patients experience severe bleeding with major trauma or surgery and spontaneous bleeding is rare.

The most common manifestation of haemophilia is bleeding into joints. Repeated bleeding into the same joint, referred to as a target joint, can prevent healing and thus cause chronic inflammation and musculoskeletal pain, reduced range of motion and diminished quality of life.

Diagnosis: Haemophilia should be suspected in individuals presenting with a history of any of these symptoms: easy bruising; "spontaneous" bleeding (i.e., bleeding for no apparent/known reason), particularly into the joints, muscles, and soft tissues; excessive bleeding following trauma or surgery. Early symptoms of joint bleeds in children at a very young age are a key indicator of severe haemophilia. If haemophilia is suspected, the clinician should obtain the patient's bleeding history and family history of abnormal or unexplained bleeding experienced by any siblings or maternal male relatives (i.e., maternal cousin, uncle, or grandfather) to assess patterns of inheritance and assist with diagnosis. Accurate diagnosis of haemophilia is essential to inform appropriate management. A definitive haemophilia diagnosis is based on a factor assay to demonstrate deficiency of FVIII or FIX.

The most challenging complication in the treatment of haemophilia is the development of anti-FVIII or FIX alloantibodies also called inhibitors, which affects approximately one-third of patients with severe haemophilia A and approximately 3-5% of those with severe haemophilia B. Such inhibitors, that neutralise the functional activity of FVIII and FIX administered for replacement therapy, impact patients' access to a safe and effective care, and predispose them to an increased risk of morbidity and mortality (Franchini, 2018). Inhibitors may occur at any time in a patient's life, but the majority of patients develop inhibitors early in life during the first 50 exposure days (EDs). People with a family history of inhibitors, patients with certain genetic mutations or certain blood types (Franchini, 2011), and non-whites are at a higher risk for developing inhibitors.

2.1.4. Management

Treatment of haemophilia A and B patients is usually with anti-homophilic factor products, replacing the deficient factor (i.e. FVIII or FIX). Prophylactic administration to maintain circulating factor levels above 1 IU/dL (1%) of normal level has resulted in a substantial reduction in bleeding frequency and its associated complications, with significant improvements to life expectancy. Preventive treatment is given prior to surgical procedures or invasive investigations (i.e. endoscopy with biopsies, tooth extractions).

For the proposed patient population who developed inhibitors, permanent eradication of inhibitors is usually first choice. ITI involves administration of factor VIII or IX in a small dose to begin with and gradually increasing the dose so that the individual's immune system learns to tolerate the clotting factor and ceases to produce inhibitors. However, an optimal regimen for ITI remains to be defined and the length of treatment is based on individual responses, ranging from months to years and comes with high treatment burden.

The current standard of care for treatment of bleeds or prevention of bleeding in those undergoing surgery in haemophilia A or B patients with inhibitors is treatment with bypassing agents (BPAs). The two products available for this are:

- recombinant factor VIIa (NovoSeven) and

- activated prothrombin complex concentrate (aPCC, or factor eight inhibitors bypassing agent [FEIBA]).

BPAs are short-acting and may need to be administered often, with long IV infusion times (25-50 minutes for FEIBA) and/or require frequent administration for prophylaxis (daily or every other day for FEIBA). Frequent administration is time-consuming and burdensome for people with haemophilia A and their caregivers. NovoSeven is indicated for episodic use only, while FEIBA is approved for episodic and prophylactic use.

For patients with haemophilia A with inhibitors, emicizumab (Hemlibra) is another option for prophylaxis of bleeding episodes. Emicizumab is a humanised bispecific monoclonal antibody that bridges activated FIX and FX to mimic the function of activated FVIII, thereby increasing thrombin formation. Such an option is not available for patients with haemophilia B with inhibitors.

2.2. About the product

The drug product LR769 (drug substance eptacog beta (activated) or Cevenfacta is an activated recombinant human coagulation Factor VII (rhFVIIa) concentrate which belongs to the pharmacotherapeutic group of Blood Coagulation Factors. LR769 is a recombinant analogue of human FVIIa, a vitamin K-dependent coagulation factor. In the presence of both calcium and phospholipids, FVIIa in a complex with tissue factor (TF) activates Factor X (FX) to Factor Xa (FXa), directly bypassing the reactions that require Factor VIII (FVIII) or Factor IX (FIX). Activation of FX to FXa initiates the common pathway of the coagulation cascade in which prothrombin is activated to thrombin, which then converts fibrinogen to fibrin to form a haemostatic plug, thereby achieving clot formation at the site of haemorrhage (haemostasis). This process may also occur in the absence of Tissue Factor on the surface of activated platelets (Hoffman, 1998).

LR769 is an activated recombinant human coagulation rhFVIIa produced by recombinant deoxyribonucleic acid (DNA) technology employing site-directed expression of the human FVII gene in the mammary gland of transgenic rabbits. The transgene containing the FVII has been stably integrated into the transgenic rabbit genome. The recombinant human FVII gene is exclusively expressed by the mammary gland under the control of a beta-casein specific promoter. Milk from these transgenic rabbits is collected and the FVII protein expressed is subsequently purified and activated during the purification process to FVIIa. The glycoprotein produced (FVII) consists of 406 amino acid residues (molecular weight 50 KDa) which is structurally similar to human plasma derived coagulation FVIIa and has similar functional properties to human plasma-derived FVIIa and to another recombinant FVIIa (eptacog alfa).

2.3. Quality aspects

2.3.1. Introduction

The Cevenfacta finished product (LR769) (active substance: eptacog beta (activated), as per INN) is an activated recombinant human coagulation Factor VII (FVIIa) produced by recombinant deoxyribonucleic acid (DNA) technology employing site-directed expression of the human FVII gene in the mammary gland of transgenic rabbits.

The finished product is a sterile lyophilised powder and solvent for solution for injection. It is supplied in vials (powder) with three dosage strengths (1 mg, 2 mg or 5 mg of eptacog beta (activated)) with a prefilled syringe (PFS) for the solvent (water for injections). The other excipients are: (powder)

arginine hydrochloride, isoleucine, trisodium citrate dihydrate, glycine, lysine hydrochloride, polysorbate 80, hydrochloric acid and (solvent) water for injections.

2.3.2. Active Substance

2.3.2.1. General information

The international nonproprietary name (INN) for the recombinant DNA derived blood-coagulation factor VII (activated), extracted from transgenic rabbits' milk is eptacog beta (activated).

Coagulation Factor VIIa (Recombinant) (rhFVIIa) is a vitamin K-dependent glycoprotein consisting of 406 amino acid residues and has a molecular weight of 50 kilodaltons (kDa). During its purification, the recombinant DNA derived Factor VII protein is activated to the serine protease Factor VIIa. Activation occurs by cleavage of the single chain molecule on the C-terminal side of the Arg152 residue, to produce an N-terminal derived light chain (LC) of 20 kDa (152 residues) and a C-terminal derived heavy chain (HC) of 30 kDa (254 residues), which remain covalently associated by a single disulfide bond.

Recombinant human FVIIa possesses a modular organisation with an N-terminal membrane-binding γ-carboxyglutamic acid (Gla)-containing domain, two epidermal growth factor (EGF)-like domains, and a C-terminal serine protease domain. Recombinant human FVIIa contains 12 disulfide bridges, seven of which are located on the light chain, four on the heavy chain, and one which enables the light and heavy chains to remain covalently bound once cleaved (interchain). The active protein is glycosylated with two N-linked glycosylation sites (one on its LC at Asn145 and one on its HC at Asn322) and two O-linked glycosylation sites (on its LC, at Ser52 and Ser60) and the molecule contains γ-carboxylated glutamic acid residues which are essential for functional activity.

2.3.2.2. Manufacture, characterisation and process controls

Manufacturers

The name(s), address(es), and responsibilities of each manufacturer (including contractors, and each production site or facility involved in the manufacture, testing and/or storage of rhFVIIa active substance (AS) have been provided. LFB Biomanufacturing (Le quartier du Rieu, Avenue des Chênes Rouges, 30100 Alès, France) is the manufacturing site responsible for the manufacture of the active substance.

Different sites are involved in the rabbit semen bank production and storage. A valid proof of GMP compliance was provided. All the manufacturing sites are GMP compliant.

Description of manufacturing process and process controls

The manufacturing process has been presented in sufficient detail. The source material is rabbit milk that is collected at milking facilities. The milk from qualified rabbits is collected and frozen. The frozen milk source material is thawed and pooled to generate the milk starting material for clarification. The pooled milk starting material is clarified. The clarified milk starting material is then viral inactivated by solvent/detergent (S/D) treatment, purified using chromatography column, concentrated, buffer exchanged and filtered into a partially purified bulk intermediate (IP). The IP is stored frozen for further processing. The IP is thawed, pooled, nanofiltered and further purified through several orthogonal chromatography steps and filtered into formulated bulk active substance (BAS). The BAS is stored frozen. Further information on the rhFVII activation process, which is supported by data has been provided.

Control of materials:

The controls which are set in order to assure that the animals, source material, and starting material (SM) are of the highest quality to continue on in processing to active substance and eventually to finished product were adequately described.

The recombinant human coagulation Factor VII (rhFVII) protein is secreted as a non-activated form into the milk of qualified rabbits with the human Factor VII (hFVII) transgene stably integrated into their genome. Two lines of animals have been used to produce rhFVIIa. Initial work was done on the material collected from animals derived from the male founder. This material was used to develop the system, for early method development, and for optimpaediatric of milking systems and protein purification development. Subsequently the production line was selected, derived from female founder R69, which has simplified genetics of the transgene integration (a single copy of the hFVII gene) with improved production of milk.

Since the same gene construct was used to generate both lines and many methods were developed using the first line, the first line-derived finished product serves as a control in some of the analyses. For this reason, the first line and R69 data are sometimes presented side by side. It is important to note that only rhFVIIa produced by the R69 line of transgenic rabbits has been developed for commercial purposes.

There are different milk production sites, that function similarly and maintain the same high standards of animal health. All sites also function similarly with respect to the collection and handling of milk.

The milk collected from transgenic rabbits carrying the hFVII gene is adequately controlled and is in line with the 'Guideline on Quality of biological active substances produced by transgene expression in animals'. The transgenic status of the female production animals is confirmed during the initial lactation period. The health of the animals can also impact the quality of the milk and is controlled by the facilities in which they are housed and the procedures surrounding their care and testing. The source material is defined as an approved pool of milk from multiple animals and collection days. In general, milk is not tested as an individual sample other than to confirm transgenic status of female rabbits for use in production during their first (and sometimes second) lactation (these samples are only tested for the presence of a minimum amount of FVII in the milk).

Mini-pools are grouped via a grouping strategy to identify the bottles required for a batch to create the source material. A representative composite is made prior to manufacturing and consists of volumetrically relative samples of the mini-pools comprising the source material bottle batch. The source material is defined as the pooled collection of mini-pools that when thawed makes up the volume required for a manufacturing run or batch.

The source material is tested as a composite, and it must meet certain criteria for quality assurance (QA) approval and release prior to being further processed. Regarding the terminology, when released, the source material becomes starting material (SM). To release SM for use in manufacturing, testing must be successfully completed on the composite that corresponds to the SM batch. The methods used to release SM, performed on the source material composite have been adequately summarised and include: factor VII concentration, factor VII activity, milk protein profile, zoonotic agents (*E. coli*, *Listeria spp*., *Salmonella spp.*), adventitious agents, bioburden and bacterial endotoxins. These source material composite test and specifications have been justified and are acceptable.

Finally, the results obtained through stability studies indicate that source material storage provides sufficient preservation of the source material for the manufacture of rhFVIIa of acceptable integrity and quality. The storage period at the recommended storage temperature is based on a combination of the SM and active substance testing results, balancing product yield with product integrity and quality.

Control of critical steps and intermediates

This section describes the controls performed on the different process steps and intermediates. They include:

- Control of milk starting material, the first process intermediate obtained after thawing and pooling of milk source material.
- In-process controls (IPCs) performed on the upstream process (USP), from milk source material to Intermediate Product (IP). The critical upstream process specifications are presented including step number, step, parameter/attribute, status (IPC/critical process parameters (CPPs)/critical material attributes (CMAs)), normal operating range (NOR), Process Performance Qualification (PPQ) results and viral clearance.
- Control of IP.
- IPCs performed on the downstream process (DSP), from IP to LR769 active substance. The downstream process specifications are presented including step number, step, parameter/attribute, status (IPC/CPP/CMA), NOR, PPQ results and viral validation.

The stability data and additional results which further confirm the observations from the previous studies, support the IP stability period.

Process validation and/or evaluation

Section 3.2.S.2.5 contains a presentation of the different studies which were conducted as part of rhFVIIa active substance process validation.

The validation programme includes different stages of process validation, in line with the European Guideline EMA/CHMP/BWP/187338/2014 on process validation for manufacture of biotechnology derived active substances. Thus, this section is organised in 3 sub-sections according to the different stages of process validation:

- Stage 1 Process Characterisation (evaluation): Section 1 contains the process robustness studies which were conducted at reduced-scale during the development of the process, in complement to the process evaluation studies described in Section 3.2.S.2.6. These studies were generated to enhance process knowledge, identify the links between process parameters and quality attributes, and establish proven acceptable ranges (PARs) for CPPs and CMAs.
- Stage 2 Process Verification (subsequent use: Process Performance Qualification (PPQ)): Section 2 contains the results of the successive PPQ exercises performed at industrial scale.
- Stage 3 continued process verification (CPV): Section 3 contains a brief overview of the CPV programme. CPV will be implemented through continuous monitoring to ensure that the purification process of rhFVII remains in a validated state.

Finally, shipping and transportation of source material, IP and active substance have been validated. A summary of these studies has been provided.

In conclusion, the data reported support consistency in production.

Manufacturing process development

Section 3.2.S.2.6 Manufacturing Process Development provides a description of the different process versions that were used throughout the development of LR769, and a summary of the comparability exercise which was implemented to validate the changes. Furthermore, this section contains a

summary of rhFVIIa active substance batches manufactured during development in chronological order starting with pilot batches from Process A up to the late stage industrial-scale batches from Process B. Finally, the development of the control strategy is presented where the applicant argues that QbD principles have been followed but does not claim a design space.

A first-generation product was obtained from a first transgenic rabbit line and purified by a standard purification process. Later in the development, a second-generation product, LR769, was developed from a new rabbit line (R69) with an improved genetic profile compared to the first-generation product. A brief comparison of characteristics of first with second generation product as well as a high-level overview of process modifications introduced from first to the second generation is given, but no dedicated comparability was presented to compare the quality profile of both materials. The second-generation process was developed at LFB to produce several pilot batches and then transferred to GMP facilities to produce first engineering batches and then further clinical batches. This process version was termed "Process A" and the GMP batches were used to supply clinical phase 1b and more than half of the pivotal phase 3 study. Later on, Process A was scaled up and further optimised to the proposed commercial Process B. Process B material was used for the second half of the pivotal phase 3 study. Process changes from Process A to Process B have been illustrated.

A risk assessment exercise was conducted to evaluate the potential consequences of these changes on quality attributes of the active substance. The initial comparability exercise to compare Process A with Process B material was based on comparison of quality attributes which are release controlled either at IP or at active substance release. Comparability criteria have been established using a statistical analysis of the pre-change representative batch results whereas for quality attributes not impacted by the changes, compliance to acceptance criteria of normal batch release was considered as an appropriate way to demonstrate comparability. In addition, a more in-depth characterpaediatric of one single batch from Process A and one single batch from Process B was provided to further support the comparability claim. No comparative stability data (comparing the degradation profile and kinetics of Process A with Process B material was provided.

At Day120 concerns regarding the quality comparability claim of Process A with Process B material were raised (Major Objection, MO). These deficiencies addressed the limited amount of in-depth characterisation data, the establishment of comparability criteria for quality attributes, which are controlled either at IP or at active substance release, and the presentation of the comparability data which made an adequate assessment difficult.

To address these concerns the following further actions were performed by the applicant:

a) Most importantly, regarding the comparison of in-depth characterisation data, the applicant has conducted an additional investigation including several clinical finished product batches manufactured from process A which were characterised in-depth and compared side by side with several clinical finished product batches manufactured from process B.

All finished product batches have been used in the clinical phase 3 trial and have been manufactured from GMP, clinical and process validation active substance batches. The provided justification for conducting the in-depth characterisation on the finished product and not on the active substance is acceptable.

This additional in-depth comparative characterisation work included standard and state-of-the-art techniques to compare the most relevant structural and functional quality attributes of the rhFVIIa molecule. The data derived thereof have been presented and indicate a comparable quality profile of material from Process A with material from Process B.

b) & c) Regarding the comparability criteria for quality attributes, which are controlled either at IP or at active substance release the applicant has clearly outlined the strategy how comparability criteria have

been established. Comparability criteria were determined using the results of different active substance batches manufactured with Process A. Process A active substance batches used for setting of comparability criteria included all GMP batches as well as engineering batches, thus representing a sufficient large historical data set from Process A material. As requested in the Major Objection the individual results from all used Process A batches are given. For each compared quality attribute, a list of historical batches results used for comparability criteria setting together with the comparability criterion and its justification has been included. In certain cases specific Process A batches were not considered to accurately reproduce historical comparability criterion determination, the provided justification for exclusion of these batches is acceptable.

It should be noted that in the MO at Day120 a recalculation of certain comparability criteria was requested, specifically for those comparability criteria which were wider than the release specifications. The applicant clarified that the comparability criteria were established tighter than or at least equal to the specifications in place for process A batches, none of the comparability acceptance criteria exceeded the release acceptance criteria applicable at the time of the comparability exercise. Specifications for the active substance have been updated throughout its development according to the modifications made to its manufacturing process and to the improvement of analytical methods. A tabulated summary of the comparability criteria set during the comparability exercise has been included into the response which compares them with the specifications in place at the time the study took place and current specification for the commercial product.

Taking these arguments as well as the fact that a retrospective recalculation of comparability criteria would not change the conclusion on comparability the response of the applicant is acceptable.

Finally, in addition to the results obtained from the first several Process B batches which have been already presented in the initial submission, data from additional Process B batches have been included into the comparability evaluation, thus enabling a sound comparability assessment based on a robust and sufficient data set. For each investigated quality attribute, a graphical presentation which shows the data distribution for process A and B batch results used during the initial comparability assessment as well as for the additional active substance Process B batches, is given. Furthermore, statistical tools were used to study data distribution in more detail. For most of the quality attributes the initial comparability results, a graphic representation of complete process B batches results present in the dossier and the TOST test confirm that data from Process A and Process B are comparable. Certain differences such as the 5% difference in the activated FVII methods could be sufficiently justified.

In summary, the deficiencies with respect to the comparability evaluation could be considered adequately solved. Additional data have been provided which demonstrate a comparable quality of Process A with Process B material. As such the Major Objection has been resolved.

Certain changes from Process A to Process B which were not included into the initial quality risk assessment in order to evaluate the potential consequences on quality attributes have been justified. No comparative stress stability data as recommended by ICH Q5E in order to compare degradation pattern and kinetics of Process A with Process B material were conducted. Instead, the applicant conducted a re-evaluation (including a head-to-head comparison) and provided a discussion of the available stability data from completed real-time/real temperature and accelerated stability studies performed for both, Process A and Process B material at active substance and product level. These discussions were performed to demonstrate a comparable stability profile of product whatever the process A or process B was used. The non-availability of comparative stress studies does not leave any uncertainties concerning comparability open. Consequently, this outstanding issue is considered solved.

To date, starting material used to generate the active substance and finished product supplies for Phase 3 clinical studies has been supplied from one site using the same rabbit line. The overall

comparability strategy to compare active substance produced from different milk collection sites is considered appropriate and sufficient to build up a robust quality bridge for the active substance produced from milk starting material from several milk collection sites.

Furthermore, changes in the control strategy during the process development have been summarised. A summary of the comparative studies conducted for the transfer of analytical methods has been submitted. Finally, the specifications for rhFVIIa active substance have been updated throughout its development according to the modifications made to its manufacturing process and to the improvement of analytical methods.

For development of the control strategy a combination of the traditional approach with inputs from the enhanced approach, mainly the implementation of quality risk management exercises and the use of process robustness studies through DoE was chosen. The resulting control strategy is based on traditional testing to meet established acceptance criteria. Although the applicant states that QbD principles have been used, no design space was derived from DoE studies. DoE studies were instead used to provide process knowledge and an adequate level of flexibility in conducting the process by establishing PARs for CPPs. In summary the development of the control strategy has been sufficiently described.

Characterisation

Recombinant human VIIa is a complex molecule composed of an N-terminal light chain of 152 AA and a C-terminal heavy chain of 254 AA held together by a single disulfide bridge (Cys135-Cys262). Recombinant human FVIIa possesses a modular organpaediatric with an N-terminal membrane-binding γ-carboxyglutamic acid (Gla)-containing domain, two epidermal growth factor (EGF)-like domains, and a C-terminal serine protease domain. The active protein contains 12 disulfide bridges and is glycosylated with two N-linked glycosylation sites and two O-linked glycosylation sites and the molecule contains γ-carboxylated glutamic acid residues (on its GLA-Domain). Consequently, a broad panel of standard and state-of-the-art analytical techniques have been used to characterise the molecule.

Primary structure included confirmation of the amino acid sequence. Post-translational modifications were investigated and included N-glycosylation, O-glycosylation, γ-carboxylation, β-Hydroxylation, phosphorylation.

Secondary structure included characterisation of disulfide bridges. Higher order structures were studied. Molecular weight was investigated, molar extinction coefficient was determined, isoform profile and purity were also studied. Recombinant human FVIIa was also characterised

Regarding the functional characterisation several *in-vitro* methods have been developed: Clotting activity of rhFVIIa was measured by the chronometric method using a commercial kit, activity of rhVII was determined with second assay termed the "amidolytic" assay but which is actually an FX activation assay. Furthermore, kinetic constants (Km and kcat) for FX and FIX activations were determined as well as the rate of inhibition of rhFVIIa by antithrombin via a kinetic inhibition assay. Binding to tissue factor was investigated by SPR (Surface Plasmon Resonance) technology, affinity parameters (Ka, Kd and KD) between TF and FVIIa were calculated. Finally, a thrombin generation time (TGT) test compared the capacity of the same antigenic quantity of FVII or FVIIa of various origins to generate thrombin in human plasma doubly depleted of FVII and FVIII or FVII and FIX.

In summary, apart from the request to include a chromogenic activity assay to determine and compare the activated FVII activity of some batches it is agreed that structural and functional features of recombinant human VIIa have been extensively studied by different techniques. In addition, descriptions of the methods used specifically for structural and functional characterisation have been provided in this section. For subset of the functional assays, a brief summary of the qualification is also

included; further information on the qualification/validation status of the methods used for characterisation of rhFVIIa has been submitted. Overall, it is agreed that the methods used for characterisation are considered suitable for their intended use.

Regarding the impurities, the applicant has summarised and discussed the available information on rhFVIIa active substance impurities. rhFVIIa active substance impurities were classified according to their origin into three categories:

- Impurities from the milk source material
- Process-related impurities (chemical leachables, and elemental impurities conducted in accordance with the ICH Q3D guideline – reference to the finished product section)
- Product-related impurities

An appropriate discussion of these impurities has been included; for selected impurities an in-depth characterisation by using a combination of orthogonal analytical techniques has been conducted. The majority of the listed impurities are controlled either via routine release testing at active substance and/or intermediate (IP) level or as in-process control. For those impurities for which no routine release or in-process tests are in place a sufficient removal during the manufacturing process could be demonstrated. For potential chemical leachables; extractables and leachables studies were provided. Extractable studies were obtained from each component supplier and the corresponding leachable studies were designed from this information using extractable data relevant to LR769 process conditions.

Finally, this section contains the description of analytical methods used to assay impurities (for those methods, which are not retained in active substance specifications).

In summary, the section on impurities has been appropriately addressed.

2.3.2.3. Specification

The active substance specifications cover appearance, identity, quality, potency, purity, impurities attributes. The active substance specifications include general quality attributes such as appearance, pH and osmolality, identity, bioburden and bacterial endotoxins, sialic acid content and the oligosaccharide profile. Furthermore, release control for purity/impurity-related quality attributes are included. Finally, rhFVII concentration as well as specific activity (calculated from rhFVII concentration and the clotting assay) are included for release testing. Rabbit FVII is controlled at the most concentrated step of the downstream process to improve method sensitivity.

The specifications include release controls for relevant physicochemical and biological quality attributes and are considered adequate for a future batch release testing of bulk active substance foreseen to be processed to the commercial finished product. For release control a panel comprised of standard and state-of the-art methods is in place. A specific assessment and discussion of the analytical portfolio has been provided.

rhFVIIa is a complex, highly post-translationally modified biomolecule, which gets activated by proteolytic cleavage, during its purification. It is composed of one light and one heavy chain, attached to each other by a disulfide bridge. 11 further disulfide bridges stabilise the higher-order structure of the protein. The active molecule carries two N-linked oligosaccharides and has two O-linked glycosylation sites. Close to its N-terminus, correctly processed FVII contains up to 10 γ-carboxylated glutamic acid residues. The protein has one phosphorylation site, and the aspartic acid at position 63 gets ß-hydroxylated. Its secondary structure composed of α-helical, ß-sheet, ß-turn and randomly ordered moieties. Its interaction with Ca2+ triggers a major structural rearrangement, which is

mandatory for its biological action. Taken together, the control of the extraordinary complexity of the molecule needs to be reflected in the analytical portfolio used to assess quality relevant properties of rhFVIIa.

The applicant proposed a complex methodological portfolio to assess and to control active substance quality. Some critical quality attributes of the API are analysed by orthogonal methods. rhFVIIa activity is measured by a clotting assay, which perfectly reflects its mechanism of action. A spectrophotometric assay is used to quantify protein strengths. The specific activity is calculated based on the ratio of biological activity and protein content. The applicant has demonstrated that the production process is able to efficiently clear Rabbit DNA far below the WHO threshold levels. Thus, host DNA is not assessed at active substance or finished product level and this is acceptable. Product related impurities like cleavage products, aggregates or degradation products are analysed. Eventually, N-linked oligo-saccharide profile is analysed and oligo-saccharide structures were confirmed. The applicant provided solid arguments supporting the absence of galactose-alpha-(1,3)-galactose motifs on the active substance. Thus, the information about the glycosylation profile of the AS is acceptable.

Taken together, this methodological portfolio gives a good insight into product purity and micro-heterogeneity. Thus, several quality attributes are covered directly or indirectly by the proposed control strategy and active substance specification. The information provided is sufficient and adequate.

Analytical methods

The analytical methods used for active substance release were adequately described and validated.

Regarding the method validation, non-compendial methods have been validated according to ICH Q2(R1). Respective validation reports and summaries have been provided. The validation data indicate that the proposed methods are suitable for the release quality control of active substance. The applicant provided sufficient evidence that the method developed to quantify rabbit milk proteins is valid for its intended use, since it recognises the majority of RMP's present in his specific bulk harvest. The applicability of compendial methods to measure appearance, pH, osmolality, bioburden, and bacterial endotoxins was confirmed for rhFVIIa samples. This is acceptable.

Batch analyses

Two different sets of batch data are presented: primary batch analyses and supportive batches. Primary data are the batches from initial process performance qualification (PPQ) and industrial scale batches manufactured by the commercial manufacturing process (Process B). The supportive batches are those manufactured at industrial scale and pilot batches from Process A and B. The specifications for these batches were the specifications used at the time of their release. The description of the methods used for the testing of these batches is included in the dossier.

Supportive batches from Process A and Process B were tested against the specifications used at the time of their release. Descriptions of historical analytical methods used for Process A and Process B active substance batches and summaries of their qualification/validation are included in this section. Although, most of the batches complied with the specification valid at that time, a few OOS values have been observed for batches from Process A. A brief explanation for these observed outliers is given.

In summary, the batch release data indicate that

- the current manufacturing process B is stable and able to deliver active substance material consistently meeting its predefined quality requirements and

- the applicant has gained a quite extensive manufacturing experience during the development of rhFVIIa.

Acceptance criteria for routine release testing have been set either to regulatory requirements, with defined limits in pharmacopoeia monographs or guidelines, or established based on data recorded from clinical, non-clinical and PPQ batches. The specification limits reflect the process capability of the commercial process and are also clinically justified. The information provided is sufficient and acceptable.

Reference standards and materials

Appropriate information on reference standards used for testing of active substance and intermediate product has been provided. Distinct reference materials for the process-related impurities have been established: manufacture and purification or the purchase of these reference materials for testing on the aforementioned process-related impurities as well as the standard used in the amidolytic activity assay have been briefly described. Documentation of the characterisation, storage conditions and formulation supportive of reference materials stability has been also provided. Whereas the amidolytic standard is purchased from commercial kits, the rabbit milk protein standard and the rabbit FVII standard were produced in-house. For in-house standards, storage periods before retesting have been defined.

Concerning the clotting assay (which is used as the potency release control for active substance and finished product), early potency (clotting) data was generated using a commercial kit. The internal standard was calibrated against the World Health Organization (WHO) international standard and by using quality control samples, also supplied as part of the kit. After assay method revalidation, an internal standard was introduced in the clotting assay. The reference standard that is used to perform the potency analysis of active substance and finished product is PRS. This internal potency standard has been calibrated versus the WHO international standard. A yearly requalification will be performed. The strategy for future implementation of new internal clotting standards (in case that the current standard expires) as well as the strategy for continuity of the potency assignment of the internal reference standard, when the current WHO standard is replaced, has been presented.

PRS is also used as the assay control for identity, oligosaccharide profile, activated FVII, monomer content, γ- carboxylation, cleaved, oxidised and non-Activated forms assays. The initial characterisation of the primary reference standard by methods used for active substance release and methods used for extensive characterisation has been conducted and is considered sufficient. An annual reference standard requalification programme has been implemented for PRS. In addition, the long-term stability protocol evaluates stability of the frozen PRS, the list of analytical tests to be performed annually is presented. Overall, the section on Reference Standards or Materials has been appropriately addressed.

Container closure system

An appropriate description of the container closure for both, the intermediate IP and active substance, has been provided. Intermediate product (IP) and formulated bulk active substance are stored frozen in heavy-walled durable bottles. The bottles are secured with a screw-cap closure. The container closure components are received pre-sterilised and comply with the Guideline on Plastic Immediate Packaging Materials (CPMP/QWP/4359/03), International Organization for Standardization (ISO) 10993 and the United States Pharmacopeia (USP) Class VI requirements for plastics. A representative supplier product certificate is included in this section.

Sterilisation of the container closure components is conducted by gamma irradiation. Reference to the performed leachables studies presented and discussed in the impurity section (3.2.S.3.2) is made.

Finally, a drawing with the dimensions of the bottle and the screw-cap closure is given.

In summary, the section 3.2.S.6 on container closure system has been sufficiently addressed and no questions are raised.

2.3.2.4. Stability

The stability studies are designed in accordance with ICH Q5C Stability testing of biotechnological/biological products.

Based on forced degradation studies, the stability indicating methods were selected for long-term stability testing including visual appearance, identity, pH, osmolality, bioburden, bacterial endotoxins, activated FVII, monomer content, rhFVIIa concentration, and specific activity (calculated using the "rhFVIIa concentration" and the clotting activity results).

Stability data for several validation batches manufactured are available. Further long-term stability data are available and have been presented.

All these active substance batches met the specification limits within the tested time and the stability studies are ongoing. No obvious trends of degradation were observed.

The proposed shelf life from the date of manufacture is supported by the submitted stability data. The containers had to be closed, protected from light in a freezer.

All results comply with the specifications and no relevant trend is observed. The results are consistent with the previously submitted data.

Based on the stability data the claimed shelf life from the date of manufacture of active substance manufactured with the commercial process is acceptable.

2.3.3. Finished Medicinal Product

2.3.3.1. Description of the product and pharmaceutical development

The finished product is a sterile lyophilised powder and solvent for solution for injection. It is supplied in vials (powder) with three dosage strengths (1 mg, 2 mg or 5 mg of eptacog beta (activated)) with a prefilled syringe (PFS) for the solvent (water for injections). The other excipients are: (powder): arginine hydrochloride, isoleucine, trisodium citrate dihydrate, glycine, lysine hydrochloride, polysorbate 80, hydrochloric acid and (solvent): water for injections.

All materials in contact with the product are commonly used in medicinal products and comply with the applicable compendial requirements.

LR769 finished product and its solvent (WFI) for reconstitution, in a pre-filled syringe, are co-packaged with a sterile CE-marked vial adapter (VA), and accessories (plunger rod and the backstop). The syringe components comply with the applicable compendial requirements.

The active substance and finished product formulation and composition are identical: arginine hydrochloride, isoleucine, glycine, lysine hydrochloride, trisodium citrate dihydrate, polysorbate 80, hydrochloric acid (HCl), nitrogen, and water for injection (WFI). Neither excipient is of human or animal origin nor novel excipients are used in the LR769 finished product formulation. The choice of excipients and their concentrations have been determined on the basis of stability of the active substance. The formulation development strategy was driven by the QTPP, and was based on former

experience and knowledge. All excipients as well as their specification comply with compendial monographs, and all methods were verified according to the relevant monographs.

Pharmaceutical Development

Appropriate formulation studies were performed to optimise the chemical and physical stability of LR769 finished product. Formulation development started with a pre-formulation screening study to evaluate the excipients contained in the original formulation and additional types of excipients, as well as small pH variations. A second formulation study was performed to justify the need for each excipient and to establish the appropriate concentrations. The justification of the formulation was conducted using a DoE approach to assess interactions between excipients. The different combinations of buffers and excipients were evaluated using stress conditions.

LR769 is a sterile white to off-white freeze-dried powder which is intended for intravenous injection following reconstitution with sterile WFI to obtain the target concentration. There are no overages in the LR769 finished product.

LR769 finished product was originally manufactured at low scale and stored frozen. A second-generation product (Process A) was developed to improve purity and potency. It was designed according to QTPP and included major improvements. Two dosage forms of lyophilised product had been initially developed. Further improvements were introduced when manufacturing process was scale-up.

These process modifications were subjected to a comparability exercise. According to the identification of all changes applied between processes, a risk assessment was conducted. Different relevant analytical methods were identified. Specific comparability criteria were established for these analytical methods. For the other quality attributes, compliance to product specifications was considered acceptable to demonstrate comparability. Results from these studies demonstrate that the process changes did not adversely impact the quality and safety of the finished product.

Lyophilisation process was developed based on thermal characterisation on the three finished product dosage strengths by differential scanning calorimetry and microscopy. The performance of the industrial equipment was validated by empty chamber temperature mapping studies, while product uniformity was verified by extended sampling studies.

The development of LR769 has been conducted following the QbD principles according to ICH guidelines Q8 to Q10, defining a QTTP and establishing the CQAs. The control strategy is based on traditional testing to meet established acceptance criteria with enhanced inputs from the process quality risk management and DoE studies. CQAs were identified and are properly controlled during the finished product manufacturing process.

The LR769 1 mg/mL finished product primary container is a Type I borosilicate glass container, with closure and aluminium crimp seal with plastic flip-off cap. All components are Ph. Eur. compliant. The physical stability of the container closure and product quality was demonstrated by performing container closure integrity testing. The finished product packaging materials were evaluated for potential extractables and leachables using a risk-based approach.

LR769 is compatible with each of the excipient materials and protects the finished product from moisture as indicated by stability data.

In-use compatibility was demonstrated by evaluating the stability of the finished product on the reconstituted solution in vials in the upside-down position. The data from the compatibility study supports that the finished product is biochemically stable for up to 24 hours at 30°C ± 2°C.

For each dosage strength, the container contains after reconstitution sufficient solution to allow withdrawal of its labelled volume. After storage leachable concentrations were below the maximum acceptable concentration and these leachables do not represent a risk for the patient safety. A shipping validation of LR769 finished product vials and LR769 VAPFS kits was performed.

Complementary studies demonstrate compatibility with the administration systems (vial adapter, syringe and infusion set). Photostability of the LR769 finished product in its secondary packaging planned for commercial supply was also demonstrated.

LR769 is supplied as a sterile lyophilised powder in single-dose glass vials and does not contain any antimicrobial preservative. The suitability of the container closure system to prevent microbiological contamination is demonstrated by the container closure integrity testing (CCIT) data, which was validated, and which is routinely applied and used as IPC on several vial samples, taken after each capping step. This is acceptable.

Taken together, the choice of materials for primary packaging and its suitability for the intended use have been sufficiently justified.

2.3.3.2. Manufacture of the product and process controls

Manufacturers

The name, address and responsibilities of the manufacturing and testing sites for LR769 finished product have been provided. All the finished product manufacturing sites are GMP compliant.

Manufacturing process

The finished product manufacturing process is described in sufficient detail. The manufacturing process to produce LR769 finished product is an aseptic fill-finish operation followed by lyophilpaediatric.

The finished product production process is composed of nine steps: active substance thawing, pooling and mixing, first filtration, aseptic filtration, filling, lyophilpaediatric, capping, cap inkjet printing and finished product visual inspection, and packaging in bulk.

Critical process parameters and their corresponding acceptance criteria for each individual process step are properly defined.

Process and control of critical steps

The CPPs acceptance criteria were established on the basis of data collected from Process Performance Qualification (PPQ) batches for the three dosage forms. Consecutive PPQ batches were performed for each finished product strength, at the intended market scale. Total processing time is not listed as CPP, but monitored and checked at the batch record level for each commercial batch, which is acceptable.

Manufacturing process development

The process was modified two times during clinical development:

An initial version was used for Phase Ia clinical development, where the finished product was stabilised with a preliminary formulation and stored frozen. For later stage clinical development, a lyophilpaediatric process was developed and the finished product became available in two strengths. This process A was carefully designed in accordance with the QTPP. Further improvements in the finished product manufacturing process took place in parallel with the active substance scale up. This latest version is the manufacturing process for market supply. The diluent (WFI) container closure

system was changed from a glass vial to a pre-filled syringe (PFS) and the vial adapter (VA) was changed accordingly to match the use of PFS to reconstitute the product.

All changes of the production process were well described. A comparability exercise based on a risk assessment demonstrated that changes from process A to process B did not impact on finished product quality.

All process steps were carefully designed and established in order to fulfil the QTPP, in order to increase its robustness and to minimise the risk of a potential impact on product quality. active substance thawing conditions were studied, optimised and justified. Sterile filtration also was developed based on product compatibility, extractables and microbial retention studies. Overfill of each dosage form was justified experimentally. The freeze-drying process was developed after having thoroughly characterised physico-chemical properties of the LR769 solution for glass, collapse and melting temperatures, as well as the lyophilised product for its glass temperature. The lyophilpaediatric parameters (pressure, temperature and duration) were developed and optimised for the freeze-drying, the primary drying and the secondary drying step, and for each dosage strength. Homogeneity of process conditions was verified on each tray under the authentic process conditions by placing temperature sensors in vials at positions representative for different zones in the lyophiliser. Stoppering conditions (gas, pressure) were investigated and set based on the QTPP. Detailed process characterpaediatric studies are reported.

Taken together, critical process parameters were identified, and a robust finished product manufacturing process was designed and implemented. The manufacturing process development was well described and seems acceptable.

Furthermore, the specifications for LR769 finished product have been updated throughout its development according to the modifications made to its manufacturing process and to the improvements of analytical methods. The specifications for commercial product were established according to the control strategy (CS) that was implemented from QbD principles. The control strategy was sufficiently explained. Acceptance criteria for commercial product were established according to the data recorded from clinical and PPQ batches.

The manufacturing process used for clinical and PPQ batches will remain unchanged for commercial batches.

Process validation

The commercial manufacturing process was validated with different consecutive PPQ batches per dosage strength and different freeze-dryers. The process does not include any isolated process intermediates. The manufacturing process validation is supported by quality by design inputs, issued from the quality risk management exercise, according to ICH Q8(R2) and Q10 guidelines. A comparability exercise was performed between freeze-dryers based on the CPPs and performance comparison related to the critical parameters. No meaningful difference was found, and all freeze dryers are considered equivalent. The process validation covers the proposed batch size range for the three dosage forms. All acceptance criteria for CPPs, complementary monitoring parameters and finished product release criteria were met for all PPQ batches for all freeze-dryers.

The applicant has reported all deviations detected during the process validation studies. They were investigated and have no impact in the process validation.

Holding times were properly validated.

All vials and vial components, as well as filling machine parts and other product-contact components, are properly prepared and sterilised. The whole process is carried out in qualified facilities, appropriately monitored, using qualified equipment.

Data for cleaning validation (Section 3.2.A.1), filter validation (Section 3.2.P.5.5 and Section 3.2.P.2.3) and validation of disposable bags (Section 3.2.P.5.5) are included in other sections of the eCTD.

Validation of the sterilisation equipment and components has been performed through heat penetration studies and distribution, using validation thermocouples and biological indicators. Different tunnel lines were validated, for the depyrogenation of LR769 vials.

Media fill trials were conducted to determine the suitability of the filling configuration used in the aseptic filling suites for the three dosages forms. The aseptic process simulations were representative of the current process and were performed with the current filling production equipment under worst case production scale and operational parameters.

Shipping validation studies were performed as two-step process, a first Operational Qualification step carried out in worst case conditions, and a final Performance Qualification considering the entire flow, climatic conditions (hot and cold period), and customs procedures which can influence the product transport. Results from these studies demonstrated that the shipping process and container system for the transportation of the LR769 (finished product vials, PFS and the whole kit) protect the integrity of the material and maintain the required temperature as confirmed by visual inspection, CCIT and temperature monitoring.

Container closure system

The container closure system of LR796 consists of Type I borosilicate glass containers, closures and aluminium crimp seals with plastic flip-off caps. The container-closure information for all three dosage forms is well described for the glass vial and stoppers.

Compatibility with the primary packaging material at long term storage conditions, as well as in-use compatibility with the reconstitution and administration systems have been sufficiently demonstrated. The information provided is sufficient and adequate.

2.3.3.3. Product specification

The release specification for LR769 finished product covers all the required attributes, including appearance, pH, osmolality, reconstitution time, particulate matter, residual moisture, content, identity, purity, potency and safety (endotoxin and sterility), as well as excipients. The specifications for the three dosage strengths are the same except for residual moisture. The shelf life specifications are identical to the release specifications with some exceptions.

The finished product formulation of LR769 is identical to the one of the active substance, no additional excipients are used in the manufacturing process of LR769 finished product and the most critical product quality attributes already specified at active substance level again are re-assessed with the same methods for finished product release at finished product level. Finished product specification for FP release and shelf life cover the complete set of finished product quality attributes. This is supported by stability data. Acceptance criteria, when identical between active substance and finished product, are adequately justified. All other acceptance criteria for analysis performed at finished product level only, were in line with compendial requirements or appear reasonable.

Potential finished product process-related impurities were identified through a risk analysis. They were assessed by extractable/leachable studies. Results from these studies demonstrate that potential extractable materials are either below the limit of quantification (LOQ) or below the maximum acceptable concentration in LR769. Therefore, they do not pose any risk to patients' health.

In addition, elemental impurities were also assessed in accordance with the ICH Q3D guideline and their concentration was also below the maximum admissible concentration. Consequently, the

presence of critical organic compounds and elemental impurities in LR769 finished product should not pose any risk to patients' health. The information provided is acceptable.

A risk assessment to evaluate the potential risk for the generation of nitrosamines in the intermediate product (IP), the active substance and the finished product manufacturing process was performed, concluding that the presence of nitrosamines in the FVII manufacturing process is unlikely. The risk is categorised as low and no further mitigation is required. This is acceptable.

The acceptance criteria for finished product specification were established on the basis of data recorded from clinical, non-clinical and PPQ batches. Specifications were established according to regulatory requirements (Ph. Eur. monographs or guidelines) and stability indicating parameters. The specification limits are clinically justified and reflect the process capability of the commercial process. This is acceptable.

Analytical methods

The analytical methods are described and include compendial and non-compendial procedures. The LR769 finished product-specific (non-compendial) analytical methods are the same as those used for the active substance and were detailed in Section 3.2.S.4.2. The compendial analytical procedures are verified according to current Ph. Eur. Monographs. Analytical procedures used exclusively for the finished product specifications are sufficiently described.

Each compendial method was verified for its suitability under the conditions of use, in accordance with current Ph. Eur. Monographs. Each LRT96-specific analytical procedure has been validated per ICH Q2 (R1) as being suitable for its intended purpose. The performance characteristics of each method was evaluated against protocol-defined acceptance criteria.

Validation reports were submitted for all non-compendial methods. Taken together, the validity of the methodological portfolio for its intended use was demonstrated.

Batch analysis

Several finished product batches were analysed. They cover PPQ batches (Process B) for all three dosage strengths and supportive batches manufactured from Process A or B and analysed according to the specifications in force at the time of their manufacturing.

All batches gave comparable data and met the acceptance criteria for release. Taken together, it appears that the finished product manufacturing process is under control and able to produce LR769 finished product of consistent and uniform quality.

Reference standard

The reference standard for the release of the finished product is the same as already described for the release of the active substance.

Container closure system (CCS)

The container closure system for all three finished product strengths was sufficiently described. Drawings of all vial and stopper sizes, as well as quality certificates were provided. In brief, the container closure system consists of Type I glass vials with closure crimped with an aluminium flip-off cap. All compounds which are in contact with the AS comply with Ph. Eur. requirements. The sterile vial adapter (VA) for reconstitution included in the secondary packaging is CE marketed. The CCS adequately protect the active substance from microbial contamination and moisture, as demonstrated in stability studies. Sterilisation and depyrogenisation of vials and stoppers have been sufficiently depicted in the process validation and evaluation section.

2.3.3.4. Stability of the product

A shelf life of 3 years when stored below 30ºC is claimed for the finished product.

The stability of LR769 finished product was evaluated according to ICH Q1A (R2), ICH Q1D and ICH Q5C guidelines.

The applicant presented primary stability data from different PPQ batches in sufficient detail: several batches each for the highest and the lowest finished product strength, and other batches for the middle finished product strength were analysed. This bracketing approach seems reasonable. Stability was assessed at 4 storage conditions. The container closure system used is identical to the one intended for the commercial product.

Stability testing was performed against finished product shelf-life specification. Methods were validated and identical to the ones used for the finished product release. Samples were assessed at finished product release at different time points afterwards. The whole stability programme was carried out in accordance with current ICH/CPMP guidelines. Long term storage was performed, which is highly endorsed.

Stability data were presented and discussed in detail. After reconstitution, chemical and physical in-use stability has been demonstrated for 24 hours at room temperature up to 30°C. The reconstituted solution should be stored in the vial. From a microbiological point of view, the product does not contain any bacteriostatic agent and must be administered within 4 hours after reconstitution. Any unused solution should be discarded 4 hours after reconstitution.

Photostability studies conducted on several batches of the 1 mg dosage form (worst case format) in their primary and secondary packaging demonstrated that, although LR769 finished product in the primary packaging (glass vial) is adversely affected by exposure to light, it was adequately protected when exposed in the secondary packaging.

Overall, the full set of long-term stability data generated throughout 48 months at three temperatures of storage on PPQ batches indicates a satisfactory stability profile in a temperature range from 5°C to 30°C. This long-term real time data supports the proposed shelf life of 36 months at a temperature not exceeding 30°C. The proposed storage condition is: "Product packaged protected from light and stored at a temperature not exceeding 30°C for 36 months. The product should not be frozen since it is packaged with a WFI glass syringe."

Post MAA, the ongoing long-term studies will be continued according to their stability protocols. All of the above considerations were correctly reflected in the SmPC.

Solvent - Water for Injections (WFI)

WFI is provided in single dose PFS for reconstitution of LR769. The PFS containing WFI are supplied in three different sizes: syringes intended to deliver 1.1, 2.2 and 5.2 mL, which are packaged with the 1 mg, 2 mg and 5 mg vials of LR769.

The process used to produce WFI in bulk and sterilised WFI is based on techniques commonly used in industrial applications. These techniques meet the specifications given in the current Ph. Eur. monograph (0169).

Sufficient information about the pharmaceutical development of sterile WFI LR769 finished product was provided. The presence of undesirable compounds has been evaluated during a long-term stability study. For the microbiological testing requirements of the relevant monographs (current edition) of the Ph. Eur. were followed.

The validation results demonstrate that the manufacturing process consistently and reproducibly produces sterile WFI in PFS that fulfils all the specified criteria for the release of a sterile single dose product. Stability data showed that WFI is stable.

2.3.3.5. Adventitious agents

The manufacturing process of rhFVIIa includes four virus reduction steps that have been validated according to the regulatory guideline 'Note for guidance on virus validation studies: the design, contribution and interpretation of studies validating the inactivation and removal of viruses' (CPMP/BWP/268/95 (revised)) using relevant model viruses. Solvent/detergent (S/D) treatment, two chromatography steps, one nanofiltration step were examined as virus reduction step in the manufacturing process of rhFVIIa. The S/D treatment and the nanofiltration are the main virus inactivation/removal steps and the two further research manufacturing steps contribute to the virus reduction.

The viral clearance studies were carried out at different laboratories in Europe. All submitted virus clearance studies are detailed and comprehensible.

As a prerequisite to viral validation, it was demonstrated, that the scaled-down model is representative of the commercial manufacturing process. The performances of trials at reduced scale were compared to the representative batch performed at manufacturing scale.

The solvent/detergent treatment was validated. The robustness of the S/D step was demonstrated for enveloped viruses under reduced concentration of S/D and reduced temperature. The operating conditions at small scale (viral clearance under normal and robustness conditions) and the current production scale are comparable.

The solvent/detergent treatment showed effectiveness in the inactivation of enveloped viruses under the normal operating conditions. A further virus deactivation study for different operating S/D conditions were performed and virus reducing was also demonstrated under this robustness operating conditions of the process.

Qualification of the one chromatography step at small scale was performed. The selected model viruses were effectively removed. Under robustness operating conditions and high-volume load the virus reduction capacity was also acceptable. The aged resin and volume load were shown to have no impact on the reduction capacity of the step. Nanofiltration as the main viral reduction step was very effective in the removal of enveloped and non-enveloped viruses. The robustness of this step was demonstrated by protein load, volume load, flow rate and volume of rinse which had no impact on the removal capacity of the step.

The virus reduction by another chromatography step was further examined. Clearing of viruses was acceptable. The robustness of the step was also demonstrated using aged resin and high protein load. It could be shown that these operating conditions have no influence for the virus reduction capacity.

Overall, with the submitted virus inactivation/clearance studies, the applicant could demonstrate that the manufacturing process of rhFVIIa is effective in inactivation/removal of a wide range of model viruses.

Additionally viral sanitisation studies for the chromatography steps of the manufacturing process of rh-FVIIa were submitted. The results from these studies demonstrated that the sanitisation procedures of the different columns are effective for the decontamination of a highly resistant non-enveloped virus and therefore more largely for other less resistant non-enveloped and enveloped viruses.

The submitted risk assessment supports the conclusion that rhFVIIa manufactured by the process described herein has a sufficient capacity to remove potential viruses, if they were to be present.

TSE

Rabbits are non-TSE-relevant animal species (according to the 'Note for guidance on minimising the risk of transmitting animal spongiform encephalopathy agents via human and veterinary medicinal products' (EMA/410/01, current revision). Additional safety measures have been implemented at the rabbit facilities e.g. the rabbits have no possible contact with other animal species and the rabbit feed is devoid from any animal-derived material.

2.3.3.6. GMO

Not applicable

2.3.4. Discussion on chemical, pharmaceutical and biological aspects

From a quality point of view a robust and well-controlled active substance and finished product manufacturing process has been set-up. An appropriate overall control strategy is in place which assures that only material fulfilling its predefined quality expectations will enter the market. This conclusion is further supported by conducted process validation results and a considerable amount of batch data from GMP batches manufactured during development. An extensive characterisation of product and its manufacturing process has been performed and indicates that the applicant has gained an in-depth knowledge of its process and product. A sufficient discussion of impurities including the risk evaluation for presence of nitrosamines at the active substance and finished product level is available.

The manufacturing process used to produce the finished product is an aseptic fill-finish operation followed by lyophilpaediatric. The finished product composition corresponds to the one of the active substance, thus leaving only active substance thawing, pooling and mixing, sterile filtration, aseptic filling, lyophilpaediatric, capping and storage of the vials as the main procedures for the finished product, provided at three different product strengths. All process steps were carefully designed, established and validated. Acceptance criteria for the commercial product were established and justified according to the data from a considerable number of clinical and PPQ batches. The finished product shelf life of 36 months when stored below 30°C (protected from light and freezing) is claimed and justified by data from adequate stability studies.

2.3.5. Conclusions on the chemical, pharmaceutical and biological aspects

The overall quality of Cevenfacta is considered acceptable when used in accordance with the conditions as defined in the SmPC.

The different aspects of the chemical, pharmaceutical and biological documentation comply with existing guidelines. The manufacturing process of the active substance is adequately described, controlled and validated. The active substance is well characterised and appropriate specifications are set. The manufacturing process of the finished product has been satisfactorily described and validated.

The quality of the finished product is controlled by adequate test methods and specifications. Adventitious agents' safety including TSE have been sufficiently assured.

2.3.6. Recommendation for future quality development

Not applicable.

2.4. Non-clinical aspects

2.4.1. Introduction

The biopharmaceutical development of Cevenfacta has been conducted in sequential phases as described in the Quality section above. Two manufacturing process versions were used during development, i.e. Process A and Process B. A comparability assessment demonstrated that the products manufactured were biochemically indistinguishable.

All nonclinical studies were performed with Process A product at the exception of the repeat toxicity study (Study 5000766) which was conducted with Process B product. The activity of LR769 (TGT, aPTT, PT) in human haemophilia A and B patient plasma study (Study 14 ENC 006) was conducted with both Process A and Process B product to demonstrate comparability between processes.

The pharmacological activity of Cevenfacta has been assessed in a series of *in vitro* and *in vivo* studies summarised below. In addition, safety pharmacology parameters were assessed in GLP toxicity studies performed in rats and *Cynomolgus* monkeys.

2.4.2. Pharmacology

2.4.2.1. Primary pharmacodynamic studies

In vitro pharmacology

In order to evaluate the specific **pharmacodynamic activity** of LR769 a comprehensive panel of *in vitro* assays was performed. These assays included amidolytic activity, activated FVII clotting activity, thrombin generation time, determination of kinetic constants for FX and FIX activation, inhibition by antithrombin and binding to tissue factor. In principle, Cevenfacta was found to be similar to the reference item NovoSeven with respect to these parameters. Please refer to the Quality Assessment Report for detailed discussion.

The functional activity of Cevenfacta was further evaluated by *in vitro* determination of the potential for **thrombin generation (TG)** as well as **prothrombin time (PT)** and **activated partial thromboplastin time (aPTT)** (Study 0LFB12). Concentrations of 0, 0.5, 1, 2, 3, 4, 6 and 10 µg/mL LR769 were employed for all assays. NovoSeven was used as reference product at the same concentrations in all assays. Whereas thrombin generation assays were performed with control plasma from healthy individuals, haemophilia A and B plasma (natural and artificial) without inhibitors, haemophilia A plasma (natural and artificial) with inhibitory antibodies as well as with double depleted FVII/FIX plasma, coagulation assays were only performed with natural plasma. Thrombin generation time (TGT) was assessed in the presence of tissue factor (TF) and phospholipids that serve as platelet substitute. In preliminary experiments the concentration of 1pM TF was determined to be ideal for the discrimination of concentration-dependent effects. With regard to endogenous thrombin potential (ETP) and thrombin peak (TP) a similar dose-dependent effect starting from the lowest dose of 0.5µg/L was observed for NovoSeven and LR769 in individual plasma samples. No statistical evaluation was performed, however, the TGT and TP of LR769 appeared to be slightly higher throughout all experiments with the difference increasing with increasing dose. The most distinct difference was

observed in two out of five haemophilia A donors with inhibitors. In addition, one of these plasmas had high ETP and TP baselines, which was explained by the applicant by mixing with artificial FVIII deficient plasma that was subjected to freeze drying and immune depletion. Coagulation was evaluated by determining PT, diluted PT (dPT) and aPTT. A shortening effect on PT and dPT was observed from the lowest concentration of NovoSeven and LR769 with no additional effect at higher concentrations. No difference between both compounds was determined. The highest change from baseline occurred in haemophilia B plasma, whereas the changes were similar in normal reference plasma, haemophilia A plasma and haemophilia A plasma with inhibitors. With regard to aPTT a dose-, however, not product-dependent reduction was observed from the lowest concentration administered (0.5 µg/mL). Only a slight change from baseline was registered in normal reference plasma. Again, the highest change from baseline occurred in haemophilia B plasma, whereas the effect was less pronounced in haemophilia A plasma and haemophilia A plasma with inhibitors. Overall, NovoSeven and LR769 were demonstrated to have similar in vitro PD effects on TGT, ETP, TP, PT, dPT and aPTT in normal plasma as well as in haemophilia B plasma, haemophilia A plasma and haemophilia A plasma with inhibitors.

In order to detect **potential differences between Process A and Process B material**, both of which were used in different *in vivo* toxicity studies, the applicant performed an additional *in vitro* PD study (Study 14 ENC 006). In this study commercial platelet poor plasma (PPP) from haemophilia A patients with or without inhibitors and haemophilia B patients were subjected to TGT, PT and aPTT assays with Process A and Process B material as well as NovoSeven as a reference. Within each plasma type all three compounds exhibited similar activity. Therefore, in vivo studies performed with both, Process A and Process B material, can be considered of comparable value for assessment.

In vivo pharmacology

In vivo pharmacology of Cevenfacta was evaluated using the **tail tip bleeding** method in **haemophilia A mice**, which have less than 1% of normal FVIII activity and, thus, prolonged bleeding time (11 TSS 003). The study was conducted with a pilot batch. Animals received 1, 2, 3, 4 and 6 mg/kg LR769. One minute after administration the tail was dissected and the tail tip was immersed into a vial containing 0.9% NaCl solution at 37°C. Endpoints analysed were the total bleeding time and blood loss over a period of 30 minutes. High inter-individual variability was observed with regard to bleeding time. Nevertheless, bleeding time and blood loss clearly decreased in a dose-dependent manner and statistically significantly differed from 0 mg/kg animals starting from 2 mg/kg or 1 mg/kg in bleeding time and blood loss, respectively. No wild-type animals were included so no conclusion on to which level of normal bleeding time and blood loss have been restored. In order to be able to compare the activity of LR769 with NovoSeven a study with identical setting was conducted using the marketed reference product (Study 11 TSS 002). Overall, both products showed similar efficacy regarding bleeding time and blood loss. No statistical differences could be determined between percent reduction of bleeding time and blood loss between Cevenfacta and NovoSeven.

An additional PD study was conducted in **haemophila A dogs** bearing a mutation in the coagulation factor VIII gene, i.e. an intron 22 inversion separating exon 22 and exon 23, causing aberrant splicing and a stop in the transcription (Study 20110067SPGPB). These dogs have a maximum of 10% FVIII activity. Three haemophilia A dogs received a dose of 100 µg/kg LR769. A toenail-bleeding model was applied and bleeding time as well as blood loss were determined pre-dose as well as 10-15 minutes and 1h, 2h, 6h and 24h post dose for 30 minutes each. Normal dogs receiving saline were included as controls. PT was reduced in animals receiving LR769 as compared to pre-dose values with the most pronounced effect (reduction by 34%) observed at 10 minutes post-dosing followed by a decline and return to baseline at 24 h post-dosing. A less pronounced effect of LR769 was observed on aPTT (a maximum of 17% after 10 minutes). Of note, a reduction of 8% in aPPT was also observed in normal dogs receiving saline.

The potential thrombogenic activity of LR769 and NovoSeven was evaluated in a **venous stasis model** employing the Wessler method in **rats** (Studies 0LFB14 and Study 0LFB11). Ligatures were set at the vena cava of anaesthetised animals that were tightened 10 seconds after i.v. administration of 0.1, 0.3 and 1 mg/kg LR769 or NovoSeven, NaCl 0.9% as a negative control or Feiba (50 IU/kg) as a positive control. After 10 minutes of stasis the vena cava was incised and inspected for thrombus formation. In case a thrombus had formed, its size and weight was determined. Thrombus formation was observed in all of the Feiba-treated animals (Wessler's score: 4.0±0.0 and mean weight: 19.7±3.3 mg), whereas all animals that received NaCl were free from thrombi. All animals administered with LR769 developed thrombi with size and weight increasing with dose: Wessler's score: 2.6±0.3, 3.6±0.2 and 4.0±0.0, weight: 6.3±2.3, 10.3±1.1 and 18.6±2.5 mg. Similar results were observed in all animals - except for one animal of the 0.3 mg/kg group - treated with NovoSeven: Wessler's score: 2.6±0.4, 3.2±0.5 and 3.9±0.1, weight: 2.1±0.9, 12.1±3.8 and 15.3±2.2 mg). Statistical evaluation revealed no difference between thrombus size and weight comparing LR769 and NovoSeven. The occurrence of thrombi in all Feiba-treated animals and their absence in animals that received NaCl demonstrated the validity of the employed animal model. Overall, evaluation of the thrombogenic activity of LR769 revealed that the thrombogenic risk is dose-dependent and comparable to marketed FVIII products such as NovoSeven.

2.4.2.2. Secondary pharmacodynamic studies

No secondary pharmacodynamic studies have been performed.

2.4.2.3. Safety pharmacology programme

No dedicated safety pharmacology studies were conducted. However, safety pharmacology data were collected during the rat and monkey GLP single and repeat toxicity studies.

2.4.2.4. Pharmacodynamic drug interactions

No pharmacodynamic drug interactions studies have been performed.

2.4.3. Pharmacokinetics

The pharmacokinetic properties of Cevenfacta was evaluated in a total of seven *in vivo* studies of which the two single dose studies in rats and monkeys were dedicated PK studies, the PK in dogs was analysed in the scope of a single dose PD study. In addition, TK parameters were reported in two repeat-dose rat and monkey studies each.

A STACLOT VIIa-rTF *in vitro* assay was validated for quantitation of factor VIIa in citrated plasma with respect to calibration curve reproducibility, whole blood:anticoagulant ratio effect, selectivity, matrix evaluation (specificity), accuracy, precision, linearity of dilution (matrix effect) and stability. All acceptance criteria were met except for the stability of LR769 in prediluted rat plasma after storage at room temperature for up to 4 hours.

Similarly, the STACLOT VIIa-rTF was also successfully validated for quantification of factor VIIa in citrated monkey plasma, however, with exceptions analogical to those in rat plasma.

For the determination of LR769 in dog plasma after single administration an ELISA method was developed and validated.

For the detection of anti-rhFVIIa antibodies in rat and monkey serum specific electro chemiluminescent immunoassays were adequately validated.

In addition, an assay to identify neutralising antibodies in rat and monkey plasma was established and validated based on potential inhibition of functional activity, i.e. reduction of clotting time in FVII deficient plasma.

Single dose PK

Pharmacokinetic parameters of Cevenfacta were evaluated after administration of single doses of 0.1, 0.2 and 0.3 mg/kg in **male Sprague Dawley rats** at 5, 15, 30 and 45 minutes and 1, 3, 6 and 24 hours post-dose (Study 461867).

In general, C_{max} increased in a dose proportional manner when comparing the lowest dose to the mid dose and in a less than dose-proportional manner when comparing the mid dose to the highest dose. $AUC_{(0\text{-}1h)}$ and $AUC_{(0\text{-}inf)}$ were comparable and increased in a more than dose-proportional manner when comparing the 0.1 and 0.2 mg/kg doses but decreased minimally from the 0.2 to the 0.3 mg/kg dose group. Of note, very high inter-individual variability was observed with regard to plasma levels in the mid-dose animals, thus, relativizing the value of the observation. Maximal exposure (t_{max}) was observed from 0.117 to 0.150h. The half-life ($t_{1/2}$) was relatively similar throughout all dosing groups with values from 0.247 to 0.311. The volume of distribution (Vd) ranged well below the total body water of rats indicating limited distribution. Clearance (CL) ranged between 262 and 398 mL/h/kg.

Pharmacokinetic parameters were also evaluated in the scope of the toenail-bleeding PD study in **haemophilia A dogs** (Study 20110067SPGPB). For PK evaluation dogs were administered 0.1 mg/kg LR769. C_{max} and $AUC_{0\text{-}t}$ were 0.888 µg/mL and 1.171 µg▪h/mL, respectively. Mean peak plasma of FVIIa activity was 1.079 µg/mL corresponding to 10.79 kg x mU/mL/U when dose-adjusted. T_{max} was 0.083 h and $t_{1/2}$ was determined at 1.34 h. Overall, FVIIa antigen concentration and activity displayed a good correlation.

For PK evaluation in ***Cynomolgus*** **monkeys** after a single dose, animals (3 female and 3 male) were administered 0.1, 0.3 and 1 mg/kg/day LR769 via i.v. bolus injection (Study 5000465). PK parameters were determined pre-dose and 5, 15 and 30 minutes and 1, 2, 6 and 8 hours post dose. In general, exposure increased with increasing dose in a more than dose-proportional manner. The maximum exposure (t_{max}) was determined to be at 5 minutes post-dose for most of the animals. $T_{1/2}$ ranged from 0.564 to 0.978 hours. CL was defined between 59 and 153 mL/hr/kg and Vd was 80.3 to 126 mL/kg. No gender differences regarding PK parameters could be identified in this study.

Repeat dose TK

In the scope of a 28-day GLP repeat-dose toxicity study in **rats** toxicokinetic parameters were evaluated (Study 504374). Animals were administered 0.1, 0.3, 1.0 and 3.0 mg/kg LR769 daily and blood was collected at 5 and 15 minutes as well as 1, 2 and 6 hours after administration on days 1 and 28. In general, exposure ($AUC_{0\text{-}inf}$) increased roughly dose-proportional after the first administration and ranged from 0.117 to 5.83 µg▪h/mL. At day 28 LR769 was only detectable in the plasma of animals of the high dose groups (1.62 and 3.08 µg/mL), therefore, TK parameter could only be determined for these animals. C_{max} was determined to be 0.164 to 6.98 µg/mL increasing with doses at day 1 and 1.53 and 2.94 µg/mL for the 1.0 and 3.0 mg/kg group, respectively, at day 28. Similarly, $t_{1/2}$ decreased with increasing doses with values between 0.416 and 0.814 hours at day 1 and 0.336 and 0.200 hours for the two highest doses at day 28. In correlation to decreased exposure with increasing number of doses the Vd decreased from day 1 to day 28 from 492 to 300 mL/kg or 605 to 281 mL/kg whereas CL increased over time in the highest dose group, i.e. 515 to 975 mL/h/kg. Anti-drug antibodies (ADA) occurred with dose-proportional incidence throughout all dosing groups with 90% ADA positive animals in the highest dose group.

TK parameters were also evaluated in the 25-day repeat dose toxicity study in rats (Study 5000172). Animals received daily doses of 6 and 11 mg/kg LR769 for 25 days. Blood samples were collected pre-dose and 5 and 15 minutes and 1, 2 and 6 hours after the infusion on days 1 and 25. C_{max} and AUC_{0-t} increased with dose and time in a more than dose-proportional manner. The difference in C_{max} between the 6 to 11 mg/kg dose was 2.5-fold on day 1 and 3-fold on day 25. AUC_{0-t} was 3 times higher in the 11 mg/kg group than in the 6 mg/kg group on day 1 and 3.6 timer higher on day 25. AUC_{0-t} increased within dosing groups by a mean of 3.12-fold at the 6 mg/kg level and a mean of 3.55-fold at the 11 mg/kg level. $T_{1/2}$ ranged from 0.433 to 0.696 h. CL generally increased with time and dose and was 91 to 507 mL/h/kg. The Vd ranged from 291 to 328 mL/kg in all study groups and was only lower, 94.6 mL/kg, in the 11 mg/kg group at day 25. As these values are well above the total blood volume of a rat, distribution beyond blood vessels is conceivable.

TK was further evaluated in the GLP-compliant 28-day repeat dose toxicity study in *Cynomologus* monkeys (Study 504376). Animals were administered 0.1, 0.3, 1.0 and 3.0 mg/kg LR769 daily for 28 days (Study 504376). Blood samples were collected pre-dose and 5 and 10 minutes and 1, 2 and 6 hours post dose on days 1 and 28. The duration of availability of LR769 in the plasma of treated animals was dose-dependent and reached 6 h for all but the lowest dose. T_{max} was 5 minutes for all dosing groups at day 1 and 28. C_{max} increased in a dose-dependent manner with a roughly dose-proportional increase from 0.3 to 3.0 mg/kg. The C_{max} values were similar between day 1 and day 28 within the particular dosing groups and ranged from 0.629 to 34.6 µg/mL. Similarly, AUC_{0-inf} and AUC_{0-t} increased in a dose-dependent fashion and roughly dose-proportional from 0.3 to 3.0 mg/mL and again similar values were calculated for the day 1 and day 28 time point within one dosing group. Only in the highest dosing group both AUC values were elevated on day 28 as compared to day 1, i.e. 34.9 vs. 46.6 µg•h/mL and 34.6 vs 44.8 µg•h/mL AUC_{0-inf} and AUC_{0-t}, respectively. $T_{1/2}$ increased with dose from 0.509 to 0.916 h on day 1 and from 0.737 to 1.28 h on day 28. CL declined from 106 to 86.5 mL/h/kg over all dose ranges on day 1 and did not follow a dose-dependent pattern on day 28, the latter of which was presumably due to very high standard deviations especially in the 0.3 mg/kg dose. Considering high standard deviations the Vd was comparable among all dose groups at both time points and ranged from 103 to 175 mL/kg.

Also the GLP-compliant 13-week repeat-dose toxicity study in male and female cynomolgus monkeys included evaluation of TK parameters (Study 5000766). Animals were administered daily infusions of 0.1, 0.3 and 1.0 mg/mL LR769. Blood samples were collected on days 1, 28, 56 and 91 at time-points between 5 minutes and 9 hours. T_{max} was between 5 and 10 minutes for all dosing groups throughout study duration in male and female animals. C_{max} and AUC_{0-inf} increased with dose and was in a comparable range for both genders. Whereas exposure remained at a similar level in all dosing groups throughout the entire study period in male animals, a decrease in exposure was observed in the highest dose group of female animals. $T_{1/2}$ was similar in both genders for all doses and time points and ranged from 0.346 to 1.63 h. CL highly varied throughout the study period in male animals with no obvious relation to dose and time point. In female animals a correlation between number of doses and CL could be observed. Similarly, Vd changed frequently without following the dose or number of administrations in male animals. In females Vd appeared to increase with dose and number of doses. Analysis of gender ratios with regard to exposure did not identify any gender differences but overall, a higher exposure in male animals except for day 1, 28 and 91 of the 0.1.mg/mL group, where exposure was higher in females.

The effect of food consumption on absorption was not evaluated for Cevenfacta.

Distribution or protein binding as well as placental transfer were not evaluated for Cevenfacta.

Furthermore, metabolism, excretion and pharmacokinetic drug interactions were not analysed.

2.4.4. Toxicology

In order to investigate potential toxicity exerted by Cevenfacta, the applicant submitted a total of two single-dose and four repeat-dose toxicity studies as well as one fertility and reproductive performance study. Local tolerance and antigenicity were evaluated in the scope of other toxicity studies. A separate predictive *in vitro* immunogenicity studies was conducted with human PBMCs.

2.4.4.1. Single dose toxicity

A GLP-compliant single dose toxicity study (Study 504374) was performed in male Sprague Dawley rats as a part of the 28-day repeat dose toxicity study. Animals received 0.1, 0.3, 1.0 and 3.0 mg/kg LR769. Parameters evaluated included clinical signs, body weights, body weight changes, food intake, clinical pathology parameters (haematology, coagulation and clinical chemistry), male reproductive functions, gross necropsy findings, organ weights, and histopathologic examinations. Details on the toxicokinetic parameters are discussed in the Quality section above. No test-article related mortality was reported for this study. Platelet counts and prothrombin time decreased in dependence on dose and time as a consequence of the pharmacodynamic activity of LR769. Minimal vascular thrombosis at the site of administration was observed in the three lower dosing groups, which was attributed to the catheterisation. The absence of thrombi in the highest dose group suggests the potential involvement of mechanical contribution by the infusion procedure to these observations. Apart from that, no changes in any of the investigated parameters were detected.

A second GLP-compliant single dose toxicity study was conducted in *Cynomolgus* monkeys that received doses of 0.1, 0.3, 1.0, 3.0 mg/kg LR769 and were necropsied two days after administration (Study 504376). Animals were evaluated for clinical signs, body weights, body weight changes, food intake, clinical pathology parameters (haematology, coagulation and clinical chemistry), gross necropsy findings, organ weights, and histopathology. TK parameters were determined and are discussed in detail in the quality section above. No deaths, clinical signs, body weight changes or alterations in food consumption were observed. Moderate, however, statistically significant shortening of prothrombin time was observed in all dosing groups from 30 to 90 minutes and in the three groups that received the highest doses also at 6h, thus, indicating a clear dose response. A transient decrease in fibrinogen levels was observed in the 1.0 mg/kg group at 60 and 90 minutes and in the 3.0 mg/kg group at 30 min pointing only vaguely towards a dose-effect relationship. No related microscopic observations were made. In addition, alanine aminotransferase was transiently elevated in one single male animal and considered of no relevance for the overall safety profile due to the isolated observation. Moderate increases in creatine kinase were observed in control animals and in monkeys that received doses of more than 0.1 mg/kg, which was attributed to potential procedure-related myocyte damages by the applicant. No changes with regard to gross pathology, organ weights and histopathology occurred. Overall, Cevenfacta can be considered well-tolerated in this study.

2.4.4.2. Repeat dose toxicity

In a GLP-compliant 28-day repeat dose toxicity study in male Sprague Dawley rats animals were administered 0.1, 0.3, 1.0 and 3.0 mg/kg/day Cevenfacta (Study 504374). A part of the animals was necropsied immediately after the dosing period and some animals after a 14-day recovery period. TK parameters were determined and are discussed in detail in the quality section above. Overall, no Cevenfacta-related effects on body weights, food consumption, ophthalmology, clinical chemistry parameters, organ weight or microscopic findings were observed. Transient, dose-dependent decrease in activity was reported for animals treated with doses starting from 0.3 mg/kg. A dose-related decrease in prothrombin time and platelet counts was also noted in animals starting from a dose of

0.3.mg/kg, which is probably attributable to the mode of action of Cevenfacta. In addition, reversible increases in white blood cells, neutrophils and monocytes were reported, however, these findings did not follow a dose-dependent pattern. Vascular and perivascular inflammatory infiltrations associated with thrombosis of variable manifestation was observed at the infusion site of animals of the control and treatment groups with an increase in incidence and severity with increasing dose. These findings persisted through the end of the recovery period in control and treatment groups and can therefore be attributed also to the trauma by infusion and not entirely to the test-article. In the 3.0 mg/kg dose a single case of a brain thrombus and two cases of pulmonary haemorrhage were observed. Although the applicant argues that the lung haemorrhages are most probably incidental, the accumulation of these three cases in the highest dose group should not be ignored. Reflecting the findings in this study, the applicant determined the local no observed adverse effect level (NOAEL) to be 1.0 mg/kg/day (on Day 28 mean Cmax value of 1.53 µg/mL and mean AUC0-inf value of 1.62 µg▪h/mL) and based on the absence of systemic toxicity, the systemic NOAEL to be equal to or greater than 3.0 mg/kg/day (on Day 28 mean Cmax value of 2.94 µg/mL and mean AUC0-inf value of 3.08 µg▪h/mL). Anti-Cevenfacta antibodies were detected in the plasma of virtually all animals at day 29 and were of neutralising character.

In a second repeat-dose toxicity study in rats animals were administered 6 and 11 mg/kg LT769 for 25 consecutive days (Study 5000172). A part of the animals was examined on day 26, the remaining animals were investigated after a 14-day recovery period. TK parameters were determined and are discussed in detail in the quality section above. No deaths or test article related effects on body weights, food consumption, clinical chemistry and urinalysis parameters were observed in the main or recovery study. Three deaths in dosing groups occurred in the TK study, however, the cause of death could not be determined at the necropsy. Decreased activity was observed in animals that received Cevenfacta with dose-related incidence and severity. Protruding penis was observed on several occasions in two animals in the high dose group with unclear significance of this finding. With regards to coagulation parameters, prothrombin time was reduced in all Cevenfacta-treated animals at a comparable rate on day 1 but not at other time points analysed as a result of the pharmacological effect. No changes of PT, aPTT or fibrinogen related to control animals were observed at the end of the treatment or recovery period, respectively. In the 11 mg/kg group several changes as compared to control animals in haematology parameters were observed at the end of the treatment period. These included decreases in platelet counts, mild increases in lymphocyte, neutrophil, monocyte and leukocyte counts in one animal, decreases in platelet counts accompanied by haematopoiesis of megakaryocytes in the sternal bone marrow in one animal and the presence thrombi. Minimal decrease in red blood cells, haemoglobin and haematocrit as well as moderate increases in platelet counts at the end of the recovery period i the high dose group were interpreted as a result of regenerative processes and not attributed to the test article by the applicant. Organs that exhibited pathological changes were abdominal blood vessels (caudal vena cava), kidney, lung, testis and epididymis. Microscopic examination identified foci of renal necrosis as a result of infarction in the 11 mg/kg group, thickening and thrombosis at the infusion site in both dose groups, dilated abdominal blood vessels related to thrombosis of adjacent vessels or as a consequence of impaired venous blood flow due to thrombosis at the infusion site and mild inflammation of and around pulmonary vessels combined with mild thrombosis. Small testis with diffuse degeneration together with small epididymis and oligo/aspermia were observed in one animal of the high dose group. Various of these pathological changes persisted until the end of the recovery period. These non-reversible changes were the thickened infusion site associated with marked thrombosis in both treatment groups, dilatation of and marked thrombosis in abdominal blood vessels (11 mg/kg), decrease in testis and epididymis weights including oligo/aspermia (11 mg/kg), minimal to mild lung thrombosis in both groups and severe thrombosis in the hepatic vein (6 mg/kg). As a consequence of marked and persistent thrombosis observed in

various organs in animals of both dosing groups the establishment of a NOAEL was not possible for this study.

A 28-day repeat dose toxicity study with a 14-day recovery period was conducted in *Cynomolgus* monkeys (Study 504376). Animals received daily infusions of 0.1, 0.3, 1.0 and 3.0 mg/kg Cevenfacta. TK parameters were determined and are discussed in detail in Section 3.2.2 of this report. No unscheduled deaths, clinical signs or effects on body weight or food consumption were observed. In addition, no ophthalmic changes or deviations from normal cardiac rhythms were noted. A moderate decrease in platelet counts associated with microscopic thrombosis of the endocardium of the right ventricle was observed in one animal of the highest dose group. Moreover, prothrombin time was decreased on day 1 for up to 90 minutes in all dosing groups. This observation was prolonged to 6h post-dose on day 1 starting from the 0.3 mg/kg group. Thus, a dose response relationship can be attributed to this effect. In addition, a transient decrease in fibrinogen was observed in animals that received doses of 1.0 mg/kg and higher. Alanine aminotransferase and creatine kinase activity mildly and transiently increased in animals given 0.3 mg/kg or ≥ 0.1 mg/kg, respectively. As creatine kinase activity was also increased in control animal it was attributed to trauma by infusion and not considered Cevenfacta-related. Apart from that, a nodule associated with thrombosis was detected after the recovery period in the right ventricle of an animal that received 3.0 mg/kg that was considered test article related. All animals developed anti-Cevenfacta antibodies during the dosing period and virtually all of these antibodies were of neutralizing character. The NOAEL for this study was set at 1.0 mg/kg/day corresponding to a mean Cmax of 9.18 µg/mL and mean AUC0-inf of 10.3 µg.h/mL on Day 28.

A second repeat-dose toxicity study was conducted in male and female *Cynomolgus* monkeys that involved daily infusion of 0.1, 0.3 and 1.0 mg/kg Cevenfacta for 13 weeks and, for a part of the animals, a 14-day recovery period. TK parameters were determined and are discussed in detail in the quality section above. No unexpected deaths or effects on body weight and food consumption were observed in animals treated with Cevenfacta. In addition, no ophthalmic changes, changes in blood pressure and electrocardiographic parameters were observed. Prothrombin time was decreased up to 30 minutes post-dose in all dosing groups as a consequence of the pharmacodynamics of Cevenfacta. This effect decreased with increasing number of administrations predominantly in females and correlated with faster systemic elimination. A decrease in aPTT was noted on day 28 30 minutes post-dose in male animals of the 1.0 mg/kg group. However, due to the isolated character of this finding it can presumably be considered incidental. Increased levels of aspartate aminotransferase, alanine aminotransferase, creatine kinase, and lactate dehydrogenase in one 1 mg/kg male were also rated non-adverse. All animals developed neutralising anti-drug antibodies. The NOAEL in this study was ≥ 1 mg/kg/day (Cmax of 11.200 and 4.260 µg/mL and AUC0-inf of 13.500 and 3.250 µg▪hr/mL in males and females, respectively). According to the applicant, this corresponds to a safety margin of 4.6 for males and 1.7 for females considering a human dose of 900 µg/kg/day and the resulting Cmax of 2.4 µg/mL.

2.4.4.3. Genotoxicity

No genotoxicity studies have been performed in line with the relevant ICH S6(R1) guideline.

2.4.4.4. Carcinogenicity

No carcinogenicity studies have been performed in line with ICH S6(R1) guideline that discourages the conduct of standard carcinogenicity studies for biotechnology-derived pharmaceuticals.

2.4.4.5. Reproductive and developmental toxicity

A GLP-compliant fertility and reproductive toxicity study was conducted in male Sprague Dawley rats that were administered 0.1, 0.3, 1.0 or 3.0 mg/kg daily. Dosing started 28 days before cohabitation and continued until a total of 46/47 doses or 55 doses, respectively. Three deaths occurred in this study one of which was probably attributable to the test item due to infusion site mass secondary to Cevenfacta administration. Apart from that no clinical signs, effects on body weight or food consumption were noted. Also organ weights and sperm counts were comparable to control animals. No microscopic abnormalities were detected in the testis, which indicated no effects on the spermatogonic cycle. Days to mating, mating, fertility indices and conception rate were comparable to control animals and, thus, not affected by the test article. Similarly, female animals paired with treated males had similar numbers of corpora lutea, implantation sites, live embryos, dead embryos, early resorptions as well as pre- and post-implantation losses when compared to control animals. Animals treated with doses of 1.0 mg/kg and higher had a comparatively high incidence of masses, thickening and firmness at the infusion sites. It was concluded that the NOAEL for male fertility and reproductive performance can be determined to be 3 mg/kg/day.

No embryo-foetal and pre- or postnatal development studies as well as juvenile toxicity studies were conducted with Cevenfacta.

2.4.4.6. Local Tolerance

No dedicated local tolerance study was performed but macroscopic and microscopic injection site analysis was included in single and repeat-dose toxicity studies in rats and in repeat-dose toxicity studies in monkeys. Rats developed occasional vascular inflammation after single administration and irreversible thrombosis when administered 3.0 mg/kg. An aggravation of these findings was observed after repeated administration of vehicle or Cevenfacta with dose-dependent increase of severity with two cases of thrombi with necrotic centre in the highest dose group. Events such a minimal to moderate thrombosis and perivascular haemorrhage persisted throughout the recovery period in control as well as test animals (3.0 mg/kg) and are likely to be at least partly attributable to mechanical trauma at the infusion site. No such observations were made in *Cynomolgus* monkeys.

2.4.4.7. Other toxicity studies

Anti-Cevenfacta antibodies were detected after multiple administrations in repeat dose toxicity studies in rats and monkeys (Studies 504374, 5000172, 504376 and 5000766). These anti-drug antibodies were of neutralising character. Based on the high homology between human and primate FVII it was investigated whether the anti-drug antibodies developed in response to Cevenfacta administration also recognise primate FVII. Indeed, it was confirmed that the primate ADA are capable to neutralise primate FVII and to inhibit its coagulant activity, which became clinically evident by increased prothrombin time. As animal studies are not considered predictive for clinical immunogenicity a predictive *in vitro* immunogenicity study (EpiScreenTM) was performed. CD8+ T cell depleted peripheral blood mononuclear cells (PBMC) from a cohort of 50 donors were cultured in the presence of Cevenfacta or NovoSeven for 8 days. Potential clinical immunogenicity expressed by a CD4+ T cell response was evaluated by T cell proliferation ([3H-thymidine uptake] and IL-2 production (ELISpot). Based on the results of this *in vitro* assay a low clinical immunogenicity is predicted for Cevenfacta.

Immunotoxicity, dependence and metabolism were not evaluated for Cevenfacta as not considered relevant for a product of this type.

Considering rabbit's milk as the platform for Cevenfacta production, it is conceivable that related **impurities** such as soluble rabbit's milk proteins and colloidal rabbit's milk proteins are potential impurities of the drug substance. The presence of such protein impurities was indirectly analysed by detection of antibodies directed against rabbit whey or casein in the serum of rats and monkeys that repeatedly received Cevenfacta. Out of 15 rat and 51 monkey samples only one rat sample was reactive to rabbit casein. Thus, although not necessarily predictive for any human immune response, the presence of impurities originating from rabbit's milk could not be determined on the non-clinical level.

The applicant provided a comprehensive risk assessment on the safety and toxicity of the **excipients** present in the drug product after reconstitution for use. These excipients are largely naturally occurring amino acids for which a sufficiently high safety margin will be met. The content of Polysorbate 80 will also be well below the permitted daily exposure. A mixture of the excipients equal to the formulation buffer was used as vehicle control in repeat-dose toxicity studies in rats and monkeys and can therefore be considered qualified.

2.4.5. Ecotoxicity/environmental risk assessment

Cevenfacta is a recombinant human FVII protein. Due to its similarity to the endogenous human FVIIa and it be considered a naturally occurring protein and the submission of ERA studies is not warranted as stated in the EMA Guideline "Environmental risk assessment of medicinal products for human use" EMEA/CHMP/SWP/4447/00 corr 2., Cevenafcta is not considered to pose a risk to the environment.

2.4.6. Discussion on non-clinical aspects

Pharmacology

In vitro and *in vivo* pharmacodynamic characterisation revealed comparable functionality of Cevenfacta and NovoSeven in all studies. *In vitro*, Cevenfacta increased thrombin generation and decreased coagulation parameters. *In vivo*, Cevenfacta efficiently reduced blood loss and bleeding time in haemophilia A mice and dogs. Moreover, thrombogenicity was comparable to NovoSeven.

An *in vitro* comparison of Process A and Process B material revealed functional similarity between the batches employed for this assay. Of note, this *in vitro* comparison only reflects functional properties of the batches but can hardly provide any information on e.g. potential pharmacokinetic differences due to formulation differences that might play a role in an *in vivo* setting.

Pharmacokinetics

Pharmacokinetic and toxicokinetic properties of Cevenfacta were evaluated in a total of three single dose and four repeat-dose studies in rats, dogs and monkeys.

After a single dose exposure increased in a roughly dose-proportional or more than dose-proportional manner.

After repeated administration (0.1, 0.3, 1.0 and 3.0 mg/kg) for 28-days in rats exposure was also dose-proportional after the first administration but decreased over time so that Cevenfacta was only detectable in animals of the high dose group at the end of the administration phase. Since 90% of animals were ADA positive, the decrease in exposure with time is very likely attributable to the development of ADA that have been demonstrated to be of neutralizing character. When higher doses, 6 and 11 mg/kg, were administered, exposure increased more than dose-proportional, i.e. more than

3-fold, over time.

Of note, AUC0-inf for the 3.0 mg/kg dose was lower after repeated administration of Cevenfacta on day 28 of Study 504374 in rats than on day 1, Cmax was lower at the end of the study period for the 1.0 and 3.0 mg/kg dose. Thus, exposure appeared to decrease after repeated-administration in rats. In contrast, exposure generally increased in Study 5000172 until day 25 when 6 or 11 mg/kg were repeatedly administered. ADA were detected in animals of both studies, but appear not to have negatively influenced exposure in the high dose study. According to the applicant's argumentation different dose levels and, as a consequence, saturation of various elimination pathways might account for that observation, which is considered plausible.

In monkeys exposure was dose-dependent and remained constant throughout the study period of 28 days. Similarly, the level of exposure remained comparable throughout the 13-week repeat dose study in male and female monkeys with the exception of the high dose group of female monkeys that had decreased exposure over time. This observation correlated well with the occurrence of ADA that, although detected in all animals that had received Cevenfacta, were present at higher titres in females. Of note, a relatively low number of animals was employed in these studies and a high SD was observed. Thus, the study results have to be interpreted with caution. Nevertheless, exposure of monkeys that received 0.3 mg/kg was comparable to haemophilia A and B patients that received 0.225 mg/kg.

Toxicology

Overall, Cevenfacta was well tolerated in all toxicity studies by rats and monkeys. General observations made in all toxicity studies were decreases in prothrombin time and platelet counts shortly after administration. Observed adverse events were largely limited to rat studies and in general attributable to exaggerated pharmacology. These events included local perivascular inflammation and thrombosis at the infusion site and deteriorated with increasing dose. As such observations were also made in control animals, a partial relation to trauma by catheterisation is also conceivable. Systemic effects were observed in rats at doses of 6 and 11 mg/kg/day. Thus, thrombosis partly associated with necrosis was observed in several organs such as abdominal blood vessels, kidney, lung, testis and epididymis. Some of these findings proved to be irreversible after the recovery period in both dosing groups. Thus, the applicant's approach to establish the local NOAEL at a dose of 1.0 mg/kg/day and the systemic NOAEL at 3.0 mg/kg/day is accepted. Of note, virtually no exposure margin to haemophilia A and B patients is established with regard to Cmax and AUC0-inf for the 1.0 and 3.0 mg/kg/day dose in rats.

Adverse events were less pronounced in *Cynomolgus* monkeys. Only one serious test-article related event was observed after repeated administration (28 days) of 3.0 mg/kg/day, which was a nodule associated with thrombosis in the endocardium of the right ventricle that was discovered after the recovery period. This event occurred at approximately the 15-fold exposure of that reported for patients receiving the 0.225 mg/kg dose. Therefore, the NOAEL for monkey studies was determined at 1.0 mg/kg/day, which corresponds to an exposure margin of 5 to the clinical exposure at a dose of 0.225 mg/kg.

Genotoxicity

No genotoxicity studies have been performed in line with the relevant ICH S6(R1) guideline which is considered acceptable.

Carcinogenicity

No carcinogenicity studies have been performed in line with ICH S6(R1) guideline that discourages the conduct of standard carcinogenicity studies for biotechnology-derived pharmaceuticals. This is

considered acceptable.

Reproductive and developmental toxicity

No effect of Cevenfacta was observed on male mating and fertility as well as conception rate at doses of up to 3 mg/kg/day.

Local Tolerance

No dedicated local tolerance study was performed but macroscopic and microscopic injection site analysis was included in single and repeat-dose toxicity studies in rats and in repeat-dose toxicity studies in monkeys.

Immunogenicity

All experimental animals of the repeat-dose toxicity studies developed anti-drug antibodies, which were of neutralising character and also recognised primate FVII. Thus, coagulation in *Cynomolgus* monkeys was impaired as expressed by an increase in prothrombin time after repeated administration of Cevenfacta. In order to predict patient immunogenicity, an in vitro assay employing human CD8+ T cell depleted PBMCs was utilised. This assay predicted low immunogenicity for Cevenfacta, which was indeed confirmed in clinical studies.

The presence of impurities from rabbit's milk was indirectly analysed by evaluating a potential immune response against rabbit whey and casein in rat and monkey serum. Of note, it is conceivable that also various components other than whey or casein represent potential impurities originating from rabbit's milk might be present in the drug product. Therefore, the applicant's approach is supportive, but of rather limited significance.

It is remarked that a huge variety of batches has been used for the non-clinical studies, even up to three different batches within one single study, which is not considered an ideal setting. However, the applicant argued that, although doses were based on the total protein content, inter-batch variabilities regarding purity did in general not exceed 10%. Thus, and considering that supra-physiological doses of FVII have been administered, a disadvantageous effect by using various batches for one experiment, is not conceivable.

Environmental Risk Assessment

The active substance is a natural substance, the use of which will not alter the concentration or distribution of the substance in the environment. Therefore, eptacog beta is not expected to pose a risk to the environment.

Considering the above data, eptacog beta is not expected to pose a risk to the environment.

2.4.7. Conclusion on the non-clinical aspects

All findings in the preclinical safety programme were related to the pharmacological effect of rFVIIa.

Overall, the applicant provided a comprehensive panel of non-clinical pharmacodynamics, pharmacokinetics and toxicity studies in order to support the MA of Cevenfacta.

2.5. Clinical aspects

2.5.1. Introduction

GCP aspects

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

The applicant 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.

- **Tabular overview of clinical studies**

Table 1 : Description of clinical efficacy and safety studies

Study ID (Location in CTD)	Total study sites, Locations	Study start, Status, Patients planned and enrolled	Design	Objectives, Primary endpoints	Study drug, Route & treatment regimen	Gender, Median age (range)	Diagnosis, Inclusion criteria
GTC-FVIIa-005-11 Phase 1b (Module 5.3.4.2)	Sites: 3 Netherlands: 1 USA: 2	09 Oct 2012 Completed 04 Jun 2013 15 planned, 15 enrolled	Phase 1b, multicenter, dose escalation of 3 doses, 10 patients at each dose level; the 15 patients enrolled each received 2 single doses at different levels, for a total of 30 doses administered	Safety, PK, PD	LR769 25, 75, or 225 µg/kg: initial 2-3 minute IV bolus infusion; single injection per dose; 2 different doses/patient, several weeks apart	Male only 33 years (20-61)	Hemophilia A or B with and without inhibitors to FVIII or FIX Adults, ≥18 years to ≤75 years
RB-FVIIa-006-13 PerSept 1 (Module 5.3.5.1)	Sites: 11 Bulgaria: 1 Georgia: 1 Poland: 1 Russia: 2 Ukraine: 2 UK: 1 USA: 3	29 Apr 2014 Completed 31 Jul 2015 25 planned, 27 enrolled	Phase 3, multicenter, randomized, open-label, crossover study of 2 treatment regimens for bleeding episodes At least 22 patients were followed for ≥6 months until ≥352 bleeding episodes recorded Objective performance criteria	Efficacy, safety, PK, immunogenicity, healthcare resource utilization	LR769 Initial 75 or 225 µg/kg ≤2 minute IV bolus dose, then 75 µg/kg single injection as needed Phase A: Initial dose for safety and PK Phase B: Treatment of bleeding episodes, repeated PK	Male only, adolescent and adult 31 years (12-54)	Hemophilia A or B with inhibitors to FVIII or FIX Adults and adolescents, ≥12 years to 75 years
LFB-FVIIa-007-14 PerSept 2 (Module 5.3.5.1)	Sites: 8 Czech Rep: 1 Georgia: 1 Mexico: 1 S. Africa: 2 Ukraine: 2 USA: 1	07 Dec 2015 Completed 30 Jun 2017 • planned, • enrolled	Phase 3, multinational, multicenter, randomized, prospective, open-label, crossover study of 2 treatment regimens for bleeding episodes At least 22 patients were to be followed for ≥6 months until ≥352 bleeding episodes had been treated. Objective performance criteria	Efficacy, safety, PK, immunogenicity, healthcare resource utilization	LR769 Initial 75 or 225 µg/kg ≤2 minutes IV bolus dose, then 75 µg/kg single injection as needed Phase A: doses for safety and PK Phase B: doses for bleeding episodes	Male only Pediatric 5 years (1-11)	Hemophilia A or B with inhibitors to FVIII or FIX Children from birth to <12 years
LFB-FVIIa-008-14 PerSept 3 (Module 5.3.5.2)	Sites: 8 Mexico: 1 Russia: 1 S. Africa: 2 Spain: 1 Ukraine: 3	25 Aug 2016 Completed 31 Aug 2017 Minimum 6 patients planned, 12 enrolled	Phase 3, multinational, multicenter, open-label, single-arm study in surgical and invasive procedures At least 12 elective surgical procedures in ≥6 patients, of which at least 6 must be major procedures	Efficacy, safety, immunogenicity	LR769 Initial dose of 200 or 75 µg/kg ≤2 minutes IV bolus infusion for major or minor procedures, respectively; repeated dosing with 75 µg/kg in intra-operative and postoperative period	Male only Pediatric and adult 20 years (2-56)	Hemophilia A or B with inhibitors to FVIII or FIX Adults and children, ≥6 months to 75 years

CTD = common technical document; FIX = coagulation factor IX; FVIII = coagulation factor VIII; ID = dentification; IV = intravenous; PD = pharmacodynamics; PK = pharmacokinetic; UK = United Kingdom; USA = United States of America

Clinical phase 1b study was conducted with Process A product, while the phase 3 studies used both Process A and Process B or process B only products.

2.5.2. Clinical pharmacology

2.5.2.1. Pharmacokinetics

Clinical studies with a PK component

Three studies with a clinical pharmacology component were conducted with Cevenfacta. Patients did not have an active bleeding at that time and had not receive treatment with any FVII(a) product within 24 hours prior to this administration.

Study GTC-FVIIa-005-11 was a Phase 1b, dose escalation study to assess the safety, pharmacokinetics (PK) and pharmacodynamics (PD) of Cevenfacta across three dose levels (25, 75, and 225 µg/kg) in a total of 15 adult male patients (mean age 33 years, range 20-61 years) with congenital haemophilia A or B with or without inhibitors. PK data were analysed using non-compartmental methods and population PK modelling.

Study RB-FVIIa-006-13 (PerSept1) was a Phase 3, multicentre, open-label, randomised, crossover study in patients with haemophilia A or B with inhibitors.

Patients received a single intravenous administration of either 75 µg/kg or 225 µg/kg of Cevenfacta as a bolus injection within 2 minutes. For PK evaluations, blood draws occurred at baseline (prior to Cevenfacta administration), 10±2 minutes, 30±5 minutes and 1, 2, 4, and 8 hours (±10 minutes) relative to the start of infusion of study drug. A repeat of the PK analyses was done in the same patients 3-6 months after the initial PK assessments (Process A), but with the product obtained from a scaled up manufacturing process (Process B), again when the patient was in a non-bleeding situation. The dose of the study drug for this repeat PK assessment was the same as used during the first evaluation. A total of 14 male patients (mean age 32 years, range 13-54 years) were included in the PK portion of this study, 7 patients each at 75 µg/kg and 225 µg/kg. Only two patients (both at 75 µg/kg) were <18 years of age. Of the 7 patients who received Process A in the 75 µg/kg group, 6 received Process B during repeat PK assessment. Of the 7 patients who received Process A in the 225 µg/kg group, 5 received Process B during repeat PK assessment. Sequential blood samples were collected for PK analysis. PK data were analysed using non-compartmental methods and population PK modelling.

Study LFB-FVIIa-007-14 (PerSept 2) was a Phase 3, multicentre, prospective, open-label, randomised, crossover study in patients with haemophilia A or B with inhibitors to FVIII or FIX. A total of 23 paediatric patients (n=10 for < 6 years old and n=13 for ≥6 years to <12 years old with overall mean age 5.59 years and range 1-11 years) were included in the PK portion of this study, 10 patients at 75 µg/kg and 13 patients at 225 µg/kg. Samples were taken pre-dose in all patients. To reduce the number of blood draws, subsequent sparse sampling was done in approximately half of the patients (sampling schedule 1) at 10±2 minutes and 1 and 4 hours (±10 minutes); the other half (sampling schedule 2) was done at 30±5 minutes and 2 and 8 hours (±10 minutes) relative to the start of infusion of study drug. The Cevenfacta data from the PerSept2 study were first analysed using a population PK approach and PK NCA parameters were derived as secondary parameters to the population PK modelling.

Table 2: Overview on clinical studies with PK component

Study	Study Objectives	Study design	Dose	Patients Number	Manufacturing Process
Phase 1b[1]	PK/PD in adult patients > 18 years old with Hemophilia A and B with or without inhibitors in a non-bleeding state	Multicenter, open-label, single-dose, dose escalation	25 µg/kg IV	10[1]	Process A
			75 µg/kg IV	10[1]	
			225µg/kg IV	10[1]	
PerSept 1	Confirmatory PK in adult and adolescent patients (> 12 years) with Hemophilia A and B with inhibitors in a non-bleeding state	Multicenter, open-label, randomized, crossover multiple doses	75 µg/kg IV	7	Process A and Process B
			225 µg/kg IV	7	
PerSept 2[2]	PK pediatric in patients from birth to <12 years with Hemophilia A and B with inhibitors in a non-bleeding state	Multicenter, open-label, randomized, crossover multiple doses	75 µg/kg IV	10	Process B
			225 µg/kg IV	13	

Source: Module 5.3.4.2, CSR Phase 1b and Module 5.3.5.1, CSR PerSept 1 and PerSept 2
Abbreviations; IV = intravenous; PK = pharmacokinetics; PD = pharmacodynamics
[1] 15 patients enrolled, 10 each received 2 single doses of LR769 (25 and 75 µg/kg, or 75 and 225 µg/kg, or 25 and 225 µg/kg)
[2] 23 patients enrolled ; 10 aged from birth to < 6 years (75 µg/kg (n=3) and 225 µg/kg (n=7) and 13 aged ≥ 6 to < 12 years (75 µg/kg (n=7) and 225 µg/kg (n=6))

LFB-FVIIA-009-19 was a Phase I, open-label, randomised, parallel, single-dose PK study of Coagulation Factor VIIa (Recombinant), Cevenfacta, in subjects with haemophilia A, with or without inhibitors to FVIII. PK and safety of a single intravenous (IV) dose of 75 or 225 µg/kg were evaluated in 28 male subjects aged 18 to 75 years, inclusive, with confirmed diagnosis of haemophilia A (with or without inhibitors to FVIII) and who were not experiencing an active bleeding episode. This study consisted of a screening visit (Day -14 to Day -1), a single-day dosing period (Day 1), and a follow-up telephone call (Day 4 ±1 day). Total study participation lasted up to 19 days. Eligible subjects were randomised (1:1) to receive 1 of the following single IV dose of Cevenfacta: 75 or 225 µg/kg. Randompaediatric was stratified by FVIII inhibitor status (with [≥5 BU] or without [<5 BU]) with a minimum of 2 and a maximum of 5 subjects with inhibitors to FVIII enrolled in each treatment group. Cevenfacta was administered as an IV bolus injection within 2 minutes. The infusion start time and stop time were recorded. Blood samples for PK assessments were collected before IMP administration and at 5, 15, and 30 minutes, and at 1, 2, 4, 6, 8, and 12 hours after the end of the infusion.

The primary objective was to evaluate the single-dose PK of Cevenfacta at 75 and 225 µg/kg in subjects with haemophilia A, with and without inhibitors to FVIII. The secondary objective was to characterise safety data collected before and after administration of a single dose of Cevenfacta. FVIIa concentrations were determined using a validated activity assay. Non-compartmental and compartmental PK analyses were performed. For this study, the PK parameters of primary interest were Cmax and AUC0-inf.

Bioanalytical Methods for PK

The clotting assay for the determination of FVIIa levels used in Studies GTC-FVIIa-005-11, RB-FVIIa-006-13, and LFB-FVIIa-007-14 (PK assay) is described below. A commercial kit for the assessment of plasma FVIIa concentrations was used which was slightly modified to be able to measure high concentrations of FVIIa in clinical samples. This assay, from which PK profiles were derived, was handled by Good Biomarker Sciences (GBS), a central laboratory in Leiden, Holland (GBS 2013-30 and 20160321).

A number of further assays was used to study pharmacodynamics parameters of Cevenfacta mainly assessed in the Phase 1b trial GTC-FVIIa-005-11. Commercial assays were used in the Study GTC-FVIIa-005-11 and were qualified or validated for use in the clinical trial.

Thrombin generation was assessed as measured by a calibrated automated thrombogram (CAT), a thrombin generation assay (TGA), which was qualified for the study. Thromboelastography, assessing clot formation and degradation was done using rotational thromboelastography (ROTEM). Other coagulation parameters assessed in Phase 1b included: activated partial thromboplastin time (APTT),

prothrombin time (PT) both as a regular assay and modified, prothrombin fragments 1+2 (PF1+2), D-dimer and thrombin antithrombin complex (TAT). All assays (PK and PD assays) have been validated/qualified and performed by Good Biomarker Sciences (GBS) in Leiden, Netherlands. Descriptions of the methods that were employed in Study GTC-FVIIa-005-11 are provided below.

PK Assay - FVIIa Activity (Clotting Assay)

PK of Cevenfacta is assessed by measuring FVIIa activity in plasma samples. The applicant for this purpose has adapted and validated the commercially available Statclot VIIa clotting assay to quantify active rhFVIIa in human plasma samples. In brief, in presence of phospholipids and calcium ions, the tested plasma is coagulated by addition of a mutated rTF, which possesses a cofactor function specific for the factor Vlla -assay principle and does not allow activation of the factor VII into factor VIIa; consequently the factor VII present in the tested plasma does not interfere in the assay. In this system the observed clotting time bears an inverse relationship with the factor VIIa level originally present in the test plasma sample. The assay was optimised during clinical development, and different assay protocols were applied.

The (endogenous) FVIIa inhibitor TFPI interfered in the original assay format, and the dynamic range of the assay was not suitable for measuring high FVIIa levels, which were reached after exogenous administration of Cevenfacta. Thus the assay matrix was replaced by TFPI and VIIa free reagent Hemoclot VII, which serves as homogenous matrix in the adapted assay. To accommodate the occurrence of high plasma factor VIIa levels in samples following administration of recombinant factor VIIa, the calibration line was extended over a 1000-fold range, but the calibration curve needed to be fitted with two functions: One for the concentration range from 0.3 to 10, and a second one for the range of 10 to 300 ng/ml FVIIa. The clotting reagent was diluted to obtain long clotting time < 240 sec observed to include baseline levels earlier and the limit set at the equipment. For very high levels above 300 ng/ml of FVIIa, a policy of dilution of the sample in 0.1% bovine serum albumin was defined.

In the initial version of the assay, and only for Phase I development the rhFVIIa was used as calibrator. From Phase III development on two different lots of commercially available NovoSeven were used as calibrators.

The validity of the latest version of the assay for its intended application was demonstrated as summarised below.

Table 3: Validity of the latest assay version

Standard curve range and units		0.33; 1; 3.3; 10; 30; 100; 300 ng/ml Novoseven®
Validated quality control range		From 2 to 100 ng/ml
Selectivity		Selective for FVIIa, no interference by FVII.
Carry-over		No effect detected
Accuracy and Precision	Factor VIIa level (100 ng/ml) (30 ng/ml) (10 ng/ml)	%CV %DEV %Total Error 10.4 8.7 19.1 8.2 8.3 16.5 4.1 12.0 16.1
Dilution linearity		300 ng/ml %CV and %DEV < 20% for 1/10 to 1/80 dilution: Pass 100 ng/ml %CV and %DEV < 20% for 1/10 to 1/80 dilution: Pass 50 ng/ml %CV < 20% for 1/10 to 1/80 dilution; Pass except once %DEV at 20.5%
Matrix interference		No hemoglobin interference up to 0.2 mM at 1:10 dilution. Higher dilution required if hemoglobin above this level to minimise interference. No effect of FVIII or FIX inhibitors.
Freeze-thaw stability <-60°C	one cycle. 1h	pass
Freeze-thaw stability <-60°C	one cycle. 24h	pass
Long term stability <-60°C	6 months	pass

Comparability of different versions of PK assays applied throughout clinical development (pivotal studies PerSept 1 and PerSept 2) was not performed, and head-to-head testing of assay reactivity of different batches of LR96 also was not done, and cannot be performed anymore, since respective samples are no more available. ISR was also not performed and cannot be performed retrospectively, also since samples are no more available. Thus, it must be kept in mind that applied methods to assess PK data from studies PerSept 1 and PerSept 2 were not fully validated.

The applicant provided further clinical PK data from a new clinical study FVIIa-009-19 based on activated FVII plasma concentrations, analysed using a different PK assay, based on STAclot VIIa-rTF reagents and measured on an automated coagulation analyser. The assay was completely validated for its precision, accuracy, selectivity, specificity, dilution linearity, prozone effect, carry over, and robustness including extended determination of frozen sample stability. Dilution linearity was confirmed. The performance of the method for activated Factor VII in human plasma was also found adequate during the bioanalysis of clinical samples, as demonstrated by the precision and accuracy for calibration and QC sample results, and by ISR (10% of total samples) and parallelism assessment. Assay validation protocols and the bioanalytical report were provided, confirming that the method was suitable for the intended use over a concentration range from 1.6 to 60 ng/ml in human plasma matrix.

Taken together, only PK data from study FVIIA-009-19 are considered valid.

PK Data Analysis

Data were analysed using non-compartmental analysis (NCA) and population PK modelling. A population PK model was initially built based on the data from the Phase 1b study and subsequently re-analysed to generate an integrated population PK model each time more data became available from the subsequent studies. The models were further updated including fixed allometric scaling and a maturation function upon request. PK data from study LFB-FVIIA-009-19 were also integrated in the analysis once they became available. In addition, for each study a separate popPK model was build. Based on the integrated popPK model, exposure-response models were developed for efficacy (successfully treated bleeding episodes at 12 hours with different severity) and safety parameter (TEAEs and ADR). During the procedure, the results of the exposure response models were also updated based on the requested update of the population PK model.

For each study the NCA analysis was performed independently from the popPK analysis, except for study PerSept 2. Since only sparse sampling was performed in this study, the NAC analysis was performed post-hoc and calculated based on the population PK model.

Evaluation and Qualification of Models

The population PK model, its requested update and the subsequent exposure-response models are briefly described in this report. The initial population PK model used pooled data from the Phase 1B study and the two Phase 3 studies PERSEPT 1 and PERSEPT 2: single dose PK data from 52 male patients (GTCFVIIa-005-11 n = 15, PERSEPT 1 n = 14, and PERSEPT 2 n = 23). Numbers of patients below 18 years of age are listed in Table 12. The updated population PK model used additional data from study LFB-FVIIA-009-19 (Study 009), a single-dose Cevenfacta study including 28 patients with haemophilia A with or without inhibitors aged between 18 to 75 years.

Table 4: Number of patients below the age of 18 years included in the PK analysis

Age range		Number of patients	Study
Neonates:	birth to 28 days	0	PERSEPT 2
Infants:	1 month to < 6 months	0	PERSEPT 2
Infants:	6 months to < 1 year	1	PERSEPT 2
Infants:	1 year to < 2 years	4	PERSEPT 2
Children:	2 years to < 6 years	6	PERSEPT 2
Children:	6 years to < 12 years	12	PERSEPT 2
Adolescents:	12 years to < 18 years	2	PERSEPT 1

For all population PK-models covariates were investigated graphically followed by a forward inclusion and backward elimination procedure. Different covariates were tested. A description of the investigation of random effects was missing. Model development was performed using standard procedures and commonly used methods were used for model evaluation, selection and investigation of the predictive performance of the models.

Initially, the final population PK model was a two-compartment model with first order elimination and a proportional error model. Weight effects on clearance (CL), volume of central component (Vc), clearance or peripheral component (Q) and volume of peripheral component (Vp) were estimated and included in the model, as well as age category effect on Vc, and study effect on the proportional error.

Upon request, the model was updated by applying fixed allometric scaling exponents on volume and clearance and evaluated a maturation function for very young children. During this update, two distinct models were considered for evaluation, an updated PK model with fixed allometric scaling exponents and an updated PK model with fixed allometric scaling exponents and maturation function for Children aged <2 years.

Fixing the exponents for the weight effect on clearance and volume of distribution to the theoretical values (0.75 for CL and 1 for V) did not significantly improve the population PK model compared to the initial PK model.

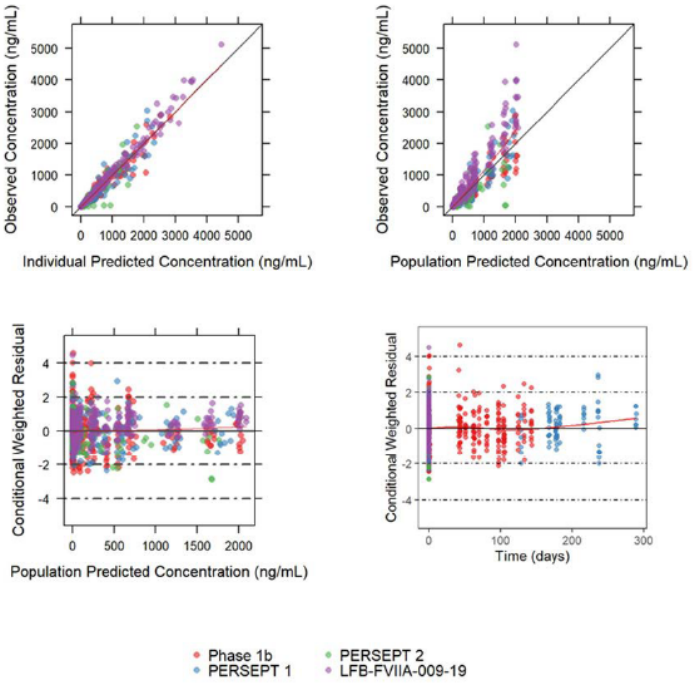
The inclusion of a maturation function was hampered by the very limited data for very young children (1 patient < 1year, 5 patients <2 years). The applicant tried to estimate the hill coefficient by fixing the age at 50% of maturation to 12 months. With the exception of the additional parameters from the sigmoidal function, PK parameter estimates of the PK model with fixed allometric scaling exponents and maturation function were then similar to estimates of the PK model with fixed allometric scaling exponents only.

Table 5. Population PK Parameters of LR769 from the Final PK Model (Fixed Allometriq Scaling Exponents abd Maturation Function for Children aged <2 years)

Parameter	Point estimate	RSE%	95% CI
Typical Values			
Clearance CL (L/h)	7.27	5.66	6.47 – 8.08
Intercompartmental clearance Q (L/h)	1.61	7.11	1.39 – 1.84
Central volume Vc (L)	7.09	5.55	6.32 – 7.86
Peripheral volume Vp (L)	2.90	6.03	2.56 – 3.25
FVII Endogenous Level (ng/mL)	1.08	10.2	0.866 – 1.30
Maturation Function on CL			
Age at 50% Maturation (month)	12.0 Fixed	n/a	n/a
Hill Coefficient	5.18	56.3	-0.538 – 10.9
Covariate Effects			
Weight on CL/Q	0.750 Fixed	n/a	n/a
Weight on Vc/Vp	1.00 Fixed	n/a	n/a
Age Category 1 on Vc (< 2 years)	0.150	33.9	0.0774 – 0.292
Age Category 2 on Vc (2 to 6 years)	0.939	16.1	0.685 – 1.29
Age Category 3 on Vc (6 to 12 years)	1.06	5.88	0.943 – 1.19

Parameter	Point estimate	RSE%	95% CI
Between Subject Variability			
On CL	0.408	12.1	0.311 – 0.505
On Vc	0.409	11.6	0.316 – 0.503
On Vp	0.235	18.4	0.150 – 0.320
On C_{ENDO}	0.724	10.5	0.575 – 0.873
Correlation CL, Vc	0.976	1.20	0.953 – 0.999
Residual Error			
Proportional (%)	21.4	6.23	18.8 – 24.0
Persept1 on Residual Error	1.54	11.9	1.22 – 1.94
Persept2 on Residual Error	1.92	16.3	1.40 – 2.65

Figure Q99a-4: Diagnostic Plots for the Final PK Model of LR769 (Fixed Allometric Scaling Exponents and Maturation Function for Children aged <2 years)



Results for PK

Table 6: Summary of results for clinical studies with PK component - NCA

Study No. (countries) CTD location	Subjects (Age: mean, range)	Dose (µg/kg) n	Mean PK Parameters Geometric Mean (geometric CV%) *Arithmetic Mean [arithmetic CV%]*					
			C_{max} (ng/mL)	AUC_{0-inf} (ng*h/mL)	CL (L/h)	Vd (L)	$T_{1/2}$ (h)	MRT (h)
Phase 1b GTC-FVIIa- 005-11 (USA, Netherlands) 5.3.3.5	N=15 males (33, 20-61)	25 n=10	230 (43) *247 (38)*	212 (41) *227 (39)*	9.0 (43) *9.6 (37)*	30 (50) *32 (36)*	2.3 (30) *2.4 (30)*	1.4 (17) *1.4 (16)*
		75 n=10	717 (32) *751 (33)*	617 (29) *639 (27)*	10 (24) *10 (22)*	30 (32) *32 (37)*	2.1 (23) *2.2 (23)*	1.4 (7.7) *1.4 (7.6)*
		225 n=10	1867 (37) *1973 (34)*	2240 (26) *2311 (28)*	7.9 (34) *8.2 (28)*	20 (40) *21 (32)*	1.8 (14) *1.8 (14)*	1.5 (8.1) *1.5 (8.1)*
Phase 3 RB-FVIIa-006-13 (PerSept 1) (USA, Russia, Bulgaria, Ukraine) 5.3.3.5	N=14 males (32, 13-54) (in the PK portion)	75 Process A n=7	426 (62) *485 (53)*	505 (65) *572 (46)*	7.9 (86) *11 (107)*	16 (103) *23 (119)*	1.4 (20) *1.4 (22)*	1.3 (18) *1.3 (19)*
		225 Process A n=7	1347 (29) *1392 (28)*	1991 (24) *2042 (25)*	8.3 (26) *8.5 (23)*	16 (30) *16 (26)*	1.3 (17) *1.3 (17)*	1.5 (16) *1.6 (15)*
		75 Process B n=6	478 (68) *566 (71)*	537 (53) *589 (44)*	7.0 (76) *8.0 (45)*	17 (81) *20 (47)*	1.7 (13) *1.7 (13)*	1.4 (15) *1.4 (15)*
		225 Process B n=5	2388 (25) *2441 (22)*	2794 (21) *2841 (20)*	5.7 (17) *5.8 (17)*	12 (22) *12 (22)*	1.4 (12) *1.4 (12)*	1.3 (9.5) *1.3 (9.5)*
Phase 3 LFB-FVIIa-007-14 (PerSept 2) (Czech Republic, Mexico, South Africa, Georgia, Ukraine, Turkey, USA) 5.3.3.5	N=23 males (5, 1-11) (PK evaluable population)	75* n=10	621 (54) *670 (28)*	363 (72) *422 (51)*	3.4 (19) *3.5 (18)*	NC	2.1 (35) # *2.2 (30) #*	NC
		225* n=13	2159 (2.3) *2160 (2.3)*	1234 (50) *1371 (50)*	3.5 (27) *3.6 (25)*		2.1 (43) # *2.3 (45) #*	

** PK sampling in the PerSept 2 study was sparse and NCA parameters were calculated based on post-hoc estimates from the population PK analysis.*
 # Elimination $T_{1/2}$
NC=not calculated

Table 7. Summary of Non-compartmental Pharmacokinetic Parameters of LR769 for Protocol LFB-FVIIA-009-19

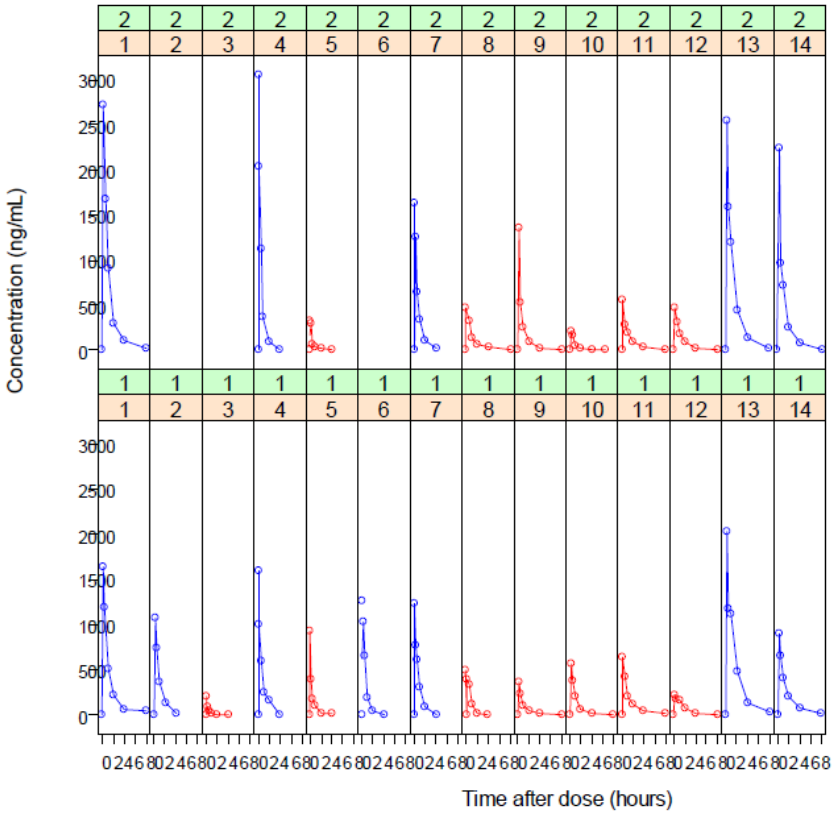
Parameter (Unit)	LR769 75 µg/kg (N = 14)	LR769 225 µg/kg (N = 14)
C_{max} (ng/mL)	938.3 (37.2)	3211.1 (22.6)
$AUC_{0\text{-}inf}$ (ng.h/mL)	1008.345 (47.3)	3571.275 (25.7)
$AUC_{0\text{-}last}$ (ng.h/mL)	997.028 (47.4)	3548.517 (25.5)
t_{max} (h)	0.120 (0.10, 0.12)	0.120 (0.08, 0.12)
$t_{1/2}$ (h)	2.341 (16.3)	2.027 (7.6)
CL (L/h)	5.126 (37.3)	4.489 (20.4)
V_d (L)	8.237 (37.0)	7.009 (21.9)
MRT (h)	1.607 (14.8)	1.560 (12.7)
AUMC (ng.h²/mL)	1634.146 (56.7)	5626.168 (34.5)
IR (ng/mL)/(µg/kg)	12.482 (36.9)	14.309 (22.7)

$AUC_{0\text{-}inf}$ = area under the plasma concentration-time curve from time 0 (dosing) to infinity; $AUC_{0\text{-}last}$ = area under the plasma concentration-time curve from time 0 (dosing) to the time of the last measurable concentration; AUMC = area under the first moment curve; C_{max} = maximum observed plasma concentration; CL = clearance; CV = coefficient of variation (%); IR = incremental recovery; MRT = mean residence time; N = number of subjects enrolled; $t_{1/2}$ = terminal elimination half-life; t_{max} = time to C_{max}; V_d = volume of distribution
Geometric mean (CV) statistics presented; for t_{max}, median (minimum-maximum) statistics presented.
Reference: Table 14.2.2

Equivalence of manufacturing process A to manufacturing process B

A manufacturing change of the drug product was introduced during clinical development and was first tested within PerSept1. For pharmacokinetic evaluation of both products, patients were first exposed to the drug from manufacturing process A and 3-6 months later, the same patients received the same drug concentration of manufacturing process B. Plasma samples were taken at the same time points after infusion for each of the two occasions. Within study Persept1 in total 11 patients were exposed to process B for PK sampling (n=14 for process A with n=7 for 75µg/kg and 225µg/kg; n=11 for process B with n=6 for 75µg/kg and n=5 for 225µg/kg).

Figure 1: Individual plasma concentration time course after iv bolus injection



Legend

red is group 75 µgµg/kg and blue is group 225 µg/kg LR769 (blue).

Green trellis numbers; occasion number (1=process A ,2= process B),

orange trellis numbers; subject numbers.

Table 8: Ratio between manufacturing processes of key PK parameters for 75µg/kg after NCA

ID	Cmax (ng/mL)			AUC last (ng*h/mL)			AUC inf (ng*h/mL)		
	A	B	B/A	A	B	**B/A**	A	B	**B/A**
	923	330	**0.36**	742.5	378.1	**0.5**	760.3	396.6	**0.5**
	488	468	**0.96**	795.4	582.9	**0.73**	802.8	603.8	**0.75**
	359	1354	**3.8**	377.9	991.2	**2.6**	382.0	1005.0	**2.6**
	574	215	**0.37**	594.3	232.9	**0.4**	601.4	238.6	**0.4**
	636	555	**0.8**	830.1	661	**0.8**	876.4	679.4	**0.77**
	216	475	**2.2**	407.5	599.6	**1.47**	416.8	611.2	**1.47**

Only patients that are reported for the exposure with process B are depicted.

Table 9: Ratio between manufacturing processes of key PK parameters for 225µg/kg after NCA

ID	Cmax (ng/mL)			AUC last (ng*h/mL)			AUC inf (ng*h/mL)		
	A	B	B/A	A	B	**B/A**	A	B	**B/A**
	1638	2724	**1.7**	1920	2960	**1.5**	2002	3021	**1.5**
	1599	3057	**1.9**	2147	3331	**1.5**	2159	3355	**1.5**
	1234	1629	**1.3**	1824	2308	**1.3**	1838	2340	**1.3**
	2039	2549	**1.25**	2989	3310	**1.1**	3037	3347	**1.1**
	895	2244	**2.5**	1373	2114	**1.5**	1414	2143	**1.5**

Only patients that are reported for the exposure with process B are depicted.

Children

Study LFB-FVIIa-007-14 (PerSept 2) included a total of 23 paediatric patients in the PK portion of this study, 10 patients at 75 µg/kg and 13 patients at 225 µg/kg. Data on PK parameters derived from post-hoc NCA are presented above.

Following the integrated popPK model the age category was found to be a significant covariate for volume of distribution (Vc in patients < 2 years, ≥ 2 to < 6 years, and ≥ 6 to <12 years was 82%, 20%, and 5% lower than Vc in patients ≥ 12 years) and clearance (CL). The body weight normalised CL determined by age category showed lower values in the paediatric population as compared to adults and adolescents with a general trend of decreased normalised CL with increased body weight among the paediatric groups. Compared with the adults and adolescents, body weight normalised CL of Cevenfacta Process B with the 225 µg/kg dose was higher by 137.5% in patients aged 2 to <6 years and by 62.5% in patients aged ≥6 to <12 years. For the 75 µg/kg dose, it was higher by 46.7% in patients aged 2 to <6 years and lower by 6.67% in patients ≥6 to <12 years; Table 10).

Table 10: Clearance of manufacturing process B, stratified by age

Dose	PK Parameter	Statistic	PerSept 2			PerSept 1
			≤ 2 years	2 to < 6 years	6 to < 12 years	> 12 years
75 µg/kg		N	2	2	6	6
	Body weight (kg)	Mean	10.10	14.75	25.72	51.83
	Clearance (L/h)	Mean (CV%)	3.03 (7.9)	3.32 (7.0)	3.70 (20.1)	8.03 (44.6)
	Weight-Normalized CL (L/h/kg)	Mean (CV%)	0.30 (7.9)	0.22 (7.0)	0.14 (20.1)	0.15 (44.6)
225 µg/kg		N	3	4	6	5
	Body weight (kg)	Mean	11.27	13.43	32.95	72.94
	Clearance (L/h)	Mean (CV%)	3.86 (3.2)	2.49 (11.1)	4.29 (12.7)	5.79 (17.1)
	Weight-Normalized CL (L/h/kg)	Mean (CV%)	0.34 (3.2)	0.19 (11.1)	0.13 (12.7)	0.08 (17.1)

Source: Supplemental Tables 15 and 16, Integrated Population PK and ER Report LR769 (09Mar2020), Module 5.3.3.5
CV% = coefficient of variation; N = number of subjects; SD = standard deviation;

Pharmacokinetic interaction studies

Pharmacodynamic interactions with other medicinal products or substances

No specific drug-drug interactions studies were conducted with Cevenfacta. However, various drug-drug interactions have been observed with medicinal products from the same therapeutic class; these

interactions were associated with an increased risk of thromboembolic events due to an interaction between activated prothrombin complex concentrates and eptacog alpha (NovoSeven). In the clinical studies with Cevenfacta, no thromboembolic events have been observed.

Relationship between plasma concentration and effect

PK/PD model: Report CHDR1201 / GTC-FVIIa-005-11

The applicant performed a pharmacometric analysis characterising the relationship between Factor VIIa (Process A) and the four PD variables Thrombin Generation Assay with platelets (AUC of peak, TGTp_AUC), activated partial thromboplastin time (aPTT), thromboelastography (ROTEM) and Prothrombin fragments 1+2 (F1+2) after administration of rhFVIIa. The PK-PD models best describing the data for TGTp and ROTEM were Hill equations (sigmoid maximal effect model), where the TGTp_AUC, or ROTEM_peak increases with increasing Factor VIIa concentration (FVIIa C). For aPPT and F1+2, a maximum effect model was most suitable, where the aPTT decreases or F1+2 increases with increasing Factor VIIa concentration. For F1+2 an effect compartment was required to account for a delay in effect.

All taken together the relationship for the above-mentioned PD markers were found to follow a saturable function of concentration: EC50 values were 87 to 1280 ng/ml. 80% of the maximum effect was achieved at concentrations between 1000-2000 ng/mL Cevenfacta. The relationship between PD markers and efficacy has not been documented.

Exposure-response analysis for efficacy

The E-R analysis for efficacy was based on data from phase 3 studies PERSEPT 1 and PERSEPT 2. Exposure parameters for activated eptacog beta were combined with the primary efficacy endpoint: Successful treatment of a bleeding episode at 12 h after first administration of the study drug. Two variables were created for the efficacy endpoint: proportion of successfully treated bleeding episodes at 12 h regardless of severity, and proportion of successfully treated mild/moderate bleeding episodes at 12 h. All bleeding events and their respective outcome were included in the analysis. Exposure parameters (AUC, C_{max}, and C_{min}) were simulated using the population PK model on the day of each event and from the time of the dose to 12 h post-dose. Upon request the E-R analysis was rerun using the updated PK models. Results remained generally similar, but it was not justified how the adequacy and predictive performance of the provided models could be considered as satisfactory.

Exposure-response analysis for safety

In the original exposure-safety response analysis, only treatment emergent adverse events (TEAEs) were analysed as their occurrence is relatively frequent in all studies (Table 11). Treatment- related TEAEs were not analysed as they were sparsely observed (e.g., no TRTEAEs were observed in PerSept 2).

Table 11. Overall Summary of Treatment Emergent Adverse Events by Study

Parameter	Phase 1b (N=15) n (%), E	PerSept 1 (N=27) n (%), E	PerSept 2 (N=25) n (%), E	PerSept 3 (N=12) n (%), E	Study 009 (N=28) n (%), E
TEAEs	11 (73.3), 39	12 (44.4), 25	17 (68.0), 68	10 (83.3), 36	6 (21.4), 7
Mild	11 (73.3), 38	4 (14.8), 12	11 (44.0), 23	8 (66.7), 16	5 (17.9), 6
Moderate	1 (6.7), 1	9 (33.3), 12	14 (56.0), 42	7 (58.3), 14	1 (3.6), 1
Severe	0, 0	1 (3.7), 1	3 (12.0), 3	3 (25.0), 6	0, 0
Treatment-related	2 (13.3), 3	2 (7.4), 7	0, 0	1 (8.3), 3	1 (3.6), 1
Serious TEAEs	0, 0	1 (3.7), 2	2 (8.0), 2	1 (8.3), 2	0, 0
Death	0, 0	0, 0	0, 0	1 (8.3), 1	0, 0

The update of the exposure-response (ER) analysis for TEAEs involved the inclusion of TEAEs reported in Study 009 with the pooled TEAE data from studies Phase 1b, PerSept 1 and PerSept 2. The original ER model for TEAEs fitted a logistic regression model relating the log-odds of a TEAE with Cevenfacta AUC0-24 at the day of the TEAE. Table 12 below shows the parameter estimates derived with the old pool of data and the updated data pool with the inclusion of Study 009. Results for the updated model did not change the relationship between the log-odds of a TEAE with Cevenfacta AUC. The significant intercept in the model suggested that the probability of experiencing TEAEs was higher than zero even in the absence of Cevenfacta.

Table 12. Parameters Estimates of the Exposure-Response Analysis ER1 based on data from PK Model with Fixed Allometric Scaling Exponents

Parameter	Statistics	Original Model	Updated Model
Intercept (logit)	Estimate (SE)	2.47 (0.906)	3.16 (0.856)
	p-value	0.00643	<0.001
$AUC_{0\text{-}24}$ of LR769 (h.ng/mL)	Estimate (SE)	-0.410 (0.164)	-0.576 (0.141)
	OR (95% CI)	0.664 (0.481, 0.916)	0.562 (0.427, 0.741)
	p-value	0.01256	<0.001

$AUC_{0\text{-}24}$ = area under the concentration-time curve from time 0 to 24 hours; CI = confidence interval; OR = odds ratio; SE = standard error.

When looking at TEAEs by age group presented in Table 13, one can observe that frequency of TEAEs was comparable between age groups with a slight trend toward more patients reporting TEAEs in the age group 6 to less than 12 years mainly due to more infections and infestations in this age group. In addition, compared to adults, lower incidence of TEAEs per infusion were observed in all paediatric age groups.

Table 13. Observed Treatment Emergent Adverse Events by Age group

Parameter	< 2 yrs (N=5)	2 to < 6 yrs (N=8)	6 to < 12 yrs (N=15)	12 to < 18 yrs (N=6)	≥ 18 yrs (N= 69)	Overall (N=103)
Patients with TEAEs	3 (60.0)	5 (62.50)	12 (80.0)	4 (66.7)	32 (46.4)	56 (53.7)
Number of TEAEs	10	27	42	14	86	179
Number of Infusions	214	616	1091	257	1268	3446
Incidence	0.047	0.044	0.038	0.054	0.068	0.052

Special populations

No pharmacokinetic data in both renally-impaired and hepatically-impaired patients are available.

There are no available data on use of Cevenfacta in elderly patients:

	Age 65-74 (Older subjects number /total number)	**Age 75-84 (Older subjects number /total number)**	**Age 85+ (Older subjects number /total number)**
PK Trials	0	0	0

2.5.3. Pharmacodynamics

Mechanism of action

The active ingredient in Cevenfacta is a recombinant analogue of human FVIIa, a vitamin K-dependent coagulation factor with a molecular mass of 50,000 Daltons. The applicant depicts three distinct pathways in which FVIIa leads to blood coagulation in haemophilia patients. In haemophilia A or B patients, FVIIa activates coagulation through the natural "TF-dependent" mechanism but the therapeutic doses required to reach haemostasis by using FVIIa are much more elevated than the normal FVIIa circulating concentration. The applicant explains that in the presence of supra-physiological doses of FVIIa, two additional coagulation pathways are induced. A second coagulation pathway "TF-independent" leads, similarly to the "TF-dependent" mode of action, to the generation of FXa at the surface of activated platelets, without the need of TF to anchor FVIIa at the cell surface and modify its structure. In addition, the use of high-FVIIa doses alleviates the natural and constant inhibition of FVIIa by the FVII zymogen. In a third pathway, FVIIa competes with activated protein C (aPC) by binding to the endothelial protein C receptor (EPCR). Thus, it is thought that FVIIa down modulates the anticoagulation by limiting the cleavage of Factor Va (the FXa co-factor) by the aPC. The applicant explains that the combination of these three pathways allows FVIIa to bypass the need of FVIIIa or FIXa restoring haemostasis even in the presence of inhibitors.

Primary and Secondary pharmacology

The pharmacodynamics parameters of Cevenfacta were mainly assessed in the Phase 1b trial GTC-FVIIa-005-11. Study GTC-FVIIa-005-11 was a dose escalation study to assess the safety, pharmacokinetics (PK) and pharmacodynamics (PD) of Cevenfacta across three dose levels (25, 75, and 225 µg/kg) in a total of 15 adult male patients (mean age 33 years, range 20-61 years) with congenital haemophilia A or B with or without inhibitors.

A set of well-established PD assays have been used in order to characterise the pharmacodynamics properties of Cevenfacta. The PD assays/parameters included Thrombin Generation Test, Prothrombin time (PT), Thrombin Generation Test with added platelets (TGTp), Rotational thromboelastometry (ROTEM-FIBTEM), Prothrombin fragments 1+2 (F1+2), D-dimers and Thrombin antithrombin complex (TAT).

In addition, in the Phase 1b trial, the relationship between plasma Cevenfacta concentration and key PD parameters including AUC of the peak of the thrombin generation assay with platelets (TGTp_AUC), aPTT, maximum clot firmness (MCF) and prothrombin fragments 1+2 was explored. The relationship between PD markers and predicted plasma concentration were estimated through PK/PD modelling using the population PK model initially built. This model was subsequently used to simulate the Cevenfacta PD effects for several dosing scenarios.

Furthermore, an *in vitro* study (Study 14ENC006) was conducted using plasma from haemophilia A and B patients with or without inhibitors (LFB Biotechnologies, Les Ulis, France). The study investigated the

in vitro effects of Cevenfacta Process A, Cevenfacta Process B and NovoSeven on the thrombin generation time (TGT), the prothrombin time (PT) and the activated thromboplastin time (aPTT).

Primary Pharmacology

The thrombin generation test with the added platelets showed that increasing levels of Cevenfacta lead to increasing formation of thrombin. In the prothrombin time assay, the prothrombin times were shortened to a similar extent with all three dose levels. Similar results were observed if this test was performed with diluted tissue factor. In the activated partial thromboplastin time assay, there was a dose dependent reduction in aPTT, with the 225µg/kg dose shortening the aPTT to approximately 35 seconds 5 min post infusion. In the rotational thromboelastometry, it was shown that there was a dose dependent effect on the clot firmness. Further, a dose dependent effect could also be observed in the formation of prothrombin fragments 1+2. There were no differences observed in the D-dimer formation.

Secondary Pharmacology

No dedicated studies/analyses were performed on the effects of Cevenfacta not related to its desired therapeutic target.

2.5.4. Discussion on clinical pharmacology

Pharmacokinetics

The applicant has submitted four studies that included the assessment of pharmacokinetics. A Phase1b study (Study GTC-FVIIa-005-11) was conducted with the product manufactured with a prior manufacturing process A in 15 male patients (age range: 20-61 years) applying three doses (25µg/kg, 75µg/kg and 225µg/kg), all patients were without inhibitors. A new manufacturing process was introduced (process B) during the first phase 3 study with PK component (Study RB-FVIIa-006-13, PerSept1). The PerSept1 study was conducted in 14 adolescent and adult, male patients (age range: 13-54 years), all with inhibitors. The assessment of PK parameters was first performed for the product manufactured with the old process A and repeated after 3-6 months for the new manufacturing process B in the same patients with the same dose as for the previous product A (repeated exposure for n=6 for 75µg/kg and n=5 for 225µg/kg). A third study (Study LFB-FVIIa-007-14, PerSept2) with PK component was conducted in male paediatric patients (age range 1-11 years) with inhibitors utilizing process B in two dose ranges (75µg/kg and 225µg/kg). A sparse sampling schedule was followed for this study in order to reduce the burden on paediatric patients. A further Phase 1 study on 28 adult subjects (18 to 75 years) with haemophilia A, with or without inhibitors to FVIII, was submitted during the assessment process (n=14 per dose of 75µg/kg and 225µg/kg). This study was primarily designed to evaluate the PK profile utilising manufacturing process B. Throughout the assessment of PK data in all studies all patients were in a non-bleeding state. In general, variability within and across studies was high. Substantial intra-subject variability was observed for the two occasions utilising process A and process B in study PerSept1 and substantial variability was observed for paediatric patients in study PerSept2, compared to adults in PerSept1. The source of variation is unclear, but low patient numbers might contribute.

Data were analysed using non-compartmental analysis (NCA) and population PK modelling. The population PK analysis was initially performed with the data from the Phase 1b study and subsequently re-analysed when more data became available from the subsequent studies. Upon request the model was again updated including fixed allometric scaling and a maturation function. Additional PK data from study LFB-FVIIA-009-19 became available and were also integrated in the analysis. For each study, the NCA analysis was performed independently from the popPK analysis, except for study PerSept2. Since

only sparse sampling was performed in this study, the NCA analysis was performed post-hoc and calculated based on the population PK model. The initial population-PK model (Certara-LFBP-PMX-Cevenfacta-1617) pooled all available single dose PK data from 52 male patients (Phase 1B n = 15, PERSEPT 1 n = 14, and PERSEPT-2 [paediatric population] n = 23). The updated model included additional data from 28 male patients (study LFB-FVIIA-009-19). The methods applied for pharmacokinetic data analysis appear appropriate and principally acceptable. However, several uncertainties arose with respect to the applied popPK model (including the subsequent exposure-response evaluation on efficacy and safety) limiting the applicability of the respective models. While most limitations of the models are related to the small sample size (overparameterpaediatric, wide CIs preventing significant results), other aspects like strong confounding between age and manufacturing process have been identified. The requested modifications together with the new data improved the initial model only slightly. Therefore, the presented models are currently not regarded as robust and conclusions based on the respective models have to be interpreted with care. Further, due to the confounding of manufacturing process and the paediatric population, it can currently not be determined whether the differences observed for the paediatric population are in relation to the manufacturing process or biological differences compared to the adult population. It is further recognised that the post-hoc NCA, as applied in study PerSept2 due to sparse data sampling, depends highly on the reliability and robustness of the prior applied model. Given the very limited number of patients and the large age range of the target population (from birth to 75 years of age (or older)), a reliable PK model is of high importance to gain as precise information as possible.

Given the identified limitations of the models and especially the very limited data in very young children (no data are available for neonates), currently the model is not expected to yield reliable information. Upon request PK simulations for the different dosing scenarios proposed in the SmPC were presented using the updated model for the different age groups: birth to < 2 years, 2 to < 6 years, 6 to < 12 years, 12 to < 18 years, and from 18 years onwards. Results indicate that infants below 2 years of age are expected to have Cmax values much higher than those achieved in older children or adults. Therefore, the adequacy of these doses for infants is doubted from the PK perspective. As a consequence of uncertain exposure and dosing recommendations, it was concluded that the paediatric indication (<12 years) will not be further pursued.

The bioavailability of Cevenfacta is considered to be 100% due to administration via intravenous bolus injection and due to its proposed similarity to the human endogenous FVIIa no further metabolic route besides proteolytic degradation is to be expected.

Within study PerSept1 striking differences were seen for mean PK parameters after receiving the higher dose and evaluation by NCA (Cmax: 1392 ng/mL for A vs. 2441 ng/mL for B, AUC0-inf: 2042 ng*h/mL for A vs. 2842 ng*h/mL for B, CL: 8.5 L/h for A vs. 5.8L/h for B, Vd: 16 L for A and 12 L for B; all considering the arithmetic mean). The impression of different PK profiles between both manufacturing processes is supported by the observed intra-subject variability in descriptive individual plasma concentrations as well as the results of the NCA on individual data. In study PerSept1 all patients treated with 225µg/kg had higher plasma concentrations at the first blood draw (10 minutes after study drug administration) when treated with manufacturing process B compared to values from process A, resulting in higher NCA values on individual level and higher point estimates on NCA PK parameters on population level. Individual plasma concentrations and individual PK parameters after NCA for patients treated with 75µg/kg also suggest a high intra-subject variability between process A and B. Whereas patients treated with the higher dose consistently had a higher exposure (Cmax and AUC) for process B compared to process A, some patients treated with the lower dose also had substantially reduced exposure from process B. It appears that this intra-individual variability resulted in comparable point estimates from NCA for the population treated with 75µg/kg in study PerSept1. Importantly, study LFB-FVIIA-009-19 provides further evidence on the to-be-marketed product from

process B on significantly more subjects compared to PerSept1 (n=28 in study LFB-FVIIA-009-19 vs. n=11 in study PerSept1). Data on Cmax and AUC for manufacturing process B confirm the previously described increased exposure for process B in comparison to process A, as assessed in study PerSept1. However, results for process B in study PerSept1 were also lower compared to the results in study LFB-FVIIA-009-19 with the same manufacturing process. In fact, results following NCA from study LFB-FVIIA-009-19 deviate substantially from PerSept1 after exposure to manufacturing process B with respect to key PK parameters (i.e. Cmax, AUC0-in, AUC0-last, volume of distribution and half-life t½). Clearance appears to be more comparable across both studies. It is recognised that variability is enormous throughout measures in both studies, as to be expected for the rather low number of tested subjects. Validity of PK assays used for studies PerSept1 and PerSept2 are questioned and as a consequence provided information in the SmPC regarding PK on adult subjects are restricted to data generated from NCA in study LFB-FVIIA-009-19. Neither of the updated models can conclude PK comparability of the two manufacturing processes A and B. It is noted that all PK measures were assessed in a non-bleeding state and a higher overall exposure of process B might have a positive effect on efficacy during bleeding state (but potentially also a detrimental effect on safety). It is further noted that comparability of process A and B appears to be more conclusive based on the newly provided Quality data. However, considering all provided evidence, data from study LFB-FVIIA-009-19 appear to be the most reliable information on PK. In conclusion, the PK profile for the to-be-marketed manufacturing process B appears to be sufficiently characterised with additional data from study LFB-FVIIA-009-19. Results from manufacturing process A are still considered to be supportive information regarding PK, despite the uncertain comparability between both manufacturing processes on PK level.

Reasons for the observed deviation in geometric mean values across studies PerSept1 and LFB-FVIIA-009-19 are currently not entirely clear. Upon request, the applicant elaborated on weight (underweight/normal/overweight/obese) and race (black/non-black) subgroups as potential factors for the observed substantial discrepancy for the PK parameters Cmax, AUC0-in, AUC0-last, volume of distribution and half-life t½ across studies after exposure to the same manufacturing process. Within study LFB-FVIIA-009-19 higher body weight is related to higher exposure for either of the available doses (75µg/kg and 225µg/kg). Similarly, black subjects appear to show higher drug exposure upon administration of the lower dose (75µg/kg), but not (or rather a bit lower exposure) after the higher dose (225µg/kg). However, small sample size in the subgroups limits robust conclusions within and across studies. It is further recognised that subject 12-<18 years were included only in study PerSept1 (2 subjects, both dosed with 75µg/kg). Presented data in the SmPC are to be restricted to NCA results from study LFB-FVIIA-009-19, but NCA data from study PerSept1 could still be considered as supportive information.

Within study PerSept1 dose-proportionality could not be demonstrated for the manufacturing process B (i.e. a 3- fold increase in dose resulted in a 5-fold increase in exposure), but was more evident for process A following NCA results. However, dose-proportionality appears conclusive within study LFB-FVIIA-009-19, which included more than double the number of participants tested form process B (ratio between 75µg/kg and 225µg/kg as summarised for NCA of PK parameters in study LFB-FVIIA-009-19: 3.4 for Cmax, 3.5 for AUC0-inf and 3.5 for AUC0-last). In summary, the totality of data on dose-proportionality leave some uncertainty with respect to manufacturing process B, which might be caused by high data variability, low patient numbers, sparse sampling and age-related differences. Approximate dose proportionality could be assumed for Cevenfacta with respect to the newly generated data in study LFB-FVIIA-009-19 (a minor over-proportional increase in exposure should be considered for the higher dose). Regarding dose proportionality in steady-state no reliable information are available, due to questioned performance of submitted models.

Pharmacodynamics

The pharmacodynamics activities of Cevenfacta were mainly evaluated in the Phase 1b trial GTC-FVIIa-005-11. The PD parameters were analysed across three different dose levels. The used PD parameters are well-established markers to describe the procoagulant activity of coagulation products. In light of the observed differences in PK parameters between Process A and B product in the PerSept 1 study and the fact that only Process A product was used in the Phase 1b study GTC-FVIIa-005-11, the applicant was asked to justify the relevance of the generated PD results for the to be commercialised product derived from Process B. The applicant justified the lack of PD data with Process B product on PK and efficacy data generated with this product. In summary, it is not considered optimal that PD data were only generated with Process A product and not with the to be commercialised Process B product. However, a further request regarding PD data would not be regarded as fruitful as direct PD bridging is impossible.

In addition to the *in vivo* analyses of PD effects in the Phase 1b study, an *in vitro* study (Study 14ENC006) was conducted using plasma from haemophilia A and B patients with or without inhibitors (LFB Biotechnologies, Les Ulis, France). The study investigated the *in vitro* effects of Cevenfacta Process A, Cevenfacta Process B and NovoSeven on the thrombin generation time (TGT), the prothrombin time (PT) and the activated thromboplastin time (aPTT).

In addition to the well-described mechanism in which FVIIa initiates the coagulation via the interaction with tissue factor at the cell surface, thereby activating Factor X to Factor Xa and initiating the common pathway of coagulation, the applicant describes two additional coagulation pathways that might be induced by supra-physiological doses of factor VIIa. One is the "TF-independent" pathway, which is similar to the "TF dependent" pathway without the need of TF to anchor FVIIa to the cell surface. In the other one, FVIIa competes with activated protein C by binding to the endothelial protein C receptor. Protein C, in a complex with Protein S, normally neutralises Factor Va, thereby impeding coagulation. Thus, supra-physiological doses of factor VIIa might down modulate anticoagulation by limiting the cleavage of factor Va by the aPC. After request, the mechanism of action was substantiated by the applicant by literature references.

For the analysis of the primary pharmacology, the applicant used a set of well-established assays to describe the PD activities of Cevenfacta. The thrombin generation test with the added platelets showed that increasing levels of Cevenfacta lead to increasing formation of thrombin. In the prothrombin time assay, the prothrombin times were shortened to a similar extent with all three dose levels. Similar results were observed if this test was performed with diluted tissue factor. In the activated partial thromboplastin time assay, there was a dose dependent reduction in aPTT, with the 225µg/kg dose shortening the aPTT to approximately 35 seconds 5 min post infusion. However, the results of this assay have to be interpreted carefully, as there is a very high inter-individual variability. In the rotational thromboelastometry, it was shown that there was a dose dependent effect on the clot firmness. However, there was also a high inter-individual variability in this assay. Further, a dose dependent effect could also be observed in the formation of prothrombin fragments 1+2, but again with a high inter-individual variability. There were no differences observed in the D-dimer formation. In conclusion, although some of the PD marker results have to be interpreted carefully due to high inter-individual variability, there seems to be a dose dependent effect of Cevenfacta on some of the PD markers. In the protocol of the Phase 1b study GTC-FVIIa-005-11, it was stated that the thrombin generation test will be performed with low and high tissue factor concentrations in order to try to mimic the in vivo physiological state. However, only the results with the addition of 0.5 pM tissue factor were presented in the CSR. It was further stated that the thrombin generation test (performed with platelet-poor plasma and initiated by addition of 0.5pM tissue factor) cannot be considered valid as there was an unfavourable signal noise ratio that hinders a proper interpretation of the results. According to the applicant, this might be due to the collection of blood with an indwelling catheter that could have led to thrombin generation or the activation of precursors. The applicant explains that the

results of the thrombin generation test with added platelets is more representative for the mode of action of rhFVIIa. The applicant was asked to comment on the absence of the thrombin generation test in the presence of high tissue factor concentration, as it might have also been more representative to the mechanism of action of Cevenfacta than the experiment with the low tissue factor. The applicant explained the absence of the thrombin generation test in the presence of high tissue factor concentration with the higher sensitivity of this assay when performed with low concentration of tissue factor. Although it is not considered optimal that pre-defined experiments in the protocol were not performed, it is not considered of crucial importance to have these experiments.

No dedicated studies/analyses were performed on the effects of Cevenfacta not related to its desired therapeutic target. As there does not seem to be an additional pharmacological effect of Cevenfacta apart from coagulation, this is regarded acceptable.

The applicant did not perform specific drug-drug interaction studies. However, for medicinal products from the same therapeutic class, various drug-drug interactions have been observed, leading to an increased risk of thromboembolic events. Although no thromboembolic events have been observed in the clinical studies conducted with Cevenfacta, the risk of thrombotic events when used simultaneously with activated or non-activated prothrombin complex concentrate or other haemostatic agents has been reflected in section 4.4 of the SmPC. Regarding the other haemostatic agents mentioned in section 4.4 of the SmPC, there is a reference made to section 4.5 of the SmPC. However, apart from activated prothrombin complex concentrates, there were no further haemostatic agents listed in section 4.5. The applicant was asked to adapt this section to reflect other haemostatic agents with which a PD interaction seems likely, e.g. factor XIII. The applicant adapted section 4.5 of the SmPC according to the recommendations. Furthermore, drug-drug interactions will be monitored in post-marketing studies (please see RMP section).

The genetic differences in PD response were not assessed in the clinical studies.

PKPD models (Report CHDR1201 / GTC-FVIIa-005-11) for Thrombin Generation Assay with platelets (AUC of peak, TGTp_AUC), Activated partial thromboplastin time (aPTT), Thromboelastography (ROTEM), and Prothrombin fragments 1+2 (F1+2) were developed using the final population PK model for 15 adult male patients treated in the Phase 1b study. However, the targeted values for these PD parameters TGTp_AUC, aPTT, thromboelastography and prothrombin fragments 1+2 and their respective targeted exposure was not clear and was asked to be specified. Furthermore, the applicant was asked to provide a discussion whether these investigated PD effects are intended to be used as reliable PD marker and thus to predict optimal dosing strategies with PKPD modelling. The applicant did not reply to the question regarding the targeted values of the PD markers which were assessed in the PKPD modelling and simulation report CHDR1201 / GTC-FVIIa-005-11. It was stated that the relationship between PD markers and efficacy has not been documented. Thus it is assumed that TGTp_AUC, aPTT, thromboelastography, and prothrombin fragments 1+2 are no reliable PD markers.

For the three markers AUC of the peak of TGT with platelets, aPTT and MCF (ROTEM-FIBTEM), there seems to be a saturated relationship between plasma concentrations and coagulation marker. The applicant provided a further plot describing the PK/PD relationship for the prothrombin fragments 1+2 (submitted in Appendix 3 of the CHDR1201 PK/PD report). The PK/PD response for this marker seems to be different from the three PD markers mentioned above. There does not seem to be a saturated relationship and the maximum effect on this PD marker is not reached even with the highest dose of 225 µg/kg. The applicant was asked to provide an explanation for the PK/PD relationship of the PD marker prothrombin fragments 1+2, being divergent from the PK/PD relationship of the other PD markers provided. The applicant has substantiated this divergence by the fact that the three techniques measuring the *in vitro* potency of eptacog beta are saturable due to the limited amount of components and time used in the *in vitro* assays. In contrast, prothrombin fragments 1+2 was

measured *in vivo*. Only a minor part of the coagulation system is engaged *in vivo* and therefore, saturation cannot be achieved. The explanation provided by the applicant can be followed. However, as it is also stated in section 5.1 of the SmPC, the PD markers do not correlate with or predict the haemostatic effectiveness of this medicinal product.

In addition to the PK/PD model the applicant performed exposure-response analyses to evaluate the relationship between exposure and efficacy and safety parameters. Data from phase 3 studies PERSEPT 1 and PERSEPT 2 were used for efficacy analysis, while data from all studies were used to investigate the relationship between exposure and safety. Two efficacy parameters were used for the analysis: The proportion of successfully treated bleeding episodes at 12 h regardless of severity and of mild/moderate bleeding episodes at 12 h. For the safety analysis TEAEs were used. Overall, the validity of the conclusions drawn from these E-R analyses are doubted as the exposure parameters (AUC and C_{max}) were derived with the updated population-PK model which is not considered reliable. Furthermore, these models are not considered reliable on their own regardless of the exposure parameter as several deficiencies were identified, including e.g. for the efficacy models, poor estimation of key parameters, high IIV, deviation of the prediction vs. the observation resulting in over-prediction. The applicant provided the requested E-R analysis by age groups. Overall, the probability of response does not seem to be clearly associated with increasing exposure (i.e. Cmax). While for adults a slight relationship between increasing exposure and probability of response might be interpreted, for infants below 2 years of age increasing Cmax was not necessarily associated with increasing probability of response. However, these results are not considered reliable based on the issues concerning the validity of the used data and the reliability of the population-PK model discussed above.

2.5.5. Conclusions on clinical pharmacology

Overall, pharmacokinetics of Process B were characterised reliably in the last study (LFB-FVIIA-009-19). Pharmacokinetics and exposure-response analyses based on data collected in earlier studies are not considered reliable since the respective PK data cannot be regarded as valid.

Although it is not considered optimal that PD data were only generated with Process A product and not with the to be commercialised Process B product, the statements made in section 5.1 of the SmPC regarding PD are acceptable. Section 5.1 of the SmPC also state that the laboratory assessments of coagulation do not necessarily correlate with or predict the haemostatic effectiveness of this medicinal product.

2.5.6. Clinical efficacy

Efficacy data are available from 3 interventional clinical studies with Cevenfacta (PerSept 1 and PerSept 2: treatment of bleeding episodes; PerSept 3: prevention of bleeding in surgical or invasive procedures). See the tabular overview at the beginning of section 2.5.1.

OPC (Objective Performance Criterion)

Since controlled studies were not feasible, the proportion of success for the pivotal studies PerSept 1 and PerSept 2 was compared to a pre specified objective performance criterion (OPC) = 0.55. This OPC was determined by reviewing the literature on the reported success of treatment with bypassing agents mainly in adult patients (Table 9).

However, due to the use of a different endpoint in the PerSept 1 and PerSept 2 studies compared with several other different endpoints described in published literature, including studies used to support the initial registration of NovoSeven, an estimate of what the OPC should be was difficult.

Several publications provided a wide range of bleeding success (25% to 93%) at different timepoints depending on the type of efficacy assessment used. An OPC of 55% was chosen, taking into account the stringent criteria for success (including elements to more objectively judge treatment success) in the PerSept 1 and PerSept 2 studies and the reported success rate for a study used to support registration of NovoSeven in the US and Europe. This OPC defined mainly in adult patients was also retained for the paediatric PerSept 2 study.

In the scientific advice procedure concluded in May 2014, the following comments were given with regard to the OPC: "CHMP supports the definition of, and the testing against an 'objective performance criterion' (OPC) when evaluating treatment success of the two considered regimens, although it is not considered a requirement for a successful MA. It is felt that - in the context of the current treatment options in this rare condition - testing against the defined OPC (0.55) should not be interpreted as a rigid trial's 'success criterion'. Neither will statistical significant superiority over the OPC lead to a registration of a regimen based on an automatism only, nor should a minor miss of the defined efficacy criterion obviate a filing. At MAA, the totality of the data available will be evaluated regarding the benefit risk ratio of each investigated dosing regimen. In this context, it will be important to obtain estimates of treatment success rates under the two considered regimens as precise as possible. Accounting for multiplicity is generally endorsed. Reported/quoted studies of a similar design provide efficacy percentages in the 70-90% range, and not often lower than 60%. When defining the OPC, it seems to be important to account for the information in how far the data from the literature refer to mild/moderate bleeding episodes. However, it is acknowledged that a three point rating scale is used in several trials, which could skew results into the more effective range."

These comments are taken into account when interpreting the provided study outcomes for both pivotal trials PerSept 1 and PerSept 2.

In addition, it is acknowledged that the identified published data describe mainly treated bleeding events in adults, and no study focussing on a paediatric population is available in order to provide at least a suitable historical control for the younger subjects.

2.5.6.1. Main studies

Study RB-FVIIa-006-13 (PerSept 1): A Phase III Study on the Safety, Pharmacokinetics, and Efficacy of Coagulation Factor VIIa (Recombinant) in Congenital Hemophilia A or B Patients with Inhibitors to Factor VIII or IX

Methods

This was a global, multicentre, Phase 3, prospective, open-label, randomised, crossover study.

- **Study Participants**

Inclusion criteria

The main inclusion criteria were: male patients with congenital haemophilia A or B with inhibitors (Bethesda Unit [BU] ≥5) or <5 BU with a known high anamnestic response or <5 BU and refractory to increased dosing of either FVIII or FIX; were ≥12 years of age (up to and including 75 years of age); and who had at least 3 bleeding episodes of any severity in the past 6 months.

Exclusion criteria

The main exclusion criteria were: any other coagulation disorder other than haemophilia A or B, being immunosuppressed (no systemic immunosuppressive medication allowed, CD4 counts should be >200/µl), platelet count <100,000 ml, known allergy or hypersensitivity to rabbits, clinically relevant hepatic and/or renal impairment, history of thrombotic events.

Patients on ITI therapy were allowed to be treated in the study as well, as long as they fulfilled the criteria for inhibitors as described above and had regular bleeding episodes.

- **Treatments**

Patients were randomised to start treatment with one of the two following study drug regimens:

• 75 µg/kg Cevenfacta treatment regimen

• 225 µg/kg Cevenfacta treatment regimen

The patients crossed over to the alternate treatment regimen every 12 weeks until the end of the study.

During Phase A, depending on their randomisation, all patients received a single IV administration of either 75 µg/kg or 225 µg/kg of Cevenfacta as a bolus injection within 2 minutes for an initial assessment of safety. During treatment Phase B (24 hours after study drug administration in Phase A), patients started with the treatment regimen assigned at randomisation consisting of 3-month periods (12 weeks).

Table 14: Dose and dosing schedule for bleeding episodes

Dose and Dosing Schedule for bleeding episodes			
	Initial Dose	**Second dose, if necessary**	**Subsequent doses**
Mild/Moderate bleeding	75 µg/kg	75 µg/kg 3 hours later	75 µg/kg every 3 hours, as necessary, for up to 21 hours
	or		
	225 µg/kg	75 µg/kg 9 hours later	75 µg/kg every 3 hours, as necessary, for up to 21 hours
Severe bleeding	75 µg/kg	75 µg/kg 2 hours later	75 µg/kg every 2 hours, as necessary, until improvement
	or		
	225 µg/kg	75 µg/kg 6 hours later	75 µg/kg every 2 hours, as necessary, until improvement

The use of other sources of FVII(a), such as aPCC (FEIBA) or NovoSeven were to be only used for rescue therapy in the event of an insufficient response to study drug.

Other agents in the treatment of a bleeding episode, such as antifibrinolytics (e.g., aminocaproic acid or tranexamic acid) were allowed.

The use of other sources of FVII(a), such as aPCC (FEIBA) or NovoSeven was only allowed when at least 24 hours had passed between the last administration of the bypassing agent and Cevenfacta administration in both Phase A and Phase B. In case the use of these products was for treatment of a bleeding episode, that specific bleeding episode was not allowed to be treated with Cevenfacta.

- **Objectives**

The general objectives of this study were to assess the safety and efficacy of two dose regimens of Cevenfacta across the full type of severity of bleeding episodes (mild, moderate, and severe), and to assess the PK of drug product produced by two different manufacturing processes (i.e., Process A and Process B).

- **Outcomes/endpoints**

For the EMA, the primary efficacy endpoint was defined as the proportion of bleeding episodes of all severity (mild, moderate, and severe) with a patient/caregiver-reported (for mild/moderate bleeding episodes) and physician-reported (for severe bleeding episodes) response of **"good" or "excellent"** at 12 hours after the initial Cevenfacta administration.

Response to treatment was rated as "none", "moderate", "good", or "excellent" (Table 15).

Table 15. Categories of response to treatment

Response	Description
None	No noticeable effect of the treatment on the bleed or worsening of patient's condition. Continuation of treatment with the study drug was needed.
Moderate	Some effect of the treatment on the bleed was noticed, e.g., pain decreased or bleeding signs improved, but bleed continued and required continued treatment with the study drug.
Good	Symptoms of bleed (e.g., swelling, tenderness, and decreased range of motion in the case of musculoskeletal haemorrhage) had largely been reduced by the treatment, but had not completely disappeared. **Symptoms had improved enough to not require more infusions of the study drug**.
Excellent	Full relief of pain and cessation of objective signs of bleed (e.g., swelling, tenderness, and decreased range of motion in the case of musculoskeletal haemorrhage). No additional infusion of study drug was required.

Source: (Amby, 2009), CSR

A response of none or moderate was usually followed by continued treatment with study drug; "good" or "excellent" meant that no further treatment was needed **or, in case of a severe bleeding episode, the dosing interval could be increased**.

Selected secondary efficacy endpoints and additional analyses:

• Time to assessment of a "good" or "excellent" response of the bleeding episodes (mild/moderate and severe, separately and combined) by the patient (and/or physician when available)

• Descriptive analysis of the number of administrations and mean total amount of Cevenfacta administered per bleeding episode

• Proportion of recurrences (defined as a bleeding in the same joint/anatomical location within 24 hours after an initial successful response)

• Failures at 24 hours

• Proportion of bleeding episodes requiring alternative treatment

• Analyses by Cevenfacta Manufacturing Process

- **Sample size**

The minimum sample size with 80% power was 22 patients with 352 mild/moderate bleedings. Assumptions included a true proportion of success of 0.70, a correlation among bleedings for a given patient of 0.1, and 8 mild/moderate bleedings per treatment regimen per patient. Each study was powered to detect a 15% point difference (from the OPC of 55% to the expected success rate of 70% for LR769) at 80% power with an alpha of 0.0125 (1-sided) for each treatment regimens. Success proportions were compared between the two treatment regimens using a 2-sided, normal approximation test. However, the comparison was not controlled for multiplicity and results were based on a nominal Type I error rate (alpha) of 0.05. Sensitivity analyses evaluating the effect of missing data (imputed as success or failure), the supportive analyses utilising the GEE and the GLMM models were performed on the primary efficacy endpoint.

- **Randomisation and Blinding (masking)**

Patients were randomised to one of the two treatment regimens (1:1 ratio) by entering the patient details in a web-based randomisation system associated with the electronic Case Report Form (eCRF). Patients remained on the initial dose regimen per randomisation for approximately 3 months before being switched to the other dose regimen.

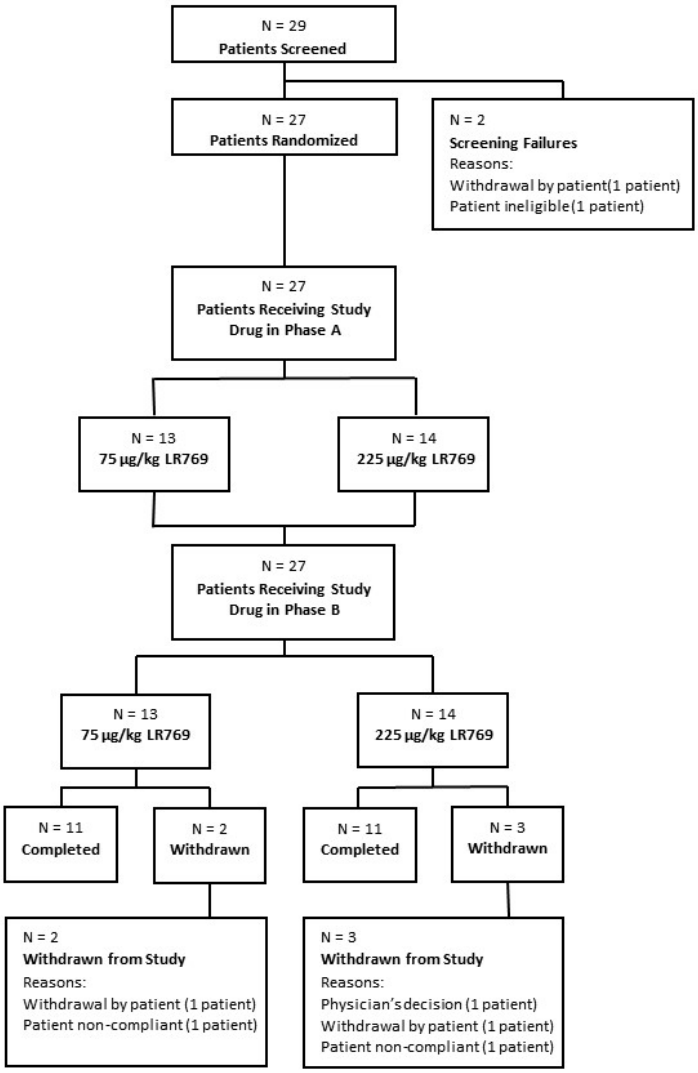
This is an open-label study.

- **Statistical methods**

The protocol-specified success was defined as statistically significant higher success compared to the Objective Performance Criterion (OPC). The study was not powered for statistical comparison between the two dose regimens. The null hypothesis (H0) for the primary efficacy endpoint was $p \leqslant 0.55$ where p is the true proportion of successfully treated mild or moderate bleeding events at 12 hours.

Results

- **Participant flow**



- **Recruitment**

For this study, patients were screened at 13 study sites: Belarus (1 site; 1 patient), Bulgaria (1 site; 2 patients), Georgia (1 site; 2 patients), Israel (1 site; 1 patient), Poland (1 site; 1 patient), Russia (2 sites; 5 patients), United Kingdom (1 site; 1 patient), Ukraine (2 sites; 12 patients), and US (3 sites; 4 patients). The patients at sites in Belarus and Israel were screen failures. Eleven sites randomised 27 patients.

- **Conduct of the study**

There were five amendments to the protocol for this study.

- **Baseline data**

Table 16: Summary of demographic and baseline characteristics (PerSept1)

Parameter	Statistic	Treatment Regimen at Randomization		Overall (N=27)
		75 µg/kg (N=13)	225 µg/kg (N=14)	
Age (years)	Mean (SD)	31.8 (12.10)	30.1 (12.98)	31.0 (12.35)
	Median	31.0	30.5	31.0
	Q1/Q3	24.0/39.0	19.0/38.0	19.0/39.0
	Minimum/Maximum	13/51	12/54	12/54
Age categorized [n (%)]	≥12 to <18 years	2 (15.4%)	3 (21.4%)	5 (18.5%)
	≥18 years	11 (84.6%)	11 (78.6%)	22 (81.5%)
Race [n (%)]	Asian	1 (7.7%)	0 (0.0%)	1 (3.7%)
	Black or African American	0 (0.0%)	1 (7.1%)	1 (3.7%)
	White	12 (92.3%)	13 (92.9%)	25 (92.6%)
Ethnicity [n (%)]	Hispanic or Latino	1 (7.7%)	0 (0.0%)	1 (3.7%)
	Not Hispanic or Latino	12 (92.3%)	14 (100%)	26 (96.3%)
BMI (kg/m^2)	Mean (SD)	20.43 (3.569)	23.23 (5.647)	21.88 (4.883)
	Median	21.43	22.55	21.95
	Q1/Q3	18.31/22.22	19.16/28.64	18.31/25.18
	Minimum/Maximum	13.7/25.2	15.4/32.7	13.7/32.7

Source: Module 5.3.5.1, CSR PerSept 1, Table 9.
Abbreviations: BMI = body mass index; Q = quartile; SD = standard deviation

Table 17: Summary of disease history (Excerpt from Table 11, CSR PerSept1)

Parameter		Treatment Regimen at Randomization		Overall (N=27)
		75 µg/kg (N=13)	225 µg/kg (N=14)	
Type of Hemophilia [n (%)]	Type A	13 (100%)	12 (85.7%)	25 (92.6%)
	Type B	0	2 (14.3%)	2 (7.4%)
Hemophilia severity grade at Screening [n (%)]	Mild	0	0	0
	Moderate	1 (7.7%)	1 (7.1%)	2 (7.4%)
	Severe	12 (92.3%)	13 (92.9%)	25 (92.6%)
Factor level (%)	Mean (SD)	0.38 (0.533)	0.35 (0.411)	0.36 (0.464)
	Median	0.10	0.20	0.10
	Q1/Q3	0.00/0.50	0.00/0.50	0.00/0.50
	Minimum/Maximum	0.0/1.8	0.0/1.0	0.0/1.8
Inhibitor status [n (%)]	BU <5	7 (53.8%)	6 (42.9%)	13 (48.1%)
	BU ≥5	6 (46.2%)	8 (57.1%)	14 (51.9%)
BU <5 but expected to have a high anamnestic response to FVIII or FIX [n (%)]	Yes	6 (46.2%)	5 (35.7%)	11 (40.7%)
	No	7 (53.8%)	9 (64.3%)	16 (59.3%)
BU <5 but expected to be refractory to increased dosing of FVIII or FIX [n (%)]	Yes	1 (7.7%)	1 (7.1%)	2 (7.4%)
	No	12 (92.3%)	13 (92.9%)	25 (92.6%)
Number of bleeding episodes during the past 6 months	Mean (SD)	14.5 (12.61)	11.0 (7.07)	12.7 (10.08)
	Median	9.0	11.0	10.0
	Q1/Q3	6.0/18.0	4.0/14.0	6.0/18.0
	Minimum/Maximum	3/50	3/24	3/50
Target joint(s)/bleeding site(s) [n (%)]	Yes	9 (69.2%)	8 (57.1%)	17 (63.0%)

- **Numbers analysed**

The Treated population was defined as all enrolled patients who received at least one study drug administration to treat a bleeding episode during Phase B (=treatment phase; Phase A was the PK phase). All analyses of efficacy were performed based on the Treated Population. At a bleeding episode level, the analysis included all bleeding episodes treated with study drug, and each such bleeding episode was analysed as treated.

- **Outcomes and estimation**

Table 18: Characteristics of bleeding episodes (PerSept1 Study)

	Treatment Regimen at the Time of Bleeding Episode		Overall (N=27)
	75 µg/kg (N=25)	225 µg/kg (N=25)	
Number of Bleeding Episodes	252	216	468
Bleeding Episode Severity			
Mild/Moderate	252 (100.0%)	213 (98.6%)	465 (99.4%)
Severe	0 (0.0%)	3 (1.4%)	3 (0.6%)
Type of Bleeding Episode			
Spontaneous	197 (78.2%)	184 (85.2%)	381 (81.4%)
Traumatic	53 (21.0%)	32 (14.8%)	85 (18.2%)
Unknown	2 (0.8%)	0 (0.0%)	2 (0.4%)
Anatomical Location			
Knee	66 (26.2%)	56 (25.9%)	122 (26.1%)
Elbow	63 (25.0%)	49 (22.7%)	112 (23.9%)
Ankle/Foot	36 (14.3%)	21 (9.7%)	57 (12.2%)
Hip	18 (7.1%)	26 (12.0%)	44 (9.4%)
Shoulder	16 (6.3%)	21 (9.7%)	37 (7.9%)
Wrist/Hand	14 (5.6%)	10 (4.6%)	24 (5.1%)
Soft tissue/Muscle	12 (4.8%)	11 (5.1%)	23 (4.9%)
Nose	4 (1.6%)	9 (4.2%)	13 (2.8%)
Oral Cavity	9 (3.6%)	3 (1.4%)	12 (2.6%)
Gastro-Intestinal	0 (0.0%)	0 (0.0%)	0 (0.0%)
Other	12 (4.8%)	10 (4.6%)	22 (4.7%)
Unknown	2 (0.8%)	0 (0.0%)	2 (0.4%)
Anatomical Location			
Target Joint	77 (30.6%)	58 (26.9%)	135 (28.8%)
Non-Target Joint	136 (54.0%)	125 (57.9%)	261 (55.8%)
Non-Joint	37 (14.7%)	33 (15.3%)	70 (15.0%)
Unknown	2 (0.8%)	0 (0.0%)	2 (0.4%)

Primary efficacy endpoint:

The observed percentage of successfully treated bleeding episodes, regardless of severity, for the 225 µg/kg regimen was greater than that for the 75 µg/kg regimen (p = 0.020).

	Treatment Regimen at the Time of Mild/Moderate Bleeding Episode		
	75 µg/kg (N=25)[1]	225 µg/kg (N=25)[1]	Overall (N=27)[1]
Number of bleeding episodes	252	216	468
Number of successes	202 (80.2%)	194 (89.8%)	396 (84.6%)
Number of failures	36 (14.3%)	14 (6.5%)	50 (10.7%)
Number of missing	14 (5.6%)	8 (3.7%)	22 (4.7%)
Success proportion [95% CI][2]	0.849 [0.740, 0.957]	0.933 [0.883, 0.983]	0.888 [0.809, 0.967]
p-value[3]	<0.001	<0.001	<0.001
p-value[4]			0.020

[1] N in the column header indicates number of patients who had at least 1 bleeding episode treated with a given dose of study drug.

[2] Analysis was based on data as observed. No missing value imputation was made.

[3] p-value from 1-sided normal approximation test of H_0: $p \leq 0.55$, where p is the true proportion of successfully treated bleeding episodes at 12 hours, with adjustment for the correlation among bleeding episodes for a given patient.

[4] p-value from 2-sided normal approximation test comparing proportions for the two treatment regimens, with adjustment for the correlation among bleeding episodes for a given patient.

Note: Stratified by actual treatment regimen at the time of the bleeding episode.

CI = confidence interval.

Secondary efficacy endpoints and additional analyses

Time to Patient Assessment of "Good" or "Excellent" Response for Mild/Moderate Bleeding Episodes

The median time to assessment of "good" or "excellent" response was approximately 3 hours shorter in the 225 µg/kg regimen (3.00 hours) compared with the 75 µg/kg regimen (5.98 hours). A comparison of results for 75 µg/kg versus 225 µg/kg showed a p = 0.001.

Number of Administrations and Total Amount of Drug Administered Per Mild/Moderate Bleeding Episode

The mean (SD) number of administrations of study drug per mild/moderate bleeding episode was 2.5 (1.75) for the 75 µg/kg regimen and 1.4 (0.96) for the 225 µg/kg regimen. A comparison of the two Cevenfacta treatment regimens for number of administrations of study drug per mild/moderate bleeding episode showed a p <0.001. For the 75 µg/kg treatment regimen, the mean (SD) total amount of study drug (µg/kg) administered per mild/moderate bleeding episode was 187.87 (131.80) µg/kg, which corresponds with approximately 2.5 mean administrations of 75 µg/kg of drug. For the 225 µg/kg treatment regimen, the mean (SD) total amount of study drug (µg/kg) administered per mild/moderate bleeding episode was 252.96 (78.97) µg/kg, which corresponds with 1.4 mean administrations of the treatment regimen for this dose group, i.e., patients received an initial injection of 225 µg/kg followed by 75 µg/kg, if needed. A comparison of the two treatment regimens for total amount of study drug administered per mild/moderate bleeding episode showed a p <0.001.

Proportion of recurrence of bleeding episodes

Bleeding recurrence was defined as a bleeding in the same joint/anatomical location within 24 hours after an initial successful response. Only one (0.2%) of the 468 bleeding episodes did recur.

Failures at 24 hours

Table 19: Description of bleeding with treatment failures 24 hours after initial administration of Cevenfacta

Patient number	Age (years)	Treatment Regimen	Severity	Cause	Location	Target joint/ bleeding site	Treated at hospital	Alternative treatment
Patient 1	30-40	75 µg/kg	Mild/moderate	Spontaneous	Other	no	no	yes
Patient 2	30-40	75 µg/kg	Mild/moderate	Spontaneous	Right knee	yes	no	yes
Patient 3	40-50	75 µg/kg	Mild/moderate	Spontaneous	Right wrist /Hand	no	no	yes
		75 µg/kg	Mild/moderate	Spontaneous	Right ankle /Foot	no	no	yes
Patient 4	30-40	225 µg/kg	Mild/moderate	Spontaneous	Oral cavity	no	no	no
		75 µg/kg	Mild/moderate	Spontaneous	Right knee	no	no	no
		75 µg/kg	Mild/moderate	Spontaneous	Right knee	no	no	no
Patient 5	50-60	75 µg/kg	Mild/moderate	Spontaneous	Left Elbow	yes	no	no
Patient 6	20-30	75 µg/kg	Mild/moderate	Spontaneous	Left shoulder	no	no	no

Source: Module 5.3.5.1 CSR PerSept 1, Listing 12.4, Listing 12.9, Listing 12.10.1, Listing 12.10.2

Proportion of bleeding episodes, regardless of severity that did not require alternative treatment

The majority (>98%) of bleeding episodes (regardless of severity) did not require alternative treatment: 98.4% (95% CI = 0.95.9%, 100%) of bleeding episodes treated with the 75 µg/kg regimen, and 99.5% (95% CI = 0.98.6%, 100%) of bleeding episodes treated with the 225 µg/kg regimen. A total of 5 bleeding episodes required alternative treatment.

Severe bleeding events

There were 3 severe bleeding episodes during the study. All 3 bleeding episodes were treated with the 225 µg/kg regimen. The locations of the severe bleeding episodes were right hip (1 episode), soft tissue/muscle (1 episode), and 'other' (renal bleed; 1 episode). None of the episodes were in a target joint, were a recurring bleed, or required alternative treatment. Two of the episodes occurred spontaneously and 1 resulted from trauma. All 3 episodes required hospitalisation.

Patient-reported assessment of "good" or "excellent" was reported for all 3 (100%) severe bleeds at 12 hours and 24 hours. Physician-reported assessment of "good" or "excellent" was reported for all 3 (100%) severe bleeds at the 12- and 24-hour timepoints.

Analyses by Cevenfacta Manufacturing Process

Process A and Process B of Cevenfacta manufacturing product were used during PerSept 1. Among the 468 bleeding episodes analysed, 70.3% of bleeding episodes were treated with Cevenfacta produced with Process A, 18.4% with Process B, and 11.3% with both processes. Only Process B Cevenfacta manufacturing product was used during PerSept 2.

Table 20: Successful Treatment of Bleeding Episodes with a "Good" or "Excellent" Response at 12 Hours After Initial Administration of Cevenfacta, Regardless of Severity, by Cevenfacta Manufacturing Process

	PerSept 1	
Manufacturing Process: Process A[1]	**75 µg/kg (N=21)**	**225 µg/kg (N=22)**
Number of Mild/Moderate/Severe Bleeding Episodes	181	148
Number of Successes	149 (82.3%)	135 (91.2%)
Number of Failures	20 (11.0%)	9 (6.1%)
Number of Missings	12 (6.6%)	4 (2.7%)
Success Proportion [95% CI]	0.882 [0.770, 0.993]	0.938 [0.870, 1.000]
Manufacturing Process: Process B[1]	**(N=14)**	**(N=10)**
Number of Mild/Moderate/Severe Bleeding Episodes	51	35
Number of Successes	41 (80.4%)	28 (80.0%)
Number of Failures	8 (15.7%)	3 (8.6%)
Number of Missings	2 (3.9%)	4 (11.4%)
Success Proportion [95% CI]	0.837 [0.696, 0.977]	0.903 [0.821, 0.985]
Manufacturing Process: Process A+B[1]	**(N=7)**	**(N=7)**
Number of Mild/Moderate/Severe Bleeding Episodes	20	33
Number of Successes	14 (70.0%)	32 (97.0%)
Number of Failures	6 (30.0%)	1 (3.0%)
Number of Missings	0 (0.0%)	0 (0.0%)
Success Proportion [95% CI]	0.700 [0.504, 0.896]	0.970 [0.769, 1.000]

Abbreviation: CI = confidence interval.
Notes: Table is stratified by actual dose regimen at the time of the bleeding episode.
[1] Cevenfacta Process A and Process B manufacturing product were used during PerSept 1.

- **Ancillary analyses**

Not applicable.

- **Summary of main efficacy results**

The following tables summarise the efficacy results from the main studies supporting the present application. These summaries should be read in conjunction with the discussion on clinical efficacy as well as the benefit risk assessment (see later sections).

Table 21: Summary of efficacy for PERSEPT 1 study

Title: A Phase III Study on the Safety, Pharmacokinetics, and Efficacy of Coagulation Factor VIIa (Recombinant) in Congenital Hemophilia A or B Patients with Inhibitors to Factor VIII or IX		
Study identifier	RB-FVIIa-006-13 (PerSept1)	
Design	Global, Multicentre, Phase 3, prospective, open label, randomised, crossover study	
	Duration of main phase:	Until at least 22 patients were followed for at least 6 months after the first treatment with Cevenfacta and until at least 352 bleeding episodes were treated. The total mean duration of exposure was 6.6 months (n=27) and 468 bleeding episodes were treated.
	Duration of Run-in phase: Duration of Extension phase:	not applicable
Hypothesis	Superiority; The protocol-specified success was defined as statistically significant higher success compared to the Objective Performance Criterion (OPC). The study was not powered for statistical comparison between the two dose regimens. The null hypothesis (H0) for the primary efficacy endpoint was $p \leqslant 0.55$ where p is the true proportion of successfully treated mild or moderate bleeding events at 12 hours.	
Treatments groups	75 µg/kg regimen	Administration of 75 µg/kg of Cevenfacta as 2-minute bolus IV infusion, followed with doses of 75 µg/kg if necessary: every 3 hours, as necessary, for up to 21 hours for mild or moderate bleeding; every 2 hours until improvement for severe bleeding episodes.
	225 µg/kg regimen	Administration of 225 µg/kg of Cevenfacta as a 2-minute bolus IV infusion, followed by doses of 75 µg/kg if necessary: every 3 hours, as necessary, from 9 hours up to 21 hours for mild or moderate bleeding; every 2 hours until improvement for severe bleeding episodes.
Endpoints and definitions	Primary endpoint	Proportion of success (using EMA definition): Proportion of successfully treated bleedings episodes regardless of severity (mild, moderate, and severe) with a patient/caregiver-reported response (for mild/moderate bleeding episodes) and physician-reported response (for severe bleeding episodes) as "good" or "excellent" at 12 hours after initial Cevenfacta administration.

	Key secondary	Time to assessment of a "good" or "excellent" response of bleeding episodes by the patient
	Key secondary	Number of administrations and total amount of drug administered per bleeding episode
Database lock	31 July 2015	
Results and Analysis		
Analysis description	**Primary Analysis**	
Analysis population and time point description	**Treated Population:** defined as all 27 enrolled patients who received at least 1 study drug administration to treat a bleeding episode during treatment	

Descriptive statistics and estimate variability

Primary efficacy endpoint according to the EMA definition:

The analysis of the proportion of successfully treated bleeding episodes with a "good" or "excellent" response, regardless of severity (i.e. including mild, moderate, and severe bleeding episodes), at 12 hours after initial administration of Cevenfacta is presented in the following table.

Table 22: Proportion of successfully treated bleeding episodes with a "good" or "excellent" response, regardless of severity, at 12 hours after initial administration of Cevenfacta

	Treatment Regimen at the Time of Bleeding Episode		Overall (N=27)
	75 µg/kg (N=25)	225 µg/kg (N=25)	
Number of bleeding episodes	252	216	468
Number of successes	204 (81.0%)	195 (90.3%)	399 (85.3%)
Number of failures	34 (13.5%)	13 (6.0%)	47 (10.0%)
Number of missing	14 (5.6%)	8 (3.7%)	22 (4.7%)
Success proportion [95% CI]	0.857 [0.750, 0.964]	0.938 [0.889, 0.986]	0.895 [0.817, 0.972]
p-value [1]	<0.001	<0.001	<0.001
p-value [2]			0.028

Notes: Table stratified by actual dose regimen at the time of the bleeding episode. Patients began Phase B treatment on the same Cevenfacta treatment regimen that they were randomised to in Phase A (either 75 µg/kg or 225 µg/kg). Thereafter, the patient was crossed over to the alternate treatment regimen every 12 weeks until the end of the study.

[1] p-value from one-sided normal approximation test of H_0: $p \leq 0.55$, where p is the true proportion of successfully treated bleeding episodes at 12 hours, with adjustment for the correlation among bleeding episodes for a given patient. The test was conducted at the 0.0125 level (adjusted from 0.025 to 0.0125 to account for multiplicity).

[2] p-value from two-sided normal approximation test comparing proportions for the two treatment regimens, with adjustment for the correlation among bleeding episodes for a given patient.

Key secondary efficacy endpoints:

Time to Patient reported Assessment of a 'Good' or 'Excellent' Response for Bleeding Episodes Regardless of Severity

The median time to response was shorter in the 225 µg/kg regimen (3.00 hours) compared with the 75 µg/kg regimen (5.98 hours).

Table 23: Time to patient assessment of "Good" or "Excellent" response for bleeding episodes regardless of severity (treated population)

	Treatment Regimen at the Time of Bleeding Episode		
	75 µg/kg (N=25)[1]	**225 µg/kg (N=25)[1]**	**Overall (N=27)[1]**
Bleeding episodes with event	240 (95.2%)	211 (97.7%)	451 (96.4%)
Censored bleeding episodes	7 (2.8%)	1 (0.5%)	8 (1.7%)
Missing	5 (2.0%)	4 (1.9%)	9 (1.9%)
Kaplan-Meier estimate (hours)			
Q1 (CI)	3.00 [3.00, 3.25]	2.97 [2.95, 3.00]	3.00 [NA, NA]
Median (CI)	5.98 [5.95, 6.00]	3.00 [NA, NA]	5.92 [3.13, 5.95]
Q3 (CI)	9.00 [8.92, 12.00]	9.00 [8.65, 9.00]	9.00 [8.92, 9.00]
Cox regression hazard			0.71

Study LFB-FVIIa-007-14 A: A Phase III Study on the Safety, Pharmacokinetics, and Efficacy of Coagulation Factor VIIa (Recombinant) in Congenital Hemophilia A or B Pediatric Patients from Birth to <12 Years Old with Inhibitors to Factor VIII or IX (PERSEPT 2)

Methods

This was a global, multicentre, Phase 3, prospective, open-label, randomised, crossover study.

- **Study Participants**

Inclusion Criteria

The main criteria for inclusion were: a diagnosis of haemophilia A or B with inhibitors (BU ⩾5, or BU <5 but either expected to have a high anamnestic response to FVIII or FIX, or expected to be refractory to increased dosing of FVIII or FIX, as demonstrated from the patient's medical history, precluding the use of FVIII or FIX; be aged from birth to <12 years old.

Exclusion Criteria

The main exclusion criteria were: any coagulation disorder other than haemophilia A or B; immunosuppression (i.e., the patient should not have received systemic immunosuppressive medication, CD4 counts at screening should have been >200/µL); a known allergy or hypersensitivity to rabbits; a platelet count <100,000/mL

- **Treatments**

Patients were randomised to start treatment with one of the two following study drug regimens:

• 75 µg/kg Cevenfacta treatment regimen

• 225 µg/kg Cevenfacta treatment regimen

The assigned treatment regimen was the dose administered in Phase A and the starting dose in Phase B before crossover to the other treatment regimen.

All levels of severity of bleeding episodes (mild, moderate, and severe) were allowed to be treated on the study.

The dosing schemes employed in this trial were the same as described above for study PerSept 1.

- **Objectives**

The general objectives of this study were to assess the safety and efficacy of two dose regimens of Cevenfacta across the full type of severity of bleeding episodes (mild, moderate, and severe), and to assess the pharmacokinetics (PK) of Cevenfacta.

- **Outcomes/endpoints**

For the EMA, the primary efficacy endpoint was defined as the proportion of bleeding episodes of all severity (mild, moderate, and severe) with a patient/caregiver-reported (for mild/moderate bleeding episodes) and physician-reported (for severe bleeding episodes) response of **"good" or "excellent"** at 12 hours after the initial Cevenfacta administration.

Selected secondary efficacy endpoints and additional analyses

• Time to assessment of a "good" or "excellent" response of the bleeding episodes (mild/moderate and severe, separately and combined) by the patient (and/or physician when available)

• Descriptive analysis of the number of administrations of Cevenfacta per bleeding episode

- **Statistical methods**

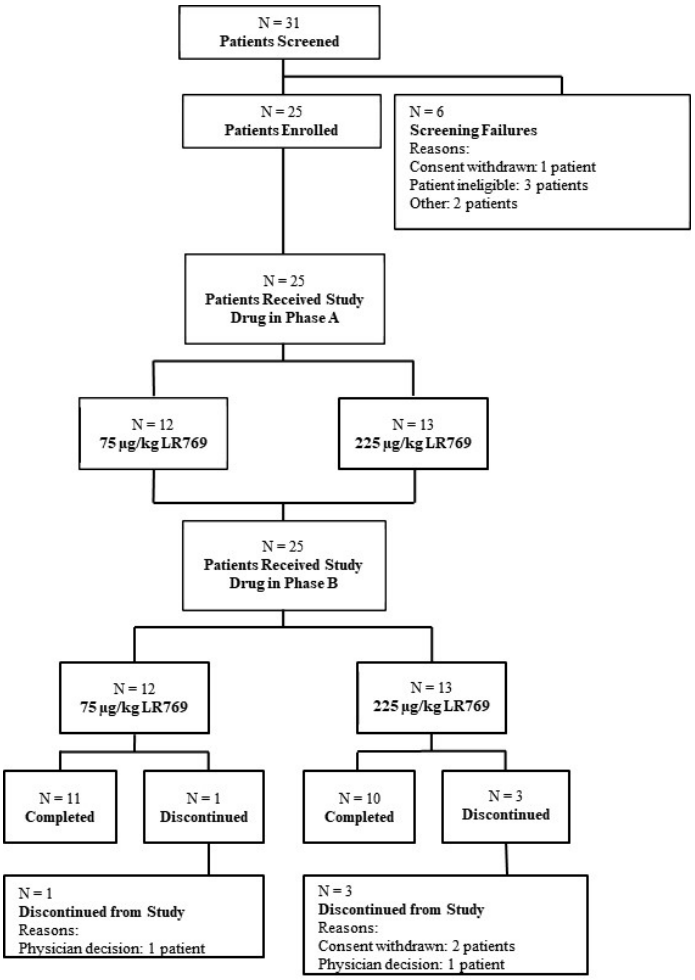
The protocol-specified success was defined as statistically significant higher success compared to the Objective Performance Criterion (OPC). The study was not powered for statistical comparison between the two dose regimens. The null hypothesis (H0) for the primary efficacy endpoint was p ≤0.55 where p is the true proportion of successfully treated mild or moderate bleeding events at 12 hours.

- **Numbers analysed**

Twenty-five enrolled and randomised patients (12 patients in the 75 µg/kg treatment regimen and 13 patients in the 225 µg/kg treatment regimen) were included in the Safety and Treated populations. The Treated population was used for efficacy analyses.

Results

- **Participant flow**



Baseline data

Table 24: Summary of demographics and baseline characteristics (safety polulation)

Parameter	Statistic	Regimen Assigned at Randomization		Overall (N=25)
		75 µg/kg (N=12)	225 µg/kg (N=13)	
Age (years)	Mean (SD)	4.9 (3.02)	4.8 (3.63)	4.9 (3.28)
	Median	5.5	4.0	5.0
	Q1/Q3	2.0/8.0	2.0/8.0	2.0/8.0
	Minimum/Maximum	1/9	1/11	1/11
Race [n (%)]	Black	4 (33.3%)	3 (23.1%)	7 (28.0%)
	White	8 (66.7%)	10 (76.9%)	18 (72.0%)
Ethnicity [n (%)]	Hispanic or Latino	1 (8.3%)	2 (15.4%)	3 (12.0%)
	Not Hispanic or Latino	11 (91.7%)	11 (84.6%)	22 (88.0%)
Weight (kg)	Mean (SD)	19.73 (7.432)	21.94 (13.391)	20.88 (10.782)
	Median	19.65	16.00	19.00
	Q1/Q3	13.50/25.70	12.50/27.00	12.50/26.90
	Minimum/Maximum	8.2/31.5	10.0/52.0	8.2/52.0
Height (cm)	Mean (SD)	104.21 (21.210)	108.60 (25.904)	106.49 (23.382)
	Median	110.25	106.00	109.50
	Q1/Q3	84.50/119.00	87.00/127.00	87.00/123.00
	Minimum/Maximum	68.0/135.0	65.0/146.0	65.0/146.0
BMI (kg/m^2)	Mean (SD)	17.74 (2.505)	17.35 (3.842)	17.53 (3.209)
	Median	17.49	16.93	17.18
	Q1/Q3	15.85/18.56	14.60/18.11	15.47/18.53
	Minimum/Maximum	15.1/24.0	11.5/24.7	11.5/24.7

Note: Stratified by treatment regimen assigned at randomization.

BMI = body mass index; N = number of patients in the treatment regimen; Q = quartile; SD = standard deviation.

Source: Table 14.1.3.1

Table 25: Summary of disease history (treated population)

Parameter		Regimen Assigned at Randomization		Overall (N=25)
		75 µg/kg (N=12)	225 µg/kg (N=13)	
Type of Hemophilia [n (%)]	Type A	11 (91.7%)	12 (92.3%)	23 (92.0%)
	Type B	1 (8.3%)	1 (7.7%)	2 (8.0%)
Hemophilia severity grade at Screening [n (%)]	Mild	0	0	0
	Moderate	0	1 (7.7%)	1 (4.0%)
	Severe	12 (100%)	12 (92.3%)	24 (96.0%)
Factor [n (%)]	FVIX	1 (8.3%)	1 (7.7%)	2 (8.0%)
	FVIII	11 (91.7%)	12 (92.3%)	23 (92.0%)
Factor level (%)	Mean (SD)	0.6 (0.33)	0.7 (0.69)	0.7 (0.54)
	Median	0.5	0.5	0.5
	Q1/Q3	0.5/1.0	0.2/1.0	0.5/1.0
	Minimum/Maximum	0/1	0/3	0/3
Inhibitor status (most recent prior to screening) [n (%)]	BU <5	2 (16.7%)	2 (15.4%)	4 (16.0%)
	BU ≥5	10 (83.3%)	11 (84.6%)	21 (84.0%)
BU <5 at screening but expected to have a high anamnestic response to FVIII or FIX [n (%)]	Yes	2 (16.7%)	4 (30.8%)	6 (24.0%)
	No	10 (83.3%)	9 (69.2%)	19 (76.0%)
BU <5 at screening but expected to be refractory to increased dosing of FVIII or FIX [n (%)]	Yes	1 (8.3%)	0	1 (4.0%)
	No	11 (91.7%)	13 (100%)	24 (96.0%)
Number of bleeding episodes during the past 6 months	Mean (SD)	4.5 (2.11)	3.5 (1.13)	4.0 (1.71)
	Median	4.0	3.0	3.0
	Q1/Q3	3.0/5.0	3.0/3.0	3.0/4.0
	Minimum/Maximum	3/10	3/6	3/10
Target joint(s)/bleeding site(s) [n (%)]	Yes	4 (33.3%)	4 (30.8%)	8 (32.0%)
	No	8 (66.7%)	9 (69.2%)	17 (68.0%)
Past ITI Therapy [n (%)]	Yes	0	1 (7.7%)	1 (4.0%)
	No	12 (100%)	12 (92.3%)	24 (96.0%)
Present ITI Therapy [n (%)]	Yes	0	0	0
	No	12 (100%)	13 (100%)	25 (100%)

Note: Stratified by treatment regimen assigned at randomization.

BU = Bethesda Unit(s); FIX = factor IX; FVIII = factor VIII; ITI = immune tolerance induction; Q = quartile; SD = standard deviation.

Source: Table 14.1.7.2, Listing 16.2.7

Summary of main efficacy results

Table 26: Summary of efficacy for trial PerSept 2

Title: A Phase III Study on the Safety, Pharmacokinetics, and Efficacy of Coagulation Factor VIIa (Recombinant) in Congenital Hemophilia A or B Pediatric Patients from Birth to <12 Years Old with Inhibitors to Factor VIII or IX (PERSEPT 2)		
Study identifier	Protocol number: LFB-FVIIa-007-14 (PerSept 2) EudraCT number: 2015-000958-38	
Design	Multinational, Multicenter, Phase 3, Prospective, Open-Label, Randomised, Crossover Study	
	Duration of main phase: Duration of Run-in phase: Duration of Extension phase:	At least 6 months and until at least 352 bleeding episodes were treated not applicable
Hypothesis	Superiority; The protocol-specified success was defined as statistically significant higher success compared to the Objective Performance Criterion (OPC). The study was not powered for statistical comparison between the two dose regimens. The null hypothesis (H0) for the primary efficacy endpoint was $p \leqslant 0.55$ where p is the true proportion of successfully treated mild or moderate bleeding events at 12 hours.	
Treatments groups	75 µg/kg dose regimen	Administration of 75 µg/kg of Cevenfacta as a ≤ 2-minute intravenous (IV) infusion, followed with doses of 75 µg/kg if necessary: every 3 hours, as necessary, for up to 21 hours for mild or moderate bleeding; every 2 hours until improvement for severe bleeding episodes. Number: 23 patients, 239 mild or moderate
	225 µg/kg dose regimen	Administration of 225 µg/kg of Cevenfacta as a ≤ 2-minute intravenous (IV) infusion, followed by doses of 75 µg/kg if necessary: every 3 hours, as necessary, from 9 hours up to 21 hours for mild or moderate bleeding; every 2 hours until improvement for severe bleeding episodes. Number: 24 patients, 307 mild or moderate and 3 severe bleeding episodes.

	Overall	Patients were randomised to start the study with either 75 µg/kg or 225 µg/kg treatment regimen of Cevenfacta. The initial dose of the assigned dose regimen of Cevenfacta was administered in Phase A (initial safety and pharmacokinetic [PK] phase) and the assigned dose regimen for the first 12-week period in Phase B (treatment phase). Thereafter, the patient was crossed over to the alternate treatment regimen every 12 weeks until the end of the study. 12 patients were randomised to receive 75 µg/kg first, then 225 µg/kg and 13 patients randomised to receive 225 µg/kg first, then 75 µg/kg.
Endpoints and definitions	**Primary endpoint**	Proportion of success (using EMA definition): Proportion of successfully treated bleedings episodes regardless of severity (mild, moderate, and severe) with a patient/caregiver-reported response (for mild/moderate bleeding episodes) and physician-reported response (for severe bleeding episodes) as "good" or "excellent" at 12 hours after initial Cevenfacta administration.
	Key Secondary	Time to assessment of a "good" or "excellent" response of bleeding episodes by the patient
	Key Secondary	Number of administrations and total amount of drug administered per bleeding episode.
Database lock	29 September 2017	
Results and Analysis		
Analysis description	**Primary Analysis**	
Analysis population and time point description	**The Treated population** (defined as all enrolled patients who received at least one study drug administration to treat a bleeding episode during treatment phase	

Descriptive statistics and estimate variability	**Primary efficacy endpoint according to the EMA definition:** The analysis of the proportion of successfully treated bleeding episodes with a "good" or "excellent" response, regardless of severity (i.e. including mild, moderate, and severe bleeding episodes), at 12 hours after initial administration of Cevenfacta is presented in the following Table. **Table 27: Bleeding episodes with a "Good" or "Excellent" patient-reported (for mild/moderate bleeding episodes) or physician-reported (for severe bleeding episodes) response at 12 hours after initial Cevenfacta**

	Treatment Regimen at the Time of Bleeding Episode		**Overall (N=25)**
	75 µg/kg (N=23)	**225 µg/kg (N=24)**	
Number of bleeding episodes	239	310	549
Number of successes	158 (66.1%)	190 (61.3%)	348 (63.4%)
Number of failures	79 (33.1%)	114 (36.8%)	193 (35.2%)
Number of missing	2 (0.8%)	6 (1.9%)	8 (1.5%)
Success proportion [95% CI]	0.667 [0.533, 0.800]	0.625 [0.500, 0.750]	0.643 [0.526, 0.761]
p-value [1]	0.043	0.120	0.060
p-value [2]			0.459

Abbreviation: CI = confidence interval

Notes: Table is stratified by actual dose regimen at the time of the bleeding episode.

[1] p-value from one-sided normal approximation test of H_0: $p \leq 0.55$, where p is the true proportion of successfully treated bleeding episodes at 12 hours, with adjustment for the correlation among bleeding episodes for a given patient. The test was conducted at the 0.0125 level (adjusted from 0.025 to 0.0125 to account for multiplicity).

[2] p-value from two-sided normal approximation test comparing proportions for the two treatment regimens, with adjustment for the correlation among bleeding episodes for a given patient.

Key secondary efficacy endpoints

Time to Patient Assessment of a 'Good' or 'Excellent' Response of the Bleeding Episodes (Regardless of Severity)

The median time to "good" or "excellent" response for bleeding regardless of severity was 9.00 hours for the 75 µg/kg regimen and 12.00 hours for 225 µg/kg treatment regimen

Table 28: Time to patient assessment of "Good" or "Excellent" response for bleeding episodes regardless of severity (treated population)

	Treatment Regimen at the Time of Mild/Moderate Bleeding Episode		
	75 µg/kg (N=23)	**225 µg/kg (N=24)**	**Overall (N=25)**
Bleeding episodes with event	233 (97.5%)	300 (96.8%)	533 (97.1%)
Censored bleeding episodes	6 (2.5%)	8 (2.6%)	14 (2.6%)
Missing	0	2 (0.6%)	2 (0.4%)
Kaplan-Meier estimate (hours)			
Q1 (CI)	5.75 [3.00, 5.92]	9.00 [NA, NA]	8.92 [8.83, 8.92]
Median (CI)	9.00 [8.92, 11.83]	12.00 [11.83, 12.00]	11.83 [9.00, 12.00]
Q3 (CI)	15.00 [14.83, 17.92]	17.92 [15.00, 20.83]	17.83 [15.00, 18.00]

Note: Table stratified by actual treatment regimen at the time of the bleeding episode.

CI = confidence interval; Q = quartile

Number of Administrations Per Bleeding Episode regardless of severity.

Table 29: Number of administrations per bleeding episodes regardless of severity (treated population)

Parameter **Statistic**	**Treatment Regimen at the Time of Bleeding Episode**	
	75 µg/kg **(N=23)**	**225 µg/kg** **(N=24)**
Number of Administrations of Study Drug per Bleeding Episode, Regardless of Severity		
N	239	310
Nmiss	0	0
Mean (SD)	3.6 (2.27)	2.8 (2.89)
Median	3.0	2.0
Q1/Q3	2.0/5.0	1.0/4.0
Min/Max	1/8	1/33

Source: Module 5.3.5.1 CSR PerSept 2 Table 14.2.6.2.1, integrated analyses Supplemental Table 14.2.7.

Abbreviations: Q = quartile; SD = standard deviation. Nmiss: number of missing data.

Note: Table stratified by actual treatment regimen at the time of the bleeding episode

Ancillary analyses

Table 30: Addendum- primary efficacy endpoints by EMA definition and stratified by age group: Bleeding episodes with a patient- reported (for mild/moderate bleeding episodes) or physician-reported (for severe bleeding episodes) response of " Good" or "Excellent" at 12 hours after initial Cevenfacta administration (treated population)

	Treatment Regimen at the Time of Bleeding Episode		Overall
	75 µg/kg	225 µg/kg	
Birth to <2 years	**(N=4)**	**(N=3)**	**(N=4)**
Number of bleeding episodes	13	19	32
Number of successes	13 (100%)	17 (89.5%)	30 (93.8%)
Number of failures	0	2 (10.5%)	2 (6.3%)
Number of missing	0	0	0
Success proportion [95% CI]	1.000 [1.000, 1.000]	0.895 [0.698, 1.000]	0.938 [0.825, 1.000]
p-value[1]	NA	<0.001	<0.001
p-value[2]			NA
≥2 years to <6 years	**(N=8)**	**(N=10)**	**(N=11)**
Number of bleeding episodes	93	128	221
Number of successes	47 (50.5%)	69 (53.9%)	116 (52.5%)
Number of failures	46 (49.5%)	58 (45.3%)	104 (47.1%)
Number of missing	0	1 (0.8%)	1 (0.5%)
Success proportion [95% CI]	0.505 [0.302, 0.709]	0.543 [0.359, 0.728]	0.527 [0.344, 0.711]
p-value[1]	0.666	0.528	0.596
p-value[2]			0.512
≥6 years to <12 years	**(N=12)**	**(N=13)**	**(N=13)**
Number of bleeding episodes	133	163	296
Number of successes	98 (73.7%)	104 (63.8%)	202 (68.2%)
Number of failures	33 (24.8%)	54 (33.1%)	87 (29.4%)
Number of missing	2 (1.5%)	5 (3.1%)	7 (2.4%)
Success proportion [95% CI]	0.748 [0.613, 0.884]	0.658 [0.497, 0.819]	0.699 [0.573, 0.824]
p-value[1]	0.002	0.094	0.010
p-value[2]			0.317

[1] p-value from 1-sided normal approximation test of H_0: $P \leq 0.55$, where p is the true proportion of successfully treated bleeding episodes at 12 hours, with adjustment for the correlation among bleeding episodes for a given patient. The test was conducted at the 0.0125 level (adjusted from 0.025 to 0.0125 to account for multiplicity).

[2] p-value from 2-sided normal approximation test comparing success proportions for the two treatment regimens, with adjustment for the correlation among bleeding episodes for a given patient.

Note: Stratified by actual treatment regimen at the time of the bleeding episode.

CI = confidence interval.

The evaluation of bleeding successes according to age subgroups shows a higher efficacy in the <2 years group, however due to the very small number of bleeds no firm conclusions can be drawn.

Table 31. Addendum- primary efficacy endpoints by EMA definition and stratified by BMI Tertile: Bleeding episodes with a patient- reported (for mild/moderate bleeding episodes) or physician-reported (for severe bleeding episodes) response of " Good" or "Excellent" at 12 hours after initial LR769 administration (treated population)

	Treatment Regimen at the Time of Bleeding Episode		
	75 µg/kg	225 µg/kg	Overall
BMI <15.85 kg/m^2	**(N=7)**	**(N=8)**	**(N=8)**
Number of bleeding episodes	57	90	147
Number of successes	34 (59.6%)	46 (51.1%)	80 (54.4%)
Number of failures	22 (38.6%)	44 (48.9%)	66 (44.9%)
Number of missing	1 (1.8%)	0	1 (0.7%)
Success proportion [95% CI]	0.607 [0.214, 1.000]	0.511 [0.234, 0.788]	0.548 [0.260, 0.836]
p-value[1]	0.388	0.608	0.506
p-value[2]			0.563
BMI ≥15.85 kg/m^2 and <17.73 kg/m^2	**(N=7)**	**(N=7)**	**(N=8)**
Number of bleeding episodes	100	106	206
Number of successes	64 (64.0%)	62 (58.5%)	126 (61.2%)
Number of failures	36 (36.0%)	40 (37.7%)	76 (36.9%)
Number of missing	0	4 (3.8%)	4 (1.9%)
Success proportion [95% CI]	0.640 [0.475, 0.805]	0.608 [0.468, 0.748]	0.624 [0.471, 0.776]
p-value[1]	0.142	0.209	0.172
p-value[2]			0.069
BMI ≥17.73 kg/m^2	**(N=9)**	**(N=9)**	**(N=9)**
Number of bleeding episodes	82	114	196
Number of successes	60 (73.2%)	82 (71.9%)	142 (72.4%)
Number of failures	21 (25.6%)	30 (26.3%)	51 (26.0%)
Number of missing	1 (1.2%)	2 (1.8%)	3 (1.5%)
Success proportion [95% CI]	0.741 [0.573, 0.909]	0.732 [0.577, 0.887]	0.736 [0.609, 0.862]
p-value[1]	0.013	0.011	0.002
p-value[2]			0.933

[1] p-value from 1-sided normal approximation test of H_0: $P \leq 0.55$, where p is the true proportion of successfully treated bleeding episodes at 12 hours, with adjustment for the correlation among bleeding episodes for a given patient. The test was conducted at the 0.0125 level (adjusted from 0.025 to 0.0125 to account for multiplicity).

[2] p-value from 2-sided normal approximation test comparing success proportions for the two treatment regimens, with adjustment for the correlation among bleeding episodes for a given patient.

Note: Stratified by actual treatment regimen at the time of the bleeding episode.

BMI = body mass index; CI = confidence interval.

The analysis of the primary endpoint according to BMI subgroups shows increasing efficacy with increasing BMI. As subjects receive a weight-based dose, an increased dose of Cevenfacta despite a similar intravascular compartment in patients with the same height but higher weight leads to better outcomes, further lending support to the notion that children might be under dosed with the adult dosing regimen.

In the responses to the D120 LoQ, the applicant provided an analysis of the primary efficacy outcome according to bodyweight category:

Table 32: primary efficacy endpoint – successful treatment bleeding episodes at 12 hours regardless of severity by age and WHO weight categories (treated population)

Statistics	Underweight		Normal		Overweight	
	75 µg/kg	225 µg/kg	75 µg/kg	225 µg/kg	75 µg/kg	225 µg/kg
Age <12 years						
N	3	3	12	13	8	8
Number of Episodes	51	59	99	131	89	120
Number (%) of Successes	29 (56.9%)	18 (30.5%)	67 (67.7%)	90 (68.7%)	62 (69.7%)	82 (68.3%)
Number (%) Failures	22 (43.1%)	41 (69.5%)	31 (31.3%)	40 (30.5%)	26 (29.2%)	33 (27.5%)
Number of Missing Responses	0 (0.0%)	0 (0.0%)	1 (1.0%)	1 (0.8%)	1 (1.1%)	5 (4.2%)
Success Proportion [97.5% CI]	0.569 [0.072, 1.000]	0.305 [0.074, 0.536]	0.684 [0.548, 0.820]	0.692 [0.551, 0.833]	0.705 [0.479, 0.930]	0.713 [0.516, 0.911]
p-value for Testing H0: $p \leq 0.55$	0.467	0.991	0.014	0.012	0.062	0.032
Age≥12 years						
N	7	7	12	11	6	7
Number of Episodes	112	67	114	100	26	49
Number (%) of Successes	102 (91.1%)	65 (97.0%)	86 (75.4%)	87 (87.0%)	16 (61.5%)	43 (87.8%)
Number (%) Failures	4 (3.6%)	2 (3.0%)	23 (20.2%)	7 (7.0%)	7 (26.9%)	4 (8.2%)
Number of Missing Responses	6 (5.4%)	0 (0.0%)	5 (4.4%)	6 (6.0%)	3 (11.5%)	2 (4.1%)
Success Proportion [97.5% CI]	0.962 [0.873, 1.000]	0.970 [0.928, 1.000]	0.789 [0.643, 0.935]	0.926 [0.839, 1.000]	0.696 [0.403, 0.988]	0.915 [0.793, 1.000]
p-value for Testing H0: $p \leq 0.55$	<0.001	<0.001	<0.001	<0.001	0.132	<0.001

The applicant provided evaluation of efficacy and estimated PK parameters in the three bodyweight categories. There was a trend towards lack of efficacy in underweight children <12 years of age, while in the other age and weight groups no comparable impact on efficacy outcomes was evident. Estimated exposure in overweight patients was comparable to that in normal weight subjects.

2.5.6.2. Analysis performed across trials (pooled analyses and meta-analysis)

Table 33. Successful treatment of bleeding episodes with a "good" or "excellent" response at 12hours after initial administration of LR769. Regardless of severity by type of haemophilia (treated population)- PerSept 1, PeSept 2 and combined studies

	PerSept 1		PerSept 2		Combined PerSept 1 and 2	
	75 µg/kg (N=25)	225 µg/kg (N=25)	75 µg/kg (N=23)	225 µg/kg (N=23)	75 µg/kg (N=48)	225 µg/kg (N=49)
Hemophilia A patient	(N=23)	(N=23)	(N=21)	(N=22)	(N=44)	(N=45)
Number of Mild/Moderate/Severe Bleeding Episodes	241	203	215	281	456	484
Number of Successes	195 (80.9%)	186 (91.6%)	141 (65.6%)	171 (60.9%)	336 (73.7%)	357 (73.8%)
Number of Failures	33 (13.7%)	11 (5.4%)	73 (34.0%)	108 (38.4%)	106 (23.2%)	119 (24.6%)
Number of Missings	13 (5.4%)	6 (3.0%)	1 (0.5%)	2 (0.7%)	14 (3.1%)	8 (1.7%)
Success Proportion [95% CI]	0.855 [0.744, 0.966]	0.944 [0.895, 0.994]	0.659 [0.522, 0.796]	0.613 [0.490, 0.736]	0.760 [0.657, 0.864]	0.750 [0.649, 0.851]
p-value[1]	<0.001	<0.001	0.059	0.159	<0.001	<0.001
p-value[2]		0.018		0.462		0.791
Hemophilia B patient	(N=2)	(N=2)	(N=2)	(N=2)	(N=4)	(N=4)
Number of Mild/Moderate/Severe Bleeding Episodes	11	13	24	29	35	42
Number of Successes	9 (81.8%)	9 (69.2%)	17 (70.8%)	19 (65.5%)	26 (74.3%)	28 (66.7%)
Number of Failures	1 (9.1%)	2 (15.4%)	6 (25.0%)	6 (20.7%)	7 (20.0%)	8 (19.0%)
Number of Missings	1 (9.1%)	2 (15.4%)	1 (4.2%)	4 (13.8%)	2 (5.7%)	6 (14.3%)
Success Proportion [95% CI]	0.900 [0.368, 1.000]	0.818 [0.807, 0.829]	0.739 [0.287, 1.000]	0.760 [0.172, 1.000]	0.788 [0.452, 1.000]	0.778 [0.396, 1.000]
p-value[1]	0.099	<0.001	0.206	0.242	0.083	0.121
p-value[2]		0.758		NA		0.876

Source: Table 14.2.1.1.10, integrated analyses
Abbreviation: CI = confidence interval.
Notes: Table is stratified by actual dose regimen at the time of the bleeding episode. Patients who completed Phase A without any safety concerns began treatment Phase B on the same LR769 treatment regimen that they were randomized to in Phase A (either 75 µg/kg or 225 µg/kg). Thereafter, the patient was crossed over to the alternate treatment regimen every 12 weeks until the end of the study.
[1] p-value from one-sided normal approximation test of H0: p ≤0.55, where p is the true proportion of successfully treated mild/moderate/severe bleeding episodes at 12 hours, with adjustment for the correlation among bleeding episodes for a given patient. The test is conducted at the 0.0125 level (adjusted from 0.025 to 0.0125 to account for multiplicity of testing).
[2] p-value from two-sided normal approximation test comparing proportions for the two treatment regimens, with adjustment for the correlation among bleeding episodes for a given patient.

Table 34. Successful treatment of bleeding episodes with a "good" or "excellent" response at 12hours after initial administration of LR769. Regardless of severity by location of bleeding (target joint, no-target joint or non-joint) (treated population) – PerSept 1, PerSept 2 and combined studies

		PerSept 1		PerSept 2		Combined PerSept 1 and 2	
		75 µg/kg (N=25)	225 µg/kg (N=25)	75 µg/kg (N=23)	225 µg/kg (N=23)	75 µg/kg (N=48)	225 µg/kg (N=49)
Target joint	Number of patients	14	12	7	7	21	19
	Number of Bleeding Episodes	77	58	33	42	110	100
	Number of Successes	59 (76.6%)	49 (84.5%)	15 (45.5%)	25 (59.5%)	74 (67.3%)	74 (74.0%)
	Number of Failures	12 (15.6%)	4 (6.9%)	18 (54.5%)	16 (38.1%)	30 (27.3%)	20 (20.0%)
	Number of Missings	6 (7.8%)	5 (8.6%)	0 (0.0%)	1 (2.4%)	6 (5.5%)	6 (6.0%)
	Success Proportion [95% CI]	0.831 [0.643, 1.000]	0.925 [0.824, 1.000]	0.455 [0.162, 0.747]	0.610 [0.212, 1.000]	0.712 [0.485, 0.938]	0.787 [0.552, 1.000]
Non-target joint	Number of patients	22	23	18	21	40	44
	Number of Bleeding Episodes	136	125	135	162	271	287
	Number of Successes	113 (83.1%)	118 (94.4%)	87 (64.4%)	90 (55.6%)	200 (73.8%)	208 (72.5%)
	Number of Failures	19 (14.0%)	5 (4.0%)	46 (34.1%)	71 (43.8%)	65 (24.0%)	76 (26.5%)
	Number of Missings	4 (2.9%)	2 (1.6%)	2 (1.5%)	1 (0.6%)	6 (2.2%)	3 (1.0%)
	Success Proportion [95% CI]	0.856 [0.742, 0.970]	0.959 [0.913, 1.000]	0.654 [0.532, 0.776]	0.559 [0.428, 0.690]	0.755 [0.655, 0.855]	0.732 [0.621, 0.844]
Non-joint	Number of patients	16	14	21	22	37	36
	Number of Bleeding Episodes	37	33	71	106	108	139
	Number of Successes	32 (86.5%)	28 (84.8%)	56 (78.9%)	75 (70.8%)	88 (81.5%)	103 (74.1%)
	Number of Failures	3 (8.1%)	4 (12.1%)	15 (21.1%)	27 (25.5%)	18 (16.7%)	31 (22.3%)
	Number of Missings	2 (5.4%)	1 (3.0%)	0 (0.0%)	4 (3.8%)	2 (1.9%)	5 (3.6%)
	Success Proportion [95% CI]	0.914 [0.829, 1.000]	0.875 [0.766, 0.984]	0.789 [0.680, 0.898]	0.735 [0.616, 0.854]	0.830 [0.751, 0.910]	0.769 [0.669, 0.868]

Source: Table 14.2.1.1.13, integrated analyses
Abbreviation: CI = confidence interval.
Notes: Table is stratified by actual dose regimen at the time of the bleeding episode. Patients who completed Phase A without any safety concerns began treatment Phase B on the same LR769 treatment regimen that they were randomized to in Phase A (either 75 µg/kg or 225 µg/kg). Thereafter, the patient was crossed over to the alternate treatment regimen every 12 weeks until the end of the study.
Two bleeding episodes from 1 patient (PerSept 1) were not included in the table since the location of bleeding was missing.

2.5.6.3. Clinical studies in special populations

Not applicable.

2.5.6.4. Supportive study

Surgery trial: Study LFB-FVIIa-008-14 (PerSept 3)

Design

This is a Phase 3 Study of the Safety and Efficacy of Coagulation Factor VIIa (Recombinant) for the Prevention of Excessive Bleeding in Congenital Haemophilia A or B Patients with Inhibitors to Factor VIII or IX Undergoing Elective Surgery or Other Invasive Procedures (PERSEPT 3).

Objectives

The primary objective of this study was to assess the efficacy of Cevenfacta to prevent excessive bleeding and achieve haemostasis in haemophilia A or B patients with inhibitors to FVIII or FIX undergoing elective surgical or other invasive procedures.

Treatments and dose

Table 35: Dose and dosing schedule in the PerSept3 study

Dose and Dosing Schedule for Major Surgical Procedures		
Day	**Dose**	**Recommended Frequency**
Day 0 (within 2 minutes of surgical incision or invasive procedure)	200 µg/kg	Initial dose immediately before surgery or start of invasive procedure
Day 0 (post first dose) – 48 hours	75 µg/kg	Every 2 hours (±5 minutes)
Days 3-4	75 µg/kg	Intervals of up to every 4 hours but not more frequently than every 2 hours
Days 5-6	75 µg/kg	Intervals of up to every 6 hours but not more frequently than every 2 hours
Days 7-10	75 µg/kg	Intervals of up to every 8 hours but not more frequently than every 2 hours
Day 11 to last administration of Cevenfacta	75 µg/kg	Intervals of up to every 12 hours, but not more frequently than every 2 hours
Dose and Dosing Schedule for Minor Surgical/Invasive Procedures		
Day	**Dose**	**Recommended Frequency**
Day 0 (within 2 minutes of surgical incision or invasive procedure)	75 µg/kg	Initial dose immediately before surgery or start of invasive procedure
Day 0 (post first dose) – 48 hours	75 µg/kg	Every 2 hours (±5 minutes) initially. Interval may be increased upon the investigator's judgment
Day 3 to Last Administration of Cevenfacta	75 µg/kg	Intervals of up to every 24 hours but not more frequently than every 2 hours

If clinically indicated because of oozing or similar findings suggesting the need for more frequent Cevenfacta infusions, the treatment interval may have been shortened in consecutive doses within the dosing guidelines (shown above). If the patient required further treatment with Cevenfacta after discharge, the patient would have administered Cevenfacta at home according to the investigator's judgment and the dosing guidelines.

Administration of an FVIIa-containing product such as aPCC (FEIBA) or NovoSeven was only permitted for rescue therapy. Other agents for the prevention of excessive bleeding during surgical or other invasive procedures, such as antifibrinolytics, were allowed.

Aspirin, NSAIDs, herbs, natural medications, and any other drug with platelet inhibitory properties, were to be discontinued at least 1 week prior to elective surgical or other invasive procedure and for the duration of treatment with Cevenfacta).

All concomitant therapies, including the use of blood products, such as red blood cells, platelets, fresh frozen plasma, fibrinogen, etc., were recorded in the patients' medical records and/or patients' diaries and in the eCRF.

Study subjects

A total of 12 patients (6 each in the minor and major surgery groups) were enrolled into the study.

Two patients were discontinued prematurely from the study. Among these patients, one patient, who underwent a minor surgical procedure, discontinued as withdrew his consent, whereas another patient, who underwent a major surgical procedure, discontinued due to a TEAE (post-procedural hematoma). This TEAE was a SAE, namely haemorrhagic anaemia and caused patient's death. This patient died due to haemorrhagic anaemia. This was the only death that occurred during the study.

Demographics and baseline characteristics

Patients ranged in age from 2 years old to 56 years old. Patients in the minor surgery group had a mean age (16 years) which was approximately one half of that of patients in the major surgery group (34 years). Due to the age difference between the surgery groups, the mean weight at screening was lower in the minor surgery group (36.72 kg) compared with the major surgery group (54.17 kg).

All 12 patients had severe haemophilia A. Five (41.7%) patients had a BU titre $\geqslant$5 at screening (by local laboratory). Six patients (50.0%) had a BU <5 but were expected to have high anamnestic response to FVIII, based on a history of anamnestic responses between 6.0 and 50.6 BU. The remaining patient (8.3%) had a BU <5 but was expected to be refractory to increased dosing of FVIII products to treat bleedings, as he had been refractory to dosing in the past.

Surgeries

Table 36: Surgical or other invasive procedures by surgery type and age (all patients)

Patient Age (years)	Surgery/Invasive Procedure	Anesthesia Type	Complication	Surgery Duration (h:min)
Minor Surgery				
<12	Circumcision	General	No	00:28
<12	Circumcision	Local	No	00:12
<12	Circumcision	General	No	00:18
40-50	Tooth extraction	Local	No	00:15
20-30	Tooth extraction	Local	No	00:10
<12	Tooth extraction	Local	No	00:02
Major Surgery				
12-20	Left transtibial amputation	General	No	03:50
50-60	Joint (hip) replacement	General	No	01:05
30-40	Orthopedic knee surgery	General	No	02:00

50-60	Amputation of the left leg at the upper third of the thigh	General	No	01:30
30-40	Removal of the endoprosthesis of the left knee joint	General	No	01:03
<12	Achilloplasty of the left ankle	General	No	00:45

Efficacy assessment

The patient's response to treatment with Cevenfacta was recorded as "excellent," "good," "moderate," or "poor." at several timepoints:

- The intraoperative efficacy of Cevenfacta was assessed by the surgeon/practitioner immediately after completion of the procedure.
- Postoperative efficacy assessments were made by the investigator or designee at 24 hours after procedure completion, at 24-hour intervals while treatment with Cevenfacta was ongoing, after the last dose of Cevenfacta, and at 48 hours after the last dose of Cevenfacta or at early termination.

The **surgeon's/practitioner's rating** of intraoperative efficacy of Cevenfacta was based on the actual blood loss compared to the maximum expected volume of blood loss in a patient without a bleeding disorder estimated and recorded prior to surgery, the amount of fluid replacement given, transfusion requirements, hemodynamic stability, etc. The response was defined as follows:

- Excellent: intraoperative blood loss that was similar to or less than expected for this type of procedure in a patient without a bleeding disorder and who underwent the same surgical or other invasive procedure; no blood component transfusion was required
- Good: intraoperative blood loss that was greater than expected (but not more than 50% greater) for this type of procedure in a patient without a bleeding disorder and who underwent the same surgical or other invasive procedure; no unexpected increased blood component transfusion requirement
- Moderate: intraoperative blood loss that was substantially greater than expected (more than 50% greater) for this type of procedure in a patient without a bleeding disorder and who underwent the same surgical or other invasive procedure, not explained by a surgical/medical issue other than haemophilia; additional blood component (within 2-fold greater than expected) transfusion was necessary
- Poor: uncontrolled intraoperative blood loss, not explained by a surgical/medical issue other than haemophilia, that required intervention (rescue therapy requirement [bypass agent or porcine FVIII], and/or increased blood component [>2-fold greater than expected] transfusion, and/or led to hypotension or unexpected transfer to the intensive care unit [ICU])

The **investigator's/designee's** rating of haemostasis on post-operative days took into account the following definition:

- Excellent: postoperative blood loss that was similar to or less than expected following this type of procedure in a patient without a bleeding disorder and who underwent the same surgical or other invasive procedure; no blood component transfusion was required
- Good: postoperative blood loss that was greater than expected following this type of procedure

in a patient without a bleeding disorder and who underwent the same surgical or other invasive procedure, not explained by a surgical/medical issue other than haemophilia; no unexpected need for blood component transfusion

- Moderate: postoperative blood loss that was substantially greater than expected following this type of procedure in a patient without a bleeding disorder and who underwent the same surgical or other invasive procedure, not explained by a surgical/medical issue other than haemophilia; additional blood component [within 2-fold greater than expected] transfusion was necessary
- Poor: uncontrolled postoperative blood loss, not explained by a surgical/medical issue other than haemophilia that required intervention (rescue therapy requirement [bypass agent or porcine FVIII], and/or increased blood component [>2-fold greater than expected] transfusion, and/or led to hypotension or unexpected transfer to the ICU)

Primary efficacy endpoint: "good" or "excellent" assessment by the investigator 48 (±4) hours after the last administration of Cevenfacta (postoperative assessment)

The final assessment (which represented the primary efficacy outcome) was performed by the investigator at the study centre **48 (±4) hours after the last dose of Cevenfacta** and was **based upon the totality of the assessments performed on the patient at each timepoint**.

Of the 12 surgical procedures performed, 9 (81.8%) procedures were reported by the investigator as successfully treated ("good" or "excellent" response) with Cevenfacta at 48 hours after the last administration of Cevenfacta, 2 (18.2%) were treatment failures ("poor" response), and 1 assessment was missing because of discontinuation from the study (withdrawal of consent) prior to the assessment at 48 hours (Table 30). The narratives for the treatment failures are described in a section below.

Table 37: Primary efficacy endpoint: "Good" or "Excellent" assessment by the investigator 48 (±4) hours after the last administration of Cevenfacta (efficacy population)

	Surgery Type		Overall
	Minor	Major	
Number of surgeries	6	6	12
Number of successes	5 (100%)	4 (66.7%)	9 (81.8%)
Number of failures	0	2 (33.3%)	2 (18.2%)
Number of missing[1]	1	0	1
Success proportion [95% CI]	1.000 [0.478, 1.000]	0.667 [0.223, 0.957]	0.818 [0.482, 0.977]

Source: Module 5.3.5.2, CSR PerSept 3, Table 16.
Abbreviation: CI = confidence interval.
Note: The table summarizes data on surgical procedure level.
Note: The 95% CI for success proportion was calculated using the Clopper-Pearson exact method.
[1] One patient in the minor surgery group was discontinued from the study due to consent withdrawal 2 days after the procedure and the start of treatment before assessment

Secondary efficacy endpoints

Number of bleeding episode requiring transfusion between the start of the procedure and 48 (±4) hours after the last administration of Cevenfacta

Only 1 patient required a transfusion for a bleeding episode between the start of the surgical procedure and 48 (±4) hours after the last administration of Cevenfacta. See the narrative below.

Number and Type of Bleeding Events at the Surgical Site Between the Start of the Procedure and 48 (±4) Hours After the Last Administration of Cevenfacta

Only 1 patient had a bleeding event (moderate) at the surgical site (right knee) between the start of the surgical procedure and 48 (±4) hours after the last administration of Cevenfacta (see below).

Number of Surgical Interventions/Re-explorations for Bleeding Between the Start of the Procedure and 48 (±4) Hours After the Last Administration of Cevenfacta

No patient required such an intervention.

"Good" or "excellent" assessment by the surgeon/practitioner for the intraoperative period and estimated actual intraoperative blood loss compared to maximum predicted blood loss

The surgeon/practitioner assessed intraoperative treatment with Cevenfacta as successful ("good" or "excellent" response) for all 12 of the minor and major surgeries (100% [95% CI = 73.5%, 100%]).

Table 38: **Overview of individual surgical or other invasive procedures by surgery type and age**

	Age year	Surgery/Invasive Procedure	Number of infusions		Intraoperative assessment (Surgeon/Practitioner)			Postoperative assessment (Investigator)							
			Preoperative Minor (75µg/kg) Major (200µg/kg)	Postoperative (75µg/kg)	Blood loss (mL)		Assessment	Bleeding	Exploration or intervention	24 h	Every 24 h	Last dose	48h after last dose	Time of Last dose assessment (hour)	Primary efficacy endpoint
					Predicted	Actual									
MINOR	40-50	Tooth extraction	1	52	3	4.5	Good	No	No	Good	Good	Good	Good	166	Success
	20-30	Tooth extraction	1	72	1	1.5	Good	No	No	Good	Good	Good	Good	263	Success
	<12	Tooth extraction	1	27	2	3	Good	No	No	Good	Good	NA (1)	NA (1)	NA (1)	Missing (1)
	<12	Circumcision	1	24	15	1	Excellent	No(2)	No	Excellent	NA	Excellent	Excellent	48	Success
	<12	Circumcision	1	24	1	1	Excellent	No	No	Excellent	NA	Excellent	Excellent	49	Success
	<12	Circumcision	1	24	3	3	Excellent	No	No	Excellent	NA	Excellent	Excellent	48	Success
MAJOR	<12	Achilloplasty of the left ankle	1	131	150	40	Excellent	No	No	Good	Excellent/ Good (3)	Excellent	Good	765	Success
	12-20	Left transtibial amputation	1	93	300	200	Excellent	No	No	Good (4)	Excellent /Good	Excellent	Good	355	Success
	50-60	Joint (hip) replacement	1	13	500	250	Excellent	No	No	Good	NA (5)	NA (5)	Poor	24	Failure
	30-40	Orthopedic knee surgery	1	63	150	50	Excellent	Yes (6)	No	Moderate (7)	Excellent (7)	Poor	Poor	164	Failure
	50-60	Amputation of the left leg at the upper third of the thigh	1	103	500	600	Good	No	No	Good	Excellent/ Good	Excellent	Good	503	Success
	30-40	Removal of the endoprosthesis of the left knee joint	1	96	500	480	Excellent	No	No	Good	Good	Good	Good	719	Success

Source: Module 5.3.5.2, CSR PerSept 3 Listing 16.2.1 , Listing 16.2.10, Listing 16.2.12, Listing 6.2.14
(1) Not Applicable: The patient discontinued from the study due to consent withdrawal and had only 2 assessments at 24 and 48 hours (both rated "good"). The patient experienced a mild bleeding 4 hours after the procedure completion reported as TEAE unrelated to LR769 for which he received aminocaproic acid (5%) BID. The last assessment was missing.
(2) This patient had a bleeding at the surgical site 14 days after the last dose, the event was reported by the investigator as TEAE unrelated to the study drug.
(3) Assessment at 168 hours ("excellent") after completion of the procedure was recorded outside the protocol-specified time window and was considered missing.
(4) Assessment at 24 hours ("good") after completion of the procedure was recorded 13 min after the protocol-specified time window of 24±2 hours) and was considered missing.
(5) Not Applicable : The patient discontinued from the study due to a TEAE within 2 days after the last dose of LR769 and he received antihemorrhagic rescue medication (52 hours after the last dose).
(6) Bleeding in the surgical site 8 days after the surgical procedure and within 2 hours after the last administration of LR769 which required transfusion and treatment with NovoSeven.
(7) Assessment at 24 hours (moderate, assessed only after 12h30), 96 ("excellent"), 120 ("excellent"), and 144 hours ("poor") after completion of the procedure were recorded outside the protocol-specified time window and were considered missing.

Amount of Cevenfacta used

Table 39: Total amount of Cevenfacta, number of administrations, and duration of treatment by surgical/invasive procedures

Parameter Statistic	Surgery Type		Overall[1, 2] (N=12)
	Minor[1] (N=6)	Major[2] (N=6)	
Total amount of LR769 (µg/kg)			
Mean (SD)	2862.5 (1521.16)	6437.5 (3050.73)	4650.0 (2961.05)
Median	1987.5	7287.5	4450.0
Q1/Q3	1875.0/3975.0	4925.0/7925.0	1875.0/7287.5
Minimum/Maximum	1875/5475	1175/10,025	1175/10,025
Number of administrations			
Mean (SD)	38.2 (20.28)	84.2 (40.68)	61.2 (38.94)
Median	26.5	95.5	58.5
Q1/Q3	25.0/53.0	64.0/104.0	25.0/95.5
Minimum/Maximum	25/73	14/132	14/132
Total duration of treatment (days)			
Mean (SD)	4.3 (3.71)	17.6 (12.36)	11.0 (11.14)
Median	2.2	18.0	6.8
Q1/Q3	2.0/6.8	6.9/30.0	2.0/18.0
Minimum/Maximum	2/11	1/32	1/32

Source: Module 5.3.5.2, CSR PerSept 3 Table 25.
Abbreviations: Q = quartile; SD = standard deviation.
Note: The table summarizes data on surgical procedure level.
[1] One patient in the minor surgery group was discontinued from the study after consent withdrawal 2 day after the procedure and the start of treatment
[2] One patient in the major surgery group was discontinued from the study one day after surgery and the start of treatment with LR769 due to hematoma.

Narratives for treatment failures:

One patient was a 40-50-year-old male with a BMI of 18.0-19.0 kg/m^2. Previous bleeding medication included FEIBA (2000 U). In the study, the patient underwent a major surgical procedure on his right knee. The patient received 200 µg/kg loading dose of Cevenfacta followed by 75 µg/kg doses of Cevenfacta every 2 hours for 4 days, and then 75 µg/kg every 4 hours thereafter. The intraoperative efficacy assessment by the surgeon was "excellent". The actual intraoperative blood loss was estimated to 50 mL compared to a maximum predicted blood loss of 150 mL. About 12 hours after completion of the procedure, the patient required administration of 4 units of red blood cells due to severe anaemia (6.4 g/dL) and the investigator reported a moderate response (assessment outside the protocol visit). No postoperative efficacy assessment at 24 hours was performed. At 48 and 72 hours after completion of the procedure the efficacy assessments were "excellent" as well as at 82 and 106 hours after completion of the procedure (assessments outside the protocol visits). Within 24 hours of the patient's last dose of Cevenfacta, i.e. 7 to 8 days after completion of the procedure, the patient had a moderate bleeding episode at the surgical site that required a transfusion with 3 units of packed red blood cells and alternative therapy with NovoSeven (90 and 270 µg/kg IV). The efficacy assessment was "poor". At 48 hours after the last dose of Cevenfacta was also "poor".

Another patient was a 50-60-year-old male who had previously participated in study RBFVIIa-006-13 (PerSept 1). In PerSept 1, he had experienced 25 mild/moderate bleeding episodes. All bleeding events were successfully treated. No bleeding episode recurred, required a visit to the hospital, or required alternative treatment. He completed his participation in PerSept 1 and he was enrolled in PerSept 3 15 months thereafter. At study entry, this patient's BMI was 31.0-32.0 kg/m^2. Previous bleeding medication included FEIBA (4000 U). He underwent venous catheter placement with a treatment with FEIBA (5000 U), which took place 8 days before he received his first dose of Cevenfacta in PerSept 3. In the study, the patient underwent a major surgical procedure of right hip replacement. He received a 200 µg/kg loading dose of Cevenfacta followed by 75 µg/kg doses of Cevenfacta every 2 hours.

The intraoperative efficacy assessment by the surgeon was "excellent." The actual intraoperative blood loss was estimated to 250 mL compared to a maximum predicted blood loss of 500 mL. At 24 hours after completion of the procedure, the efficacy was assessed as "good." Post-procedural hematoma formation was observed the day after the surgery. The patient's haemoglobin decreased to 111 g/L, (158 g/L at screening) which was considered abnormal and clinically significant. The increased hematoma was assessed as Cevenfacta inefficacy leading to a withdrawal of study drug 1 day after completion of the procedure and discontinuation from the study. This patient's imputed efficacy response was classified as "poor" for the 48 [±4] hours after the last dose of Cevenfacta timepoint assessment.

Rescue medication with FEIBA (4500 U IV three times daily) was administered after the early termination visit. Nonsteroidal anti-inflammatory drugs (NSAIDs) were administered without pain relief; analgesia was achieved with fentanyl (25 µg/hour, subcutaneous) and trimeperidine 2% (1 mL IV). The post-procedural hematoma was considered by the investigator to be possibly related to treatment with Cevenfacta.

Three days after the surgery, the patient experienced acute haemorrhagic anaemia resulting from a gastrointestinal haemorrhage, which complicated his haemophilia A. He suffered cardiopulmonary arrest and died. An autopsy revealed severe anaemia of the visceral organs, a large intermuscular haematoma of the right hip, signs of gastrointestinal haemorrhage, acute haemorrhagic anaemia, and interstitial pulmonary oedema. There were no signs of chronic stomach ulcer or cirrhosis. The investigator considered the haemorrhagic anaemia and gastrointestinal haemorrhage to be serious and probably related to treatment with Cevenfacta due to temporal association and disseminated intravascular coagulation (DIC). However, there was no clinical evidence, nor any autopsy findings to indicate DIC, and the patient had been switched from Cevenfacta to FEIBA approximately 3 days before the gastrointestinal haemorrhage. Analysis performed by the sponsor and the data monitoring committee concluded that the postoperative administration of NSAIDs followed by gastrointestinal haemorrhage and acute haemorrhagic anaemia, coupled with the fact that the terminal half-life of Cevenfacta is approximately 2 hours, suggested that these serious adverse events were unlikely to be related to treatment with Cevenfacta. Of note, with the responses to the D120 LoQ, it was confirmed that no postoperative NSAIDs were administered. The latest intake of an NSAID was one week before the surgery. Regarding the question why acute haemorrhagic anaemia was mainly attributed to the gastrointestinal haemorrhage, the autopsy report was provided indicating that the participant lost up to 2,500 mL blood in the gastric lumen, small gut and colonic loops.

2.5.7. Discussion on clinical efficacy

Design and conduct of clinical studies

The provided efficacy data for Cevenfacta comprise results from three clinical trials investigating either the treatment of bleeding events (PerSept1: patients ≥ 12 years, PerSept2: <12 years) or the prevention of excessive bleeding during elective surgery or invasive procedures (PerSept3: patients ≥6 months to ≤75 years) in subjects with haemophilia A or B with inhibitors.

In both PerSept1 and 2, subjects were randomly assigned to one of two dosing regimens, which differed by the strength of the initial bolus dose and the intervals of the subsequent infusions. One dosing scheme was to administer 75 µg/kg, followed by (if necessary) additional 75 µg/kg administrations every 3 hours for up to 21 hours (for severe bleeding events: every 2 hours until improvement). The alternative dosing scheme involved a high bolus infusion of 225 µg/kg. If necessary, this was followed by a second dose of 75 µg/kg 9 hours later and additional doses every 3 hours until up to 21 hours. For severe bleeding events, the second dose (75 µg/kg) was scheduled 6

hours after the bolus infusion and the intervals of the subsequent doses were shortened to 2 hours. Every 3 months, patients crossed over to the alternate treatment regimen.

In the **PerSept1** trial, a total of 27 patients were enrolled at 11 different study sites, mainly in Eastern Europe and the US, and received Cevenfacta for the treatment of in total 468 bleeding episodes (465 mild/moderate, 3 severe). The **PerSept2** trial enrolled 25 patients from 8 sites in Europe, America and South Africa. The CSR includes data on 549 treated bleeding events (546 mild/moderate, 3 severe).

Among the 52 patients enrolled in the on-demand treatment studies (PerSept1 + PerSept2), there were only 4 haemophilia B patients (severe, with inhibitors). The remaining patients were patients with haemophilia A with inhibitors (45x severe, 3x moderate). In PerSept1, ~50% of patients had BU ≥5, and ~40% of patients had BU <5 but were expected to have a high anamnestic response to FVIII or FIX. The other had BU <5 but were expected to be refractory to increased doses. In PerSept 2: ~24% of patients had BU <5 but were expected to have a high anamnestic response to FVIII or FIX, and 4% of patients had BU <5 but were expected to be refractory to increased dosing of FVIII or FIX. The other patients had BU ≥5.

The **PerSept3** trial presents data from 12 patients with severe haemophilia A with inhibitors, who underwent 12 surgeries/invasive procedures (6 minor, 6 major surgeries) at 8 sites in 5 countries (South Africa, Mexico, Eastern Europe). For minor procedures, the subjects received an initial dose of 75 µg/kg within 2 minutes of the surgical incision or invasive procedure. This was followed by subsequent administration of 75 µg/kg every 2 hours and increasing intervals during the following days, based on the judgement of the investigator. For major surgeries, the initial dose prior to surgical incision was 200 µg/kg, followed by 75 µg/kg every 2 hours for 48 hours. The intervals for the subsequent days/weeks were more flexible.

The in- and exclusion criteria selected a patient population with haemophilia A or B with inhibitors with either a high BU titre or a high anamnestic response when displaying titres <5 BU. In the absence of a specific guideline for factor VII products, the BWP and CHMP agreed that the "Guideline on clinical investigation of recombinant and human plasma-derived factor IX products" (EMA/CHMP/BPWP/144552/2009 Rev. 1), can be regarded as an appropriate reference for different aspects of the development of Cevenfacta. The in- and exclusion criteria and number of recruited patients for the three PerSept trials are in line with this guidance and repeated scientific advice given by the CHMP.

Due to very small target patient population a non-inferiority trial with an active comparator was not considered feasible and a placebo control not possible due to ethical reasons. Therefore a non-controlled study design was accepted by CHMP in frame of a scientific advice procedure (EMA/CHMP/SAWP/424687/2011), also because no claim beyond bleeding control is sought. Further, historical control with bleeding control rates from trials with NovoSeven and FEIBA was deemed sufficient for benefit-risk assessment. In order to formalise this historical control, the applicant defined a pre-specified objective performance criterion (OPC) = 0.55, against which the proportion of success for the pivotal studies were compared. This OPC was determined by reviewing the literature on the reported success of treatment with bypassing agents. The identified published data describe treated bleeding events mainly in adults with only few paediatric subjects included. In addition, a three-point rating scale is used in several trials, which could skew results into the more effective range. CHMP recognised these uncertainties in the scientific advice procedure and stated that at MAA, the totality of the data available will be evaluated regarding the benefit risk ratio of each investigated dosing regimen.

A discrepancy was noted with regard to patients with high anamnestic response to FVIII or FIX between the inclusion criteria and the claimed indication (FVIII or IX inhibitor titre BU<5 for inclusion criteria and high-response inhibitors to FVIII or IX (BU≥5) in the claimed indication). This discrepancy

in the wording of the indication was amended by the applicant. The inclusion of patients on ITI is accepted; eptacog beta is not expected to increase the inhibitor titre and the intensive FVIII or FIX administration may increase the anamnestic response to FVIII or FIX. Unlike PERSEPT 1 and 2, patients receiving ITI therapy were excluded from PERSEPT 3. The applicant justified the difference on ITI therapy between PerSept 1and 2 and PerSept 3 by the difficulty to pursue such treatment in patients hospitalised for surgery.

Efficacy was assessed by the patient/caregiver and recorded in the patient diary and, if treated in the hospital, also by the physician. A 4-point haemostatic scale for the response assessment was used as recommended in the Guidelines for clinical development of recombinant FVIII and FIX. The four categories of response to treatment "none", "moderate", "good" and "excellent" were based on the assessment of pain and objective signs of bleed (i.e. swelling, tenderness and decreased range of motion in the case of musculoskeletal haemorrhage). It was mentioned in the dossier that a visual analogue scale (VAS) to rate pain was completed to assess response of pain to treatment in the patient diary. Nevertheless the assessment of the other parameters relative to signs of bleed were not mentioned. In the D120 LoQ it was asked how these parameters were recorded by the patient/caregiver in order to rate the response to treatment of a bleeding episode as "excellent," "good," "moderate," or "none." The applicant indicated that the criteria relative to signs of bleed such as swelling, tenderness and decreased ROM assessed by the patient for mild/moderate bleeding and physician for severe bleeding have not been collected and rated individually and that they were part of the global 4-point scale. Signs of bleed are indeed considered as subjective criterion while the overall product consumption and the pain as assessed by a VAS, both recorded, allowed a more objective assessment in the 4-point scale.

The primary efficacy endpoint for the PerSept1 and PerSept2 studies was defined as the proportion of bleeding episodes regardless of severity (mild, moderate and severe) with a patient/caregiver-reported (for mild/moderate bleeding episodes) and physician-reported (for severe bleeding episodes) response of "good" or "excellent" on the 4-point haemostatic scale at 12 hours after initial administration of Cevenfacta.

In the PerSept1 and PerSept2 trials, the study duration was specified as "until at least 352 bleeding episodes had been treated and at least 6 months had passed since first administration". However, substantially higher numbers of bleeding episodes were reported in the final CSRs (PerSept1: 468, PerSept2: 549). The mean duration of exposure was 6.6 months in PerSept1, and 11.2 months in PerSept2. According to the protocol of PerSept1, an interim analysis was planned after 80% (or 282 bleeding episodes) of the initial planned sample size of 352 bleeding episodes had been treated. This meeting was to discuss an analysis prepared by an independent statistician on the conditional power of the study and the need for a sample size re-estimation. No results of this interim analysis is provided, despite the substantial deviations from the study protocol. The studies are unblinded and subjectivity is involved in the assessment of the primary endpoint, both of which violates the recommendations in the EMA guideline on METHODOLOGICAL ISSUES IN CONFIRMATORY CLINICAL TRIALS PLANNED WITH AN ADAPTIVE DESIGN. The applicant was asked to provide an explanation for the lack of adherence to the study protocol and to demonstrate that the alterations were not done in a data-driven manner. In the responses to the D120 LoQ, the applicant provided background information from the DMC meetings. The study ended upon the study completion of the 27 patients already treated at the time of the third DMC Meeting. These 27 patients ultimately registered a total of 468 bleeding episodes (465 mild/moderate and 3 severe).

Furthermore, the applicant was asked to provide additional efficacy analyses for both PerSept (1+2) studies, including only the first 352 bleeding events, as initially planned in the original protocol. In the responses, the applicant only addressed the PerSept1 study. The sensitivity analysis after 352 bleeding events shows very similar point estimates and confidence intervals compared to the primary endpoint.

No further concern is raised regarding the PerSept1 study.

However, the overrun of bleeding episodes was even higher for the PerSept2 trial. In total, 549 bleeding episodes were treated. The applicant was asked to provide the same sensitivity analysis for PerSept2, including a justification for the overrun. Of note, the mean treatment duration of exposure during PerSept 1 was 6.6 months (n=27), while the mean duration of exposure was 11.2 months (n=25) during PerSept2. In the responses to the D180 LoOI, the applicant convincingly explained that a lower than expected median bleeding rate (observed rate 1.4 BEs/month vs assumed rate 2.67 BEs/month) caused the longer mean duration of exposure in PersSept2, compared to PerSept1. Two subjects with an unusually high number of BEs (these 2 participants experienced in total 120 BEs) did also strongly contribute to the overrun. No sensitivity analysis was provided for PerSept2, since the applicant decided to exclude the respective population from the label, which is acceptable.

Several changes to the statistical methods were done as part of PerSept 1 protocol amendments. Due to the open-label nature of study, the applicant was requested to comment on the timing of these amendments with regards to patient enrolment and data accumulation. As requested, the applicant provided further clarifications regarding the timing of protocol amendments and therefore of the main changes in statistical methods with regards to patient enrolment. The content and impact of each protocol amendment was described, and the number of patients enrolled, the number of treated bleeding episodes and the point estimates for the primary endpoint are summarised at the time of each protocol amendment. It is noted that some of the key changes in statistical methods, introduced with protocol amendments 1 and 2, were implemented before first patient enrolled. It is agreed that such changes can be considered independent of the subsequent trends in the accumulating data.

Other methodological issues were raised regarding the lack of proper control of multiplicity, a clear justification for the usage of the OPC of 55%, or the consequence of treatment withdrawal with respect to further treatment and bleeding outcome.

Not all methodological issues were resolved in the end. For example, for people who are withdrawn from treatment with the study drug, the remaining bleeding episodes (after withdrawal) should be documented and included as failure in the efficacy assessment. The responses by the applicant could also not clarify whether ALL bleeding events during the whole study period have been treated with Cevenfacta or whether some of the events were treated with alternative treatments (without documentation). The difficulty of evaluating events that were not reported is acknowledged, but the concern arises whether or not the reporting of bleeding events is independent of the perceived efficacy of their treatment. An introduction of bias cannot be ruled out, especially because most patients were treated at home. The estimate of the rate of treatment failure in the population of bleeds that were reported could not be representative of the overall rate of failure. The applicant has also not provided adequate reasoning for the value of the OPC from a clinical or methodological perspective. However, these issues are not further pursued, since the main aspects of the study design have been agreed with during several previous EMA-SA procedures.

Missing data were excluded from the primary analysis of the phase 3 studies, which could result in biased primary analysis estimates. The applicant performed sensitivity analyses where missing assessments were not excluded to assess the robustness of the main results. In order to better understand the potential implications of missing data, the applicant was requested to provide further clarifications regarding the reasons for missing assessments. The applicant describes the <5% missing rate as being acceptable and argues that a primary analysis based on observed cases is standard practice. This is not agreed, and missing data should generally be accounted for in the primary analysis, especially when missing not at random (MNAR) data patterns are suspected, as in the present situation. Indeed, the review of bleeding episodes with missing responses indicates, as acknowledged by the applicant, an estimation bias with an overestimation of the proportion of success. Due to the

limited information and absence of collected reason for missing data, this bias cannot be precisely quantified. Therefore, as part of the D180 LoOI, it was requested that the SmPC summary table should be updated for the primary analysis results (point and interval estimations) based on the analysis where bleeding episodes with missing assessments are considered as failures. The applicant changed the respective table accordingly.

In the PerSept3 trial, the primary efficacy endpoint was the percentage of surgical or other invasive procedures with a "good" or "excellent" response to Cevenfacta treatment 48 (±4) hours after the last administration of Cevenfacta as assessed by the investigator.

The patient's response to treatment with Cevenfacta was recorded as "excellent," "good," "moderate," or "poor" at several timepoints:

• The intraoperative efficacy of Cevenfacta was assessed by the surgeon/practitioner immediately after completion of the procedure.

• Postoperative efficacy assessments were made by the investigator or designee at 24 hours after procedure completion, at 24-hour intervals while treatment with Cevenfacta was ongoing, after the last dose of Cevenfacta, and at 48 hours after the last dose of Cevenfacta or at early termination.

The evaluation of response to treatment was in line with the Guidelines on the clinical investigation of FVIII and FIX products stating that response should be assessed as "none", "moderate", "good" or "excellent" by the physician including efficacy of haemostasis, loss of blood, and requirements for transfusion. The response to treatment were to be assessed by two different operators, which is acknowledged since different physicians are involved in intra- and post-operation but this may induce variability in evaluation. The postoperative efficacy assessment timepoints (i.e., at 24 [±2] hours after completion of the surgical procedure, and then every 24 [±2] hours while treatment was ongoing, at the time of the last dose, at 48 hours after the last dose, and at early termination) should be justified in light with the administration of treatment that is done more frequently. The applicant's justification of the timing of the efficacy assessments was mainly based on the two studies supporting the approval of Novoseven, which is acknowledged in the lack of dedicated guideline. The issue was not further pursued.

The pre-operative and operative doses for major surgery are 200 µg/kg immediately before the surgery, followed by 75 µg/kg every 2 hours for the duration of the surgery with further recommendations for post-operative doses. The applicant was asked to clarify the rationale for the 200 µg/kg pre-operative dose. In the responses, the applicant cited a publication (UK consensus protocol for the use of FVIIa in orthopaedic surgeries, Giangrande et al., 2009), which recommends the use of a bolus dose between 120–180 µg/kg of NovoSeven to cover surgery. The applicant describes that the reason for picking the 200 µg/kg dose was based on the intention to remain close to both the cited study and the Phase 1 PK/PD study. From an efficacy point of view, the decision to study the 200 µg/kg dose for prevention of bleeding during major surgeries is understood.

Efficacy data and additional analyses

The study designs and populations of the available published clinical trials with other bypassing agents differ in terms of several important aspects, such as the definition and time point of the primary endpoints, modality of treated bleeds (e.g. only joint bleeds) and the included subjects (e.g. mostly adults) from the PerSept studies. This clearly hampers the comparability of the obtained results with those of the published trials and limits the usefulness of the predefined OPC.

In **PerSept1,** the primary endpoint is met for both dose regimens with a proportion of mild/moderate/severe bleeding episodes that were successfully treated at 12 hours of 85.7% (95% CI = 75.0%, 96.4%) for the 75 µg/kg regimen and 93.8% (95% CI = 88.9%, 98.6%) for the 225 µg/kg

regimen (p<0.001). A higher success proportion is shown with the 225µg/kg dose regimen compared to the 75 µg/kg dose. It is however noted that no imputation was made for missing values in the primary efficacy analysis, with a number of missing bleeding episodes of 22 (4.7%). Assigning missing assessments as failures would be the more conservative approach and appears more appropriate. This results in a proportion of 89.8% successfully treated bleeding episodes (194/216 bleedings) for subjects receiving an initial dose of 225 µg/kg, compared to 80.2% (202/252) for the dose of 75 µg/kg. These point estimates are similar to published results with NovoSeven and FEIBA and also comparable to expected outcomes for factor VIII or IX treatment in haemophilia without inhibitors. The subgroup analysis by inhibitor level shows a lower successfully treated bleeding in the low titre group compared to the high titre group for both dose regimens. The discrepancy observed in the successful treatment between patients with low titre inhibitors and high titre inhibition could not be clearly justified by the applicant that suggests a possible impact of the immune response (type of antibodies, epitope specificity, kinetics, mechanisms of inhibition of FVIII function, etc.) or genetic factors. It was noted that this discordance across the two subpopulations was also observed in PerSept 2. The issue was not further pursued.

In terms of time to assessment of a successful response (= 'good' or 'excellent' assessment) there was a clear difference between the two treatment regimens, with a median of 3 hours for the 225 µg/kg group and 6 hours for the 75 µg/kg group. As expected, a lower number of study drug administrations were necessary for the 225 µg/kg group (mean 1.4, median 1.0 administrations) compared to the 75 µg/kg group (mean 2.5, median 2.0 administrations). On the other hand, the higher bolus infusion of 225 µg/kg resulted in a higher total amount of study drug administered (mean 252.96 µg/kg, median 225.09 µg/kg) compared to the lower dose bolus infusion of 75 µg/kg (mean 187.87 µg/kg, median 149.68 µg/kg) for the treatment of mild/moderate bleeding events.

The posology section of the currently proposed SmPC indicates both treatment regimen, while suggesting that dose, frequency and duration of Cevenfacta therapy should be based on the patient's clinical response and haemostasis evaluation. This is in line with the SmPC of NovoSeven and flexibility based on individual response is endorsed. Further, this may also have a dose sparing effect in individuals with sufficient response to the lower dosed bolus infusion.

One patient reported 4 bleeding events (2x right elbow, 2x right knee) on mid Q4 2014. Based on the provided information, these bleeding events might have been rated as bleeding recurrence. The applicant was asked in the D120 LoQ to comment and to provide more information about these events. In the responses, the applicant clarified that the second bleedings occurred more than 24 hours after the last treatment of the previous bleeding. Therefore, these events did not meet the criteria of a bleeding recurrence (as defined in the protocol).

During the PerSept1 trial, a new manufacturing product was introduced (commercial product, upscaled Process B). In principle, the results of the PerSept1 trial suggest that Cevenfacta is sufficiently efficacious for the treatment of bleeding episodes. However, the presented efficacy results are compromised by the fact that only a relatively small fraction of patients received product of the commercial Process B. Of the 468 bleeding episodes in PerSept1, only 18.4% were treated with product from process B and ~11.3% with a mixture of products from both processes. There was a high intra-subject variability for PK parameters such as C_{max} and AUC. A reduced efficacy was noted for the 225 µg/kg dosing regimen for Process B (~80%) compared to process A (~90%) in PerSept 1, therefore the bridging of outcomes observed with the clinical trial material to the commercial material is not straightforward. Considering that there were also some questions regarding the quality comparability exercise, two major objections were raised, one for the quality comparability exercise, and another overarching major objection regarding the PK and efficacy aspects.

The MO regarding the quality comparability was solved by the applicant.

Comparability of clinical data: The applicant pointed out that the haemostatic response did not differ statistically between Process A and Process B as the 97.5% CIs for the proportion of success overlap with each other. This is also the case if missing assessments are imputed as failure for the analysis. The applicant provided a detailed overview of the efficacy assessments for subjects who were treated with products from both manufacturing processes. Efficacy assessment at 12 hours was available for 14 patients totalling 275 bleeding episodes, 196 treated with Process A and 79 treated with Process B. Each individual subject was discussed separately. The detailed overview of the treatment success in patients who received products from both manufacturing processes is reassuring and it can be agreed that no meaningful differences were observed. A comparison of safety data was provided as well and no further concern did arise.

Despite the concluded comparability based on provided Quality data, comparability of the pharmacokinetic profile between process A and B cannot be concluded. However, data on efficacy and safety do not raise further concern on potential differences on applied manufacturing processes.

Considering all the provided information, especially also the fact that the MO on the quality comparability was sufficiently addressed, this overarching major objection with respect to the clinical issues concerning the change in the manufacturing process during development was considered as resolved.

Only 3 severe bleedings were treated during the trial PerSept1 (traumatic intramuscular, spontaneous right hip and, spontaneous renal haemorrhages). All three bleeding episodes achieved haemostasis at 12 hours after the initial administration of Cevenfacta and did not require alternative treatment or retreatment. However, one patient was treated with a much higher dose than pre-specified in the protocol, one patient was concomitantly treated with an antihaemorrhagic (etamsylate) drug, and for one event it was initially not entirely clear why it was attributed as severe. The applicant was asked to provide more information regarding the concomitant treatment with etamsylate and to further elaborate why the bleeding event in one subject was considered as severe. The applicant clarified that the severe bleeding event was caused by a tongue bite. The event was considered as severe by the investigator due to its location in the mouth region and its traumatic origin. This is in line with the Classification of severity of bleeding episodes. It was also clarified that treatment with sodium etamsylate (in another patient) was initiated on the same day as the severe renal bleeding started (mid Q2 2015) and was continued for 3 days. According to the protocol, such concomitant treatment with sodium etamsylate (or other antihaemorrhagic drugs such as tranexamic acid) was not disallowed. Concomitant administration of etamsylate may confound the treatment effect of Cevenfacta. However, it is acknowledged that this treatment was allowed according to the protocol. In the real world situation, it would not be unusual to concomitantly administer other antihaemorrhagic agents such as antifibrinolytics (tranexamic acid) as haemostatic support in some cases (as also suggested in the WFH guideline for the management of haemophilia).

There were a total of 154 minor protocol deviations reported for 25 patients (12 patients in the 75 µg/kg dose group and 13 patients in the 225 µg/kg dose group) during the study, mainly related to study procedures or assessments that were not performed according to the schedule in the protocol (75.3%). Missing efficacy assessment as part of protocol violation related to study procedure or assessment-related is considered as having an impact on efficacy analysis, taking into account that missing data are excluded from the primary analysis. The applicant was asked to discuss how the minor and/or major protocol violations related to compliance in study drug administration impacted the response to treatment of the bleeding episodes and efficacy results. The impact on efficacy of a large majority of protocol deviations related to compliance in study drug (47 of 83) occurring in two subjects could regrettably not be assessed due to the lack of assessment or record of efficacy data. From the 83 protocol deviations related to compliance in study drug reported in PerSept 1, only 29 were recorded during the treatment of bleeding episodes and were considered by the applicant to have a potential

impact on efficacy. Additional dosing administration after a good/excellent assessment occurred in 8 bleeding episodes and are not expected to have an impact to the efficacy as assessed by the primary endpoint since the total number of IMP dose received before response was still compliant with the protocol recommendation for the treatment, but can affect the outcome of the secondary endpoint "number of administrations and total amount of drug administered per bleeding episode". Moreover a good assessment was reached before the 12 hours timepoint of the primary endpoint in both 8 bleeding episodes with additional dosing administration. Indeed the relevance of the sensitivity analysis regarding the effect of additional dosing administration on the primary endpoint when considering the bleeding episodes as failure if the assessment was preceded by additional dosing administration after good/excellent assessment at a previous assessment timepoint (N=8) is unclear, since additional dose administrations after improvement are not expected to impact efficacy. The point estimates in the SA are consistent with those from PA for the primary endpoint.

It is noted that concomitant medications were administered twice as often to patients in the 75 µg/kg treatment regimen (92.3%) than to patients in the 225 µg/kg treatment regimen (42.9%). In particular analgesics and antihaemorrhagics treatment were more administered in the 75 µg/kg treatment regimen (38.5% and 46.2% respectively) compared to the 225 µg/kg treatment regimen (21.4% and 0 respectively). Blood coagulation factor other than FEIBA or Novoseven were administered in 4 (30.8%) subjects in the 75 µg/kg treatment regimen vs 0 in the 225 µg/kg treatment regimen. A total of 3 (11.1%) patients received a concomitant bypassing agent (FEIBA or Novoseven) during the study: 2 (15.4%) subjects in the 75 µg/kg treatment regimen and 1 (7.1%). The applicant was asked to discuss the more frequently use of concomitant medications in patients in the 75 µg/kg treatment regimen compared to the 225 µg/kg treatment regimen, in particular analgesics and antihaemorrhagics, in light of the response to Cevenfacta treatment of bleeding episodes. Although the discrepancies observed in the tables in the PerSept 1 CSR did not reflect the actual concomitant treatment use since these tables were stratified by treatment regimen assigned at randompaediatric, it is however noted that the use of rescue therapy was higher with the 75 µg/kg regimen than the 225µg/kg regimen, i.e. 4 vs 1 bleeding episodes respectively. Also concomitant medication other than bypassing, medical history or adverse event during the treatment of bleeding episodes (Table Q123-1) were administered in 4 patients for 5 bleeding episodes of which 4 were treated with the 75µg/kg regimen (NSAIDs for haemorrhage-related pain, antifibrinolytic and antibiotics for gingival infection associated to bleeding for 2 bleeding episodes and FVIII for bleeding prophylaxis) and one treated with the 225 µg/kg regimen (antihaemorrhagics and corticosteroids for a severe renal bleeding). Nevertheless, despite the higher numerical use of concomitant medications due to bleeding related events with 75 µg/kg compared to 225 µg/kg, the small number of cases prevents any clear conclusion on its relation to the efficacy of Cevenfacta. Of the 6 cases of analgesics, anti-inflammatory and antirheumatic products, or antihaemorrhagic treatment that were started at the same time or during a bleeding episode, 5 had available assessments and 3 of them were for bleeding episodes or associated pain. The limited number of cases does not allow to highlight any imbalance across the 2 dose regimens. There were 94 bleedings episodes with ongoing concomitant treatment with analgesics, anti-inflammatory and antirheumatic products, and or antihaemorrhagics of which comparable number of successfully treated bleedings in the 75 µg/kg and 225 µg/kg regimens (36 and 31 respectively) but higher number of unsuccessfully treated bleedings in the 75 µg/kg regimen compared to the 225 µg/kg regimen (20 vs 4). However the use of these concomitant treatment started before the occurrence of the bleeding episode leading to the use of Cevenfacta so a lack of efficacy could not justify the discrepancy in the observed unsuccessfully treated bleeding episodes across the 2 dose regimens.

With the D120 LoQ, the applicant was asked to provide separate efficacy results for mild and moderate bleeding episodes. In PerSept1, the majority of bleeding events was moderate in severity (~78%). Overall, the efficacy point estimates were higher for mild bleedings (treatment success: 93.3% for

both dose regimens combined) compared to moderate bleedings (treatment success: 82.8% for both dose regimen combined), which is not surprising. Interestingly, this difference was mainly caused by a weaker efficacy readout with the 75 µg/kg dose regimen (treatment success: 78%).

Table 40. Primary efficacy endpoint – successful treatment of mild and moderate bleeding episodes at 12 hours by FDA and EMA definitions

	Mild Bleedings			Moderate Bleedings		
Statistics	75 µg/kg (N=16)	225 µg/kg (N=16)	Overall (N=22)	75 µg/kg (N=23)	225 µg/kg (N=25)	Overall (N=25)
EMA definition						
Number of Episodes	52	47	99	200	166	366
Number (%) of Successes	48 (92.3%)	45 (95.7%)	93 (93.9%)	156 (78.0%)	147 (88.6%)	303 (82.8%)
Number (%) of Failures	2 (3.8%)	1 (2.1%)	3 (3.0%)	32 (16.0%)	12 (7.2%)	44 (12.0%)
Number of Missing Responses	2 (3.8%)	1 (2.1%)	3 (3.0%)	12 (6.0%)	7 (4.2%)	19 (5.2%)
Success Proportion [95% CI] (1)	0.960 [0.837, 1.000]	0.978 [0.931, 1.000]	0.969 [0.901, 1.000]	0.830 [0.675, 0.985]	0.925 [0.850, 0.999]	0.873 [0.759, 0.988]
p-value (2)	<0.001	<0.001	<0.001	<0.001	<0.001	<0.001
p-value (3)		NA			0.041	
FDA definition						
Number of Episodes	52	47	99	200	166	366
Number (%) of Successes	47 (90.4%)	45 (95.7%)	92 (92.9%)	155 (77.5%)	146 (88.0%)	301 (82.2%)
Number (%) of Failures	3 (5.8%)	1 (2.1%)	4 (4.0%)	33 (16.5%)	13 (7.8%)	46 (12.6%)
Number of Missing Responses	2 (3.8%)	1 (2.1%)	3 (3.0%)	12 (6.0%)	7 (4.2%)	19 (5.2%)
Success Proportion [95% CI] (1)	0.940 [0.811, 1.000]	0.978 [0.931, 1.000]	0.958 [0.874, 1.000]	0.824 [0.669, 0.980]	0.918 [0.845, 0.992]	0.867 [0.752, 0.983]
p-value (2)	<0.001	<0.001	<0.001	<0.001	<0.001	<0.001
p-value (3)		0.449			0.034	

In **PerSept 2**, 546 of the 549 treated bleeding events were classified as mild/moderate. None of the three severe bleeding episodes that occurred during the study was assessed as a success. Two were treatment failures and for the third, the 12-hour assessment is missing. However, from the narratives it is clear that for each severe bleed in the first days no assessment better than moderate was reported. The very low number of severe bleeding episodes occurring in the study prevents any conclusion on the efficacy of eptacog beta for severe bleedings; nevertheless the efficacy results for these severe bleeding episodes are mentioned in the SmPC.

66.1% of bleeding events treated with the 75µg/kg dose were successfully treated at 12 hours, as well as 61.3% of bleeds treated with the 225µg/kg dose in the total population. For both dosing schemes, the lower confidence intervals are below 55% as defined by the OPC, thus the study has formally failed its primary analysis. As mentioned in the description of the OPC in the introduction of the efficacy section, this fact alone will not lead to an automatic rejection of the trial outcomes as supportive of an indication in the investigated age group. Due to the fact that the OPC was defined using published outcomes of bleeding events treated with NovoSeven or FEIBA mostly in adults and often using a 3-point bleeding scale, the relevance of this threshold to the paediatric population is unclear and should not constitute the main reason to reject a label in children <12 years of age.

An analysis of the primary outcome for the two age cohorts showed the following results: For the <6-year-old subjects, these values are 56.6% and 58.5% for 75µg/kg and 225µg/kg, respectively. For the 6 to <12-year-old patients, the proportions are 73.7% and 63.8% for the two different dosing schemes. The lower bounds of the confidence intervals are below the pre-specified 55% in both age groups, except for the 75µg/kg dose in the older cohort.

It is established that younger children display a faster protein metabolism than older children or adults and usually a higher dose of coagulation factor VIII or IX is necessary to treat bleeding events in children with haemophilia compared to adults. Despite the fact that a faster clearance of Cevenfacta was observed in paediatric subjects (CL based on a median weight of 19 kg was 3.68 L/h (~194 mL/h/kg; 25.1 %CV) in PerSept 2, while CL based on a median weight of 67.4 kg was 7.62 L/h (~113 mL/h/kg; 26.4 %CV) in the PerSept 1 study), the same dose and interval as in adults was used for children in both age cohorts. A trend towards better treatment outcomes was observed in the 6 to <12 cohort, supporting the notion that the selected dose and /or dosing interval should have been adapted for children. The analysis of the primary endpoint according to BMI subgroups shows increasing efficacy with increasing BMI. Due to weight-based dosing, an increased dose of Cevenfacta despite a similar intravascular compartment is administered in patients with the same height but higher weight and leads to better outcomes, further indicating that children might be underdosed with the adult dosing regimen.

The median time to assessment of a good or excellent response was 9 hours for the 75µg/kg dose and 12 hours for the 225µg/kg dose. As for the lower dose, a repeat administration was allowed every 3 hours, this signifies the need for 3 doses of 75µg/kg (at 0, 3 and 6 hours) until success. For the higher dose, the initial treatment of 225µg/kg could be followed with a 75µg/kg dose at 9 hours, and the outcome of this endpoint signifies that the initial higher dose and at least one additional dose are needed for resolution of the bleed. It is apparent that a more frequent administration of Cevenfacta leads to an earlier resolution of the bleeding event in children <12 years of age. However, compared to outcomes from PerSept 1, where a median of 3 hours for the 225 µg/kg group and 6 hours for the 75 µg/kg group passed until a good/ excellent response was reported, these values emphasise the inferior bleed control in younger children compared to adolescents and adults.

In order to show if there is a substantial difference in efficacy, the applicant was asked to provide separate efficacy results for mild and moderate bleeding episodes for PerSept2.

In their responses to the D120 LoQ, the applicant submitted the following analysis:

Table 41: **Primary efficacy endpoint – Successful treatment of mild and moderate bleeding episodes at 12 hours, by FDA and EMA definitions.**

	Mild Bleedings			Moderate Bleedings		
Statistics	75 µg/kg	225 µg/kg	Overall	75 µg/kg	225 µg/kg	Overall
EMA definition (All Patients)						
N	14	20	20	18	19	20
Number of Episodes	64	98	162	175	209	384
Number (%) of Successes	61 (95.3%)	93 (94.9%)	154 (95.1%)	97 (55.4%)	97 (46.4%)	194 (50.5%)
Number (%) of Failures	3 (4.7%)	3 (3.1%)	6 (3.7%)	76 (43.4%)	109 (52.2%)	185 (48.2%)
Number of Missing Responses	0 (0.0%)	2 (2.0%)	2 (1.2%)	2 (1.1%)	3 (1.4%)	5 (1.3%)
Success Proportion [95% CI] (1)	0.953 [0.881, 1.000]	0.969 [0.918, 1.000]	0.963 [0.912, 1.000]	0.561 [0.383, 0.738]	0.471 [0.286, 0.655]	0.512 [0.351, 0.673]
p-value (2)	<0.001	<0.001	<0.001	0.446	0.832	0.702
p-value (3)		0.589			0.241	
EMA definition (Excluding underweight patient)						
N	14	20	20	17	18	19
Number of Episodes	64	98	162	157	181	338
Number (%) of Successes	61 (95.3%)	93 (94.9%)	154 (95.1%)	96 (61.1%)	93 (51.4%)	189 (55.9%)
Number (%) of Failures	3 (4.7%)	3 (3.1%)	6 (3.7%)	59 (37.6%)	85 (47.0%)	144 (42.6%)

	Mild Bleedings			Moderate Bleedings		
Statistics	75 µg/kg	225 µg/kg	Overall	75 µg/kg	225 µg/kg	Overall
Number of Missing Responses	0 (0.0%)	2 (2.0%)	2 (1.2%)	2 (1.3%)	3 (1.7%)	5 (1.5%)
Success Proportion [95% CI] (1)	0.953 [0.881, 1.000]	0.969 [0.918, 1.000]	0.963 [0.912, 1.000]	0.619 [0.470, 0.769]	0.522 [0.340, 0.705]	0.568 [0.428, 0.707]
p-value (2)	<0.001	<0.001	<0.001	0.150	0.632	0.389
p-value (3)		0.589			0.257	

While the success proportion of mild bleeding events is clearly in favour of treatment with eptacog beta at both the 75µg and the 225µg dose, the success proportion for moderate bleeding events is only 55.4% for the 75µg dose and 46.4% for the 225µg dose. This increases to 61.1% and 51.4% for the lower and higher dose, respectively, when excluding the underweight subject. The analysis of outcomes of mild versus moderate bleeding events underlines that for mild bleeds either dosing regimen was efficacious in children. For moderate bleeds however, the repeated administration of 75µg is clearly preferable, but the success proportion is still distinctly lower than that observed in subjects ⩾ 12 years of age, even if the underweight subject is excluded from the analysis.

The mean and median number of administrations for mild/moderate bleeds was 3.6 and 3.0 for the 75µg/kg dose, respectively. For the 225µg/kg dose, the mean and median are 2.6 and 2.0, respectively. In PerSept 1, for the 75 µg/kg dose a mean and median of 2.5 and 2.0 administrations and for the 225 µg/kg dose a mean and median of 1.4 and of 1.0 administrations were necessary until a successful outcome. As rapid bleed control is essential to minimise pain as well as tissue and joint destruction, these inferior outcomes cast doubt on a potential label in children below 12 years of age. The applicant was asked to discuss why, despite differences in PK parameters, the same dose and interval used in adults was selected for both younger age cohorts and to further investigate the observed differences in efficacy between the two populations studied in PerSept 1 and PerSept 2, especially with regard to time to good or excellent assessment, dose administered and use of other haemostatic agents.

In their responses to the D120 LoQ, the applicant clarified that the choice of identical dosing schedules in paediatric and in adult subjects was based on safety concerns, the wide range of doses of eptacog alfa used in children as reported in the literature and the positive review of the first 132 bleeding events by the data monitoring committee. This cautious approach is acknowledged.

The applicant further argued that several factors may have substantially influenced the observed results and should be taken into account for the assessment of the totality of the provided data from PerSept 2:

- Underweight subject was a <6-year-old child, who is likely to have been underdosed due to weight based dosing. The provided post hoc analysis excluding this subject shows indeed a substantially higher success proportion at 12 hours for both DRs (75µg 53.2% -> 67.8%; 225µg 52.9% -> 67.1%). This effect underlines the importance of an adequate dosing recommendation for underweight children.

- The analysis of time to good or excellent response showed that after the 12 hours time point, most bleeding episodes gradually resolved (75µg and 225µg: 15 hours 84.9% and 91.1% respectively; 18 hours 87.7% and 93.0% respectively; 21 hours are 90.5% and 94.4% respectively) until nearly all were successfully treated at 24 hours (75µg: 94.4%; 225µg: 95.8%). Furthermore, the applicant points out that for children the response to treatment is rated by the caregivers. Due to the fact that younger children are not able to communicate a change in symptoms as clearly as older children or adults, and due to caregivers likely being more cautious and applying extra doses in order to unequivocally stop the bleeding event, this could also lead to a longer time and more doses used until successful treatment is reported. This phenomenon was also reported by Gruppo et al (2013) in their

publication of the Dosing Observational Study in haemophilia, which describes home treatment with recombinant activated factor VII in congenital haemophilia with inhibitors.

- In addition, to highlight the relevance of the results of PerSept 2 compared to paediatric data generated with NovoSeven, the 4-point efficacy grading scale was transformed into the 3-point scale used in Croteau et al (2016). Croteau et al describe and analyse all available data for paediatric patients treated with NovoSeven supporting the US license. This transformation results in a percentage of successes at 12 hours of 98.7% for the 75µg dose and 97.4% for the 225µg dose. While it is difficult to compare results across different studies, this analysis illustrates the anticonservative effect of introducing a 3-point scale for haemostatic efficacy assessment and is accepted as supportive.

A comparative analysis of the secondary efficacy outcomes shows the same trend as that seen for the primary efficacy endpoint, i.e. the younger age cohorts experience a longer time to good or excellent response, need more administrations and more bleeding episodes required alternative treatment. The trend towards a better efficacy of the 75µg/kg dosing regimen is evident throughout all reported outcome measures.

The youngest participants in study PerSept 2 were 5 children 1 year of age. There are no data available in even younger patients and outcomes from older children would have to be extrapolated to this youngest age cohort in order to support a label. The population PK model indicates that in children below 2 years of age, Cmax is strikingly higher than in adults, and AUC is also predicted to be higher than in children 2-<6 years of age. The applicant has provided dosing simulations that would use a longer duration of infusion in children below 1 year of age in order to achieve a flattening of Cmax into a range comparable to that seen in adults. However, due to doubts about the accuracy of the population PK model, and about the reliability of available paediatric PK data in general, this proposal cannot be accepted.

There were four amendments to the protocol of the PerSept2 study that were not considered to have an impact on the efficacy analyses. Since all study patients experienced protocol violations, the applicant was asked to summarise by category and comment on them. The applicant reported 76 protocol deviations related to the study medication (74 initially recorded plus 2 additional identified during the treatment); none of these reported deviations are considered to have impacted the efficacy of Cevenfacta. There were 10 protocol deviations that were considered to potentially underestimate the efficacy of Cevenfacta by the applicant. A total of 30 protocol deviations were considered by the applicant to potentially overestimate the efficacy (11 with the 75µg/kg regimen and 19 with the 225µg/kg regimen) of which 20 that were IMP administration after a "good/excellent" assessment; since the treatment was to be administered until the bleeding episode was successfully treated (i.e. "good/excellent" assessment) it appears unlikely this deviation could affect the efficacy of Cevenfacta.

Concomitant medications were administered more often to patients in the 75 µg/kg regimen (91.7%) than to patients in the 225 µg/kg treatment (76.9%) but unlike PerSept 1 study the unbalance was less pronounced (11/12 patients received concomitant medications in 75 µg/kg group vs 10/13 in 225 µg/kg group). In total FEIBA/Novoseven were administered to 6/25 (24%) patients. It is noted that these bypassing agents were more administered in the 225 µg/kg regimen than the 75 µg/kg regimen (30.8% and 16.7% respectively). More bypassing agents were administered to the patients ⩾6 to <12 of age than <6 years old, 5/12 patients (41.7%) and 1/13 patient (7.7%) respectively. The unbalance in use of rescue therapy among the two dose regimens and the two age groups was discussed by the applicant in light of the efficacy results. It is noted that the use of rescue therapy was higher with the 75 µg/kg regimen than the 225µg/kg regimen, i.e. 4 vs 1 bleeding episodes respectively. Despite the higher numerical use of concomitant medications due to bleeding related events with 75 µg/kg compared to 225 µg/kg, the small number of cases prevents any clear conclusion on its relation to the efficacy of Cevenfacta.

The number of bleeding episodes in children that required alternative treatment was small, one bleed in the 225µg/kg group in the age group <6 and 12 bleeds in the ages group 6 to <12, with 6 in each dosing regimen. No firm conclusions can be drawn from these sparse data.

In the **PerSept3 study**, the number of performed surgeries is in line with scientific advice by the CHMP and fulfils the requirements outlined in the factor IX guideline. The reported minor surgery procedures were circumcisions and tooth extractions (3 each). The major surgeries included orthopaedic procedures such as two orthopaedic knee surgeries, two leg amputations, and a hip replacement. These surgeries can be considered as a sufficiently challenging model.

Three patients in the minor surgery group were previously enrolled in PERSEPT 2 and 2 patients in the major surgery group were previously enrolled in PERSEPT 1. Since the submitted summary of clinical efficacy and clinical overview both mentioned that two patients in the minor surgery group previously participated in the PERSEPT 2 study and data from PERSEPT 2 study mentioned that two patients had a drug interruption to undergo a surgical procedure and were enrolled in Study PERSEPT 3, the applicant was asked to clarify the situation of the third patient. The applicant confirmed that the third patient from PerSept 3 did not participate in PerSept 2 (screen failure).

The primary efficacy endpoint for this study was the percentage of surgical or other invasive procedures with a "good" or "excellent" response to Cevenfacta treatment 48 (±4) hours after the last administration of Cevenfacta as assessed by the investigator. Of the 12 surgical procedures performed, 9 (81.8%) procedures were reported by the investigator as successfully treated at the timepoint of the primary endpoint. Since no hypothesis for the primary efficacy endpoint was made, it cannot be concluded if the endpoint was met.

The assessments of intraoperative efficacy by the surgeon/practitioner were either "good" or "excellent" for all procedures. For minor surgeries, the mean (SD) number of study drug administrations was 38.2 (20.98) and the mean (SD) treatment duration was 4.3 (3.71) days. For major surgeries, patients received mean 84.2 (40.68) administrations of Cevenfacta with a mean treatment duration of 17.6 (12.36) days.

According to the provided data, there was one patient (minor surgery: tooth extraction) who discontinued the study due to withdrawal of consent before the final assessment. This missing assessment was not imputed as treatment failure for the primary analysis. The documented reason for withdrawal (2 days after the tooth extraction) was based on the perception of the parents that they did not see effect from the treatment, which means this could theoretically qualify for an AE of "lack of efficacy". However, the latest efficacy assessment by the Investigator (on the same day) was "good". Since there was no assessment by the Investigator at the time of withdrawal, it remains unclear whether this missing assessment should be imputed as failure. The applicant was asked to describe efficacy during PerSept3 in section 5.1 of the SmPC only in a descriptive manner, without showing point estimates. The data from PerSept3 is limited and stating for example an efficacy of 100% for minor surgeries (which is questionable as described above) would suggest more security than justified.

One patient (knee surgery) had a moderate bleeding episode within 24 hours of the last dose of study drug (i.e. 7 to 8 days after surgery) and required a red blood cell transfusion and rescue treatment with NovoSeven, resulting in a "poor" assessment for the primary endpoint. Based on the provided information, it seems that treatment with Cevenfacta might have been discontinued too early. The applicant was asked to comment on this case and to provide more detailed information regarding the time of the last administration of Cevenfacta and the occurrence of the bleeding episode. The applicant states that one subject might have received suboptimal treatment due to his low weight (BMI 18.0-19.0 kg/m2). This is considered as not completely unlikely, considering that in the PerSept2 trial a clearly reduced efficacy readout was noted in subjects with a reduced BMI. Further, the dosing interval was extended to every 4 hours despite a previous post operative bleeding and the persistence of the

infection/inflammation markers. In addition, this patient would probably have benefited from a closer follow up as the evaluation at 120 h was missing and a delay of 36 h elapsed between the last "excellent" assessment (106 h) and the "poor" assessment at 140 h, which can be agreed with. The provided information underlines the importance of close follow-up during the postoperative phase. Upon request, the applicant included a statement in section 4.2. of the SmPC as follows: close follow-up is important for early detection of potential postoperative bleeding events that may require adjustment of the dosing intervals.

One patient underwent a right hip replacement. The day after the procedure, the patient developed a hematoma and the haemoglobin value decreased to 111 g/l (158 g/l at screening). These events led to discontinuation from the study and the imputed efficacy at the primary endpoint was rated as "poor". The patient received rescue medication with FEIBA (4500 U IV three times daily). Three days after the surgery, the patient experienced acute haemorrhagic anaemia resulting from a gastrointestinal haemorrhage. He suffered cardiopulmonary arrest and died. Both the Sponsor and the DMC concluded that the serious events of gastrointestinal haemorrhage and acute haemorrhagic anaemia were likely related to postoperative administration of NSAIDs. However, the patient received paracetamol, which is actually not an NSAID. Paracetamol is recommended for treatment of postoperative pain in patients with haemophilia, according to the Comprehensive Care Guideline of the World Federation of haemophilia (WFH). The applicant was asked to further elucidate why the event of acute haemorrhagic anaemia was mainly attributed to the gastrointestinal haemorrhage, although the autopsy revealed a large hematoma of the right hip, but only signs of gastrointestinal haemorrhage. One should also consider that no NSAID was applied. In the responses, it was clarified that the latest intake of an NSAID was one week before the surgery, which might have affected platelet activity after surgery, according to the DMC. In the DMC meeting summary (03 January 2017), it is mentioned that there were discrepancies in the recordings made by the Investigator. The DMC expressed their concern about the overall management of the postoperative bleeding complication in this subject at this site and recommended that no new subjects be recruited at this site. Regarding the reason why acute haemorrhagic anaemia was mainly attributed to the gastrointestinal haemorrhage, the autopsy report was provided indicating that the participant lost up to 2,500 mL blood in the gastric lumen, small gut and colonic loops.

The uncertainties regarding the dose recommendations for treatment of severe bleeding episodes and the prevention of bleedings following major surgeries were raised as a combined major objection. Although efficacy could be limited in these difficult clinical situations, the posology is considered closely related to efficacy and warrants additional justification. The proposed intervals for postoperative administrations following major surgeries are overall a bit wider than it is suggested for NovoSeven.

Treatment of severe bleeding episodes:

PK modelling data was provided, which basically shows that certain concentrations (Cmax to achieve probability of response of 70%) are regularly reached after administration Cevenfacta in different scenarios. This alone is however not sufficient to infer efficacy. For example, these concentrations (or even higher) were also reached in younger children (PerSept2) and a clearly reduced efficacy was noted compared to the older population recruited in PerSept1.

Importantly, the population PK model is not considered reliable, which is consequently also the case for the results obtained from the E-R analyses.

The clinical data obtained in PerSep1 and PerSept3 (successful treatment of 3 severe BEs and prevention of intraoperative bleeding during 6 major surgeries) suggests that Cevenfacta is efficacious in treating severe bleeding episodes in adults and probably adolescents. Due to the limited data, a detailed estimation of efficacy for the treatment of severe bleeding episodes cannot be made.

During PerSept1, both dosing regimen (with shorter intervals) were allowed for the treatment of severe BEs, in principle. Table 1 in section 4.2 of the SmPC recommends only the dosing regimen with the higher bolus dose (225 µg/kg). Since the 225 µg/kg regimen showed a clearly higher success rate for treatment of moderate bleeding events at the primary endpoint (compared to the 75 µg/kg dose), it may be reasonable to assume that this dose regimen could achieve a better result in treating severe bleeding episodes as well. It should also be mentioned that all 3 severe BEs were treated with this regimen and one patient was treated with a much higher dose than pre-specified in the protocol. Further, if one would consider the intraoperative efficacy during major surgeries as model for severe bleedings, it can be taken into account that the preoperative dose of 200 µg/kg is close to the 225 µg/kg bolus.

Overall, it can be acceptable not restricting the indication for adults and adolescents (i.e., including also the treatment of severe bleeding episodes). Considering all these aspects, the proposed recommendation to include only the regimen with the higher bolus dose in 4.2 is supported.

However, the acceptability of including children below 12 years of age (regardless of severity of the bleeding episode) was questioned. Cevenfacta was not efficacious for the treatment of severe bleeding episodes in children below 12 years of age, as none of the three severe BEs treated resulted in haemostatic response at both the 12 and 24 hours after initiation of treatment. A new major objection was raised. With the responses to the LoOI, the applicant has decided to exclude children below 12 years of age from the indication.

Prevention of bleeding episodes following major surgeries:

The applicant provided PK modelling data to justify the currently proposed dosing regimen. However, the population PK model and the results obtained from the E-R analyses are not considered reliable.

The applicant cites different publications (Shapiro et al, 1998; Shapiro et al., 2012; Ertruran et al., 2019). The paper by Ertruran et al. outlines the high proportion of bleeding complications caused by orthopaedic surgeries in patients with inhibitors and discusses several uncertainties related to these procedures and mentions the justified anxiety of those involved in the care of such patients. The publication by Shapiro et al. (2012) also discusses that a high percentage of haemophilia treatment centre staff feels uncomfortable or very uncomfortable performing non-orthopaedic (29% in total) or orthopaedic (49% in total) surgical procedures. The paper by Shapiro et al. from 1998 describes a randomised trial of two doses (35 vs. 90 µg/kg with defined intervals) of NovoSeven in haemophilia patients with inhibitors undergoing surgery. Of the 29 recruited subjects, intraoperative haemostasis was achieved in 28/29 patients, satisfactory haemostasis after the first 48 hours was reported by 26/29 participants and 23/29 participants successfully completed the study. Of note, the higher dose regimen performed better, as 13/14 patients were successfully treated at the end of the study. The proposed dosing for Cevenfacta is closer to the high dose regimen in the study by Shapiro et al., although the suggested bolus dose is higher (200 µg/kg).

Among the 6 major surgeries performed during PerSept3, intraoperative efficacy was sufficient for all patients. However, 2 subjects had postoperative complications. The subject who died during the postoperative period after a hip replacement surgery is extensively discussed in a section above. Another patient with major (knee) surgery reported a moderate bleeding event at the surgical site 7 days after the procedure. The provided information suggests that this patient would probably have benefited from a closer follow up, as efficacy assessments were either missing or outside the protocol-specified time points. In order to avoid that re-bleedings are detected too late, the applicant was asked to add an additional statement to the dosing table (Table 2) in section 4.2 of the SmPC.

The provided information underlines the importance of close follow-up during the postoperative phase. The applicant included a corresponding statement in section 4.2 of the SmPC.

2.5.8. Conclusions on the clinical efficacy

The efficacy for the treatment of bleeding episodes in subjects >12 years of age is considered as sufficient.

For children <12 years of age the efficacy of Cevenfacta was not convincingly demonstrated. The analysis of outcomes of mild versus moderate bleeding events underlines that for mild bleeds either dosing regimen was efficacious in children. For moderate bleeds however, the repeated administration of 75µg is clearly preferable, but the success proportion is still distinctly lower than that observed in subjects ⩾12 years of age, even if the underweight subject is excluded from the analysis. The influence of low bodyweight on the proportion of successfully treated bleeds is evident from the cohort of children <6 years of age, in which the subject had a very low bodyweight for his age and was very likely underdosed due to the weight-based dosing scheme. PK modelling data intended to support an adequate dosing regimen in underweight children, however, cannot be accepted due to doubts about the adequacy of the model and the reliability of paediatric PK data in general.

The optimal dosing regimen as well as the efficacy for children below the age of 2, and especially for infants below 1 year of age, are still uncertain. The youngest participants in study PerSept 2 were 5 children 1 year of age. The applicant has submitted conflicting data on the number of treated bleeding events in this age category. There are no data available in even younger patients and outcomes from older children would have to be extrapolated to this youngest age cohort in order to support a label. The population PK model indicates that in children below 2 years of age, Cmax is strikingly higher than in adults, and AUC is also predicted to be higher than in children 2-<6 years of age. The applicant has provided dosing simulations that would use a longer duration of infusion in children below 1 year of age in order to achieve a flattening of Cmax into a range comparable to that seen in adults. However, due to doubts about the accuracy of the population PK model and about the reliability of available paediatric PK data from PerSept 2 in general this proposal cannot be accepted.

The efficacy in severe bleeding events in children below 12 years of age is not established.

In their response to the D180 LoOI, the applicant clarified that due to the lack of additional data which could support the efficacy and dosing recommendations of Cevenfacta in younger children, it was decided to exclude the age cohort of children below 12 years of age from the indication.

2.5.9. Clinical safety

2.5.9.1. Patient exposure

Clinical safety of Cevenfacta been evaluated in 4 clinical studies, i.e. Phase 1b (n=15), PerSept 1 (n=27), PerSept 2 (n=25), and PerSept 3 (n=12).

Of the 75 subjects, 15 are patients with haemophilia A without inhibitors, who participated in the phase 1b study. The other 60 subjects are patients with haemophilia A with inhibitors (n=56) or patients with haemophilia B with inhibitors (n=4).

During the assessment period, the results of a further study, LFB-FVIIA-009-19, which evaluated the single dose PK of Cevenfacta in 28 adult subjects suffering from haemophilia A, became available. 4 of the subjects had evidence of inhibitors >5 Bethesda units during the study.

The incidence of inhibitors in haemophilia B is considerably less frequent compared to haemophilia A and consequently such patients are more difficult to recruit into a clinical study.

13 subjects were <6 years, 15 subjects were between 6 and <12 years, 6 were between 12 and <18 years, and 41 were >18 years of age, with an age range from 1 to 61 (1-56 in target patients with inhibitors).

Four patients in PerSept 3 also participated in previous studies (2 patients in PerSept 1 and 2 in PerSept 2). As noted in table footnotes, these patients are counted uniquely under each treatment regimen column in both PerSept 3 and their respective former studies; however, the Overall numbers (N=75) count each patient only once.

Across all studies, 3418 infusions of Cevenfacta were administered (676 with Cevenfacta Process A, 2627 with Cevenfacta Process B and 115 with both manufacturing Processes), representing 1117 treatment episodes with a mean (SD) number of treatment episodes per patient of 14.9 (16.60).

A treatment episode was defined as any one of the following:

1. Single Cevenfacta administration in Phase 1b or Phase A of PerSept 1 and PerSept 2;

2. Single Cevenfacta administration for purpose of pharmacokinetics (PK) in Phase B of PerSept 1;

3. All Cevenfacta administrations from just prior to the surgical incision or invasive procedure through the end date/time of the surgery/procedure in PerSept 3; or

4. All Cevenfacta administrations for purposes of treating a given bleeding episode in Phase B of PerSept 1 and PerSept 2, or after the end date/time of surgery/procedure in PerSept 3.

The mean (SD) total amount of Cevenfacta administered was 4584.0 (5186.37) µg/kg. The mean (SD) number of infusions per patient was 45.6 (54.51) and the total duration of treatment was 12.8 (11.65) days.

The median duration of treatment was 1 day for each dose in Phase 1b, each with a minimum and maximum of 1 day. In the pooled results from PerSept 1 and 2, the median duration was 5.1 days (75µg/kg) and 6.6 days (225 µg/kg), and ranged from a minimum of 0 days to a maximum of 17 days in the 75 µg/kg dose group, and from 1 to 30 days in the 225 µg/kg dose group.

In PerSept 3, the median duration of treatment was 7.2 days for those receiving 75 µg/kg and 1.0 day for those receiving the loading dose of 200 µg/kg on the day of their surgical or invasive procedure, as would be expected per protocol. The minimum number of days treated for those receiving 75 µg/kg was 1 day, with a maximum of 32 days. Duration of treatment for all those who received 200 µg/kg loading dose was 1 day.

2.5.9.2. Adverse events

The clinical studies of Cevenfacta defined several categories of AEs. An AE was considered a treatment-emergent adverse event (TEAE) if it occurred or worsened after the first dose of study drug. Non-TEAEs were AEs that occurred after signing the informed consent but before the first study drug administration. An AE was considered treatment-related if it had a definite, probable, or possible relationship to the study treatment, or if the relationship to study treatment was missing.

In addition, the Phase 1b, PerSept 1, and PerSept 2 studies analysed "treatment-associated" adverse events (TAAEs). The purpose of defining TAAEs was to capture all AEs within a defined time period relative to dosing, whether or not the AEs were considered to be treatment-related. More precisely, in Phase 1b, the time window for TAAE definition was 36 hours post infusion. In PerSept 1 and PerSept 2, an AE was considered to be TAAEs if it occurred between the start of treatment of a bleeding episode and the end of treatment of the bleeding episode, up to and including 24 hours after the last administration of study drug for that bleeding episode, or if it occurred within 24 hours after study

drug administration for PK purposes. In PerSept 3, TAAEs were not defined or measured separately in the statistical analysis plan (SAP) for the study.

In the Cevenfacta programme, a number of prospective AEs were identified as adverse events of special interest (**AESIs**) based on the haemophilia population, and/or experience with coagulation factors, and/or because Cevenfacta belongs to a group of biotechnology-derived therapeutic proteins. These were **thromboembolic events**, **hypersensitivity reactions**, and **immunogenicity** or antidrug antibodies (ADAs).

The definitions of treatment-emergent and treatment-associated adverse events as well as the selection of adverse events of special interest are endorsed.

The most frequent TEAEs by SOCs reported in at least 10% of patients were:

- Infections and infestations in 25.3% of patients (mostly from PerSept 2), the most frequent TEAEs were nasopharyngitis in 7 (9.3%) patients, bronchitis and rhinitis in 4 (5.3%) patients, and respiratory tract infection viral and tonsillitis in 2 (2.7%) patients each.

- Injury, poisoning and procedural complications in 11 (14.7%) patients, the most frequent TEAEs were procedural pain in 5 (6.7%) patients, wound secretion in 3 (4.0%) patients and anaemia postoperative in 2 (2.7%) patients.

- Nervous system disorders in 11 (14.7%) patients, the most frequent TEAEs were headache in 6 (8.0%) patients and dizziness in 2 (2.7%) patients.

- Gastrointestinal disorders in 10 (13.3%) patients, the most frequent TEAEs were vomiting and diarrhoea in 3 (4.0%) patients each and nausea in 2 (2.7%) patients.

- Respiratory, thoracic and mediastinal disorders in 8 patients (10.7%), the most frequent TEAEs were cough in 4 (5.3%) patients and oropharyngeal pain in 2 (2.7%) patients.

No specific pattern is discernible from the analysis of TEAEs by SOCs. The distribution of TEAEs by SOC was consistent with the patients' age in each study and the clinical setting in which the product was used. Infections and infestations and gastrointestinal disorders were mostly reported in the paediatric patients in PerSept 2 while injury, poisoning and procedural complications were more frequent in PerSept 3. Nervous system disorders were mainly from Phase 1b.

Table 42: Treatment-emergent adverse events and treatment-related adverse events by system organ class (safety population) – Integrated analyses

All Studies		
	TEAE	**TRTEAE**
	Overall	Overall
	(N=75)	(N=75)
System Organ Class	n (%), E	n (%), E
Any Event	**50 (66.7), 172**	**5 (6.7), 13**
Blood and lymphatic system disorders	7 (9.3), 8	1 (1.3), 1
Cardiac disorders	1 (1.3), 1	0 (0.0), 0
Ear and labyrinth disorders	2 (2.7), 5	0 (0.0), 0
Gastrointestinal disorders	10 (13.3), 18	1 (1.3), 1
General disorders and administration site conditions	7 (9.3), 12	1 (1.3), 6
Immune system disorders	1 (1.3), 1	0 (0.0), 0
Infections and infestations	19 (25.3), 41	0 (0.0), 0
Injury, poisoning and procedural complications	11 (14.7), 22	1 (1.3), 1
Investigations	5 (6.7), 8	1 (1.3), 1
Metabolism and nutrition disorders	1 (1.3), 1	0 (0.0), 0
Musculoskeletal and connective tissue disorders	6 (8.0), 13	0 (0.0), 0

Neoplasms benign, malignant and unspecified (incl cysts and polyps)	1 (1.3), 1	0 (0.0), 0
Nervous system disorders	11 (14.7), 18	0 (0.0), 0
Psychiatric disorders	1 (1.3), 1	0 (0.0), 0
Respiratory, thoracic and mediastinal disorders	8 (10.7), 12	0 (0.0), 0
Skin and subcutaneous tissue disorders	1 (1.3), 1	0 (0.0), 0
Vascular disorders	6 (8.0), 9	0 (0.0), 0

172 treatment emergent adverse events were observed during the phase 1b study and PerSept 1,2 and 3. Many AEs were infections like nasopharyngits or diarrhoea, which are prevalent in children, or commonly occurring events, like headache. Only a minority of TEAE were assessed as related, which can be agreed. Most of these events represented local or systemic infusion reactions, and were graded as mild.

Table 43: Description of treatment-related treatment emergent adverse events (safety population) – Integrated analyses

Study reference	Patient's details: Gender/Age (years)/BMI (kg/m²)	Dose of the study drug (µg/kg)*/ Manufacturing process	Events details						Action taken with study drug
			Preferred term	TAAE	Outcome	Duration	Severity	Serious	
Phase 1b	M/20-30/22.00-23.00	25/A	Dizziness	Yes	Resolved	11 minutes	Mild	No	Dose not changed
		75/A	Dizziness	Yes	Resolved	3 minutes	Mild	No	Dose not changed
	M/50-60/26.00-27.00	25/A	Headache	Yes	Resolved	2 hours 10 minutes	Mild	No	Dose not changed
PerSept 1	M/30-40/25.00-26.00	75/A	Infusion site discomfort	Yes	Resolved	3 hours	Mild	No	Dose not changed
			Infusion site discomfort	Yes	Resolved	3 hours	Mild	No	Dose not changed
			Infusion site discomfort	Yes	Resolved	3 hours	Mild	No	Dose not changed
			Infusion site discomfort	Yes	Resolved	1 minute	Mild	No	Dose not changed
			Infusion site haematoma	Yes	Resolved	4 days	Mild	No	Dose not changed
			Infusion site haematoma	Yes	Resolved	3 days	Mild	No	Dose not changed
	M/12-20/15.00-16.00	225/A+B	Increase body temperature	Yes	Resolved	2 days	Moderate	No	Dose not changed
PerSept 3	M/50-60/31.00-32.00	75/B	Post procedural haematoma	Yes	Not resolved	Ongoing	Severe	No	Drug withdrawn
			Blood loss anaemia[1,2]	No	Fatal	-	Severe	Yes	Not applicable
			Gastrointestinal haemorrhage[2]	No	Not resolved	Ongoing	Severe	Yes	Not applicable

Source: Module 5.3.4.2, CSR Phase 1b, Listings 2.1 and 2.13 in Appendix 12.2.1; Module 5.3.5.1, CSR PerSept 1, Listings 12.4, 12.10.1 and 12.11.1; Module 5.3.5.2, CSR PerSept 3, Listings 16.2.5 and 16.2.15.1

**The last treatment dose/regimen received prior to the start of the AE.*

[1]Hemorrhagic anaemia reported in CSR PerSept 3 was recoded as Blood loss anaemia (MedDRA v.23.0)

[2]Probably related by Investigator assessment and unrelated per DMC and Sponsor's reassessment

AE = adverse event, BMI = body max index; CSR = clinical study report, M = male; MedDRA = Medical Dictionary for Regulatory Activities; TAAE = Treatment- associated adverse event

Phase Ib: 1 patient experienced dizziness under both 25 µg/kg and 75 µg/kg of Cevenfacta, both events were mild of short duration and the patient recovered. 1 patient experienced, 3 hours after receiving 25

µg/kg of Cevenfacta, a mild headache lasting approximately 2 hours and from which he recovered. Additionally, one patient experienced, during drug infusion, symptoms including tachycardia, flushing, tremor, dysgeusia, chest discomfort which were assessed as unrelated to the study drug by the Investigator. Upon review of clinical signs and symptoms and temporal association, the Sponsor considered that this patient may have developed "infusion related reaction" to Cevenfacta.

PerSept 1: 1 patient experiencing 6 drug-related TEAEs at 75 µg/kg including 4 events of infusion site discomfort and 2 events of infusion site haematoma, all occurred during 4 bleeding episodes and all were mild in severity. 1 child of 12 years old experiencing 1 increased body temperature 4 hours after receiving 225 µg/kg Cevenfacta which was moderate in severity and resolved 2 days later.

PerSept 3: One patient who underwent major hip replacement surgery, experienced 3 drug-related TEAEs all severe in nature (post procedural haematoma, serious blood loss anaemia, and serious gastrointestinal haemorrhage).

LFB-FVIIA-009-19: 1 TEAE (mild headache in one subject) was assessed to be related to Cevenfacta and resolved without medication.

Analysis by dose regimens:

Table 44. Overview of Treatment-emergent Adverse Events (Safety Population) – Integrated Analysis

	Phase 1b			Combined PerSept 1 and 2		PerSept 3		All Studies				
Dose Parameter	25 µg/kg (N1=10, N2=10) n (%) E, I	75 µg/kg (N1=10, N2=10) n (%) E, I	225µg/kg (N1=10, N2=10) n (%) E, I	75 µg/kg (N1=48, N2=1500) n (%) E, I	225 µg/kg (N1=50, N2=1154) n (%) E, I	75 µg/kg (N1=12, N2=725) n (%) E, I	200 µg/kg (N1=6, N2=9) n (%) E, I	25 µg/kg (N1=10, N2=10) n (%) E, I	75 µg/kg (N1=66, N2=2235) n (%) E, I	200 µg/kg (N1=6, N2=9) n (%) E, I	225 µg/kg (N1=60, N2=1164) n (%) E, I	Overall (N1=75, N2=3418) n (%) E, I
TEAEs	8 (80.0), 21, 2.100	5 (50.0), 10, 1.000	5 (50.0), 8, 0.800	20 (41.7), 44, 0.029	21 (42.0), 53, 0.046	10 (83.3), 34, 0.047	2 (33.3), 2, 0.222	8 (80.0), 21, 2.100	35 (53.0), 88, 0.039	2 (33.3), 2, 0.222	26 (43.3) 61, 0.052	50 (66.7) 172, 0.050
TAAEs[a]	3 (30.0), 5, 0.500	4 (40.0), 9, 0.900	2(20.0), 4, 0.400	7 (14.6), 13, 0.009	9 (18.0), 14, 0.012	9 (75.0), 28, 0.039	2 (33.3), 2, 0.222	3 (30.0), 5, 0.500	20 (30.3), 50, 0.022	2 (33.3), 2, 0.222	11 (18.3) 18, 0.015	28 (37.3) 75, 0.022
Serious TEAEs	0 0, 0.000	0 0, 0.000	0 0, 0.000	1 (2.1), 2, 0.001	2 (4.0), 3, 0.003	1 (8.3) 2, 0.003	0 0, 0.000	0 0, 0.000	2 (3.0), 4, 0.002	0 0, 0.000	2 (3.3) 3, 0.003	4 (5.3) 7, 0.002
Serious TAAEs[a]	0 0, 0.000	0 0, 0.000	0 0, 0.000	0 0, 0.000	1 (2.0), 2, 0.002	0 0, 0.000	0 0, 0.000	0 0, 0.000	0 0, 0.000	0 0, 0.000	1 (1.7) 2, 0.002	1 (1.3) 2, 0.001
Treatment-related TEAEs[b]/Adverse Reactions	2 (20.0), 2, 0.200	1 (10.0), 1, 0.100	0 0, 0.000	1 (2.1), 6, 0.004	1 (2.0), 1, 0.001	1 (8.3) 3, 0.004	0 0, 0.000	2 (20.0), 2, 0.200	3 (4.5), 10, 0.004	0 0, 0.000	1 (1.7) 1, 0.001	5 (6.7) 13, 0.004
TEAEs leading to study drug withdrawal	0 0, 0.000	0 0, 0.000	0 0, 0.000	1 (2.1), 1, 0.001	0 0, 0.000	1 (8.3), 1, 0.001	0 0, 0.000	0 0, 0.000	2 (3.0), 2, 0.001	0 0, 0.000	0 0, 0.000	2 (2.7) 2, 0.001
TEAEs leading to death	0 0, 0.000	0 0, 0.000	0 0, 0.000	0 0, 0.000	0 0, 0.000	1 (8.3) 1, 0.001	0 0, 0.000	0 0, 0.000	1 (1.5), 1, 0.000	0 0, 0.000	0 0, 0.000	1 (1.3) 1, 0.000

Source: Appendix B2, Table 14.2.3.1.1
All AEs were assigned to the last treatment dose/regimen received by the patient prior to the start of the AE.
[a]For AEs occurring in the Phase 1b study, during Phase A of the PerSept 1 or PerSept 2, or from the initial dose of LR769 just prior to the surgical incision or invasive procedure through end of surgery/procedure in the PerSept 3 study, an AE was considered to be a TAAE if it occurred within 24 hours after administration of LR769. For AEs occurring during Phase B of the PerSept 1 or PerSept 2, or after end of surgery/procedure in PerSept 3, an AE was considered to be a TAAE if it occurred between the start of treatment of a bleeding episode or procedure and the end of treatment of the bleeding episode or procedure, up to and including the 24 hours after the last administration of LR769 for that bleeding episode or procedure, or if it occurred within 24 hours after LR769 administration for PK purposes (PerSept 1).
[b]An AE was considered treatment-related if it had a definite, probable, or possible relationship to LR769 or if the relationship to LR769 was missing.
AE = adverse event; E = number of events; I = incidence of the event, calculated as number of events/number of administrations of the given treatment/dose regimen; n (%) = number and percentage of patients with the event; N1 = number of patients in the Safety Population who had at least 1 treatment episode treated with the given treatment regimen; N2 = number of administrations of the given treatment regimen; PK = pharmacokinetic; TAAE = treatment-associated adverse event; TEAE = treatment-emergent adverse event

2.5.9.3. Serious adverse event/deaths/other significant events

SAEs

Of the 75 treated patients, 4 (5.3%) experienced a total of 7 SAEs.

In addition to the SAEs leading to death for one patient in PerSept 3, 3 other patients treated with Cevenfacta experienced 4 treatment-emergent nonfatal SAEs while on study: 1 patient in PerSept 1 and 2 patients in PerSept 2. These SAEs are summarised briefly below and all were classified as unrelated to treatment with Cevenfacta.

Phase 1b

In the Phase 1b study, no patient experienced an SAE.

PerSept 1

In PerSept 1, one patient in the 75 µg/kg treatment regimen experienced 2 treatment-emergent nonfatal SAEs (acute tonsillitis and subarachnoid haemorrhage). The Investigator considered these SAEs to be unrelated to treatment with Cevenfacta.

PerSept 2

Two patients (8.3%, both in the 225 µg/kg treatment regimen) in PerSept 2 each experienced 1 treatment-emergent nonfatal SAE. One patient was in the birth to <6-year-old age group and 1 patient was in the ≥6 to <12-year-old age group.

The <2-year-old patient was diagnosed with dysentery that was moderate in severity and was classified as an SAE by the Investigator because it was a medically important event (acute infection). The patient was treated with ciprofloxacin. Another <12-year-old patient experienced paresis due to an intracranial bleed that was severe and classified as an SAE by the Investigator, due to prolonged hospitalisation.

PerSept 3

In PerSept 3, one patient experienced 3 TRTEAEs (post procedural hematoma, haemorrhagic anaemia (recoded as blood loss anaemia (MedDRA v.23.0), and gastrointestinal haemorrhage). The blood loss anaemia and gastrointestinal haemorrhage were considered by the Investigator to be SAEs. These events were initially reported as unlikely related and were subsequently updated to be probably related to Cevenfacta by the Investigator. The independent DMC reviewed the SAEs and was not in agreement with the Investigator's subsequent assessment. The DMC reviewed the medical management records and assessed the 2 SAEs as unlikely related to Cevenfacta. Concurrent Sponsor review reached a similar conclusion to the DMC. The patient died due to blood loss anaemia. See Section Deaths below for a complete narrative of this patient.

No other patient in PerSept 3 experienced an SAE.

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No subject in this single dose study experienced an SAE.

The 5 SAEs reported from studies PerSept 1 and 2 are either infections or bleeding events and their sequelae. It is agreed with the assessment of the investigator that these SAEs can be classified as unrelated to Cevenfacta.

From the review of the narrative of the one patient experiencing SAEs in PerSept 3, however, the initially diagnosed blood loss anaemia appears to be due to the postoperative haematoma. A decrease in haemoglobin from 158g/L to 111g/L at 24 hours after surgery and before withdrawal of Cevenfacta was observed. Therefore, even if the final lethal event, i.e. the gastrointestinal haemorrhage, happened during treatment with FEIBA, the initial blood loss anaemia can be attributed to lack of effect of Cevenfacta. According to the WHO classification of anaemia severity, a haemoglobin value of 111g/L is classified as mild anaemia, therefore not fulfilling the SAE definition. However, this event can be considered as a related treatment-associated adverse event.

The two SAEs of gastrointestinal haemorrhage and blood loss anaemia happened shortly after withdrawal of Cevenfacta and initiation of treatment with FEIBA.

Deaths

Of the 75 patients treated with Cevenfacta in clinical studies, 1 patient in PerSept 3 died following discontinuation of treatment with Cevenfacta. This patient had successfully completed PerSept 1 before enrolling in PerSept 3.

The patient was diagnosed with severe haemophilia A in the late 1950s. In the PerSept 1 study, this patient experienced 25 mild or moderate bleeding episodes between his first dose (Mid Q4 2014) and early Q3 2015. The first 10 episodes were treated in the 225 µg/kg treatment regimen, the next 6 in the 75 µg/kg treatment regimen, and the final 9 in the 225 µg/kg treatment regimen. All but 1 of the bleeding episodes were spontaneous. Patient reported efficacy 12 hours after initial Cevenfacta administration was "excellent" for the first 2 episodes, and "good" for all 23 of the subsequent episodes. No bleeding episode recurred, required a hospital visit, or required alternative treatment. The patient did not experience any TEAE during the PerSept 1 study. He completed his participation in PerSept 1 in early Q3 2015.

The patient was enrolled in PerSept 3 in early Q4 2016, underwent venous catheter placement 2 days after, and received his first dose of Cevenfacta (200 µg/kg loading dose, per protocol) ,another 8 days later (D0), the same day he underwent the major surgical procedure of right hip replacement. His initial Cevenfacta dose was followed by 75 µg/kg doses every 2 hours from D0 to D1 , as allowed by protocol. There were no surgical complications, and the surgeon's intraoperative efficacy assessment was "excellent." At 24 hours after surgery completion, efficacy was assessed as "good."

Post procedural hematoma formation was observed on D1, despite infusions of Cevenfacta. The patient's haemoglobin was normal at screening (158 g/L), prior to the surgery; 24 hours post procedure it had decreased to 111 g/L, which was considered abnormal and clinically significant. The increased hematoma was assessed by the Investigator as Cevenfacta inefficacy. Cevenfacta was withdrawn and the patient was discontinued from the study due to the post procedural hematoma. The patient received rescue treatment with FEIBA following his early termination visit.

On D3, the patient experienced acute post haemorrhagic anaemia (MedDRA v.23.0 PT blood loss anaemia) resulting from a gastrointestinal haemorrhage, which complicated his haemophilia A (note that gastrointestinal bleeding was not in the medical history for this patient). He suffered cardiopulmonary arrest and died that same day. The autopsy outcome was massive gastrointestinal blood loss.

These SAEs (blood loss anaemia; gastrointestinal haemorrhage) were initially reported as unlikely related and were subsequently updated to be probably related to Cevenfacta by the Investigator. The independent DMC reviewed the SAEs and was not in agreement with the Investigator's subsequent assessment. The DMC reviewed the medical management records and assessed the 2 SAEs as unlikely related to Cevenfacta. Concurrent Sponsor review reached a similar conclusion to the DMC. The patient died due to blood loss anaemia.

2.5.9.4. Laboratory findings

Haematology

Most haematology laboratory parameters evaluated during the clinical studies of Cevenfacta showed no apparent trends or clinically significant changes, other than those expected based on the pharmacologic action of the study drug.

Clinical Chemistry

Most clinical chemistry laboratory parameters evaluated during the clinical studies of Cevenfacta showed no apparent trends or clinically significant changes, other than those expected based on the pharmacologic action of the study drug. Based on grade 3 threshold of CTCAE v.5.0, some markedly abnormal values were recorded for alanine aminotransferase (ALT), aspartate aminotransferase (AST), sodium and total serum calcium in the Phase 3 studies.

The patient showing abnormally high ALT and AST values suffered from hepatitis C and had elevated levels already at baseline, which peaked at week 12 and then decreased without intervention.

The applicant was asked to provide more information on the two paediatric patients who experienced very low calcium levels. In their response to the D120 LoQ, the applicant summarised the current knowledge on the association of hypocalcaemia and coagulopathy. At the time being it is not established if the hypocalcaemia represents a sequel of a trauma or bleeding event or if a pre-existing hypocalcaemia worsens the extent of bleeding.

It can be assumed that clinicians will monitor laboratory parameters in those patients who undergo major surgery or experience a major bleeding event as a matter of course.

Coagulation

Coagulation parameters showed no apparent trends or clinically significant changes, other than those expected in haemophilia patients and based on the pharmacologic action of the study drug.

2.5.9.5. Safety in special populations

Subgroup analysis by age at enrolment

Of the 75 patients included, 28 were children, 6 were adolescents and 41 were adults. Although inclusion was permitted for patients aged up to 75 years, no patient older than 65 years was enrolled in any study of Cevenfacta.

The overall frequency of TEAEs was quite similar between age groups with a slight trend toward more TEAEs in children aged from 6 to less than 12 years. The proportion of patients reporting TEAE was 61.5% in patient aged less than 6 years (0.045 TEAEs per infusion), 80% in patients aged from 6 to less than 12 years (0.038 TEAEs per infusion), 66.7% in adolescents (0.054 TEAEs per infusion) and 63.4% in adults (0.064 TEAEs per infusion).

The age range of all enrolled patients was 1 to 61 years (1-56 years in target patients with inhibitors). The safety of Cevenfacta administration in elderly subjects has not been investigated. Due to concurrent risk factors, the incidence of thromboembolic events in these patients is likely to be higher.

Subgroup analysis by BMI

Of the 75 treated patients included, 32 were classified as underweight (BMI <18.5 kg/m2) but most of them were children or adolescents and only 2 patients were adults (in PerSept 3), 27 patients had normal weight (18.5 kg/m2 to <25 kg/m2), 13 patients were overweight (25 kg/m2 to <30 kg/m2) and 4 patients were obese (≥30 kg/m2).

Despite the differences observed in the incidence and the nature of TEAEs between the different groups of BMI, the pattern of TEAEs remained consistent with the patients age in each category of BMI and with the clinical setting in which the drug product was used.

Subgroup analysis by disease history

The incidence of TRTEAEs (patient level) was comparable in the categories of the subgroups type of haemophilia (Type A, Type B) or severity (moderate, severe), FVIII/FIX level (< Median [0.5%], ≥ Median [0.5%]), or level of inhibitor (BU <5, BU ≥5). No TRTEAE was reported in more than 1 patient in any category of these subgroups.

Pregnant or breastfeeding women

Eptacog beta (activated) was evaluated only in male patients. Also, there are no available data on use of eptacog beta (activated) in pregnant women. No information on labor, delivery, or the effects of eptacog beta (activated) on nursing mothers or breast-fed infants is available to-date.

2.5.9.6. Immunological events

Screening and confirmatory assays were setup based on common antibody-bridging- assay protocols. Method validation reports for the assessment of immunogenicity including drug-interference studies were provided and confirm that the applied protocols were suitable for the intended use, and aligned with respective EMA guideline on immunogenicity assessment of therapeutic proteins in force at the time-point when the study was performed.

Immunogenicity against Cevenfacta was low, with only two transiently positive ADA samples in the entire study programme. A single positive test against colloidal rabbit milk protein in one subject in PerSept 2 could not be replicated and is most likely a false positive.

No hypersensitivity events were reported in any of the four clinical studies.

2.5.9.7. Safety related to drug-drug interactions and other interactions

The increased risk of thromboembolic events with concomitant use of aPCC/PCC is expected for Cevenfacta.

2.5.9.8. Discontinuation due to adverse events

The only case that involved an AE leading to discontinuation in any clinical study with Cevenfacta was that for one patient in PerSept 3, who discontinued from Cevenfacta treatment due to post procedural haematoma and subsequently withdrew from the study due to blood loss anaemia. The patient later died. The cause of death was blood loss anaemia secondary to gastrointestinal haemorrhage. The post procedural haematoma was considered by the Investigator to be possibly related to treatment with Cevenfacta. Further details are provided in under the heading of SAE.

2.5.9.9. Post marketing experience

Cevenfacta was approved in the United States of America on 01 April 2020. At the time of the initial marketing authorisation application submission, Cevenfacta has not been launched in this territory, and therefore, no patients have been exposed to this medicinal product.

Available data for the US market include 16 users and 2 subjects have enrolled in a PASS. No AEs were reported.

2.5.1. Discussion on clinical safety

The clinical safety of Cevenfacta has been investigated in four clinical trials which enrolled 75 patients (4 patients enrolled in two studies, PerSept 3 and PerSept 1 or PerSept 2, respectively). The 15 subjects of the phase 1b study were patients with haemophilia A without inhibitors. In the phase 3 studies, 56 subjects were patients with haemophilia A with inhibitors, and 4 subjects suffered from haemophilia B with inhibitors. 13 subjects were <6 years, 15 subjects were between 6 and <12 years, 6 were between 12 and <18 years, and 41 were >18 years of age, with an age range from 1 to 61 (1-56 in target patients with inhibitors). Additionally, a single dose PK trial in 28 subjects suffering from haemophilia A, of whom 4 subjects displayed evidence of a high titre inhibitor against FVIII, was submitted during the review process.

The overall demographics, disease characteristics, concomitant diseases and medications were consistent with those of the general population of patients with haemophilia and inhibitors. The BMI and BSA were generally typical for the age ranges enrolled.

As usually observed in such patients, the most frequent medical histories (61.3% of the patients) were from the system organ class (SOC) "Musculoskeletal and Connective Tissue Disorders". The majority of patients (81.3%) were taking medication to treat bleedings, and as expected, the most frequent were analgesics (42.7% of the patients) and blood and coagulation factors (in 34.7% of patients).

The overall profile particularly regarding concomitant medication used in the course of the clinical studies is considered consistent with respective study population and does not indicate any additional safety concerns.

The main exclusion criteria in all 4 trials were immunosuppression, having a platelet count <100,000/ml, a known allergy or hypersensitivity to rabbits, or a history of thromboembolic events. The latter two conditions are adequately reflected in section 4.3 of the SmPC.

The presented safety database is small, but this is owed to the fact that patients with haemophilia and inhibitors are rare, especially those who suffer from haemophilia B. Therefore, the very low number of patients with haemophilia B with inhibitors and the low numbers of patients with haemophilia A with inhibitors can be accepted as post-marketing safety follow-up via EUHASS and PEDNET registry is planned (please see RMP section).

During the clinical trials, 172 adverse events were captured, of which less than 10% (n=13) were assessed as related. Many of the TEAE were infections like nasopharyngitis or diarrhoea, which are prevalent in children, or commonly occurring events, like headache. Most of the events assessed as related represented local or systemic infusion reactions, and were graded as mild. In single dose PK study LFB-FVIIA-009-19, one instance of mild headache was assessed as treatment related.

The following AEs were identified as adverse events of special interest (AESIs): thromboembolic events, hypersensitivity reactions, and immunogenicity or antidrug antibodies (ADAs). No AESIs were reported in any of the four clinical studies.

Of the 7 serious adverse events, 5 SAEs were reported from studies PerSept 1 and 2 are either infections or spontaneous or traumatic bleeding events and their sequelae. It is agreed with the assessment of the investigator that these SAEs can be classified as unrelated to Cevenfacta.

The two SAEs of gastrointestinal haemorrhage and blood loss anaemia leading to death of one patient in PerSept 3 happened shortly after withdrawal of Cevenfacta and initiation of treatment with FEIBA. However, an assessment of the relatedness of these events to the treatment with Cevenfacta is difficult and the applicant was asked to provide more insights into this event. The applicant provided the autopsy report and the DMC meeting minutes concerning this event. In the DMC meeting summary

(03 January 2017), it is mentioned that there were discrepancies in the recordings made by the Investigator. The DMC expressed their concern about the overall management of the postoperative bleeding complication in this subject at this site and recommended that no new subjects be recruited at this site. In summary, despite persistent bleeding at the surgical site, no revision of the wound was performed in order to identify and manage bleeders. The gastrointestinal bleed started approximately two days after initiation of FEIBA, therefore a direct relationship is unlikely.

Evaluations of safety laboratory parameters and immunogenicity data did not reveal worrying signals. In two paediatric subjects low calcium levels were observed. The applicant provided the current knowledge on the association of hypocalcaemia and coagulopathy. At the time being it is not established if the hypocalcaemia represents a sequel of a trauma or bleeding event or if a pre-existing hypocalcaemia worsens the extent of bleeding. Therefore, no further helpful recommendation can be made in the SmPC, especially as it can be assumed that clinicians will monitor laboratory parameters in those patients who undergo major surgery or experience a major bleeding event as a matter of course.

Due to weight-based dosing, an increased or decreased dose of Cevenfacta despite a similar intravascular compartment is administered in patients with the same height but differing weight, which could lead to either lack of efficacy or safety consequences. The applicant was therefore asked to discuss if a minimum dose for underweight and a maximum dose for overweight patients should be specified or if at least a statement alerting the treating physician that dose based on bodyweight may require adjustment in underweight or overweight patients is warranted in the SmPC. During the evaluation, the applicant provided evaluation of efficacy and estimated PK parameters in the three bodyweight categories. There was a trend towards lack of efficacy in underweight children <12 years of age, while estimated exposure in overweight patients was comparable to that in normal weight subjects. It is acknowledged that the current PK model is not optimal, but additional reassurance towards comparable safety is provided by the 284 treated bleeding episodes in overweight subjects in studies PerSept 1 and 2.

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

2.5.2. Conclusions on the clinical safety

The clinical safety profile of Cevenfacta as demonstrated in its clinical trial programme is considered manageable, and able to support the granting of a marketing authorisation.

2.6. Risk Management Plan

2.6.1. Safety concerns

The applicant proposed the following summary of safety concerns in the RMP:

Table 45: Summary of safety concerns

Important identified risks	None
Important potential risks	Anaphylactic reactions* Thromboembolic events Immunogenicity
Missing information	Patients with hepatic or renal impairment Elderly patients Pregnant and breastfeeding women

2.6.2. Pharmacovigilance plan

Table 46: On-going and planned additional pharmacovigilance activities

Study **Status**	**Summary of objectives**	**Safety concerns addressed**	**Milestones**	**Due dates**
Category 1 - Imposed mandatory additional pharmacovigilance activities which are conditions of the marketing authorisation				
None				
Category 2 – Imposed mandatory additional pharmacovigilance activities which are Specific Obligations in the context of a conditional marketing authorisation or a marketing authorisation under exceptional circumstances				
None.				
Category 3 - Required additional pharmacovigilance activities				
Collaboration with the EUHASS registry Planned	To further characterise the safety profile in patients exposed to eptacog beta (activated) and to estimate the event rates of the following important risks (anaphylactic reactions, thromboembolic events immunogenicity, as well as in patients with hepatic or impairment, elderly patients, pregnant and breastfeeding women.	Anaphylactic reactions Thromboembolic Immunogenicity Patients with hepatic or renal impairment Elderly patients Pregnant and breastfeeding women	Start of data collection: Yearly data collection: Yearly Report:	To be confirmed at the end of the centralised procedure Each year, from 1-January to 31-December Q1 of next year for 5 years

Study Status	Summary of objectives	Safety concerns addressed	Milestones	Due dates
Collaboration with the PedNet registry Planned	To generate information regarding the use and the safety of eptacog beta (activated) in patients from 12 years old (including those with hepatic or renal impairment) in the post-authorisation setting. Safety endpoints of interest will include hypersensitivity reactions, thromboembolic events, immunogenicity and drug-drug interactions with activated or non-activated prothrombin complex or other haemostatic agents, but all adverse events reported to the PedNet registry in patients exposed to eptacog beta (activated) will be summarised.	Anaphylactic reactions Thromboembolic events Immunogenicity Patients with hepatic or renal impairment	Start of data collection: Yearly data collection: Yearly Report:	To be confirmed at the end of the centralised procedure Each year, from 1-January to 31-December Q1 of next year for 5 years

2.6.3. Risk minimisation measures

Table 47: Description of routine risk minimisation measures by safety concern

Safety concern	Routine risk minimisation activities
Important identified risks	
None.	None
Important potential risks	
Anaphylactic reactions	• Routine risk communication: Patient Leaflet (PL) section 4 • Routine risk minimisation activities recommending specific clinical measures to address the risk: SmPC sections 4.3 & 4.4, PL sections 2 & 4 • Other routine risk minimisation measures beyond the Product Information:

	Pack size: None Legal status: None
Thromboembolic events	• Routine risk communication: Patient Leaflet (PL) section 4 • Routine risk minimisation activities recommending specific clinical measures to address the risk: SmPC sections 4.4 & 4.5, PL sections 2 & 4 • Other routine risk minimisation measures beyond the Product Information: Pack size: None Legal status: None
Immunogenicity	• Routine risk communication: Patient Leaflet (PL) section 4 • Routine risk minimisation activities recommending specific clinical measures to address the risk: SmPC sections 4.4, PL sections 2 & 4 • Other routine risk minimisation measures beyond the Product Information: Pack size: None Legal status: None
Missing information	
Patients with hepatic or renal impairment	• Routine risk minimisation measures: SmPC section 4.4 PL section 2 • Additional risk minimisation measures: None
Elderly patients	• Routine risk minimisation measures: SmPC section 4.4 PL section 2 • Additional risk minimisation measures: None
Pregnant and breastfeeding women	• Routine risk minimisation measures: SmPC section 4.6

	PL section 2 • Additional risk minimisation measures: None

2.6.4. Conclusion

The CHMP considers that the risk management plan version 2 is acceptable.

2.7. Pharmacovigilance

2.7.1. Pharmacovigilance system

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

2.7.2. 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.

2.8. Product information

2.8.1. User consultation

The results of the user consultation with target patient groups on the package leaflet submitted by the applicant show that the package leaflet meets the criteria for readability as set out in the *Guideline on the readability of the label and package leaflet of medicinal products for human use.*

3. Benefit-Risk Balance

3.1. Therapeutic Context

3.1.1. Disease or condition

The indication sought is treatment of bleeding episodes and for the prevention of bleeding in those patients undergoing surgery or invasive procedures, in children and adults congenital haemophilia A or B patients with:

- High-response inhibitors to coagulation factors VIII or IX (i.e. ≥5 Bethesda Units (BU)), including those expected to have a high anamnestic response to factor VIII or factor IX administration.
- Low-response inhibitors (BU<5) but expected to be refractory to increased dosing of FVIII or FIX.

3.1.2. Available therapies and unmet medical need

The current standard of care for treatment of bleeds or prevention of bleeding in those undergoing surgery in haemophilia A or B patients with inhibitors is treatment with bypassing agents. The two products available for this are:

- recombinant factor VIIa (NovoSeven) and
- activated prothrombin complex concentrate (aPCC, or factor eight inhibitors bypassing agent [FEIBA]).

For patients with haemophilia A with inhibitors, emicizumab (Hemlibra) is an option for **prophylaxis** of bleeding episodes. Emicizumab is a humanised bispecific monoclonal antibody that bridges activated FIX and FX to mimic the function of activated FVIII, thereby increasing thrombin formation. Such an option is not available for patients with haemophilia B with inhibitors.

3.1.3. Main clinical studies

A total of four clinical studies were submitted to support the MAA of Cevenfacta. There was a Phase 1b Study in patients with haemophilia A or B with or without inhibitors assessing the safety and PK/PD of Cevenfacta. The three efficacy trials (PerSept1-3) enrolled haemophilia A or B patients with inhibitors.

Study GTC-FVIIa-005-11: Phase 1b, dose-escalation, multicentre, open-label, multinational study assessing safety, PK, PD of Cevenfacta in adult patients with congenital haemophilia A or B in a non-bleeding state. 15 patients were enrolled.

LFB-FVIIA-009-19: Phase I, open-label, randomised, parallel, single-dose PK study in subjects with haemophilia A, with or without inhibitors to FVIII. PK and safety of a single intravenous (IV) dose of 75 or 225 µg/kg of the commercial manufacturing process were evaluated in 28 male subjects aged 18 to 75 years, inclusive, with confirmed diagnosis of haemophilia A (with or without inhibitors to FVIII) and who were not experiencing an active bleeding episode.

PerSept1: Phase 3, multicentre, randomised, open-label, crossover study of two treatment regimens for bleeding episodes (patients ≥12 years of age); The trial consisted of two phases: Phase A: PK and safety; Phase B: treatment of bleeding episodes, repeated PK for product of the commercial manufacturing process. 27 patients were enrolled.

PerSept2: Phase 3, multicentre, randomised, open-label, crossover study of two treatment regimens for bleeding episodes (patients <12 years of age); the trial consisted of two phases: Phase A: PK and safety; Phase B: treatment of bleeding episodes. 25 patients were enrolled.

PerSept3: Phase 3, multicentre, single-arm, open-label, study in surgical/invasive procedures; ≥12 procedures in ≥6 patients; ≥6 major procedures (patients aged ≥6 months to ≤75 years). 12 patients were enrolled (4 patients participated in earlier trials (2 from PerSept1 and 2 from PerSept2) and were counted uniquely).

3.2. Favourable effects

From a quality point of view a robust and well-controlled drug substance and drug product manufacturing has been set-up. An appropriate overall control strategy is in place which assures that only material fulfilling its predefined quality expectations will enter the market. This conclusion is further supported by conducted process validation results and a considerable amount of batch data from GMP batches manufactured during development. An extensive characterisation of product and its

manufacturing process has been performed and indicates that the applicant has gained an in-depth knowledge of its process and product.

The phase 3 trial **PerSept1** includes data from treatment of 468 bleeding episodes (465 mild/moderate, 3 severe) in 27 subjects above the age of 12 years. The proportion of successfully treated bleeding episodes was higher for the **225 µg/kg** dose regimen (**89.8%**), compared to the **75 µg/kg** regimen (**80.2%**).

In terms of time to assessment of a successful response (= 'good' or 'excellent' assessment) there was a clear difference between the two treatment regimens, with a median of **3 hours** for the **225 µg/kg** group and **6 hours** for the **75 µg/kg** group.

Less study drug administrations were necessary for the **225 µg/kg** group (**mean 1.4, median 1.0** administrations) compared to the **75 µg/kg** group (**mean 2.5, median 2.0** administrations). For patients on the 225 µg/kg regimen, approximately **85%** were successfully treated with **a single administration of 225 µg/kg** Cevenfacta.

The higher bolus infusion of 225 µg/kg resulted in a higher total amount of study drug administered per bleeding episode (mean 252.96 µg/kg, median 225.09 µg/kg), compared to the lower dose bolus infusion of 75 µg/kg (mean 187.87 µg/kg, median 149.68 µg/kg) for the treatment of mild/moderate bleeding events.

In study **PerSept2,** 549 treated bleeding events (546 mild/moderate, 3 severe) occurred in 25 subjects <12 years of age. Of these bleeds, **66.1%** of bleeding events treated with the **75µg/kg** dose (n=239) were successfully treated at 12 hours, as well as **61.3%** of bleeds treated with the **225µg/kg** dose (n= 310). For the <6-year-old subjects, these values are 56.6% and 58.5% for 75µg/kg and 225µg/kg, respectively. For the 6 to <12-year-old patients, the proportions are 73.7% and 63.8% for the two different dosing schemes.

The median time to assessment of a good or excellent response was **9 hours** for the **75µg/kg** dose and **12 hours** for the **225µg/kg** dose. As for the lower dose, a repeat administration was allowed every 3 hours, this signifies the need for 3 doses of 75µg/kg (at 0, 3 and 6 hours) until success. For the higher dose, the initial treatment of 225µg/kg could be followed with a 75µg/kg dose at 9 hours, and the outcome of this endpoint signifies that the initial higher dose and at least one additional dose are needed for resolution of the bleed.

The mean and median number of administrations for mild/moderate bleeds was **3.6** and **3** for the **75µg/kg** dose, and **2.6** and **2** for the **225µg/kg** dose, respectively.

The **PerSept3** trial provides data from 12 surgical procedures, including 6 major (2x leg amputation, 2x knee surgery, 1x hip surgery, 1x achilloplasty) and 6 minor (3x circumcision, 3x tooth extraction) surgeries in patients between the age of 2 to 56 years.

The **intraoperative assessment** by the surgeon/practitioner was **"good" or "excellent" for all 12 procedures**. This assessment was based on the blood volume loss, the amount of fluid replacement given, transfusion requirements, and hemodynamic stability. However, of the 12 surgical procedures performed, **9 (81.8%) procedures** were reported by the investigator as **successfully treated** ("good" or "excellent" response) with Cevenfacta at 48 hours after the last administration (=primary endpoint) of Cevenfacta, 2 (18.2%) were treatment failures ("poor" response), and 1 assessment was missing because of discontinuation from the study (withdrawal of consent) prior to the assessment at 48 hours.

For minor surgeries, the mean (SD) number of study drug administrations was 38.2 (20.98) and the mean (SD) treatment duration was 4.3 (3.71) days. For major surgeries, patients received mean 84.2 (40.68) administrations of Cevenfacta with a mean treatment duration of 17.6 (12.36) days.

3.3. Uncertainties and limitations about favourable effects

The applicant provided further clinical PK data from a new clinical study FVIIa-009-19 based on activated FVII plasma concentrations, analysed using a different PK assay. An indirect comparison of the NCA results obtained by the two different methods in two different studies (method GBS 2013-30 for Phase 3 studies versus method AI-01587 for the new Study 009-19) was attempted to assess the degree of comparability / similarity of PK data using the same to-be marketed Process B and same doses. Overall, these data did not give reassurance on the comparability of PK data collected with the two analytical methods and ultimately reinforce doubts regarding the reliability of the analytical method used in Phase 3 studies. Conclusively, PK data collected in these two studies were excluded from the PK package and only data from the new clinical study FVIIa-009-19 were considered for PK characterisation purpose of the of Cevenfacta product.

In the phase III trial differences in clinical performance characteristics have been observed between product generated with process version A and B. Regarding quality, a number of deficiencies in the conduct of the comparability exercise have been noted in the initial dossier. These deficiencies left a considerably high level of uncertainty on the quality comparability claim of Process A with Process B (intended commercial process) material open. To address these deficiencies the applicant:

#) conducted an additional comparative in-depth characterisation of clinical/GMP/process validation material manufactured with both process versions,

#) provided acceptable clarifications on establishment of comparability criteria,

#) and included the whole available batch release data set from both process versions to re-evaluate comparability.

In summary, the new data provided with the responses support the comparability claim.

During the **PerSept1** trial, a new manufacturing product was introduced (upscaled process B). The above presented efficacy results are compromised by the fact that only a relatively small fraction of patients received product of the commercial process B. Of the 468 bleeding episodes in PerSept1, only 86/468 (18.4%) were treated with product from process B and 53/468 (11.3%) with a mixture of products from both processes.

For the 75 µg/kg regimen, the proportion of successfully treated bleeding events was similar between both processes (process A: 82.3%, process B: 80.4%). The success proportion was lower for process B with the 225 µg/kg regimen (process A: 91.2%, process B: 80.0%). However, the comparability of efficacy results between the processes is limited due to the much lower number of bleedings treated with process B. Initial major concerns regarding the comparability have been resolved (please see clinical discussion).

In study **PerSept 2**, a clear difference in the proportion of successfully treated bleeding events to the outcomes of PerSept 1, where patients aged 12 and above were investigated, is evident (66.1% vs. 80.2% for the 75µg/kg dose and 61.3% vs. 89.8% for the 225µg/kg dose).

Despite the fact that a faster clearance of Cevenfacta was determined in paediatric subjects, the same dose and interval as in adults was used for children in both age cohorts. A trend towards better treatment outcomes was observed in the 6 to <12 cohort, supporting the notion that the selected dose and /or dosing interval should have been adapted for children.

The analysis of the primary endpoint according to BMI subgroups shows increasing efficacy with increasing BMI. Due to weight-based dosing, an increased dose of Cevenfacta despite a similar intravascular compartment is administered in patients with the same height but higher weight and

leads to better outcomes in those subjects and could conversely cause a lack of efficacy in underweight subjects.

The median time to assessment of a good or excellent response was 9 hours for the 75µg/kg dose and 12 hours for the 225µg/kg dose. However, compared to outcomes from PerSept 1, where a median of 3 hours for the 225 µg/kg group and 6 hours for the 75 µg/kg group passed until a good/ excellent response was reported, these values emphasise the inferior bleed control in younger children compared to adolescents and adults. It can however not be excluded that these outcomes might be influenced by the assessment of bleeding response being done by the parent or caregiver for paediatric subjects

In an analysis of outcomes of mild versus moderate bleeding events, the success proportion of mild bleeding events is clearly in favour of treatment with eptacog beta at both the 75µg and the 225µg dose, the success proportion for moderate bleeding events is only 55.4% for the 75µg dose and 46.4% for the 225µg dose.

The efficacy in severe bleeding events in children below 12 years of age is not established due to only three severe bleeds being treated in study PerSept 2, of which none were a success. Further uncertainties concern the optimal dose for children below 2 years of age and especially for infants <1, for whom no data are available. No reliable population PK model was available to provide support for dosing recommendations in any of the above-mentioned issues.

In their response to the D180 LoOI, the applicant has clarified that children below 12 years of age will be excluded from the indication, as there are no further data available to support dosing recommendations and efficacy in this age group.

Some **methodological concerns** for both **PerSept1 and 2** regarding the primary efficacy estimand were raised, particularly specifying how the intercurrent events withdrawal from assigned treatment and initiation of alternative/rescue therapy are to be addressed.

Not all methodological issues were resolved in the end. For example, for people who are withdrawn from treatment with the study drug, the remaining bleeding episodes (after withdrawal) should be documented and included as failure in the efficacy assessment. The responses by the applicant could also not clarify whether ALL bleeding events during the whole study period have been treated with Cevenfacta or whether some of the events were treated with alternative treatments (without documentation). The difficulty of evaluating events that were not reported is acknowledged, but the concern arises whether or not the reporting of bleeding events is independent of the perceived efficacy of their treatment. An introduction of bias cannot be ruled out, especially because most patients were treated at home. The estimate of the rate of treatment failure in the population of bleeds that were reported could not be representative of the overall rate of failure. The applicant has also not provided adequate reasoning for the value of the OPC from a clinical or methodological perspective. However, these issues were not further pursued since the main aspects of the study design have been agreed with during several previous EMA-SA procedures. The efficacy table in section 5.1 of the SmPC was updated, showing the primary efficacy results based on an analysis where bleeding episodes with missing assessments are considered as failures.

Further, a planned interim analysis to potentially re-assess the study's sample size raised several concerns. The number of reported bleeding events by far exceeded the pre-specified numbers. Therefore, the applicant was asked to explain the overrun and the decision making regarding the interim analysis. Further a primary efficacy analysis including only the first 352 bleeding events, as initially planned in the original protocol, was requested. In their responses, the applicant provided background information from the DMC meetings. The explanation of the overrun was sufficiently convincing for both trials (PerSept1 and PerSept2, see discussion section). For PerSept1, a sensitivity

analysis after 352 bleeding events shows very similar point estimates and confidence intervals compared to the primary endpoint. No such sensitivity analysis was provided for PerSept2, since the applicant decided to exclude the respective population from the label, which is acceptable.

The open-label and uncontrolled study design and limited size of PerSept 1 (N = 27), PerSept 2 (N = 25) and PerSept 3 (N = 12) make any interpretation of efficacy results challenging.

There were 2 treatment failures in the **PerSept3** surgery study. One patient (knee surgery) had a moderate bleeding episode within 24 hours of the last dose of study drug (i.e. 7 to 8 days after surgery) and required a red blood cell transfusion and rescue treatment with NovoSeven. The second treatment failure for a hip surgery resulted in death of a patient (due to a GI bleeding, according to the autopsy). It is not straightforward to assess to what extent lack of efficacy of Cevenfacta contributed to the fatal outcome 3 days after surgery, especially because the patient also received treatment with FEIBA due to a bleeding at the surgery site, starting 1 day after surgery. Overall, the provided information underlines the importance of close follow-up during the postoperative phase. Upon request, the applicant included a statement in this regard in section 4.2. of the SmPC.

The data for **treatment of severe bleeding episodes** is sparse. Only 6 severe bleeding events occurred in both on-demand treatment studies. The 3 severe bleedings in PerSept1 were successfully treated. However, confounding factors (e.g. much higher dose than pre-specified, concomitant treatment with antihaemorrhagic drug) influenced the outcome assessment. None of the 3 severe bleeding episodes in PerSept2 were considered successfully treated. The uncertainties regarding the dose recommendations for treatment of severe bleeding episodes and the prevention of bleedings following major surgeries were raised as a combined major objection. The responses are discussed in the discussion on clinical efficacy. Overall, it is acceptable not restricting the indication for adults and adolescents (i.e., including also the treatment of severe bleeding episodes). Table 1 in section 4.2 recommends only the dosing regimen with the higher bolus dose (225 µg/kg), which is supported based on the available data.

3.4. Unfavourable effects

During the clinical trials, 172 adverse events were captured, of which less than 10% (n=13) were assessed as related. Many of the TEAE were infections like nasopharyngitis or diarrhoea, which are prevalent in children, or commonly occurring events, like headache. Most of the events assessed as related represented local or systemic infusion reactions and were graded as mild.

The following AEs were identified as adverse events of special interest (AESIs): thromboembolic events, hypersensitivity reactions, and immunogenicity or antidrug antibodies (ADAs). No AESIs were reported in any of the four clinical studies.

Of the 7 serious adverse events, 5 SAEs were reported from studies PerSept 1 and 2 and are either infections or spontaneous or traumatic bleeding and their sequelae. It is agreed with the assessment of the investigator that these SAEs can be classified as unrelated to Cevenfacta. Two related SAEs (gastrointestinal haemorrhage and blood loss anaemia) were reported from PerSept3.

Evaluations of safety laboratory parameters and immunogenicity data did not reveal worrying signals.

3.5. Uncertainties and limitations about unfavourable effects

The available safety database is small (n= 75) due to the fact that patients with haemophilia and inhibitors are rare, especially those who suffer from haemophilia B. Therefore, the very low number of patients with haemophilia B with inhibitors (n=4) and the low numbers of patients with haemophilia A with inhibitors (n=56) can be accepted as post-marketing safety follow-up via EUHASS and PEDNET registry is planned (please see RMP). The age range reached from 1 to 61 (1-56 in target patients with inhibitors), thus clinical experience in elderly patients, who are likely to have more cardiovascular risk factors promoting the incidence of thromboembolic events, is missing. The current safety database was further limited by the exclusion of patients with a higher risk of thromboembolic events, as well as severe comorbidities such as liver and/or renal impairment, active malignancy and immunosuppression. Patients with known allergy or hypersensitivity to any component of to the product or to rabbit protein and patients with platelet count below 100 000/µL were also excluded from the clinical studies.

The two related SAEs of gastrointestinal haemorrhage and blood loss anaemia leading to the death of one patient in PerSept 3 happened shortly after withdrawal of Cevenfacta and initiation of treatment with FEIBA. However, an assessment of the relatedness of these events to the treatment with Cevenfacta is not straightforward and the applicant was asked to provide more insights into this event, where the main safety concern is lack of efficacy. The applicant provided the autopsy report and the DMC meeting minutes concerning this event. In the DMC meeting summary (03 January 2017), it is mentioned that there were discrepancies in the recordings made by the Investigator. The DMC expressed their concern about the overall management of the postoperative bleeding complication in this subject at this site and recommended that no new subjects be recruited at this site. In summary, despite persistent bleeding at the surgical site, no revision of the wound was performed in order to identify and manage bleeders. The gastrointestinal bleed started approximately two days after initiation of FEIBA, therefore a direct relationship is unlikely.

Due to weight-based dosing, an increased or decreased dose of Cevenfacta despite a similar intravascular compartment is administered in patients with the same height but differing weight, which could lead to either lack of efficacy or safety consequences. The applicant was therefore asked to discuss if a minimum dose for underweight and a maximum dose for overweight patients should be specified or if at least a statement alerting the treating physician that dose based on bodyweight may require adjustment in underweight or overweight patients is warranted in the SmPC. The applicant provided evaluation of efficacy and estimated PK parameters in the three bodyweight categories. There was a trend towards lack of efficacy in underweight children <12 years of age, while estimated exposure in overweight patients was comparable to that in normal weight subjects. It is acknowledged that the current PK model is not optimal, but additional reassurance towards comparable safety is provided by the 284 treated bleeding episodes in overweight subjects in studies PerSept 1 and 2.

In two paediatric subjects low calcium levels were observed and more information was requested. The applicant has adequately summarised the current knowledge on the association of hypocalcaemia and coagulopathy. At the time being it is not established if the hypocalcaemia represents a sequel of a trauma or bleeding event or if a pre-existing hypocalcaemia worsens the extent of bleeding. Therefore, no further helpful recommendation can be made in the SmPC, especially as it can be assumed that clinicians will monitor laboratory parameters in those patients who undergo major surgery or experience a major bleeding event as a matter of course.

3.6. Effects Table

Table 48: Effects Table for Cevenfacta in the treatment of bleeding episodes and for the prevention of bleeding in those patients undergoing surgery or invasive procedures

Effect	Short Description	Unit	Dose 1	Dose 2	Uncertainties/ Strength of evidence	References
Favourable Effects						
Treatment of Bleeding Events	4-point scale; Excellent or Good = Treatment success	%	**75µg/kg**	**225µg/kg**	Low patient numbers due to rarity of the disease; Only 4 patients suffering from haemophilia B with inhibitors; Only 3 severe bleeds treated in each trial	Section on Clinical Efficacy 3.3.5
PerSept 1 ≥12 yoa n=27			80.2% (252 BEs)	89.8% (216 BEs)	Comparability Material from Process A with Process B	
PerSept 2 <12 yoa n=25			66.1% (239 BEs)	61.2% (310 BEs)	Underdosing compared to adolescents or adults	
Time to treatment success	Median Duration in h	h				
PerSept 1 ≥12 yoa			5.98	3.00		
PerSept 2 <12 yoa			9.00	12.00		
Number of administrations per BE	Median #	n				
PerSept 1 ≥12 yoa			2.0	1.0		
PerSept 2 <12 yoa			3.0	2.0		
Surgery: Investigator Assessment 48h after last treatment	4-point scale; Excellent or Good = Treatment success	%	Minor surgeries n=6	Major Surgeries n=6		
PerSept 3 n=12			100%	66.7%		
Unfavourable Effects						
Safety Database n=75		All dose levels				Section on Clinical Safety 3.3.8
Adverse Events of Special Interest	Allergic Reactions / Hypersensitivity	None			Small safety database	

Effect	Short Description	Unit	Dose 1	Dose 2	Uncertainties/ Strength of evidence	References
	Binding Antibodies/ Neutralising Antibodies	2 transient ADAs/ 0 neutralising Antibodies				
	Thrombotic events	None				
Death		1 subject in PerSept 3			Relatedness difficult to ascertain, event happended 2 days after end of treatment with Cevenfacta	

Abbreviations: BE… Bleeding Event, h…hour, n…number

3.7. Benefit-risk assessment and discussion

3.7.1. Importance of favourable and unfavourable effects

The currently available treatment options for haemophilia patients with inhibitors are very limited. Timely control of spontaneous or traumatic bleeding events is essential to delay and/or prevent irreversible tissue and joint damage. The submitted data from PerSept1 show that Cevenfacta provides satisfactory efficacy and sufficiently quick onset of effect in **patients ≥12** years of age. For the dose regimen with a higher bolus infusion (225 µg/kg), a better efficacy was noted in terms of proportion of success, time until success, and number of administrations needed, compared to the lower bolus dose (75 µg/kg). In contrast, the lower bolus dose resulted in a reduced amount of used Cevenfacta. The current version of the SmPC enables some flexibility in dosing, based on the patient's individual response, which is endorsed and may lead to a dose sparing effect in some patients.

For **children <12** years of age the observed efficacy of Cevenfacta was not convincingly demonstrated. The analysis of outcomes of mild versus moderate bleeding events underlines that for mild bleeds either dosing regimen was efficacious in children. For moderate bleeds however, the repeated administration of 75µg is clearly preferable, but the success proportion is still distinctly lower than that observed in subjects ≥12 years of age, even if the underweight subject is excluded from the analysis. The influence of low bodyweight on the proportion of successfully treated bleeds is evident from the cohort of children <6 years of age, in which subject had a very low bodyweight for his age and was very likely underdosed due to the weight-based dosing scheme. PK modelling data intended to support an adequate dosing regimen in underweight children however, cannot be accepted due to doubts about the adequacy of the model and the reliability of paediatric PK data from trial PerSept 2 in general.

The efficacy in **severe bleeding** events in **children below 12** years of age is **not established**.

The applicant clarified in their responses to the D 180 LoOI, that children below 12 years of age will be excluded from the indication, as no further data are available to support dosing recommendations and efficacy in this age group.

The surgery trial PerSept3 shows that Cevenfacta is efficacious for intraoperative haemostasis during minor and major surgeries. However, there were 2 cases of treatment failures due to bleeding events in the postoperative phase. The applicant included a statement in the posology section to inform about

the importance of close follow-up to enable early detection of potential postoperative bleeding events that may require adjustment of the dosing intervals.

Only a minority of TEAE were assessed as related and most of these events represented local or systemic infusion reactions and were graded as mild. The serious adverse events were mainly either infections or spontaneous or traumatic bleeding. The adverse events of special interest (AESI) were defined as thromboembolic events, hypersensitivity reactions, and immunogenicity or antidrug antibodies (ADAs). No AESI were reported in any of the four clinical studies. However, the safety database is small due to the rarity of the disease. Post-marketing safety follow-up is planned via EUHASS and PEDNET registries.

3.7.2. Balance of benefits and risks

The safety and efficacy of Cevenfacta can be considered as favourable in patients ≥**12 years of age**.

3.7.3. Additional considerations on the benefit-risk balance

While no difference regarding safety was noted in patients <12 years of age, Cevenfacta was clearly less efficacious in terms of time until and proportion of successfully treated bleeding events compared to children ⩾12 years of age and adults. Additional review of the totality of the data shows that for children <12 years, the efficacy of both proposed dosing regimens of Cevenfacta was sufficiently shown for mild bleeding events only. With regard to efficacy in moderate and severe bleedings as well as the optimal dosing regimen for children below 2 years and for children with a low bodyweight for their age, substantial uncertainties remain and preclude a positive benefit risk balance.

The age group of children <12 years of age is excluded from the indication, therefore the benefit risk balance in the remaining target population of adolescents ⩾12 years and adults is positive.

3.8. Conclusions

The overall benefit/risk balance of Cevenfacta is positive, subject to the conditions stated in section 'Recommendations'.

4. Recommendations

Similarity with authorised orphan medicinal products

The CHMP by consensus is of the opinion that Cevenfacta is not similar to Alprolix and Idelvion within the meaning of Article 3 of Commission Regulation (EC) No. 847/2000. See Appendix on Similarity.

Outcome

Based on the CHMP review of data on quality, safety and efficacy, the CHMP considers by consensus that the benefit-risk balance of Cevenfacta is favourable in the following indications:

Cevenfacta is indicated in adults and adolescents (12 years of age and older) for the treatment of bleeding episodes and for the prevention of bleeding in those undergoing surgery or invasive procedures in the following patient groups:

- in patients with congenital haemophilia with high-responding inhibitors to coagulation factors VIII or IX (i.e. ≥5 Bethesda Units (BU));

- in patients with congenital haemophilia with low titre inhibitors (BU <5), but expected to have a high anamnestic response to factor VIII or factor IX administration or expected to be refractory to increased dosing of FVIII or FIX.

Conditions or restrictions regarding supply and use

Medicinal product subject to medical prescription.

Other 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 marketing authorisation holder (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.

New Active Substance Status

Based on the review of available data, it is considered that eptacog beta (activated) is not a new active substance in comparison to the known active substance eptacog alfa (activated) previously authorised in the European Union as NovoSeven on 23/02/1996 as it is not demonstrated that it differs significantly in properties with regard to safety and efficacy from the previously authorised substance.

Paediatric Data

Furthermore, the CHMP reviewed the available paediatric data of studies subject to the agreed Paediatric Investigation Plan P/0214/2017 and the results of these studies are reflected in the Summary of Product Characteristics (SmPC) and, as appropriate, the Package Leaflet.