24 September 2015
EMA/671791/2015
Committee for Medicinal Products for Human Use (CHMP)

Assessment report

ELOCTA

International non-proprietary name: efmoroctocog alfa

Procedure No. EMEA/H/C/003964/0000

Note

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

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List of abbreviations

ADA	anti-drug (rFVIIIFc) antibody
ADR	adverse drug reaction
AE	adverse event
ALT	alanine aminotransferase
ADME	absorption, distribution, metabolism, excretion
APC	activated Protein C
aPTT	Activated partial thromboplastin time
AUC	Area under the curve
AST	aspartate aminotransferase
AUC_{inf}	area under the concentration-time curve from time zero to infinity
BDD	B-domain deleted
BU	Bethesda unit
CABS	chromosomal aberrations
Cmax	maximum plasma activity
DKO	double knockout
DNAUC	dose-normalized area under the curve
DP	Drug Product
DS	Drug Substance
eCRF	electronic case report form
ED	exposure day
ED50	effective dose
ELISA	Enzyme-linked immunosorbent assay
EMA	European Medicines Agency
EPD	electronic patient diary
F	female
FAS	full analysis set
FcRn	neonatal Fc receptor
FVIII	coagulation factor VIII
GLP	Good Laboratory Practice
Hb	Haemoglobin
HCT	haematocrit
HCV	hepatitis C virus
HemA	haemophilia A
HEK	human embryonic kidney
HIV	human immunodeficiency virus
IgG	immunoglobulin G
IgG1	Immunoglobulin G1
IU	International unit
IR	incremental recovery
IQR	interquartile range
IV	intravenous
kD	kilodalton

KO	knockout
MAA	marketing authorisation applicant/application
MRT	mean residence time
NA	not applicable
NIRC	New Iberia Research Center
NOAEL	no observed adverse effect level
PD	Pharmacodynamics
PK	Pharmacokinetic/Pharmacokinetics
PTP	previously treated patient
RBC	red blood cell
rFVIII	recombinant Factor VIII
rFVIIIFc	recombinant human coagulation factor VIII, Fc fusion protein
ROTEM	rotational thromboelastography
SAE	serious adverse event
SAS	safety analysis set
SC	single chain
SC rFVIIIFc	single chain isoform of rFVIIIFc
SD	study drug or standard deviation
SmPC	summary of product characteristics
SOC	system organ class
SPR	surface plasmon resonance
$t_{1/2}$	half-life
TEAE	treatment-emergent adverse event
TESAE	treatment-emergent serious adverse event
Tg	transgenic
TVT	tail vein transection
Vss	volume of distribution at steady state
VWF	von Willebrand Factor
WBC	white blood cell
WBCT	Whole blood clotting time

1. Background information on the procedure

1.1. Submission of the dossier

The applicant Biogen Idec Ltd submitted on 9 October 2014 an application for Marketing Authorisation to the European Medicines Agency (EMA) for ELOCTA, through the centralised procedure falling within the Article 3(1) and point 4 of Annex of Regulation (EC) No 726/2004. The eligibility to the centralised procedure was agreed upon by the EMA/CHMP on 20 February 2014.

ELOCTA, was designated as an orphan medicinal product EU/3/10/783 on 20 September 2010 in the following indication: Treatment of haemophilia A

The applicant applied for the following indication:

ELOCTA is a long-acting recombinant coagulation factor for the treatment and prophylaxis of bleeding in patients with haemophilia A (congenital factor VIII deficiency). ELOCTA does not contain von Willebrand factor, and is therefore not indicated in patients with von Willebrand disease. ELOCTA can be used for all age groups.

The legal basis for this application refers to:

Article 8.3 of Directive 2001/83/EC - complete and independent application. The applicant indicated that efmoroctocog alfa was considered to be a new active substance.

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 test(s) or study(ies).

Information on Paediatric requirements

Pursuant to Article 7 of Regulation (EC) No 1901/2006, the application included an EMA Decision(s) P/0077/2014 on the agreement of a paediatric investigation plan (PIP).

At the time of submission of the application, the PIP P/0077/2014 was not yet completed as some measures were deferred.

Information relating to orphan market exclusivity

Similarity

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

New active Substance status

The applicant requested the active substance efmoroctocog alfa contained in the above medicinal product to be considered as a new active substance in itself, as the applicant claims that it is not a constituent of a product previously authorised within the Union

Protocol Assistance

The applicant received Protocol Assistance from the CHMP on 13 December 2012. The Protocol Assistance pertained to quality, non-clinical and clinical aspects of the dossier.

Licensing status

ELOCTA has been given a Marketing Authorisation in the Unites States on 6 June 2014, Australia on 27 June 2014, Canada on 22 August 2014, Japan on 26 December 2014.

A new application was filed in the following countries: South Africa, Israel, Taiwan, Brazil, New Zealand, Switzerland and Colombia.

1.2. Steps taken for the assessment of the product

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

Rapporteur: Jan Mueller-Berghaus Co-Rapporteur: Sol Ruiz

- The application was received by the EMA on 9 October 2014.
- The procedure started on 29 October 2014.
- The Rapporteur's first Assessment Report was circulated to all CHMP members on 19 January 2015 The Co-Rapporteur's first Assessment Report was circulated to all CHMP members on 20 January 2015
- During the meeting on 12 February 2015 the Pharmacovigilance Risk Assessment Committee (PRAC) adopted the PRAC Advice on the submitted Risk Management Plan (
- During the meeting on 26 February 2015, the CHMP agreed on the consolidated List of Questions to be sent to the applicant. The final consolidated List of Questions was sent to the applicant on 27 February 2015
- The applicant submitted the responses to the CHMP consolidated List of Questions on 21 May 2015.
- The Rapporteurs circulated the Joint Assessment Report on the applicant’s responses to the List of Questions to all CHMP members on 29 June 2015
- During the meeting on 09 July 2015 the Pharmacovigilance Risk Assessment Committee (PRAC) adopted the PRAC Advice on the submitted Risk Management Plan
- During the CHMP meeting on 23 July 2015, the CHMP agreed on a list of outstanding issues to be addressed in writing and/or in an oral explanation by the applicant
- The applicant submitted the responses to the CHMP List of Outstanding Issues on 21 August 2015.

- The Rapporteurs circulated the Joint Assessment Report on the applicant's responses to the List of Questions to all CHMP members on 2 September 2015
- During the meeting on 10 September 2015 the Pharmacovigilance Risk Assessment Committee (PRAC) adopted the PRAC Advice on the submitted Risk Management Plan
- During the meeting on 21 to 24 September 2015 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 ELOCTA.

2. Scientific discussion

2.1. Introduction

Haemophilia A is an inherited sex-linked disorder of blood coagulation in which affected males (very rarely females) do not produce functional coagulation FVIII in sufficient quantities to achieve satisfactory haemostasis. The incidence of congenital haemophilia A is approximately 1 in 10,000 births. Disease severity is classified according to the level of FVIII activity (% of normal) as mild (>5% to <40%), moderate (1% to 5%) or severe (<1%). This deficiency in FVIII predisposes patients with haemophilia A to recurrent bleeding episodes in joints, muscles or internal organs, either spontaneously or as a result of accidental or surgical trauma.

Without adequate treatment these repeated haemarthroses and haematomas lead to long-term sequelae with severe disability. Other less frequent, but more severe bleeding sites, are the central nervous system, the urinary or gastrointestinal tract, eyes and the retro-peritoneum. Patients with haemophilia A are at high risk of developing major and life-threatening bleeds after surgical procedures, even after minor procedures such as tooth extraction.

The development of cryoprecipitate and subsequently FVIII concentrates, obtained by fractionation of human plasma, provided replacement FVIII and greatly improved clinical management and life expectancy of patients with haemophilia A. Current treatment approaches focus on either prophylactic or on demand factor replacement therapy with plasma-derived FVIII or recombinant FVIII products. In the short term, prophylaxis can prevent spontaneous bleeding and in the long term, prophylaxis can prevent bleeding into joints that will eventually lead to debilitating arthropathy.

Prophylaxis with FVIII concentrates is currently the preferred treatment regimen for patients with severe haemophilia A, especially in very young patients. The majority of patients receiving prophylaxis are treated 3-times weekly or every other day at a dose of 25–40 international units (IU)/kg (or 15–25 IU/kg in an intermediate dose regimen), although an escalating dose regimen is also used. However, on-demand treatment is still the predominant replacement approach in many countries.

The most serious complication in the treatment of haemophilia A is the development of neutralising antibodies (inhibitors) against FVIII, rendering the patient resistant to replacement therapy and thereby increasing the risk of unmanageable bleeding, particularly arthropathy, and disability.

ELOCTA (efmoroctocog alfa) is a recombinant human coagulation factor VIII Fc fusion protein (rFVIIIFc) consisting of B-domain deleted FVIII covalently attached to the Fc domain of human immunoglobulin G1

(IgG1) thus aiming at prolongation of plasma half-life. It has been developed as a long-acting version of recombinant FVIII (rFVIII) for the control and prevention of bleeding episodes, routine prophylaxis, and perioperative management (surgical prophylaxis) in individuals with hemophilia A.

ELOCTA is formulated as powder for intravenous administration in a single-use vial. Each single-use vial contains nominally 250, 500, 750, 1000, 1500, 2000, or 3000 International Units (IU) of rFVIIIFc for reconstitution with a solvent (Sterile Water for Injections), which is provided in a pre-filled syringe.

In 2013, national scientific advice was sought from the United Kingdom Medicines and Healthcare Products Regulatory Agency (MHRA), Swedish Medicinal Products Agency, and German Paul-Ehrlich-Institute. No substantial deviations from the advices provided could be identified.

On 2 April 2014, the Paediatric Committee (PDCO) of the European Medicines Agency adopted a favourable opinion on the modification of an agreed paediatric investigation plan (PIP) (P/0077/2014) and a partially completed compliance procedure was finalised on 16-18 July 2014 (EMEA-C1-001114-PIP01-10-MO2). Completed studies, Study 997HA301 and Study 8HA02PED, and the initiation of Study 8HA01EXT are considered compliant with EMA Decision P/0077/2014.

2.2. Quality aspects

2.2.1. Introduction

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

ELOCTA is formulated as a sterile, non-pyrogenic, preservative-free, lyophilized, white to off-white powder to cake for intravenous administration in a single-use vial. Each single-use vial contains nominally 250, 500, 750, 1000, 1500, 2000, or 3000 International Units (IU) of rFVIIIFc for reconstitution with liquid diluent (Sterile Water for Injection), which is provided in a pre-filled syringe.

The finished medicinal product consists of a package containing a rFVIIIFc drug product vial, a pre-filled diluent (SWFI) syringe and medical devices (a plunger rod, a vial adapter (used as a transfer device during reconstitution), an infusion set, alcohol swabs, plasters and gauze pad for intravenous administration).

2.2.2. Active Substance

General information

In summary, the Applicant submitted sufficient information on nomenclature and general properties.

Structure

The active substance of Elocta, efmoroctocog alfa, is a recombinant human coagulation factor VIII, Fc fusion protein (rFVIIIFc) comprised of a single molecule of B-domain deleted human Factor VIII (BDD FVIII) fused to the dimeric Fc region of human IgG1 with no intervening linker sequence.

The rFVIIIFc protein has a molecular weight of approximately 220 kDa. rFVIIIFc is synthesized as 2 polypeptide chains, one chain consisting of BDD FVIII fused to the N-terminal of human IgG1 Fc domain the other chain consisting of the same Fc region alone.

The two subunits of rFVIIIFc, FVIIIFc single chain and Fc single chain, are associated through disulfide bonds in the hinge region of Fc as well as through extensive noncovalent interactions between the Fc fragments.

Manufacture, characterisation and process controls

Manufacturer

The manufacturing and testing sites of the active substance and the responsibilities of each site were listed in the dossier. Valid GMP certificates were presented for all sites.

Description of manufacturing process and process controls

The description of the active substance manufacturing process is considered adequate. Main production steps include fermentation, purification, steps for virus inactivation and virus removal, concentration, formulation, filtration and filling. The batch size was defined. Process flow diagrams for the different steps of the manufacturing process were provided.

Control of materials

The lists of compendial and non-compendial raw materials used during the production of rFVIIIFc were included in the dossier. For non-compendial materials, the control test that have been performed and the in-house specifications were also submitted.

No materials of animal origin are used during the cell banking or in the manufacture of the rFVIIIFc active substance.

In general, the description and control of the expression construct is in accordance with guideline ICH Q5B (Quality of Biotechnological Products: Analysis of the Expression Construct in Cell Lines Used for Production of r-DNA-Derived Protein Products). The origin and the description of coding sequences as well as the cloning strategy for the expression plasmid were given.

A two-tiered cell-banking system is used, consisting of a MCB and a WCB which are both stored at two different locations. The documentation provided supports in general compliance with guideline ICH Q5D (Quality of Biotechnological Products: Derivation and Characterization of Cell Substrates Used for Production of Biotechnological/Biological Products).

Control of critical steps and intermediates

Following early product and process development, a product risk assessment was performed to identify Critical Product Quality Attributes (CQA). Once CQAs were identified, initial process and product risk assessments were performed and used in conjunction with early manufacturing and development knowledge to identify and rank parameters that may potentially affect process consistency and product quality. Based on these assessments, a subset of parameters was selected for further evaluation in statistically designed process characterization studies using scaled-down models of the manufacturing steps. The results of the characterization studies were used to further refine the parameter classification. A control strategy was then

developed for parameters based upon their final classification, i.e. critical, key, non-key. Although this classification is not in line with ICH terminology, it was considered acceptable for the control strategy of this particular product. In addition, the process controls and the acceptable ranges for the operation of critical steps in the rFVIIIFc active substance manufacturing process were indicated.

The selected control parameters for the different cell culture steps were considered appropriate to ensure manufacturing process consistency and performance within the expected ranges.

The control strategy for the different rFVIIIFc purification steps was presented.. In addition, the in-process controls and tests for these steps were shown with the action limits and/or in-process specifications. The selected control parameters for the different chromatographic steps are considered appropriate to ensure manufacturing process consistency. Overall, the control strategy was considered acceptable.

Process validation

In general, the active substance manufacturing process is considered sufficiently validated. Process validation was comprised of impurity clearance validation, process consistency validation, chromatography and filter lifetime validation and the stability evaluation of process intermediates.

Clearance of process impurities was either directly confirmed by measurement in manufacturing scale process intermediates or by measurement in laboratory scale spiking studies or both.

Manufacturing process development

The manufacturing process development has been sufficiently outlined. The description and the comparisons of active substance manufacturing processes and batch utilization of material used for clinical and nonclinical studies were submitted. Operating parameters known to impact process consistency and product quality were maintained between the pilot and full scale processes. Comparability of the rFVIIIFc active substance batches manufactured using the commercial process and the clinical active substance batches was demonstrated by release test results, in-process testing, and a variety of characterization assays.

Characterisation

rFVIIIFc was extensively characterised by physicochemical methods in accordance with guideline ICH Q6B. The structural characterisation and the physicochemical properties confirmed the expected properties for a recombinant FVIIIFc product. In general, the characterization performed was considered appropriate for this complex fusion molecule. The panel of tests was comprehensive and covered most of its structural and functional attributes. The comparability between representative batches from development and commercial manufacture (including process validation batches) as well as with rFVIIIFc reference materials was demonstrated.

The biological activity was analysed by the FVIII one stage clotting assay (activated partial thromboplastin time (aPTT)), the FVIII chromogenic assay and the FcRn binding assay. Additional in vitro functional tests were performed comprising the binding to von Willebrand factor and the generation of Factor Xa.

Since it is anticipated that the potency of modified products measured by the one stage clotting assay (aPTT) may be dependent on the choice of the aPTT reagent, the ISTH recommends for all new FVIII products to perform a study including assay variations (different aPTT reagents) for FVIII testing when using the coagulation assay. Respective studies were provided by the Applicant in Module 5 (no significant dependence on the aPTT reagent was observed).

In addition, the impurity profile regarding product- and process-related impurities was appropriately investigated. Detailed results and discussions regarding the identity and levels of individual impurities as well as the safety assessment for the process-related-impurities based on the clearance validation were provided.

Specification

The rFVIIIFc active substance specifications used for release and stability testing are considered appropriate including adequate tests for integrity, potency, purity and quality. The release and stability parameters and their specifications are in accordance with guideline ICH Q6B and seem adequate for the control of the active substance as shown with the provided batch analysis data.

The acceptance criteria for the control parameters are based on historical data including preclinical and clinical batches from process development as well as from process validation batches and further commercial batches.

Analytical methods

The active substance is tested using pharmacopoeia and non-pharmacopoeia analytical methods. Method validations were provided.

Reference materials

The strategy for establishing and maintaining reference standards for release and stability testing of commercial rFVIIIFc active substance and drug product was sufficiently described.

A primary reference standard (PRS) was established in order to ensure that the quality of the active substance remains consistent and to avoid a drift in quality over time. Working reference standards (WRS) are established for routine release and stability testing of active substance which are qualified against the primary reference standard, and the stability of both reference materials is monitored to assess the suitability of these reference standards over their lifetime.

The potency of PRS was assigned by chromogenic assay to the WHO 8th International Factor VIII Concentrate Standard by a statistically valid assay. Thus, traceability to the International Standard was considered established and the use of International Units (IU) for potency labelling of rFVIIIFc justified. This is in line with CHMP guidance (EMA/CHMP/BWP/85290/2012) and the official communication from the SCC (Hubbard, 2013).

The PRS has undergone release testing and extensive characterization studies A critical criterion for the selection of PRS was the consistent specific activity values measured by two distinct assays: activated partial thromboplastin (aPTT) coagulation assay and FVIII chromogenic assay. This will allow its use as potency calibration standard using either assay.

Container closure system

Sufficient information on container closure system of the active substance was submitted. rFVIIIFc active substance is stored frozen in a container made of polycarbonate equipped with polypropylene cap. The container closure system has been evaluated by means characterization of extractable and leachables substances. All testing performed indicate the container closure is appropriate for use for the storage of rFVIIIFc active substance.

Stability

The applicant submitted sufficient active substance stability data which justify approval of a shelf life of 36 months at -70 °C ± 10 °C.

Comparability exercise for Active Substance

Extensive comparability studies in compliance with the guideline ICH Q5E were performed in order to investigate the impact of process changes introduced during development on the product quality. The process changes and their rationale were appropriately described. The stability data, the release results, the in-process testing and characterization of rFVIIIFc clinical and commercial active substance batches indicated that these materials are comparable. Therefore, the active substance manufactured by the validated manufacturing process intended for commercial production is representative of active substance manufactured for clinical use. Furthermore, the process can be considered consistent and reproducible and yields active substance of adequate quality.

New Active Substance

The Applicant stated that, efmoroctocog alfa, is a biological substance not previously authorised as a medicinal product in the European Union and requested that efmoroctocog alfa contained in the Elocta to be considered a new active substance (NAS) in itself.

Efmoroctocog alfa is a fully recombinant fusion protein comprising B-domain deleted (BDD) human FVIII covalently linked to the Fc domain of human immunoglobulin G1 (IgG1).

Based on the assessment of the submitted data CHMP concluded that efmoroctocog alfa is a new active substance that has not been authorised European Union previously. From a quality perspective, it can be regarded as a NAS in itself.

2.2.1. Finished Medicinal Product

Description of the product and pharmaceutical development

Description and composition of drug product

The rFVIIIFc drug product and its composition have been adequately described. The rFVIIIFc drug product is a sterile lyophilized powder for solution for injection for intravenous administration, and is presented in seven different strengths. All strengths are presented in aseptically filled single use vials in nominal strengths from 250 to 3000 IU/vial. The finished product is formulated with L-Histidine, sodium chloride, calcium chloride dihydrate, sucrose, polysorbate 20, sodium hydroxide and hydrochloric acid.

The lyophilized powder is reconstituted with nominal 3 mL sterilized water for injections (SWFI) supplied in a sterile pre-filled syringe of USP/Ph. Eur. type I glass.

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

Pharmaceutical development

The pharmaceutical development has been sufficiently described.

Briefly, in the different stages of drug product development material produced at the commercial scale was used. . Comparability studies indicated that phase 1+2 and, in particular, phase 3 clinical trial material and commercial product were manufactured by the same process and were of comparable quality.

A formulation buffer has been developed with components free of human-and animal-derived material. Development studies on the lyophilisation process have led to a robust commercial freeze-drying process which resulted in a product with consistent quality attributes that were comparable to drug product generated at pilot scale.

Manufacture of the product and process controls

Manufacturer

The drug product manufacturing, release testing and secondary packaging sites were listed in the dossier and GMP certificates were submitted.

Description of manufacturing process and process controls

The finished product manufacturing process has been adequately described and flow charts submitted.

Briefly, the manufacturing process covers the following steps: thawing and pooling of active substance, compounding of drug product, sterile filtration, filling, lyophilisation, stoppering and crimping, visual inspection and bulk packaging (vials), quarantine storage, bulk packaging (finished medicinal product assembly) and shipping.

With respect to process control, the rationale for the classification of process parameters and quality attributes appeared reasonable and the action limits or specifications were adequately set. Based on the outcome it seems that the entire rFVIIIFc drug product manufacturing can be run under well controlled and aseptic conditions to assure a sterile finished product of consistent quality.

The process hold times for intermediates and finished product have been sufficiently justified based on data from the validated full scale process, media fills, and from small scale stability studies.

Process validation

Based on knowledge gained during development and early full scale production batches, so-called input parameters and output parameters were defined and were classified according to their criticality. This criticality is based on a risk analysis with respect to the impact of a parameter on process performance and product quality. The approach is in line with ICH Q8(R2) Guideline on pharmaceutical development.

During process validation the commercial manufacturing process, commercial batches were evaluated for process consistency, hold time, and aseptic manufacturing conditions. The applicant has demonstrated that the manufacturing process of rFVIIIFc drug product operates within established parameters and performs reproducibly under controlled conditions, leading to a product that meets all quality attributes. Therefore the presented data provide assurance that the commercial manufacturing process has been successfully validated.

The media fill runs demonstrated that aseptic manufacturing conditions could be maintained, also when performing simulated interventions during filling as “worst case” conditions.

Control of excipients

Only excipients manufactured and tested according to Ph. Eur. are used. No novel excipients or excipients of human or animal origin are used for the manufacture of rFVIIIFc drug product.

Product specification

The information presented in section Control of Drug Product was sufficiently detailed to provide assurance that the quality of the drug product is well controlled. A risk based approach (FMECA) has been applied in line with ICH Q9 Quality risk management to define analytical parameters which were considered critical with respect to the quality of the drug product. Acceptance criteria for critical quality attributes were derived from structure-activity relationship, animal studies, clinical experience, safety considerations, compendial requirements, and experience from literature. Based on the outcome of this analysis a set of control parameters for drug product release and stability testing was defined. Overall, this set of release tests appeared sufficient to assure drug product quality and safety. However, it is recommended that the Applicant re-evaluates the protein content specification of the drug product, as soon as data from 30 lots of each dosage size are available (see 2.2.6).

Analytical methods

All test methods applied during batch release (and stability testing) are compendial or were validated in line with ICH Q2(R) recommendations.

The Ph. Eur. FVIII chromogenic assay was adequately re-validated against the in house reference standard to support the applicability of this assay to the rFVIIIFc fusion protein. As an outcome, the parameter linearity and all other parameters tested on the drug product passed the validation acceptance criteria, indicating that the compendial method can be used in potency determination of rFVIIIFc drug product.

Batch analysis

The release test results were considered adequate. All results met the release specifications in place at time of testing.

Reference materials

The reference standard used for testing of the drug product is the same as the reference standard used for testing of the active substance (see above).

Container closure system

The container closure system has been sufficiently described. The rFVIIIFc drug product vial for all dosage sizes from 250 IU to 3000 IU per vial is a 10 ml Ph.Eur type I glass vial, closed with a chlorobutyl rubber stopper, sealed with an aluminium flip-off cap.

Stability of the product

Sufficient stability data were submitted to support the shelf life claim given in the SmPC.

A 36-month shelf life was proposed for rFVIIIFc lyophilized drug product (all strengths:250 through 3000 IU/vial) when stored at 2 to 8 ºC, with allowance of short-term storage for up to 6 months at room temperature (not to exceed 30 ºC) within the proposed 36-month shelf life.

The stability of rFVIIIFc drug product has been investigated in line with ICH Q 5C.

A stability study to evaluate in use shelf life with vials at the end of shelf life justifies the proposed in use shelf life of 6 h at RT (not to exceed 30°C).

In line with ICH Q5C photo-stability studies were performed which indicated that the lyophilised product is light sensitive, requiring proper storage of the product in its outer carton. Respective information is given in the product information.

Adventitious agents

TSE compliance

Compliance with the TSE Guideline (EMEA/410/01 – rev. 3) has been sufficiently demonstrated. The active substance is produced in a serum-free fermentation medium. No other material of bovine origin is added during fermentation process of rFVIIIFc. The MCB which has been established is free from TSE-risk substances.

Virus safety

As stated above, the fermentation of rFVIIIFc takes place in a serum-free medium and no other material of bovine origin is added during fermentation process of rFVIIIFc. This minimizes a possible contamination for adventitious viruses. The cells used for production of rFVIIIFc have been sufficiently screened for viruses. These tests failed to demonstrate the presence of any viral contaminant in the MCB of rFVIIIFc.

There is sufficient capacity within the manufacturing process of rFVIIIFc for reduction of viral particles. The purification process of rFVIIIFc includes several steps for inactivation/removal of enveloped viruses. The effectiveness of these steps has been sufficiently demonstrated. Studies of reuse of chromatography resins have been provided.

In summary, the virus safety of rFVIIIFc has been sufficiently demonstrated.

Drug product - Solvent WfI in a pre-filled Syringe

The drug product solvent is sterilised Water for Injections (sWFI). The container closure system consists of a glass vial, a plunger stopper and a closure system of a tip cap with a Luer lock and a tamper-evident seal.

The information provided in the dossier for the solvent showed that the sWFI is manufactured under GMP compliant conditions using a validated process.

The sWFI in a 3 ml pre-filled syringe (3 ml fill volume) meets E.P. requirements for sterile WFI and has a shelf life of 60 month when stored at 2-8°C. Within this 60 months shelf-life, the sWFI may be stored at room temperature (not to exceed 30°C) for up to 6 months when packaged with the rFVIIIFc drug product. The proposed shelf life conditions were supported by real time stability data.

2.2.1. Discussion on chemical, pharmaceutical and biological aspects

Overall, the different aspects of the chemical, pharmaceutical and biological documentation comply with existing guidelines.

The fermentation, recovery and purification of the active substance, efmoroctocog alfa, are adequately controlled and validated. Appropriate active substance specifications have been set. The physicochemical and biological characteristics of the active substance have been well characterised using state-of the-art methods.

The manufacturing process of the drug product has been described and validated in sufficient detail. The quality of the drug product is controlled by adequate test methods and specifications. The data presented support the shelf-life proposed for the active substance and drug product.

No excipients or raw materials of human or animal origin are used in the manufacturing process and therefore the risk of contamination with viral or TSE agents is considered negligible.

In summary, the information provided in the application demonstrates consistent batch-to-batch production achieving a well-defined quality of the finished medicinal product.

2.2.2. Conclusions on the chemical, pharmaceutical and biological aspects

The quality of Elocta is considered to be acceptable when used in accordance with the conditions defined in the SmPC. Physicochemical and biological aspects relevant to the uniform clinical performance of the product have been investigated and are controlled in a satisfactory way. Data has been presented to give reassurance on viral/TSE safety.

2.2.3. Recommendation(s) for future quality development

In the context of the obligation of the MAHs to take due account of technical and scientific progress, the CHMP recommends the following points for investigation:

1. It is recommended that the applicant should re-evaluate the protein content specification of the drug product, as soon as data from 30 lots of each dosage size are available. A time line should be specified and a re-evaluation report should be sent to the Competent Authority

2.3. Non-clinical aspects

2.3.1. Introduction

The non-clinical program included pharmacokinetic (PK), pharmacodynamic, and toxicology studies performed in mice, rats, dogs, and monkeys.

Pivotal repeat-dose toxicology studies including PK assessments were conducted as GLP studies while primary pharmacodynamics, other PK studies and pilot toxicology studies were conducted as non-GLP studies.

2.3.2. Pharmacology

Primary pharmacodynamic studies

The non-clinical pharmacology evaluation of rFVIIIFc focused on the primary pharmacodynamics (PD) of rFVIIIFc with the aim to evaluate rFVIIIFc as a treatment for acute bleeding, as well as a long-acting pro-

coagulant agent for prophylaxis therapy. To support drug manufacturing changes, in vivo comparability studies were conducted to complement analytical and biochemical evaluation of rFVIIIFc. In addition, a purified non-processed single chain isoform of rFVIIIFc (SC rFVIIIFc) was evaluated.

In vitro pharmacology studies were performed to demonstrate that rFVIIIFc is similar to rFVIII (Xyntha and ReFacto) in biochemical activity assays. In vivo pharmacology studies were performed to evaluate the clotting activity of rFVIIIFc in HemA mice and dogs, as well as to evaluate the acute and prophylactic efficacy of rFVIIIFc in HemA mice bleeding models.

The fusion of recombinant BDD FVIII to the Fc domain of IgG1 has been shown to decrease the in vivo clearance of this protein. rFVIIIFc was characterized in a series of in vitro biochemical binding and activity assays using pure proteins, phospholipids, and plasma, which were chosen to correlate with its pro-coagulant function in vivo.

In vitro studies

Table 6: Summary of non-clinical in vitro pharmacology studies with rFVIIIFc

Study Number and Title	Test System	Key Findings
R-FR8-009 Kinetics of Thrombin Activation of FVIIIFc, Nonprocessed FVIIIFc, and BDD FVIII by SDS-PAGE	Human α-thrombin	The thrombin activation profiles determined for rFVIIIFc; purified, SC rFVIIIFc (nonprocessed isoform); and BDD rFVIII (ReFacto) were comparable.
R-FR8-010 Protein C Inactivation of rFVIIIFc, Nonprocessed rFVIIIFc, and BDD FVIII	Human APC	The cleavage of the A2 domain by APC and inactivation of the active forms of rFVIIIFc, SC rFVIIIFc (nonprocessed isoform), and BDD rFVIII (ReFacto) were comparable.
R-FR8-017 Biochemical In Vitro Assays for the Characterization of FVIIIFc, Nonprocessed FVIIIFc, and BDD FVIII	Human platelets, human FIXa, human FX, phospholipid vesicles	The affinity (K_d) for FIXa during formation of the Tenase complex was similar for rFVIIIFc, SC rFVIIIFc (nonprocessed isoform), and BDD rFVIII (ReFacto). The K_m and V_{max} for FX activation by tenase on phospholipids or activated platelets was similar for rFVIIIFc, SC rFVIIIFc, and BDD rFVIII.
R-FR8-028 SPR Analysis of the Affinity for VWF of rFVIIIFc DS, SC rFVIIIFc, and BDD rFVIII	Human VWF	The affinity (K_d) of binding to VWF was similar for rFVIIIFc, SC rFVIIIFc (nonprocessed isoform), and BDD rFVIII (Xyntha) by SPR (0.34, 0.31 and 0.26 nM, respectively).
R-FR8-029 Susceptibility of rFVIII Variants to Thrombin-mediated Release from VWF	Human VWF, human α-thrombin	Thrombin increased the release rate for rFVIIIFc, SC rFVIIIFc (nonprocessed isoform), and BDD rFVIII (Xyntha) from VWF and rFVIIIFc was 3-fold more responsive than SC rFVIIIFc to the thrombin concentration.
R-FR8-024-R2 Evaluation of Single Chain rFVIIIFc activity by One Stage (aPTT) Assay, Automated Chromogenic Substrate Assay and Thrombin Generation Assay	Human FVIII-depleted plasma with and without human VWF	The activities of rFVIIIFc, SC rFVIIIFc (nonprocessed isoform), and purified processed rFVIIIFc were all similar in the chromogenic activity assay, but SC rFVIIIFc had 60% reduced activity compared to rFVIIIFc in the aPTT assay in the presence of VWF compared to rFVIIIFc.
R-FR8-011 Binding of rFVIIIFc to FcRn: Biacore analysis	Human, monkey, rat and mouse FcRn	The affinity (K_d) by SPR for rFVIIIFc binding to soluble FcRn varied for FcRn from human, monkey, rat, and mouse (51.7, 52.1, 11.7 and 10.7 nM, respectively).

APC = activated protein C; aPTT = activated partial thromboplastin time; BDD = B domain-deleted; FcRn = neonatal Fc receptor; SC = single chain; SPR = surface plasmon resonance; VWF = von Willebrand factor

Description of single chain rFVIIIFc (SC rFVIIIFc) in rFVIIIFc

In preparations of rFVIIIFc drug substance (DS), a fraction of the total rFVIIIFc is not cleaved at Arg 1648, leading to the generation of the single chain isoform (SC rFVIIIFc). rFVIIIFc contains ≤40% SC rFVIIIFc. In order to characterize the single chain isoform of rFVIIIFc, a preparation of 100% SC rFVIIIFc was purified from rFVIIIFc.

In vitro functional characterization (R-FR8-009, R-FR8-010, R-FR8-017, R-FR8-028, R-FR8-029, R-FR8-024-R2, R-FR8-011

The potency of rFVIIIFc was measured with both chromogenic and aPTT assays and found to be comparable. In order to further characterize the in vitro activity of rFVIIIFc, both rFVIIIFc and SC rFVIIIFc were compared to rFVIII in a series of biochemical assays. The thrombin activation profiles for rFVIIIFc, SC rFVIIIFc and BDD rFVIII (ReFacto) were similar based on SDS-PAGE and sequence analysis. In activity assays, the affinities (Kd) for FIXa during formation of the tenase complex and the Km and Vmax for FX activation by tenase on phospholipids or activated platelets were similar for rFVIIIFc, SC rFVIIIFc and BDD rFVIII. The cleavage of the A2 domain by APC and inactivation of the active forms of rFVIIIFc, SC rFVIIIFc and BDD rFVIII were similar. The results of these biochemical mechanism studies were all consistent with the potency of rFVIIIFc in the aPTT and chromogenic activity assays.

The activities of rFVIIIFc, SC rFVIIIFc and purified processed rFVIIIFc were all similar in the chromogenic activity assay and in the aPTT assay in the absence of VWF. However, up to a 60% reduction in activity was observed for SC rFVIIIFc in the aPTT assay in the presence of VWF when compared to rFVIIIFc. Therefore, studies were performed to compare the interaction of rFVIIIFc, SC rFVIIIFc and rFVIII with VWF.

The binding of VWF to rFVIIIFc, SC rFVIIIFc and rFVIII was measured by Real-time SPR analysis and was compared and the binding kinetics and the affinities (Kd) for VWF all were found to be similar for rFVIIIFc, SC rFVIIIFc and BDD rFVIII by SPR (0.34, 0.31 and 0.26 nM, respectively).

Thrombin cleavage increases the rate of release of FVIII from VWF by up to 160-fold by release of the acidic a3 domain. The addition of α-thrombin to rFVIIIFc, SC rFVIIIFc or BDD rFVIII (Xyntha) bound to VWF increased the off-rate in a thrombin concentration dependent manner. The release rate of SC rFVIIIFc from VWF was found to be 3-fold less responsive than rFVIIIFc and BDD rFVIII to the thrombin concentration. This decreased responsiveness of SC rFVIIIFc to release from VWF by thrombin is due to delayed release of the acidic a3 domain following cleavage at Arg 1689. Because the site at Arg 1648 is still intact in SC rFVIIIFc, the release of the a3 domain requires cleavage at both Arg 1689 and Arg 740 by thrombin.

The affinity of rFVIIIFc for the extracellular domains of purified human, cynomolgus monkey, mouse and rat FcRn were determined. Half-maximal binding was found to be ~50 nM for human and cynomolgus monkey FcRn and ~11 nM for rat and mouse FcRn. The finding that rFVIIIFc bound more tightly to murine than human and monkey FcRn is consistent with literature reports for human IgG molecules.

In vivo studies

Table 7: Summary of non-clinical in vivo pharmacology studies with rFVIIIFc

Study No. and Title	Species	Single Dose (unless noted); route of administration	Key Findings
Whole Blood and Plasma Clotting Studies			
R-FR8-014 Pharmacodynamics of Factor VIII-Fc and ReFacto® in Factor VIII-deficient Mice by Whole Blood Clotting Time (WBCT) and Chromogenic Activity	HemA mice	rFVIIIFc or BDD rFVIII (ReFacto): 50 IU/kg, IV	rFVIIIFc resulted in prolonged clotting activity compared to BDD rFVIII (ReFacto) in HemA mice as measured by WBCT, with significant activity of rFVIIIFc up to 96 hours post-dose versus a loss in activity between 24 to 48 hours for BDD rFVIII.
R-FR8-016 Pharmacodynamics and WBCT after administration of a single dose IV of nonprocessed FVIIIFc in FVIII-deficient animals (Studies SYN829 and SYN826)	HemA mice	SC rFVIIIFc (present at 21.8 to 32.3% of rFVIIIFc DP): 50 IU/kg, IV	The clotting activity of SC rFVIIIFc (nonprocessed isoform) was similar to rFVIIIFc in HemA mice.

Study No. and Title	Species	Single Dose (unless noted); route of administration	Key Findings
N-FR8-010-R1 Comparability of the Efficacy of rFVIIIFc Liquid Drug Product and Lyophilized Drug Product in FVIII-Deficient Mice by Whole Blood Rotational Thromboelastomy in vitro and ex vivo	HemA mice	rFVIIIFc (liquid DP or lyophilized DP) or rFVIII (Xyntha or Advate): 50 IU/kg, IV	Clotting activity (ROTEM) versus time profiles were comparable for rFVIIIFc liquid DP and rFVIIIFc lyophilized DP. rFVIIIFc (liquid and lyophilized DP) were comparable to rFVIII (Xyntha and Advate) for acute clotting activity (<24 hours), but rFVIIIFc demonstrated greater clotting activity relative to rFVIII at later timepoints (72 to 96 hours).
N-FR8-013 Comparability Prolonged Efficacy (ex vivo ROTEM) of rFVIIIFc (VLA5 versus RVS2 DP) Study in Hemophilia A Mice	HemA mice	rFVIIIFc (lyophilized DP from VLA5 and RVS2 manufacturing processes) or rFVIII (Advate): 25 IU/kg, IV	Clotting activity versus time profiles were comparable for rFVIIIFc lyophilized DP from both the VLA5 and RVS2 manufacturing processes. rFVIIIFc DP were comparable and as effective as rFVIII (Advate) acutely (<24 hours). rFVIIIFc DP demonstrated comparable long lasting clotting relative to rFVIII at later timepoints (72 to 120 hours).
N-FR8-003 Pharmacodynamics and Pharmacokinetics of FVIIIFc and ReFacto® in Hemophilia A Dogs	HemA dogs	rFVIIIFc: 125 IU/kg, IV rFVIII (Xyntha/ReFacto): 114 or 120 IU/kg, IV	Administration of a single dose of rFVIIIFc corrected clotting in HemA dogs through 96 hours. rFVIIIFc demonstrated sustained clotting activity compared to BDD rFVIII (ReFacto). Administration of rFVIIIFc corrected clotting through 72 or 102 hours post-dose, while BDD rFVIII corrected clotting through 48 hours post-dose.

Study No. and Title	Species	Single Dose (unless noted); route of administration	Key Findings
Efficacy Studies			
R-FR8-019-R1 Acute Efficacy of rFVIIIFc Lyophilized Drug Product in the Tail Clip Bleeding Model of Hemophilia A Mice	HemA mice; normal mice (C57BL/6 strain)	rFVIIIFc or rFVIII (Advate): 24, 72 or 216 IU/kg, IV	Acute bleeding protection and a significant reduction in blood loss was demonstrated for rFVIIIFc and rFVIII (Advate) in HemA mice at all 3 doses compared to vehicle control. Both high dose HemA mice treatment groups were similar to normal mice (C57BL/6 strain). Acute efficacy of rFVIIIFc and rFVIII were comparable and both were equally effective in a model of episodic (on-demand) treatment in HemA mice.
N-FR8-012 Comparability Acute Efficacy Study of rFVIIIFc (VLA5 versus RVS2 DP) in the Tail Clip Bleeding Model of Hemophilia A Mice	HemA mice	rFVIIIFc (lyophilized DP from VLA5 and RVS2 manufacturing processes): 25, 50 or 100 IU/kg, IV	A significant reduction in blood loss compared to vehicle control was found for all 3 doses of rFVIIIFc lyophilized DP from both the VLA5 and RVS2 manufacturing processes. Blood loss across doses did not differ significantly and the acute efficacy in HemA mice was comparable between VLA5 and RVS2.

Study No. and Title	Species	Single Dose (unless noted); route of administration	Key Findings
R-FR8-022-R1 FVIIIFc Prophylactic Efficacy in Hemophilia A Mouse Tail Vein Transection (TVT) Model	HemA mice	rFVIIIFc or rFVIII (Advate): 0, 4, 12 or 36 IU/kg, IV	A significant improvement in survival and re-bleed rates were found for rFVIIIFc compared to rFVIII (Advate) at 12 IU/kg when both were dosed 24 hours pre-TVT. A similar dose response based on survival and re-bleed rates was found for rFVIIIFc dosed 48 hours pre-TVT versus rFVIII dosed 24 hours pre-TVT. The duration of prophylactic efficacy for rFVIIIFc was 2-fold longer than rFVIII in HemA mice.
R-FR8-023-R1 In vivo Efficacy of Nonprocessed (Single Chain) rFVIIIFc in the Tail Vein Transection Model in Hemophilia A Mice	HemA mice	SC rFVIIIFc and rFVIIIFc (with 25.1% SC): 0.46, 1.38, 4.6 µg/kg; (4.39, 13.2, 43.9 IU/kg)	A similar dose response based on survival and re-bleed rates was demonstrated for rFVIIIFc and SC rFVIIIFc (nonprocessed isoform), both dosed 48 hours pre-TVT. SC rFVIIIFc was fully active in vivo with a prophylactic efficacy profile comparable to rFVIIIFc.

BDD = B domain-deleted; DP = drug product; HemA = haemophilia A; IV = intravenous; ROTEM = rotational thromboelastography; SC = single chain; TVT = tail vein transection; WBCT = whole blood clotting time

Clotting activity in treated HemA mice by WBCT (R-FR8-014 and R-FR8-016)

Recombinant FVIIIFc was compared for clotting efficacy with ReFacto in FVIII-deficient mice using a single intravenous dose of 50 IU/kg (n=6) and measuring whole blood clotting time (WBCT). FVIII-deficient mice given rFVIIIFc maintained normal clotting times for over 96 hours with 67% of mice clotting normally through 115 hours, whereas 100% of mice given ReFacto lost clotting capacity at 42 hours post-injection showing a 2.7 fold improvement in WBCT with rFVIIIFc compared to ReFacto.

Similarly, in chromogenic assay studies using a single 50 IU/kg intravenous dose, FVIII deficient mice had FVIII activity through 72 hours with rFVIIIFc and no detectable FVIII activity with Advate or ReFacto at 48 hours. Factor VIII-deficient mice given rFVIIIFc showed a dose response in FVIII activity levels at 50 IU/kg and 250 IU/kg. However, mice given 1000 IU/kg had similar FVIII activity levels as mice given the 250 IU/kg dose, which may be due to saturation of VWF binding sites at the highest dose with concomitant rapid clearance of unbound rFVIIIFc via clearance receptors for FVIII.

Clotting activity of NP rFVIIIFc was evaluated in study R-FR8-016 in FVIII-deficient mice using chromogenic activity assays and WBCT. Using a single intravenous dose of 250 IU/kg, NP rFVIIIFc had similar activity as rFVIIIFc DS in chromogenic activity assays. Further, after a single intravenous dose of 50 IU/kg, normal clotting activity was maintained for 96 hours with NP rFVIIIFc, which had a similar WBCT profile as rFVIIIFc

DS. Thus, in mice with severe hemophilia A, NP rFVIIIFc and rFVIIIFc exerted similar capacities for reducing the time to clot formation ex vivo.

Clotting activity in treated HemA mice by ROTEM (N-FR8-010-R1 and N-FR8-013)

rFVIIIFc DP liquid and lyophilized, Xyntha, and Advate had comparable effects on clot formation and stability. At 72 and 96 hours, rFVIIIFc DP (liquid and lyophilized) significantly improved clotting compared to Advate and Xyntha. Results from a second whole blood clotting study in HemA mice demonstrated in vivo comparability of rFVIIIFc from the VLA5 manufacturing process and lyophilized DP from the RVS2 manufacturing process and Advate, having similar acute activity versus Advate (up to 24 hours) and prolonged activity at later timepoints.

Clotting activity of rFVIIIFc and ReFacto in HemA dogs (N-FR8-003)

In a crossover design study, 4 dogs with severe hemophilia A were given a single intravenous dose of 114-120 IU/kg ReFacto and 3 days later a single dose of 125 IU/kg rFVIIIFc. Blood clotting was measured using both WBCT and chromogenic activity assays. With rFVIIIFc, WBCT corrected to normal for 72-102 hours, whereas ReFacto, supported normalization of WBCT for 48 hours. Chromogenic assay studies show that the terminal half-life for rFVIIIFc was 15.4 ± 0.3 hours compared to ReFacto with 7.4 hours. Pharmacodynamic profiles of the clotting activity over time for rFVIIIFc and ReFacto correlated well with the concentration of rFVIII (ELISA). Overall, in dogs with severe hemophilia A, initially both rFVIIIFc and FVIII similarly reduced blood clot formation time, however, rFVIIIFc increased the duration of this effect 1.5-2.1 fold as compared to ReFacto.

Efficacy studies of rFVIIIFc in bleeding models in HemA mice

The activity of rFVIIIFc in the acute bleeding model was found to be comparable to Advate as anticipated from their similar in vitro biochemical activities in coagulation assays. In the prophylactic model, rFVIIIFc was observed to result in approximately 2-fold longer protection than Advate, based on the effective dose (ED50) for survival, which is consistent with the prolonged whole blood clotting activity in HemA mice.

Acute efficacy of rFVIIIFc in the tail clip bleeding model of HemA mice (R-FR8-019-R1 and N-FR8-012)

The acute clotting efficacy of lyophilized rFVIIIFc DP and Advate were compared using a well-established tail clip bleeding model. Following an intravenous administration of 24, 72, or 216 IU/kg at 5 minutes prior to the tail clip, the blood loss from FVIII-deficient mice treated with rFVIIIFc or Advate was measured gravimetrically and the percentage of the protected population was calculated. Both rFVIIIFc and Advate treatments result in a significant reduction of blood loss as well as the increase in the percent of protected population. Overall, in the dose range (24 – 216 IU/kg) tested, rFVIIIFc and Advate have shown comparable efficacy by both measurements.

A second acute efficacy study in HemA mice was used to compare the efficacy of lyophilized DP from the VLA5 and RVS2 manufacturing processes. Animals were given a single IV dose of 0, 25, 50, or 100 IU/kg rFVIIIFc DP from VLA5 at the 2000 IU/vial strength or RVS2 at the 3000 IU/vial strength. Mice given either DP from VLA5 or RVS2 had reduced blood loss in a dose-dependent manner with significant reductions in bleeding at 25, 50, and 100 IU/kg. Statistical analyses comparing the results obtained using DP from both processes demonstrated that there were no differences at any of the doses tested. Thus, rFVIIIFc DP from VLA5 and RVS2 demonstrated comparable acute efficacy in a HemA mice tail clip bleeding model.

Prophylactic efficacy of rFVIIIFc in a tail vein transection model of HemA mice (R-FR8-022-R1 and R-FR8-023-R1)

The HemA mice tail vein transection (TVT) model was used to compare the abilities of rFVIIIFc and Advate to prevent bleeding and mortality when administered 1 or 2 days prior to TVT in HemA mice. A single 12 IU/kg IV infusion of rFVIIIFc administered 24 or 48 hours before TVT was compared to Advate administered 24 hours before TVT. Mice were observed for 24 hours post-TVT and scored for both survival and re-bleeding following the initial clot formation. Overall, the data showed that a single dose of rFVIIIFc corrects the FVIII deficiency and protects against severe bleeding approximately 2-fold longer compared to a single dose of Advate. There was no significant difference in re-bleeding rate or survival for HemA mice dosed with rFVIIIFc at 48 hours before injury and those dosed with Advate 24 hours pre-TVT. The responses for the high and low doses (36 and 4 IU/kg) were similar and both survival and re-bleeding rates were not significantly different for rFVIIIFc at 48 hours and Advate at 24 hours.

The TVT model was also used to compare the prophylactic efficacy of pure SC rFVIIIFc with that of rFVIIIFc containing 25.1% of the single chain isoform. The whole blood clotting activity observed for rFVIIIFc and SC rFVIIIFc indicated a similar ability of each to correct the clotting deficiency in HemA mice. Both rFVIIIFc and SC rFVIIIFc were dosed at 0.46, 1.38 and 4.6 µg/kg at 48 hours prior to TVT injury. For rFVIIIFc, these 3 doses corresponded to 4.39, 13.2 and 43.9 IU/kg, respectively. A similar dose response was observed for both rFVIIIFc and SC rFVIIIFc, based on either the re-bleeding rates or survival (Figure 10). No differences were found for either parameter at any of the 3 doses tested.

Overall, comparison of rFVIIIFc and rFVIII in a prophylactic efficacy model in HemA mice demonstrated a 2-fold prolonged efficacy for rFVIIIFc versus Advate. Additionally, SC rFVIIIFc is equally efficacious to rFVIIIFc and the presence of SC rFVIIIFc in rFVIIIFc contributes fully to the prolonged efficacy observed for rFVIIIFc.

Secondary pharmacodynamic studies

No secondary pharmacodynamic studies have been submitted.

Safety pharmacology programme

Based on its mechanism of action as a replacement factor to restore coagulation activity, separate safety pharmacology studies to investigate possible effects of rFVIIIFc on the cardiovascular, respiratory, or central nervous systems were not performed (See discussion on non-clinical aspects). The 2 fusion partners that comprise rFVIIIFc are human factor VIII and the Fc domain of human IgG1. Human factor VIII is well characterized in the clinic as a replacement therapy in haemophilia A patients. The Fc domain is found on many drugs, including dozens of therapeutic antibodies. For these reasons, separate safety pharmacology studies were judged to be unnecessary for rFVIIIFc.

Cardiovascular measurements (ECGs and heart rate) were included in the 4-week repeat-dose toxicology studies in monkeys. Effects on the respiratory and central nervous system were indirectly determined from clinical observations.

Pharmacodynamic drug interactions

No PD drug interaction studies have been submitted.

2.3.3. Pharmacokinetics

Table 8: List of non-clinical pharmacokinetic studies

Overview			Test Article: rFVIIIFc	
Type of Study	**Test System**	**Method of Administration**	**Testing Facility**	**Study Number**
Absorption				
Single-dose PK	HemA mice	IV	Biogen Idec	R-FR8-014
Single-dose PK	Normal mice; FcRn-KO mice; hFcRn-Tg mice; HemA mice	IV	Biogen Idec	R-FR8-018
Single-dose PK	HemA mice	IV	Biogen Idec	N-FR8-009-R1
Single-dose PK	HemA mice	IV	Biogen Idec	N-FR8-011
Single-dose PK	HemA mice	IV	Biogen Idec	R-FR8-016
Single-dose PK	Sprague Dawley rats	IV	Biogen Idec	N-FR8-004
Single-dose PK	HemA dogs	IV	Francis Owen Blood Research Lab, UNC, Chapel Hill, NC	N-FR8-003
Single-dose PK	Cynomolgus monkeys	IV	New Iberia Research Center, Lafayette, LA	N-FR8-006
Single-dose PK	Cynomolgus monkeys	IV	Battelle, Columbus, OH	N-FR8-007-R2
Repeat-dose toxicology/PK (GLP)	Sprague Dawley rats	IV	Battelle, Columbus, OH	CN53610
Repeat-dose toxicology/PK (GLP)	Cynomolgus monkeys	IV	Battelle, Columbus, OH	CN53056
Repeat-dose toxicology/PK (GLP)	Cynomolgus monkeys	IV	Battelle, Columbus, OH	N110486
Biodistribution of ^{125}I-rFVIIIFc	HemA mice; Double-KO (DKO) mice (FVIII-KO and VWF-KO)	IV	MPI Research, Mattawan, MI	R-FR8-027
Transplacental transfer of rFVIIIFc	Pregnant HemA mice and fetuses	IV	Biogen Idec	R-FR8-041

DKO = double knockout; FcRn = neonatal Fc receptor; GLP = good laboratory practice; HemA = haemophilia A; IV = intravenous; KO = knockout; PK = pharmacokinetics; Tg = transgenic; VWF = von Willebrand factor

Plasma levels of rFVIIIFc were determined by a sandwich enzyme-linked immunosorbent assay (ELISA) to measure circulating drug based on mass in µg/mL and a chromogenic activity assay based on cofactor activity in IU/mL. The presence of anti-rFVIIIFc antibodies in rat or cynomolgus monkey plasma was determined using a bridging ELISA method in which anti-rFVIIIFc IgG bridges between a biotin-labeled rFVIIIFc and a labeled rFVIIIFc. This anti-drug antibody ELISA was used to measure anti-rFVIIIFc antibody formation in GLP repeat dose PK and toxicology studies in rats and monkeys.

Absorption

All non-clinical PK evaluations of rFVIIIFc were performed using intravenous (IV) administration, which matches the intended route of administration for individuals with haemophilia A. PK parameters of rFVIIIFc were assessed in normal, HemA, FcRn-KO, and hFcRn-Tg mice; Sprague Dawley rats; HemA dogs; and cynomolgus monkeys. rFVIIIFc was administered either by IV bolus injection (rodents) or by IV infusion (dog and monkey).

Normal and HemA mice (R-FR8-014 and R-FR8-018))

The PK parameters of rFVIIIFc were compared to those for ReFacto and Advate, all at a dose of 50 IU/kg, in HemA mice. In this study, the elimination half-life of rFVIIIFc (11.1 hours) was greater than either ReFacto (5.0 hours) or Advate (7.1 hours). The PK parameters of rFVIIIFc were compared at 3 dose levels, 50, 250, and 1000 IU/kg, which resulted in a similar elimination half-life (12.6, 14.5, and 12.3 hours, respectively) over a 20-fold dosing range of the drug. Overall, the elimination half-life of rFVIIIFc was between 2.22-fold to 2.90-fold greater compared to ReFacto and between 1.56-fold to 2.04-fold greater compared to Advate in HemA mice.

The PK parameters of rFVIIIFc and Xyntha were also compared at 125 IU/kg in HemA mice. The elimination half-life for rFVIIIFc was found to be 12.34 hours, which was 1.63-fold greater than the elimination half-life for Xyntha of 7.58 hours. In the same study, PK parameters for rFVIIIFc and Xyntha were compared at 125 IU/kg doses in normal mice (C57BL/6 strain). The elimination half-life measured for rFVIIIFc was 8.51 hours, which was 1.96-fold greater than the elimination half-life for Xyntha of 4.34 hours.

FcRn-KO and hFcRn-Tg mice (R-FR8-018)

The PK parameters for rFVIIIFc and Xyntha were compared after a single 125 IU/kg dose in FcRn-KO and hFcRn-Tg mice in order to characterize the mechanism of action of the prolonged elimination half-life observed in mice. The elimination half-life of the rFVIIIFc and Xyntha were similar in the FcRn-KO mice and were determined to be 5.81 hours for rFVIIIFc and 6.63 hours for Xyntha. In contrast, in the hFcRn-Tg mice (in which the knocked-out murine FcRn is replaced with human FcRn), the elimination half-life of rFVIIIFc increased to 10.65 hours, while the Xyntha elimination half-life was found to be 4.36 hours, which is similar to the value in the FcRn-KO mice. In mice expressing human FcRn in the absence of murine FcRn, the elimination half-life for rFVIIIFc was 2.45-fold longer than the elimination half-life of Xyntha.

Overall, these observations show that the addition of the human Fc domain of IgG1 to rFVIII allows binding to human FcRn, resulting in a prolonged elimination half-life of rFVIIIFc relative to Xyntha in a mouse model.

Non-clinical comparability studies in HemA mice (N-FR8-009-R1, N-FR8-007-R2 and N-FR8-011)

To support the change from the liquid to the lyophilized DP formulation, PK parameters were determined for each formulation in HemA mice and in monkeys. HemA mice (2 males and 2 females per time point, 28 total/treatment group) were administered a single 250 IU/kg IV dose of either rFVIIIFc liquid DP or rFVIIIFc lyophilized DP. The PK parameters were comparable for the liquid DP and lyophilized DP, including the elimination half-life (18.5 and 19.3 hours), the MRT (23.9 and 22.8 hours), the C_{max} (4.73 and 6.06 IU/mL) and the $AUC_{0-\infty}$ (90.7 and 123.6 IU•hr/mL), respectively.

To support the change from the VLA5 to the RVS2 lyophilized process, PK parameters were determined in HemA mice for each process. Male HemA mice (4 per time point, 32 total/treatment group) were administered a single 200 IU/kg IV dose of each of the 3 DP samples (VLA5 2000 IU/vial from the 10,000 vial lot scale, RVS2 2000 IU/vial from the 40,000 vial lot scale, and RVS2 3000 IU/vial from the 40,000 vial lot scale). All PK parameters were similar for VLA5 2000 IU/vial, RVS2 2000 IU/vial and RVS2 3000 IU/vial, including the elimination half-life (19.4, 18.3, and 18.5 hours), the MRT (21.7, 21.0 and 21.3 hours), the C_{max} (4.26, 3.99 and 3.75 IU/mL) and the $AUC_{0-\infty}$ (76.8, 76.1 and 70.0 IU•hr/mL), respectively.

PK of single chain rFVIIIFc in HemA mice (R-FR8-008 and R-FR8-016)

In order to characterize the single chain isoform of rFVIIIFc, a preparation of 100% SC rFVIIIFc was purified from rFVIIIFc containing SC rFVIIIFc. The PK parameters of a 250 IU/kg dose of pure SC rFVIIIFc were determined in HemA mice and found to be comparable with rFVIIIFc. The elimination half-life of pure SC rFVIIIFc was 13.8 hours, which is similar to the average of values for rFVIIIFc in HemA mice (15.7 ± 3.4 hours).

Single-dose PK characterization of rFVIIIFc in rats (N-FR8-004)

The PK parameters of rFVIIIFc were determined in normal Sprague Dawley rats. Animals were administered a single IV dose of 1000 IU/kg which was the highest dose proposed to be tested in the repeat-dose toxicology studies. The PK analysis was based on the mean values of plasma rFVIIIFc concentration at each time point and the elimination half-life was determined to be 8.0 hours. This is longer than the elimination half-life reported in the literature for full-length rFVIII in rats which is 5.5 hours for Kogenate. Based on the literature value, rFVIIIFc is predicted to have a 1.45-fold longer elimination half-life in rats.

Single-dose characterization of rFVIIIFc in dogs (N-FR8-003)

The PK parameters of rFVIIIFc were evaluated in HemA dogs. A single 125 IU/kg IV dose of rFVIIIFc was administered to 2 dogs. When the concentration of rFVIIIFc in plasma was measured by ELISA, the elimination half-lives were 17.3 and 16.6 hours (average = 17.0 hours). Similarly, when rFVIIIFc was measured using the chromogenic activity assay, the elimination half-lives were 15.1 to 15.7 hours (average = 15.4 hours).

Two dogs also received a single dose of BDD rFVIII (ReFacto), 114 IU/kg for 1 dog and 120 IU/kg for the other, followed by rFVIIIFc (125 IU/kg) 72 hours later in a crossover design. The elimination half-life determined from the ELISA data for ReFacto were 7.0 hours and 6.7 hours (average = 6.85 hours). Similarly, when ReFacto was measured by the chromogenic activity assay, the elimination half-life were 7.5 and 7.2 hours (average = 7.35 hours). The elimination half-lives for rFVIIIFc in the crossover study were 15.7 and 13.3 hours (average = 14.5 hours) by ELISA and 15.2 and 15.7 hours (average = 15.5 hours) by chromogenic activity assay.

The average elimination half-life of rFVIIIFc for the 4 dogs was 15.7 ± 1.7 hours (ELISA) and 15.4 ± 0.32 hours (activity). The elimination half-life for rFVIIIFc is 2.10-fold to 2.29-fold longer than ReFacto in HemA dogs. The ELISA concentration data was compared with the activity assay data for rFVIIIFc in dogs, by dividing the average $AUC_{0-\infty}$ from the activity assay data (25.9 ± 6.5 IU·hr/mL) by the $AUC_{0-\infty}$ from the ELISA data (2.48 ± 0.97 µg·hr/mL). The resulting estimate of the specific activity of the rFVIIIFc circulating in vivo (10,450 IU/mg) is similar to the specific activity of the rFVIIIFc used for this study, 9119 IU/mg. Based on this calculation, the circulating rFVIIIFc was fully active in this study in HemA dogs.

Single-dose PK characterization of rFVIIIFc in monkeys (N-FR8-006 and N-FR8-007-R2)

rFVIIIFc and Xyntha were administered as a single IV dose at 125 IU/kg in a crossover study design in cynomolgus monkeys. Three monkeys received Xyntha on Day 0 and rFVIIIFc on Day 3, while 3 other monkeys received rFVIIIFc on Day 0 and Xyntha on Day 4. Plasma samples were collected pre-dose and after dosing at 0.25, 4, 12, 24, 36, 48 and 72 hours for measurement of rFVIIIFc or Xyntha by ELISA and the chromogenic activity assay. Unlike the results observed in the other animal models, the plasma concentration over time profiles were similar for rFVIIIFc compared to Xyntha. The elimination half-lives were also similar

for rFVIIIFc and Xyntha based on the ELISA (11.9 ± 1.7 and 12.7 ± 4.4 hours, respectively) or the activity assay (16.1 ± 6.9 and 12.5 ± 1.7 hours, respectively).

In a comparability study in cynomolgus monkeys (4 animals per treatment group), the liquid and lyophilized formulations of rFVIIIFc were compared with respect to all PK parameters. The animals were administered a single 125 IU/kg IV dose of either rFVIIIFc liquid DP or rFVIIIFc lyophilized DP and plasma levels were determined using both the ELISA and the capture chromogenic activity assay. All PK parameters were comparable for the 2 formulations based on both assays.

The average elimination half-life in monkeys was 11.82 ± 1.11 and 12.97 ± 0.81 hours (ELISA) and 12.6 ± 0.7 and 14.8 ± 1.5 hours (activity) for the liquid DP and lyophilized DP, respectively. The ELISA concentration data was compared with the activity assay data for the liquid DP and lyophilized DP, by dividing the average $AUC_{0-\infty}$ from the activity assay data (47.2 ± 11.5 and 46.7 ± 15.9 IU·hr/mL) by the $AUC_{0-\infty}$ from the ELISA data (5.559 ± 1.197 and 6.537 ± 1.334 µg·hr/mL). The resulting estimate of the specific activities of the rFVIIIFc circulating in vivo (8491 and 7143 IU/mg) is similar to the specific activities for the rFVIIIFc liquid DP and lyophilized DP (10,268 and 8697 IU/mg, respectively) used for this study. Based on this calculation, the circulating rFVIIIFc DPs were fully active in this study in monkeys.

Repeat-dose PK characterization of rFVIIIFc in rats (CN53610)

In a 4 week GLP toxicology study [CN53610] in Sprague Dawley rats, rFVIIIFc was administered IV every other day over a 4 week period for a total of 14 doses at 50, 250 or 1000 IU/kg to evaluate the systemic and local effects and the PK of rFVIIIFc. Each treatment group included 3 males and 3 females per time point. Blood was collected pre-dose and at the predetermined time points up to 96 hours (0.25, 1, 4, 8, 12, 24, 36, 48, 72 and 96 hours). Plasma samples were analyzed for rFVIIIFc concentration using a validated ELISA method. The PK analysis was based on mean values of rFVIIIFc plasma concentrations. Blood samples for immunogenicity evaluation were obtained from the same animals, once pre-study and just prior to dosing on Days 11, 19, 27 and 57 for plasma analysis of anti-rFVIIIFc antibodies. Anti-drug antibodies were determined using a validated anti-drug antibody ELISA method.

The systemic exposure for rFVIIIFc was evaluated using C_{max} and $AUC_{0-\infty}$ values. With a 5-fold and 20-fold increase in dose from low to mid- to high dose groups, C_{max} was approximately proportional between the 3 dose groups (5.9-fold and 15.4-fold, respectively), but $AUC_{0-\infty}$ was observed to be less than proportional (3.4-fold and 6.1-fold increase in $AUC_{0-\infty}$, respectively). Group mean C_{max} and $AUC_{0-\infty}$ values were similar between males and females for a given dose, with the exception of the high dose group that had higher C_{max} and $AUC_{0-\infty}$ values for males.

Group mean elimination half-life values were 13.5 and 13.4hours for the low dose, 21.3 and 11.5 hours for the mid-dose, and 11.8 and 7.95 hours for the high dose, for males and females, respectively. As dose level increased, there was a trend toward increased clearance that was most notable at the high dose level (2.6-fold comparing high dose to low dose levels) and there was also a rise in the volume of distribution as the dose level increased (2.6-fold comparing high dose to low dose levels).

Repeated administrations of rFVIIIFc resulted in a limited number of evaluable data points, due to most values being below the limit of quantitation. Therefore, no PK parameters were evaluated for Day 27. Nearly all of the animals receiving rFVIIIFc at all dose levels developed antibodies against rFVIIIFc (22/24 in the low dose group, 20/24 in the mid-dose group and 22/24 in the high dose group). Therefore, the unmeasurable levels of rFVIIIFc on Day 27 in all groups treated with rFVIIIFc were likely due to the development of anti-rFVIIIFc antibodies.

Repeat-dose PK characterization of rFVIIIFc in monkeys (CN53056 and N110486)

Two 4-week GLP toxicology studies were conducted in cynomolgus monkeys; one study used the liquid formulation of rFVIIIFc and the other study used the lyophilized formulation of rFVIIIFc. In both studies, rFVIIIFc was administered IV every other day for a total of 14 dose administrations at 50, 250 and 1000 IU/kg to evaluate the systemic and local effects and the PK of rFVIIIFc. In both studies, the vehicle and high dose groups included 5 monkeys/sex/group, while the low and the mid-dose groups had 3 monkeys/sex/group. PK profiles were characterized after the first dose (Day 1) and the last dose (Day 27).

On Day 1, systemic exposure parameters for rFVIIIFc were evaluated using C_{max} and $AUC_{0-\infty}$ values. Both of these parameters increased with an increase in dose and were approximately proportional for both studies. Group mean C_{max} and $AUC_{0-\infty}$ values were similar between males and females for given dose. For the liquid formulation, the C_{max} values for males and females, respectively, were 0.158 ± 0.018 and 0.123 ± 0.001 µg/mL in the low dose group, 0.873 ± 0.051 and 0.813 ± 0.070 µg/mL in the mid-dose group, and 2.82 ± 0.160 and 2.82 ± 0.260 µg/mL in the high dose group. The group mean AUC0–∞ values for males and females, respectively, were 2.53 ± 0.510 and 1.46 ± 0.020 µg·hr/mL in the low dose group, 10.4 ± 1.90 and 11.2 ± 2.90 µg·hr/mL in the mid-dose group and 42.5 ± 4.20 and 32.5 ± 4.50 µg·hr/mL in the high dose group. Comparable results were observed for the lyophilized formulation.

For the liquid formulation, individual elimination half-lives ranged from 6.65 to 21.7 hours among all the dose groups and averaged 11.7 ± 1.2, 11.2 ± 1.2 and 13.6 ± 1.2 hours for the low, mid- and high dose groups, respectively. For the lyophilized formulation, individual elimination half-lives ranged from 9.08 to 18.4 hours among all the dose groups and averaged 12.1 ± 2.2, 13.4 ± 2.8 and 11.9 ± 1.9 hours for the low, mid- and high dose groups, respectively.

After repeat doses of rFVIIIFc in monkeys, there were 5 monkeys in each study that had measurable rFVIIIFc in the pre-dose samples on Day 27, which is likely due to some drug accumulation. Several of the monkeys in the high dose groups and some in the mid-dose groups did not have a sufficient number of data points with measurable a plasma concentration of rFVIIIFc to evaluate PK. Overall, C_{max} and $AUC_{0-\infty}$ values increased in an approximately dose-proportional manner, with the exception of the high dose group that had lower C_{max} and $AUC_{0-\infty}$ values compared to both the low and mid-dose groups for both studies. In the study using the lyophilized formulation, a single male in the high dose group showed a high $AUC_{0-\infty}$, while the $AUC_{0-\infty}$ for the other 4 animals could not be calculated due to insufficient data. Compared to Day 1, the low dose groups had similar PK parameters on Day 27 in both studies, while the middose groups had a slightly lower C_{max} and $AUC_{0-\infty}$ values and the high dose groups had markedly lower group mean C_{max} and $AUC_{0-\infty}$ values on Day 27.

In the study using the liquid formulation, 2 of 6 animals in the mid-dose group and 9 of 10 animals in the high dose group developed anti-rFVIIIFc antibodies. In the study using the lyophilized formulation, 1 of 6 animals in the low dose group, 4 of 6 animals in the mid-dose group, and 6 of 10 animals in the high dose group developed anti-rFVIIIFc antibodies. The development of antibodies to the human rFVIIIFc fusion protein is expected due to species differences. The development of anti-drug antibodies in the mid-and high dose groups was considered responsible for the reduced systemic exposure of rFVIIIFc after 4 weeks of repeat dosing in both studies.

Distribution

Single-dose biodistribution of rFVIIIFc in mice (R-FR8-027 and R-FR8-041)

The biodistribution of ^{125}I-rFVIIIFc was determined in a quantitative whole body autoradiography study (QWBA) in mice. Following IV administration, ^{125}I-rFVIIIFc is cleared and degraded in the liver in both HemA mice with circulating VWF and in double knockout (DKO) mice with the combined FVIII-KO and VWF-KO traits. However, VWF stabilizes rFVIIIFc in the blood and delays liver uptake in HemA mice relative to DKO mice.

Based on the percentage of the initial dose per organ (%ID/organ), rFVIIIFc distributes into the liver to a greater extent in the absence of VWF in DKO mice compared to the liver distribution in the presence of VWF in HemA mice. The organs with the greatest %ID are blood, liver, muscle, bone, and kidney for both HemA and DKO mice. Comparison of the %ID/organ at 5 and 30 minutes in HemA mice (blood: 36.1 and 34.1%; liver: 7.22 and 11.1%; muscle: 3.12 and 2.95%; bone: 2.70 and 1.69%; and kidney: 2.04 and 2.10%) to the %ID/organ at 5 and 15 minutes in DKO mice (blood: 28.4 and 19.3%; liver: 29.2 and 30.5%; muscle: 3.59 and 2.57%; bone: 3.64% at 15 min only; and kidney: 1.63 and 2.32%) shows that the liver is the major clearance organ.

Based on the ^{125}I-rFVIIIFc biodistribution, the liver is the dominant clearance organ in both HemA and DKO mice. The presence of VWF appears to stabilize ^{125}I-rFVIIIFc in the blood and delays liver uptake in HemA mice relative to DKO mice as deduced from the relative lower ratio of ^{125}I-signal in the liver to blood in HemA mice when compared to DKO mice.

In 2 separate studies, 3 or 4 pregnant mice were dosed with either 400 IU of rFVIIIFc or BDD FVIII (approximately 13,000 IU/kg), 3 to 4 hours before the fetuses were extracted. FVIII activity could be measured in all 9 fetal blood samples from pups removed from mothers dosed with rFVIIIFc. The measured FVIII activity was 1.1% ± 0.65% of the FVIII activity found in the maternal circulation after dosing (from 0.2% to 1.9%). In contrast, no FVIII activity could be detected in 9 fetal blood samples from pups removed from mothers dosed with BDD FVIII.

Metabolism

Metabolism studies have not been submitted (See discussion on non-clinical aspects)

Excretion

Excretion studies have not been submitted (See discussion on non-clinical aspects)

Pharmacokinetic Drug Interactions

No PK drug interaction studies have been performed with rFVIIIFc. (See Discussion on non-clinical aspects)

Other pharmacokinetic studies

Placental transfer study

Study R-FR8-041 evaluated the possibility of placental transfer of rFVIIIFc in HemA mice, based on the role of neonatal Fc receptor in the transplacental transfer of protective IgG molecules frommaternal to foetal circulation. In this study, female HemA mice were treated with rFVIIIFc or BDD rFVIII at day 19 of gestation. Analysis carried out by the chromogenic activity assay indicated that a small amount of rFVIIIFc was

transferred to the foetuses obtained from the mothers receiving rFVIIIFc, not observed for BDD rFVIII treatment.

2.3.4. Toxicology

Table 9: Toxicology studies

			Overview			Test Article: rFVIIIFc	
Type of Study	**Species and Strain**	**Method of Administration**	**Duration of Dosing**	**Doses (IU/kg)**	**GLP Compliance**	**Testing Facility**	**Study Number**
Single-Dose Toxicity	Cynomolgus Monkeys	IV	Single dose	0; 3000; 10,000; 20,000	No	NIRC Lafayette, LA	N-FR8-005
Repeat-Dose Toxicity	Sprague Dawley Rats	IV	2 ½ weeks	1000	No	Syntonix[a] Waltham, MA	N-FR8-004
	Cynomolgus Monkeys	IV	2 ½ weeks	50, 250, 1000	No	NIRC Lafayette, LA	N-FR8-001
	Sprague Dawley Rats	IV	4 weeks	0, 50, 250, 1000	Yes	Battelle Columbus, OH	CN53610
	Cynomolgus Monkeys	IV	4 weeks	0, 50, 250, 1000	Yes	Battelle Columbus, OH	CN53056
	Cynomolgus Monkeys	IV	4 weeks	0, 50, 250, 1000	Yes	Battelle Columbus, OH	N110486
Other Toxicity Studies (Comparative Immunogenicity)	HemA Mice	IV	2 ½ weeks	0, 50, 250, 1000	No	Syntonix[a] Waltham, MA	R-FR8-015
	HemA Mice	IV	4 weeks	0, 50	No	Biogen Idec Waltham, MA	N-FR8-018

[a] Syntonix was acquired by Biogen Idec
CABS = chromosomal aberrations; GLP = Good Laboratory Practice; HemA = haemophilia A; IV = intravenous; NA = not applicable; NIRC = New Iberia Research Center

Single dose toxicity

Non-GLP single-dose acute toxicology and PK study (N-FR8-005)

One single-dose toxicology study was conducted with rFVIIIFc in monkeys to determine the single dose tolerance and toxicity in cynomolgus monkeys at higher doses of rFVIIIFc (3000, 10,000, and 20,000 IU/kg) compared to those used in repeat-dose toxicology studies (50, 250 and 1000 IU/kg). The highest dose used in the single-dose toxicology study (20,000 IU/kg) is approximately 300-fold higher than a routine prophylactic dose used to treat patients and exceeds the binding capacity of VWF in monkeys.

Single doses of rFVIIIFc were well-tolerated. There were no effects of these high doses of rFVIIIFc on coagulation parameters (fibrinogen, aPTT, and PT), thrombogenic markers (fibrinogen and platelets), haematology parameters, or clinical chemistry analyses. There were no effects on organ weights, nor were there any histopathological changes attributed to effects of rFVIIIFc. The no observed adverse effect level (NOAEL) was defined as the highest dose tested, 20,000 IU/kg.

Repeat dose toxicity

rFVIIIFc was evaluated for adverse toxicological effects following repeat dosing in rats and monkeys. Non-GLP pilot studies were conducted in both species to determine the tolerability of repeat dosing and to assess development of antibodies to rFVIIIFc. Based on information from the pilot studies, a 4-week GLP repeat-dose study was conducted in rats and two 4-week GLP repeat-dose studies were conducted in monkeys.

Non-GLP pilot toxicology studies (N-FR8-004 and N-FR8-001)

In the repeat-dose, non-GLP study in rats animals were dosed IV at 1000 IU/kg on SD0 to characterize first dose PK properties. Subsequent doses were administered every other day from SD5 to SD17. This dosing regimen was well-tolerated. The elimination half-life from a pooled plasma profile was 8 hours. By SD27, 9 of 10 rats had developed antibodies to rFVIIIFc. 4 of 9 rats had antibodies specific to FVIII moiety, and 2 of 9 rats had antibodies specific to the Fc portion of the test article.

In a second repeat-dose, non-GLP study in cynomolgus monkeys, a total of 9 cynomolgus monkeys were divided into 3 dose groups (50, 250 and 1000 IU/kg) and received 8 IV doses on SD0, 5, 7, 9, 11, 13, 15 and 17. Each animal received its first bolus IV dose of rFVIIIFc on SD0 to characterize first dose PK properties. Subsequent IV doses were administered every other day starting on SD5. PK profiles were monitored using chromogenic and one-stage aPTT). The use of these activity assays provides support that administered rFVIIIFc protein retained its FVIII-specific activity in the circulation. Residual levels of rFVIIIFc (including endogenous FVIII) were measured prior to dose administration on SD9, 11, 13, 15 and 17 and post-dosing on SD21 and 27 by the one-stage aPTT clotting assay. Anti-drug antibodies were measured using a bridging ELISA at selected timepoints during the study.

Following the first dose on SD0, maximum plasma FVIII activity levels were approximately linear with dose using both the chromogenic assay and the one-stage aPTT assay. Individual elimination half-lives based on the chromogenic assay ranged from 6 to 19 hours, with a mean value of 13.3 hours. Using the one-stage aPTT assay, individual elimination half-lives ranged from 5 to 34 hours, with a mean value of 17.9 hours. Results were comparable for both assays.

Pre-dose levels of FVIII activity (measured using the one-stage aPTT assay) decreased over time, indicating the presence of anti-rFVIIIFc antibodies which cross-reacted with endogenous FVIII. By the end of the study, antibodies to rFVIIIFc were detected in 7 of the 9 treated monkeys.

GLP repeat-dose toxicology studies (CN53610, CN53056, N110486)

rFVIIIFc was evaluated for systemic and local toxicological effects in Sprague Dawley rats in a 4-week repeat-dose GLP study using the liquid formulation. Rats were selected because they are a standard species used in toxicology studies. The highest dose selected for the toxicity studies was 1000 IU/kg. Animals received IV doses of rFVIIIFc every other day for 4 weeks (total of 14 doses). The terminal necropsy occurred 2 days after the last dose on SD29, and the recovery necropsy was 1 month later (SD57). The dose levels, 50, 250, and 1000 IU/kg, were well-tolerated for the 4 weeks of dosing. There were no effects on any in-life parameters (clinical observations, body weights, food consumption, ophthalmic examinations), laboratory evaluations (haematology, serum chemistry, coagulation), or post-mortem analyses (gross necropsy, organ weights, histopathology). There were no effects of rFVIIIFc at the injection site (tail vein). Antibodies to rFVIIIFc developed during the 4-week dosing period (which was expected for the fully human protein in these nonhuman species); the development was independent of gender and dose level. An increase in aPTT (approximately 20% to 25%) was seen in mid and high dose males and in high dose females on SD29. These increases may represent cross-reactivity of antirFVIIIFc antibodies with endogenous FVIII, but the magnitude of the change in aPTT values was insufficient to cause any adverse clinical signs in the rats.

Overall, repeat-dosing of rFVIIIFc in rats was well-tolerated for 4 weeks with a NOAEL defined as the highest dose tested, 1000 IU/kg. The development of antibodies and corresponding ablation of exposure in most of the treated animals precluded longer dosing periods in this species.

A 4-week repeat-dose GLP toxicology study was conducted with the liquid formulation of rFVIIIFc to evaluate systemic and local toxicological effects in cynomolgus monkeys. Monkeys were selected as a pharmacologically relevant species since the binding of the Fc portion of the molecule to FcRn is most similar to human. Animals received IV doses of rFVIIIFc every other day for 4 weeks (total of 14 dose administrations). The terminal necropsy occurred 2 days after the last dose (SD29), and the recovery necropsy was 1 month later (SD57).

Toxicology parameters evaluated in this study included in-life observations (clinical observations, body weights, food consumption, ophthalmic examinations, electrocardiograms (ECGs)), laboratory evaluations (haematology, serum chemistry, coagulation), immunogenicity (antibodies to rFVIIIFc), and post-mortem analyses (gross necropsy, organ weights, histopathology). Local tolerance was also monitored by gross and microscopic evaluations of the injection sites. There were no adverse toxicological findings directly related to effects of rFVIIIFc in this study.

Antibodies to rFVIIIFc developed in a dose-related pattern starting on SD11. Five of 10 high dose animals developed antibodies by SD19, and by SD27, 8 of 10 high dose animals were antibody-positive. Two animals dosed at 250 IU/kg developed antibodies (one was transiently positive on SD19). Anti-rFVIIIFc antibodies were not detected in the low dose animals (50 IU/kg).

A second 4-week repeat-dose GLP toxicology study in cynomolgus monkeys was conducted with the lyophilized formulation of rFVIIIFc. The study design was identical to the first 4-week study in monkeys, but based on clinical abnormalities seen in the first study, greater care was taken in handling the animals when collecting blood for laboratory evaluations as it was possible that some animals could develop antibodies that might cross-react with endogenous FVIII and render them susceptible to bleeding (i.e. acquired haemophilia).

As seen in the first toxicology study in cynomolgus monkeys, antibodies to rFVIIIFc developed in a dose-related manner and caused indirect adverse effects. Development of these antibodies altered the PK parameters following the last dose on SD27. Increased aPTT values during the dosing period (SD19, 27 and 29) provided supporting data that that antibodies to rFVIIIFc cross-reacted with endogenous FVIII.

After eliminating indirect toxicological effects that were considered due to development of antirFVIIIFc antibodies formation, there were no direct toxicological effects of repeat dosing with rFVIIIFc in monkeys. Body weights, food consumption, ophthalmic examinations, and ECGs were within normal limits for all dose groups. Organ weights were not adversely affected by rFVIIIFc. Histopathological observations, with the exception of effects associated with SC haemorrhage, were within normal limits for monkeys treated with rFVIIIFc.

Overall, there were no adverse toxicological findings directly related to effects of rFVIIIFc following 4 weeks of repeated dosing. SC haemorrhage following blood collections and subsequent adverse events were considered due to anti-rFVIIIFc antibodies that cross-reacted with endogenous FVIII in some animals and prevented them from regaining haemostasis. Thus, the NOAEL for direct effects of rFVIIIFc was defined as the highest dose tested, 1000 IU/kg. The development of antibodies, along with ablation of exposure and acquired haemophilia, in most of the antibody-positive animals precluded longer dosing periods in this species.

Genotoxicity

Genotoxicity studies have not been submitted (See Discussion on non-Clinical aspects).

Carcinogenicity

Carcinogenicity studies have not been submitted (See Discussion on non-Clinical aspects)

Reproduction Toxicity

Reproduction toxicity studies have not been submitted (See Discussion on non-Clinical aspects)

Toxicokinetic data

Local Tolerance

Local tolerance was evaluated in the 4-week repeat-dose toxicology studies in rats and monkeys by gross and microscopic examination of the IV injection sites. In comparison to microscopic findings in control animals, there were no exacerbated local reactions due to administration of rFVIIIFc. There were no injection site reactions in either control or treated rats. In monkeys, all dose groups (including the control groups) had microscopic findings of haemorrhage, inflammation, and/or fibrosis, consistent with IV injections.

Other toxicity studies

Antigenicity

Two comparative immunogenicity studies were conducted in HemA mice. The first study compared rFVIIIFc to ReFacto (rFVIII), while the second study compared rFVIIIFc lyophilized DP from the VLA5 manufacturing process (2000 IU/vial from the 10,000 vial lot scale) to rFVIIIFc lyophilized DP from the RVS2 manufacturing process (3000 IU/vial from the 40,000 vial lot scale). The route of administration was IV in both studies.

Non-GLP comparative immunogenicity studies (R-FR8-015 and N-FR8-018)

A non-GLP repeat dose comparative immunogenicity study was conducted in FVIII-deficient mice (R-FR8-015). Six doses of rFVIIIFc, or recombinant human FVIII (ReFacto) were administered intravenously twice weekly for 3 weeks at 50, 250, or 1000 IU/kg. FVIII chromogenic activity was measured in plasma pre-study and 1 hour after the first and sixth doses. After the sixth dose, 3/6 animals receiving 50 IU/kg rFVIIIFc and all of the animals treated with 50 IU/kg ReFacto had measurable FVIII activity. In the 250 and 1000 IU/kg dose groups, results were similar for both rFVIIIFc and ReFacto after the last dose, with the FVIII activity below the limit of quantitation for all but 1 animal treated with 250 IU/kg rFVIIIFc. There was a dose-dependent increase in the incidence and titer of anti-drug antibodies for both rFVIIIFc and ReFacto in this study. At the 50 IU/kg dose level, 3/5 mice treated with rFVIIIFc tested positive for anti-drug antibodies and 1/6 mice treated with ReFacto were positive on Day 32. Treatment with 250 IU/kg rFVIIIFc resulted in 5/6 animals testing positive for anti-drug antibodies on Day 16 with titers ranging from 50 to 200 and treatment with 250 IU/kg ReFacto resulted in 1/6 mice testing positive (titer = 50). However on Day 32, all animals in both the rFVIIIFc and ReFacto 250 IU/kg groups were positive for anti-drug antibodies with titers ranging from 50 to 800 for rFVIIIFc and 50 to 3200 for ReFacto. Repeated administration of 1000 IU/kg rFVIIIFc or ReFacto induced antibody formation in all mice on Days 16 and 32 and with similar titer ranges.

A second immunogenicity study in HemA mice was conducted to compare rFVIIIFc lyophilized DP from the VLA5 manufacturing process (2000 IU/vial from the 10,000 vial lot scale) to rFVIIIFc lyophilized DP from the RVS2 manufacturing process (3000 IU/vial from the 40,000 vial lot scale). Vehicle control animals did not develop antibodies to rFVIIIFc. One animal in each group dosed with rFVIIIFc developed antibodies (on SD14

for DP from RSV2 and on SD28 for DP fromVLA5). Thus, the immunogenic potential of rFVIIIFc lyophilized DP from the VLA5 and RVS2 manufacturing processes were comparable in HemA mice.

2.3.5. Ecotoxicity / environmental risk assessment

No environmental risk assessment was submitted.

2.3.6. Discussion on non-clinical aspects

Pharmacology

The specific activity of rFVIIIFc was found to be comparable to reported values for a number of rFVIII products by both FVIII-specific aPTT (1-stage clotting assay) and chromogenic assays. Additional in vitro characterization assays were performed to examine the function of rFVIIIFc in the coagulation cascade, to ensure that the normal function of the clotting factor was not compromised by the presence of the Fc domain at the carboxyl terminus. rFVIIIFc was compared to another commercially available rFVIII product for binding to vWF, activation by thrombin, interaction with FIXa, phospholipids and platelets, interaction with FXa, and inactivation by APC. In all of these assays, the function of rFVIIIFc was comparable to the other rFVIII product.

In vivo clotting activity was measured via WBCT and chromogenic assay in hemophilic mice and dogs. In both models rFVIIIFc revealed similar acute clotting efficacy as the comparators, however, rFVIIIFc increased the duration of this effect 2.7 and 1.5-2.1 fold as compared to other commercially available rFVIII products, respectively. As the pharmacodynamic assays have been performed with liquid DS, a study comparing liquid and lyophilized DS material resulted in similar efficacy. The acute clotting efficacy of lyophilized rFVIIIFc DP and another rFVIII product were compared using a well-established tail clip bleeding model demonstrating comparable efficacy and a 2-fold prolonged efficacy for rFVIIIFc versus comparator.

Pharmacokinetics

In all nonclinical PK studies, rFVIIIFc was administered either by IV bolus injection or infusion in order to model the route of administration in the clinic. The analytical methods include assays to measure plasma concentrations of rFVIIIFc (ELISA) and assays to measure FVIII activity (chromogenic activity assays).

The PK parameters of rFVIIIFc were assessed in several species (mice, dogs, rats and monkeys). Monkeys were chosen as a species in which to test comparability because the affinity of rFVIIIFc for human FcRn and monkey FcRn are similar.

The elimination half-life for rFVIIIFc was found to be a minimum of 1.5-fold to greater than 2.5-fold longer than the elimination half-life for full-length rFVIII or BDD rFVIII, by direct comparison (normal mice, hFcRn-Tg mice, HemA mice, HemA dogs), or by reference to published data (rat).

Studies in FcRn-KO and hFcRn-Tg mice demonstrated that the prolonged elimination half-life of rFVIIIFc is dependent on interaction with the FcRn receptor; both C_{max} and $AUC_{0-\infty}$ were shown to be dose proportional over a wide dose range in rats and monkeys, while the elimination half-life did not vary with dose in these species or in mice (50 to 1000 IU/kg). PK of purified SC rFVIIIFc was similar to the PK of rFVIIIFc. Different drug products (liquid and lyophilized) produced by alternative manufacturing process (VLA5 and RVS2) used during clinical development were found to be comparable.

A study performed with radiolabeled product showed the blood, lungs, kidneys, myocardium, urinary bladder and urine as the tissues where radioactivity was detected. Additional studies in HemA mice and DKO mice indicated that VWF is necessary to stabilize rFVIIIFc.

The role of neonatal Fc receptor in the transmission of rFVIIIFc was shown, indicating that the mechanism of transplacental transfer occurs by the FcRn pathway.

In line with guideline ICH S6 Guideline (1997) and Addendum (ICH S6(R1), 2012), metabolism, excretion and pharmacokinetic drug interactions studies are not required for the development of this type of product.

Pharmacokinetic single-dose studies carried out in dogs (HemA dogs) confirmed the prolonged elimination half-life of rFVIIIFc (ELISA average data = 14.5 hours and chromogenic activity assay average data = 15.5 hours) compared to BDD rFVIII (ELISA average data = 6.85 hours and chromogenic activity assay average data = 7.35 hours.

In the 4-week GLP study carried out in rats administered with rFVIIIFc (50, 250 and 1000 IU/Kg), the half-lives values were 13.5 and 13.4 hours for the low dose, 21.3 and 11.5 for the mid-dose; and 11.8 and 7.95 hours for the high-dose (males and females respectively). In the same study, rFVIIIFc repeated dosing resulted in the appearance of anti-rFVIIIFc antibodies, which affected the pharmacokinetic parameters.

In the repeat-dose 4-week study in monkeys the PK was similar in animals that did not develop anti-drug antibodies, but a decrease in $AUC_{0-\infty}$ or elimination half-life and an increase in CL were observed in monkeys that did develop anti-drug antibodies. The development of ADAs (dose-dependent) was reported, irrespective of the manufacturing process. This finding modified the exposure of rFVIIIFc, which produced drug levels that were below quantification levels after 4 weeks.

The study performed with radiolabeled product showed the blood, lungs, kidneys, myocardium, urinary bladder and urine as the tissues where radioactivity was detected. The liver clears and degrades rFVIIIFc and VWF stabilizes rFVIIIFc in the blood and delays liver uptake based on a biodistribution study with ^{125}I-rFVIIIFc in mice.

The PK parameters of a liquid and lyophilized formulation were found to be comparable in HemA mice and monkeys, and the PK parameters of lyophilized DP from 2 manufacturing processes (VLA5 and RVS2) were found to be comparable to each other in HemA mice, thus supporting the use of the different formulations and manufacturing processes in GLP toxicology studies and clinical studies, and the suitability of RVS2 for commercialization.

In summary, these PK studies demonstrate that rFVIIIFc has an extended half-life and support the potential of rFVIIIFc to provide a prolonged protective haemostatic effect with less frequent dosing compared to FVIII. Type and amount of non-clinical pharmacokinetic studies are considered sufficient and appropriate to support marketing authorisation.

Toxicology

The highest dose tested in animals in repeat-dose studies, 1000 IU/kg, is 10 times the highest anticipated clinical dose. There were no adverse toxicological findings directly related to effects of rFVIIIFc, either macroscopic or microscopic, up to the highest dose tested in the 4-week repeat-dose studies, and up to the highest dose tested in the single-dose toxicology study, 20,000 IU/kg. Thus, the NOAEL for non-immunogenic-related toxicities was considered to be 1000 IU/kg for both rats and monkeys.

The repeat-dose studies showed the appearance of anti-rFVIIIFc antibodies as the main toxicological finding occurred in both species (rats and monkeys). In the case of monkey species, the development of anti-rFVIIIFc antibodies was observed in a dose-dependent manner (50-1000 IU/Kg).The presence of these antibodies was also detected after the recovery period at the highest dose, i.e. 1000 IU/Kg, which corresponds to a HED value of 324 IU/Kg (safety margin of 6.5-fold to the recommended clinical dose for long-term prophylaxis of 50 IU/Kg).

Local tolerance was evaluated within repeated dose toxicology studies. The Applicant reported microscopic findings of haemorrhage, inflammation and/or fibrosis even in control groups, which it was considered consistent with IV injections.

A comparability study between rFVIIIFc and BDD rFVIII, resulted in a similar profile in terms of anti-rFVIIIFc antibodies development and the reduction of clotting activity in a dose-dependent manner. This immunotoxicological finding was in line with the one occurred in monkeys, in which the appearance of ADAs was also reported. Consequently, clotting activity (aPTT increased) and haematological parameters (decreases in red blood cells, haemoglobin and haematocrit) were altered in antibody-positive animals. No differences were reported between different rFVIIIFc lyophilized drug products (VLA5 and RVS2).

According to ICH S6 guideline recommendations, the omission of studies on genotoxicity, carcinogenicity and reproductive and developmental toxicity is justified.

According to the “Guideline on the environmental risk assessment of medical products for human use” substances like amino acids, peptides, proteins, carbohydrates and lipids are exempted from the guideline since they are unlikely to result in significant risk to the environment; Elocta is thereby exempted and an environmental risk assessment is not required.

Overall, the safety of rFVIIIFc has been adequately characterized in animals. No adverse toxicological findings directly related to effects of rFVIIIFc, either macroscopic or microscopic, up to the highest dose tested have been reported. Non-clinical data reveal no special hazard for humans based on acute and repeated dose toxicity studies (which included assessments of local toxicity and safety pharmacology). Studies to investigate genotoxicity, carcinogenicity, toxicity to reproduction or embryo-foetal development have not been conducted. In a placental transfer study, ELOCTA has been shown to cross the placenta in small amounts in mice. This information has been included in the SmPC section 5.3.

2.3.7. Conclusion on the non-clinical aspects

The non-clinical development of Elocta was performed in accordance with current guidelines. In general, type and amount of pharmacodynamic, pharmacokinetic and toxicology studies are considered sufficient and appropriate to support marketing authorisation.

2.4. Clinical aspects

2.4.1. Introduction

GCP

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

Study ID	Study Objective	Design	Subjects entered/ completed	Diagnosis Incl. criteria	Duration/ Study Status
998HA101	Assess the safety and PK of a single administration of rFVIIIFc at 2 dose levels (25 and 65 IU/kg)	Phase 1/2a, first-in-human, Active comparator (Advate)	19 enrolled / 16 completed	PTPs ≥12 years with severe haemophilia A	1 day (single dose); 28-day follow-up / ***completed***
997HA301	Evaluate the safety and characterize the PK profile of rFVIII. Assess the efficacy of rFVIIIFc for prophylaxis, episodic treatment and perioperative management.	Phase 3; Arm 1 (individualised prophylaxis with sequential PK subgroup and comparator Advate), Arm 2 (weekly prophylaxis with 65 IU/kg), Arm 3 (episodic dosing); Major surgery subgroup	165 enrolled / 153 completed	PTPs ≥12 years with severe haemophilia A	Up to 75 weeks for subjects in the sequential PK subgroup and up to 67 weeks for all other subjects for screening, treatment, and follow-up / ***completed***
8HA02PED	Evaluate safety, efficacy, and PK of rFVIIIFc in paediatric patients	Twice weekly prophylaxis with dose adjustment up to a maximum of 80 IU/kg every 3 days	35 subjects <6 years of age and 34 subjects 6 to <12 years of age	PTPs <12 years with severe haemophilia A	~28 weeks for treatment and follow-up periods (at least 50 EDs) / ***completed***

8HA01EXT	Evaluate the long-term safety and efficacy of rFVIIIFc	Individualised prophylaxis; weekly prophylaxis with 65 IU/kg; episodic dosing; surgery	211 enrolled as of 06 Jan 2014; 0 completed	Adult and paediatric PTPs with severe haemophilia A who have completed Study 997HA301, Study 8HA02PED or any other study with rFVIIIFc	Up to 4 years or until rFVIIIFc is commercially available in participating countries / ***ongoing***
997HA307	Characterise PK of rFVIIIFc at 2 vial strengths (1000 and 3000IU). Evaluate safety of rFVIIIc.	For PK assessment, injection of 50 IU/kg at both strengths (1000 and 3000IU) in an interval of 5–28 days. Subsequently prophylactic or episodic dosing of rFVIIIc.	12 planned; 5 enrolled as of 30th May 2014 (only 4 received both PK doses)	PTPs ≥ 12 years old with severe haemophilia	Up to 6 months following PK assessments / ***ongoing***

2.4.2. Pharmacokinetics

Methods

Determination of FVIII activity of human plasma samples

The most commonly assay used in clinical laboratories for measuring the activity of FVIII in plasma samples is the one-stage clotting assay. An alternative method for determining FVIII activity in plasma is the two-stage chromogenic assay.

Immunogenicity assays

An anti-drug antibody (ADA) assay was designed to quantify both neutralizing and non-neutralizing antibodies in treated patients plasma samples designed to detect all immunoglobulin classes, including antibodies that are targeted only to the FVIII portion or the Fc portion of the drug product. The assay was validated according to international guidelines.

The Nijmegen-Modified Bethesda Assay (ISTH reference method for factor VIII inhibitor testing) was used for quantifying neutralizing antibodies titers. This assay measures the decrease in FVIII activity in a one-stage assay when a patient sample containing neutralizing antibodies is mixed with a normal plasma sample. The titer of the inhibitor sample is determined from the reduction in FVIII activity compared to a control inhibitor-free plasma mix. For high titer inhibitor samples, dilutions are tested to arrive at a reduction near 50%, which is defined as 1 Bethesda unit (BU). Sample inhibitor titer is expressed as Bethesda Unit BU/mL. In

these clinical studies, a titer of <0.6 BU/mL was reported as “negative.” Titers from ≥0.6 BU/mL to 5 BU/mL are considered positive (‘low titer’). Samples with >5 BU/mL are considered ‘high titer’.

Pharmacokinetic data analysis

The PK parameters were to be derived from FVIIII activity measured using one stage clotting (aPTT) and chromogenic substrate assays:

-Incremental recovery (K) post-injection

-Area under the plasma concentration versus time curve from time zero to infinity (AUC_{0-INF})

-Maximum plasma activity (Cmax)

-Elimination half-life (t½)

-Mean residence time (MRT)

-Clearance (CL)

-Volume of distribution (V)

To assess the duration of therapeutic effect of FVIII, the following parameters were to be assessed:

Time to 1% and to 3% above baseline FVIII from completion of injection.

Statistical analysis

Summary descriptive statistics were to include the number of non-missing values, mean, geometric mean, standard deviation, percent coefficient of variation, minimum, and maximum. These analyses were to be repeated for the one-stage clotting and chromogenic assays.

An analysis of variance (ANOVA) model with factors for study treatment and subject was to be used to compare rFVIIIFc to Advate for the analysis of selected PK parameters including but not limited to t1/2, AUC, and time to reach 1% above baseline FVIII activity. The analysis was to be performed for each dose level separately. PK parameters were to be log-transformed for these analyses and estimated means, mean differences, and confidence intervals on the log-scale were to be exponentiated to obtain estimates for geometric means, geometric mean ratios, and confidence intervals, respectively, on the original scale.

Absorption

Bioavailability

No bioavailability studies were submitted (See discussion on clinical pharmacology).

Bioequivalence

Two formulations of the rFVIIIFc drug product have been used in the clinical studies. A frozen liquid formulation was used in the Phase 1/2a study, and a lyophilised formulation (intended for commercialisation)

was used in the subsequent studies. The comparability of the two drug products was evaluated in vitro as well as in the context of non-clinical studies.

The lyophilised rFVIIIFc formulation from the VLA5 manufacturing process was used in Studies 997HA301 and 8HA01EXT and from the RVS2 manufacturing process in Studies 8HA02PED and 8HA01EXT. The primary difference between the VLA5 and RVS2 manufacturing processes was in drug product scale (change from 10,000 to 40,000 vials/lot, respectively). rFVIIIFc from the RVS2 manufacturing process is proposed for commercial use.

Distribution

No distribution studies were submitted (see discussion on Clinical pharmacology)

Elimination

No elimination studies were submitted (see discussion on Clinical pharmacology)

Dose proportionality and time dependencies

Pharmacokinetics of of rFVIIIFc was evaluated in three of the overall five clinical studies with rFVIIIFc: in a single-dose, Phase 1/2a study (998HA101); a multiple-dose, Phase 3 study in adults and adolescents ≥12 years of age (997HA301); and a multiple-dose, Phase 3 study in children <12 years of age (8HA02PED). In studies 998HA101 and 997HA301, PK of rFVIIIFc was compared to Advate. In study 8HA02PED, PK of rFVIIIFc was compared to PK of prior FVIII therapy in a subset of subjects.

Pharmacokinetics in target population

Study 998HA101 was a Phase 1/2a study to compare PK of escalating single doses of rFVIIIc with Advate® in previously treated patients (PTPs) ≥12 years of age with severe haemophilia A. The study population included 1 Asian (at Site 200, Hong Kong); all other subjects were white (at US sites). The median age of all subjects was 30.5 years (range: 23 to 61 years), and median weight was 78.3 kg (range: 54 to 111 kg). The median age and weight were higher in the 25 IU/kg dose group than in the 65 IU/kg dose group: 42 years vs. 30 years; and weight 88.3 kg vs. 75.8 kg, respectively. The overall history of exposure ranged from >100 to 6000 exposure days (EDs). Seven of 16 subjects were using Advate at the time of study entry. Twelve of 16 subjects were following a prophylaxis regimen, requiring FVIII replacement 2 to 3 times per week. All subjects were required to have a minimum 4-day washout period from their current FVIII product prior to their initial dose of Advate.

Dosing was sequential: a single dose of Advate was administered at 25 or 65 IU/kg followed 3 or 4 days later, respectively, to ensure a sufficient washout time, by an equal dose of rFVIIIFc. Plasma FVIII activity was measured in subjects before rFVIIIFc injection; 10 and 30 minutes; and 1, 3, 6, 9, 24, 48, 72, 96, 120, and 168 hours (7 days) after an injection of 25 IU/kg of rFVIIIFc, with additional samples at 192, 216, and 240 hours (10 days) after injection for subjects dosed at 65 IU/kg of rFVIIIFc. Plasma FVIII activity was measured at the same time points after Advate treatment, through 72 hours for the 25 IU/kg group and 96 hours for the 65 IU/kg group.

16 subjects were enrolled: 6 subjects received 25 IU/kg and 10 subjects received 65 IU/kg. All 16 subjects were included in the PK analysis of Advate. However, only 15 subjects were included in the PK analysis of rFVIIIFc because of incomplete PK sampling for 1 subject.

Results of the PK evaluation are summarised as follows:

PK Parameters by Chromogenic Assay for rFVIIIFc and Advate Per Dose Group (Study 998HA101, Phase 1/2a)

PK Parameter	Dose: 25 IU/kg (N=6)			Dose: 65 IU/kg (N=9)		
	Advate Geom. Mean [95% CI]	rFVIIIFc Geom. Mean [95% CI]	Geom. Mean Ratio [95% CI] (p-value)	Advate Geom. Mean [95% CI]	rFVIIIFc Geom. Mean [95% CI]	Geom. Mean Ratio [95% CI] (p-value)
C_{max_OB} (IU/dL)	75.5 [65.5, 87.1]	76.5 [64.9, 90.1]	1.01 [0.940, 1.09] (p = 0.686)	175 [143, 215]	182 [146, 227]	1.04 [0.900, 1.20] (p = 0.571)
AUC_{inf} (h*IU/dL)	1056 [822, 1358]	1659 [1300, 2117]	1.57 [1.38, 1.80] (p<0.001)	2265 [1672, 3070]	4277 [2956, 6190]	1.89 [1.61, 2.21] (p<0.001)
$t_{½}$ (h)	10.5 [8.49, 12.9]	16.7 [13.8, 20.1]	1.59 [1.35, 1.87] (p<0.001)	10.8 [8.16, 14.2]	19.8 [14.3, 27.5]	1.84 [1.60, 2.12] (p<0.001)
MRT (h)	15.0 [12.2, 18.6]	23.9 [19.8, 28.9]	1.59 [1.35, 1.87] (p<0.001)	15.84 [11.7, 20.4]	28.5 [20.5, 39.6]	1.85 [1.61, 2.12] (p<0.001)
CL (mL/h/kg)	2.35 [1.80, 3.06]	1.49 [1.16, 1.92]	0.636 [0.557, 0.727] (p<0.001)	2.87 [2.12, 3.89]	1.52 [1.5, 2.20]	0.530 [0.453, 0.620] (p<0.001)
V_{ss} (mL/kg)	35.5 [30.5, 41.3]	35.9 [30.4, 42.3]	1.01 [0.898, 1.14] (p = 0.822)	44.5 [36.7, 54.1]	43.4 [38.2, 49.4]	0.975 [0.863, 1.10] (p = 0.653)
IR (IU/dL per IU/kg)	3.05 [2.62, 3.54]	3.09 [2.61, 3.66]	1.01 [0.940, 1.09] (p = 0.679)	2.70 [2.20, 3.31]	2.80 [2.24, 3.50]	1.04 [0.900, 1.20] (p = 0.571)

AUCinf = area under the curve from time zero to infinity; CI = confidence interval; CL = clearance; Cmax_OB = maximum observed activity, occurring at Tmax (baseline and residual drug subtracted); FVIII = coagulation factor VIII; Geom. Mean = geometric mean; IR = incremental recovery; MRT = mean residence time; PK = pharmacokinetic; rFVIIIFc = recombinant coagulation factor VIII Fc fusion protein; t½ = half-life; Time 1% = time after dose when FVIII activity has declined to 1 IU/dL above baseline; Time 3% = time after dose when FVIII activity has declined to 3 IU/dL above baseline; Tmax = time to maximum concentration or activity; Vss = volume of distribution at steady state.

Estimated means, 95% CI for means, and mean differences were transformed to obtain estimated geometric means, 95% CI for geometric means, and geometric mean ratios, respectively.

Study 997HA301

Study 997HA301 (See also Clinical Efficacy section) was a Phase 3 study to evaluate the safety, PK, and efficacy of rFVIIIFc lyophilized powder administered as an IV injection to previously treated subjects with severe hemophilia A. In total, 165 adult and adolescent subjects ≥12 years of age were enrolled. The study evaluated an individualized prophylaxis regimen (Arm 1), a weekly prophylaxis regimen (Arm 2), and an episodic (on-demand) regimen (Arm 3).

For all subjects, PK assessments for rFVIIIFc were based on plasma FVIII activity levels that were determined by the one-stage clotting (aPTT) assay and two-stage chromogenic substrate assay.

The PK analysis was performed on FVIII activity versus time data obtained following IV infusion. A compartmental analysis and noncompartmental analysis (NCA) were to be conducted.

PK parameters calculated were to include but not be limited to: dose-normalized AUC (DNAUC); half-life; CL; MRT; Vd; incremental recovery; time to reach 1% above baseline FVIII activity based on both the one-stage clotting assay and the two-stage chromogenic assay; time to reach 3% above baseline FVIII activity based on both the one-stage clotting assay and the two-stage chromogenic assay.

The Pharmacokinetic Analysis Set (PKAS) was defined as all subjects in Arms 1, 2, or 3 who had completed evaluable sampling timepoints (through at least the 48-hour timepoint for the Advate profile or the 72-hour timepoint for the rFVIIIFc PK profiling) to allow the acceptable determination of the terminal half-life.

The Sequential PK Subgroup was defined as subjects who had evaluable PK profiles for both Advate and baseline rFVIIIFc and/or evaluable PK profiles for both baseline rFVIIIFc and the repeat rFVIIIFc profile. Prior to the first dose of rFVIIIFc or Advate (for subjects in the sequential PK subgroup of Arm 1), all subjects were to undergo a washout of FVIII-containing products of at least 96 hours. For adolescent subjects, a 72-hour washout was to be allowed;

Comparison of Advate and rFVIIIFc PK Parameters - Compartmental Methods – Chromogenic Assay (Study 997HA301, adults and adolescents ≥12 years of age), Sequential PK Subgroup

PK parameter	rFVIIIFc Geom. Mean (n=27) (95% CI)	Advate Geom. Mean (n=27) (95% CI)	Geom. Mean Ratio (95% CI)
Cmax (IU/dL)	130.78 (103.63, 165.05)	136.95 (117.62, 159.46)	0.95 (0.73, 1.24)
DNAUC (IU*h/dL per IU/kg)	47.45 (41.55, 54.18)	28.05 (24.85, 31.65)	1.69 (1.54, 1.85)
Elimination t1/2 (h)	20.89 (18.23, 23.93)	13.67 (12.31, 15.18)	1.53 (1.34, 1.74)
CL (mL/h/kg)	2.108 (1.846, 2.407)	3.566 (3.159, 4.024)	0.59 (0.54, 0.65)
MRT (h)	24.96 (22.41, 27.80)	15.94 (14.70, 17.27)	1.57 (1.47, 1.67)
Vss (mL/kg)	52.6 (47.4, 58.3)	56.8 (51.5, 62.7)	0.93 (0.84, 1.02)
IR (IU/dL per IU/kg)	2.4912 (2.2762, 2.7265)	2.5589 (2.3247, 2.8168)	0.97 (0.90, 1.06)
In Vivo Recovery (%)	101.224 (93.355, 109.756)	104.161 (95.016, 114.185)	0.97 (0.90, 1.05)
Time 1% (days)	5.010 (4.525, 5.548)	3.220 (2.970, 3.491)	1.56 (1.47, 1.65)
Time 3% (days)	3.612 (3.250, 4.015)	2.306 (2.120, 2.509)	1.57 (1.47, 1.67)

Note 1: Includes subjects who have evaluable PK profiles for both Advate and baseline rFVIIIFc.
2: CI = confidence interval; CL = clearance; Cmax = maximum activity; DNAUC = dose-normalized area under the curve; Geom. Mean = geometric mean; IR = incremental recovery; MRT = mean residence time; PK = pharmacokinetic; t1/2 = half-life; Time 1% = time after dose when FVIII activity has declined to 1 IU/dL above baseline; Time 3% = time after dose when FVIII activity has declined to 3 IU/dL above baseline; Vss = volume of distribution at steady state.

Pharmacokinetic properties were evaluated in 28 subjects (≥ 15 years) receiving rFVIIIFc at a single dose of 50 IU/kg of ELOCTA. Pharmacokinetic samples were collected pre-dose and then subsequently at 7 time points up to 120 hours (5 days) post-dose.

Pharmacokinetic parameters after 50 IU/kg dose of ELOCTA are presented in Tables 10 and 11.

Table 10: Pharmacokinetic parameters of ELOCTA using the one-stage clotting assay

Pharmacokinetic parameters[1]	ELOCTA (95% CI)
	N=28
Incremental Recovery (IU/dL per IU/kg)	2.24 (2.11-2.38)
AUC/Dose (IU*h/dL per IU/kg)	51.2 (45.0-58.4)
C_{max} (IU/dL)	108 (101-115)
CL (mL/h/kg)	1.95 (1.71-2.22)
$t_{1/2}$ (h)	19.0 (17.0-21.1)
MRT (h)	25.2 (22.7-27.9)
V_{ss} (mL/kg)	49.1 (46.6-51.7)

[1] Pharmacokinetic parameters are presented in Geometric Mean (95% CI)
Abbreviations: CI = confidence interval; C_{max}= maximum activity; AUC = area under the FVIII activity time curve; $t_{1/2}$= terminal half-life; CL = clearance; V_{ss} = volume of distribution at steady-state; MRT = mean residence time.

Table 11: Pharmacokinetic parameters of ELOCTA using the chromogenic assay

Pharmacokinetic parameters[1]	ELOCTA (95% CI)
	N=27
Incremental Recovery (IU/dL per IU/kg)	2.49 (2.28-2.73)
AUC/Dose (IU*h/dL per IU/kg)	47.5 (41.6-54.2)
C_{max} (IU/dL)	131 (104-165)
CL (mL/h/kg)	2.11 (1.85-2.41)
$t_{1/2}$ (h)	20.9 (18.2-23.9)
MRT (h)	25.0 (22.4-27.8)
V_{ss} (mL/kg)	52.6 (47.4-58.3)

[1] Pharmacokinetic parameters are presented in Geometric Mean (95% CI)
Abbreviations: CI = confidence interval; C_{max}= maximum activity; AUC = area under the FVIII activity time curve; $t_{1/2}$= terminal half-life; CL = clearance; V_{ss} = volume of distribution at steady-state; MRT = mean residence time.

Special populations

Impaired renal function

N/A

Impaired hepatic function

N/A

Gender

Males with severe haemophilia A were enrolled into the PK studies.

Race

Patients of race white, black, Asian and others have been enrolled in the clinical trial; in principal PK differences are not expected.

Paediatric population

Pharmacokinetic parameters of ELOCTA were determined for adolescents in study 997HA301 (pharmacokinetic sampling was conducted pre-dose followed by assessment at multiple time points up to 120 hours (5 days) post-dose) and for children in study 8HA02PED (pharmacokinetic sampling was conducted pre-dose followed by assessment at multiple time points up to 72 hours (3 days) post-dose). Tables 12 and 13 present the pharmacokinetic parameters calculated from the paediatric data of subjects less than 18 years of age.

Table 12: Pharmacokinetic parameters of ELOCTA for paediatrics using the one-stage clotting assay

Pharmacokinetic parameters[1]	Study 8HA02PED		Study 997HA301*
	< 6 years	6 to < 12 years	12 to < 18 years
	N = 23	N = 31	N = 11
Incremental Recovery (IU/dL per IU/kg)	1.90 (1.79-2.02)	2.30 (2.04-2.59)	1.81 (1.56-2.09)
AUC/Dose (IU*h/dL per IU/kg)	28.9 (25.6-32.7)	38.4 (33.2-44.4)	38.2 (34.0-42.9)
$t_{½}$ (h)	12.3 (11.0-13.7)	13.5 (11.4-15.8)	16.0 (13.9-18.5)
MRT (h)	16.8 (15.1-18.6)	19.0 (16.2-22.3)	22.7 (19.7-26.1)
CL (mL/h/kg)	3.46 (3.06-3.91)	2.61 (2.26-3.01)	2.62 (2.33-2.95)
V_{ss} (mL/kg)	57.9 (54.1-62.0)	49.5 (44.1-55.6)	59.4 (52.7-67.0)

[1] Pharmacokinetic parameters are presented in Geometric Mean (95% CI)
Abbreviations: CI = confidence interval; AUC = area under the FVIII activity time curve; $t_{1/2}$ = terminal half-life;
CL = clearance; MRT = mean residence time; V_{ss} = volume of distribution at steady-state
*Pharmacokinetic parameters in 12 to <18 years included subjects from all the arms in Study I with different sampling schemes

Table 13: Pharmacokinetic parameters of ELOCTA for paediatrics using the chromogenic assay

Pharmacokinetic parameters[1]	Study 8HA02PED		Study 997HA301*
	< 6 years	6 to < 12 years	12 to < 18 years
	N = 24	N = 27	N = 11
Incremental Recovery (IU/dL per IU/kg)	1.88 (1.73-2.05)	2.08 (1.91-2.25)	1.91 (1.61-2.27)
AUC/Dose (IU*h/dL per IU/kg)	25.9 (23.4-28.7)	32.8 (28.2-38.2)	40.8 (29.3-56.7)
$t_{½}$ (h)	14.3 (12.6-16.2)	15.9 (13.8-18.2)	17.5 (12.7-24.0)
MRT (h)	17.2 (15.4-19.3)	20.7 (18.0-23.8)	23.5 (17.0-32.4)
CL (mL/h/kg)	3.86 (3.48-4.28)	3.05 (2.62-3.55)	2.45 (1.76-3.41)
V_{ss} (mL/kg)	66.5 (59.8-73.9)	63.1 (56.3-70.9)	57.6 (50.2-65.9)

[1] Pharmacokinetic parameters are presented in Geometric Mean (95% CI)
Abbreviations: CI = confidence interval; AUC = area under the FVIII activity time curve; $t_{1/2}$ = terminal half-life;
CL = clearance; MRT = mean residence time; V_{ss} = volume of distribution at steady-state
* Pharmacokinetic parameters in 12 to <18 years included subjects from all the arms in Study I with different sampling schemes
In comparison with adolescents and adults, children less than 12 years of age may have a higher clearance and a shorter half-life which is consistent with observations of other coagulation factors. These differences should be taken into account when dosing.

For subjects in study 8HA02PED with PK dosing with both pre-study FVIII and rFVIIIFc, a comparison of the PK parameters was performed by calculating the ratio of the rFVIIIFc PK parameter to the prior FVIII for each subject.

In the subset of subjects whose prior therapy was Advate (8 subjects in the <6 years of age cohort and 8 subjects in the 6 to <12 years of age cohort), the geometric mean of the intra-subject ratio of rFVIIIFc to Advate for t½ was 1.749 (95% CI: 1.470, 2.081) and 1.426 (95% CI: 1.191, 1.707) for the <6 years of age cohort and 6 to <12 years of age cohort, respectively.

In subjects whose prior therapy was Helixate/Kogenate (6 subjects in the <6 years of age cohort and 6 subjects in the 6 to <12 years of age cohort), the geometric mean of the intra-subject ratio of rFVIIIFc to Helixate/Kogenate for t½ was 1.798 (95% CI: 1.070, 3.023) and 1.781 (95% CI: 1.048, 3.026) for the <6 years of age cohort and 6 to <12 years of age cohort, respectively.

In the subset of subjects whose prior therapy was Haemosolvate (6 subjects in the 6 to <12 years age cohort), the geometric mean of the intra-subject ratio of rFVIIIFc to Haemosolvate for t½ was 1.837 (95% CI: 1.538, 2.193).

Study 8HA02PED (See also Clinical Efficacy)
Study 8HA02PED was an open-label, Phase 3, multicenter evaluation of the safety, PK, and efficacy of rFVIIIFc for routine prophylaxis and control of bleeding in PTPs <12 years of age with severe hemophilia A.

Sixty subjects were enrolled into the PK subgroup (25 subjects <6 years of age and 35 subjects 6 to <12 years of age). A washout period with no FVIII treatment was required prior to administration of prestudy FVIII and prior to the administration of rFVIIIFc. Eligible subjects underwent a PK evaluation of prestudy FVIII (50 IU/kg; unless they were exempt because they had a satisfactory PK assessment performed within 14 months prior to the Screening Visit), followed by a PK evaluation of rFVIIIFc (50 IU/kg). Blood sampling schedules were as follows:

-Samples for PK assessment of prestudy FVIII were obtained predose and at 30 (±5) minutes and 3 (±0.5), 24 (±3), and 48 (±4) hours following prestudy FVIII dosing.

-Samples for PK assessment of rFVIIIFc were obtained predose and at 30 (±5) minutes and 3 (±0.5), 24 (±3), 48 (±4), and 72 (±7) hours following rFVIIIFc dosing.

NCA was performed for baseline and for residual drug-corrected FVIII activity data from both the one-stage and chromogenic assays using Phoenix WinNonlin software

Actual sampling times, doses, and injection durations were used for PK analyses. Actual doses were used for the analysis of FVIII profiles following rFVIIIFc dosing, whereas nominal doses were used for the PK analysis of prestudy FVIII. Nominal sampling times and doses were used for the creation of tables, listings, and figures. The key PK parameters estimated included IR, DNAUC, t½, MRT, CL, and Vss.

Any subject with adequate rFVIIIFc PK data was included in the Pharmacokinetic Analysis Set (PKAS).The PKAS, defined as all subjects with adequate PK data by either assay, comprised 55 subjects overall. Analyses performed for the PK subgroup using both the one-stage aPTT clotting and chromogenic assays included a summary of FVIII activity levels for rFVIIIFc at scheduled PK timepoints for the PKAS, a summary of FVIII activity levels for prestudy FVIII and rFVIIIFc for subjects who had complete and evaluable PK profiles for both prestudy FVIII and rFVIIIFc, a listing of PK parameters derived from NCA for both prestudy FVIII and rFVIIIFc for the All-Enrolled Analysis Set, the descriptive statistics of PK parameters of rFVIIIFc for the PKAS, a listing of the ratio of rFVIIIFc to prestudy FVIII for select PK parameters for all subjects included in the PKAS, the plots of FVIII activity versus time profiles for rFVIIIFc and prestudy FVIII for each subject in the PKAS and The mean-activity-versus-time profiles for prestudy FVIII and rFVIIIFc for subjects who had complete and evaluable PK profiles for both prestudy FVIII and rFVIIIFc.

In total, 60 subjects enrolled into the PK subgroup (25 subjects in the <6 years of age cohort and 35 subjects in the 6 to <12 years of age cohort). Of the 60 subjects in the PK subgroup, 5 subjects were exempted from PK assessment with prestudy FVIII as they had historical data from a prior PK assessment with FVIII

As specified in the 8HA02PED protocol, these subjects were still required to complete a PK assessment with rFVIIIFc, and only the rFVIIIFc data, if evaluable, were included in the PK summary.

Two of the 60 subjects in the PK subgroup withdrew following the PK assessment for prestudy FVIII.

Fifty-three subjects (23 subjects in the <6 years of age cohort and 30 subjects in the 6 to <12 years of age cohort) received PK assessments with both prestudy FVIII and rFVIIIFc prior to beginning prophylaxis treatment with rFVIIIFc.

A total of 55 subjects (91.7%), 55 subjects (91.7%), and 51 subjects (85.0%) had a complete and evaluable PK profile for prestudy FVIII, rFVIIIFc, or both, respectively.

There were 19 subjects in the <6 years of age cohort and 27 subjects in the 6 to <12 years of age cohort with complete and evaluable PK profiles for both FVIII and rFVIIIFc within the same individual as measured by the one-stage assay. Using the chromogenic assay, 22 subjects in the <6 years of age cohort and 25 subjects in the 6 to <12 years of age cohort had complete and evaluable PK profiles for both prestudy FVIII and rFVIIIFc within the same individual chromogenic assay.

Population PK analysis

Data from studies 998HA101 (phase 1/2a adults), 997HA301 (phase 3 adults) and 8HA02PED (phase 3 children) were used to conduct a population PK analysis.

The rFVIIIFc modeling dataset included 16 subjects ≥12 years of age from the Phase 1/2a study, 164 subjects from the Phase 3 study in adults and adolescents ≥12 years of age, and 69 subjects from the Phase 3 study in children <12 years of age including subjects (from the Phase 3 studies) with episodic trough and peak measurements.

The Advate modeling dataset included 16 subjects from the Phase 1/2a study and 30 subjects from the Phase 3 study in adults and adolescents ≥12 years of age.

Mixed-effects modelling with maximal likelihood parameter estimation methods were used to evaluate the population characteristics of rFVIIIFc. Activity data, measured by the one-stage clotting assay (aPTT, LLOQ was 0.5 IU/dL), was used as a marker of rFVIIIFc PK. NONMEM versions 7.1.2 and 7.2 were used for population PK analysis with Intel Fortran compiler, version 11.1.048 and version 12.1. Simulations of various dosing scenarios for dose regimens that might be used in prophylaxis, for the treatment of bleeding episodes, and in perioperative care were presented.

The simulations from the model using only data from adults and adolescents ≥12 years of age showed that:

- For prophylaxis: A dose of 50 IU/kg every 4 days would show up to 77.4% of the patients with troughs above 1%. Increasing the time interval to 5 days would decrease this percentage to around 50% of patients.

- For minor to moderate bleeding, the recommendations of the WFH of having peaks between 40 and 60 IU/dL would be achieved with initial doses of 20-30 IU/kg of rFVIIIFc.

- For severe bleeding, considering a target of a peak of 80-100 IU/dL, the starting dose should be 40-50 IU/Kg of rFVIIIFc.

- For the perioperative treatment, a single treatment simulation has been performed, and therefore, no extrapolation to any dosing regimen could be performed.

The simulations from the model using only data from paediatrics to adults were similar.

Study 997HA307

Additionally to the three studies mentioned above, a further study (997HA307) was being conducted to evaluate safety and compare the PK of rFVIIIFc from the 3000 and 1000 IU vial strengths. Interim results – which were later confirmed by the final PK results- are presented in the following table:

Table 14 **PK Parameters (Geometric Mean and 95% CI) for FVIII Activity – Noncompartmental Methods - Two Stage Chromogenic Assay**

PK parameters (geometric mean and 95% CI) for FVIII activity - non-compartmental methods - two-stage chromogenic assay
Pharmacokinetic Analysis Set

PK Parameter		1000 IU (N=17)	3000 IU (N=18)
AUCinf (IU*h/dL)	n	15	16
	Geo. Mean	2649.0	2628.0
	95% CI	(2230.2, 3146.5)	(2206.2, 3130.5)
IR (IU/dL per IU/kg)	n	17	18
	Geo. Mean	2.633	2.426
	95% CI	(2.326, 2.981)	(2.128, 2.765)
Cmax (IU/dL)	n	17	18
	Geo. Mean	132.61	122.29
	95% CI	(116.85, 150.50)	(106.80, 140.03)
t1/2 (h)	n	15	16
	Geo. Mean	18.58	19.10
	95% CI	(16.35, 21.12)	(16.44, 22.19)
CL (mL/h/kg)	n	15	16
	Geo. Mean	1.899	1.915
	95% CI	(1.602, 2.250)	(1.612, 2.275)
Vss (mL/kg)	n	15	16
	Geo. Mean	45.88	48.94
	95% CI	(41.31, 50.96)	(42.13, 56.86)
MRT (h)	n	15	16
	Geo. Mean	24.17	25.56
	95% CI	(21.16, 27.60)	(22.15, 29.50)

NOTE 1: Abbreviations: Geo. Mean = Geometric mean, CI = Confidence interval, AUCinf = area under the concentration-time curve to infinity, IR = incremental recovery (K-value), Cmax = maximum plasma activity, t½ = terminal half-life, CL = clearance, Vss = volume of distribution at steady state, MRT = mean residence time.
2: Data cutoff was 17Nov2014.
3: 95% confidence interval on the geometric mean based on the t-statistic back-transformed from the log scale.

SOURCE: FACTOR8HA/997HA307/INTERIMPK2/IN-T-PK-NONCOMP-CHROM-PKAS.SAS
DATE: 16MAR2015

Pharmacokinetic interaction studies

N/A

Pharmacokinetics using human biomaterials

N/A

2.4.3. Pharmacodynamics

Mechanism of action

No clinical pharmacodynamic studies on the mechanism of action have been submitted

Primary and Secondary pharmacology

Subjects at selected sites in the Phase 3 study in adults and adolescents ≥12 years of age (997HA301) had global haemostasis assays performed, including an exploratory thrombin generation assay (TGA) and, dependent upon the selected sites' testing capabilities, whole blood rotational thromboelastometry (ROTEM). There were wide inter- and to some extent also intra-subject variances in thrombin generation potential.

2.4.4. Discussion on clinical pharmacology

In haemophilia, pharmacokinetic data are the most important surrogate endpoints for efficacy of a new factor VIII product (EMA/CHMP/BPWP/144533/2009) and PK is assessed for factor VIII activity (FVIII:C).

Bioavailability studies are not applicable as per the intravenous route of administration for which bioavailability is assumed to be 100%; distribution, elimination and metabolism studies are not required in accordance with the guideline for the type of product.

rFVIIIFc PK investigation was conducted in at least 12 previously treated patients from each of the relevant age groups (≥12 years, 6 to <12 years and <6 years of age), fulfilling the minimum patient numbers as required by the guideline on clinical investigation of FVIII products.

The overall PK evaluation of rFVIIIFc shows adequate results for all age groups investigated.

The chosen primary PK parameters, dose-normalized AUC, IR, t1/2, Vd and clearance, are in line with EMA guideline requirements. Dosing for treatment of bleeds and for surgery are based on targeting a specific peak FVIII level and maintaining the FVIII activity level above a certain trough level for a specified period of time. "Peak" levels are measured in PK studies as the maximal concentration (C_{max}). C_{max} is most influenced by the dose administered. In addition, it was determined the times after dosing when FVIII activity had declined until 1 IU/dL above baseline (Time 1%) and 3 IU/dL above baseline (Time 3%) as surrogate measures for driving the dosing interval in prophylaxis regimen at the doses of 25 IU/Kg, 65 IU/Kg and 50 IU/Kg in adults and children.

In the PK studies in subjects ≥12 years of age (998HA101 and 997HA301), rFVIIIFc PK was compared to PK of Advate where prolongation of half-life and reduction of clearance of rFVIIIFc can be observed. The extent and relevant extrapolations from this PK pattern are further discussed under clinical efficacy.

In the PK studies in subjects ≥12 years of age (998HA101 and 997HA301), rFVIIIFc PK was compared to PK of Advate and a more favourable PK profile is stated for rFVIIIFc by the MAA. Compared to Advate, prolongation of half-life and reduction of clearance of rFVIIIFc can indeed be recognised. In this context, though, a possible imbalance in PK sampling for rFVIIIFc (with a sampling time of at least 120 hours) compared to Advate (sampling time 72 hours) has to be discussed. Relatively more sampling time points with FVIII activity levels near individual baseline and/or lower limit of quantification (LLQ) of the assay for rFVIIIFc than for Advate could have biased the PK analysis. As a response to the List of Questions (LoQ), the applicant has provided an additional analysis of the PK subgroup of Study 997HA301, for which results are proposed to be depicted in the SmPC. The 120 hours sampling time point of rFVIIIFc was excluded in this analysis, which is considered a reasonable approach to account for possible imbalances in PK sampling. Depending on the type of analysis (compartmental vs non-compartmental) and assay (with different LLQs), indeed a certain impact of in-/ or exclusion of the late 120 hours sampling time point of rFVIIIFc can be recognised. Resulting rFVIIIFc half-life ranges from ~17.5 to ~20.5 hours in Study 997HA301, which, however, is still regarded as an acceptable range in view of the variety of PK analysis types that were used. The applicant's additional

analysis could show that the possible impact of imbalanced sampling in Study 997HA301 is negligible. It has however been acknowledged, that already between marketed (r)FVIII products, variance of PK parameters exists.

In the Phase 1/2a Study (998HA101), doses of 25 IU/kg and 65 IU/kg were administered for PK evaluation. Under a dose of 65 IU/kg, geometric mean of Cmax is 175 IU/dl and 182 IU/dl for Advate and rFVIIIFc, respectively. Elevated factor VIII activity levels >150 IU/dl may constitute a risk factor for (venous) thromboembolism (Jenkins et al. 2012). In the proposed SmPC, these doses up to 65 mg/dl and for children even doses up to 80 mg/dl are recommended for rFVIIIFc long term prophylactic treatment.

In the PK analysis in trial 8HA02PED, consistent with the known impact of increased CL of coagulation factors in younger patients, a shorter t½ of rFVIIIFc was observed as age decreased. In general, the clearance was higher in group of children younger than 6 years than in those between 6 and less than 12 years (3.8600 ml/h/Kg and 3.0490 ml/h/Kg respectively). DNAUCs was lower in the youngest children (25.90 IU x h/dl per IU/ Kg and 32.80 IU x h/dl per IU/ Kg, respectively). The geometric mean t½ for rFVIIIFc for subjects in the PKAS was 12.277 (95% CI: 10.988, 13.718) hours in the youngest age cohort and 13.451 (95% CI: 11.445, 15.808) hours in the group of older children, by one stage clotting assay. IR values were slightly lower in children younger than 6 years of age. These data suggest that prophylaxis in children can need another dosing interval on the prophylaxis regimen different to the adults. An analysis of variance (ANOVA) with factors for study treatment (pre-study FVIII versus rFVIIIFc) and subject is required to know the comparability with pre-study FVIII.

The repeat PK evaluation after continuous treatment in the pivotal trial 997HA301,after the first injection of rFVIIIFc. Results showed similar PK parameters and thus satisfies the guideline requirement of demonstrating no decrease in FVIII activity after prolonged use. PK parameters of rFVIIIFc as important surrogates of rFVIIIFc efficacy have been explored and are in principle considered satisfactory. Summing up, the IR of rFVIIIFc is similar to that of the currently available therapies (approximately 2 IU/dL per IU/kg). The PK profile of rFVIIIFc is stable with repeat dosing and the lengthening of the half-life would support less frequent intravenous administrations. Consistent with the known impact of increased CL of coagulation factors in younger patients a shorter t½ of rFVIIIFc was observed as age decreased.

Overall PK evaluation of rFVIIIFc shows appropriate results. Also prolongation of half-life and reduction of clearance of rFVIIIFc could be shown in the PK analysis. As an important finding is however to be considered, that under recommended prophylactic doses of 65 IU/kg, elevated factor VIII activity levels >150 IU/dl were observed, since these may constitute a risk factor for thromboembolism especially in elderly patients (See Clinical Safety). With these considerations in mind, for long term prophylaxis, the recommended dose in the SmPC, is 50 IU/kg every 3 to 5 days. The dose may be adjusted based on patient response in the range of 25 to 65 IU/kg. In some cases, especially in younger patients, shorter dosage intervals or higher doses may be necessary. (see Clinical efficacy)

In the SmPC, ELOCTA dosing for treatment of bleeding episodes is recommended as 20-40 (IU/dL) for early haemarthrosis, muscle bleeding or oral bleeding; 30-60 (IU/dL) for more extensive haemarthrosis, muscle bleeding or haematoma; 60-100 (IU/dL) for Life threatening haemorrhages.

When used in surgery the recommended dosing is 60-100 (IU/dL) in case of minor surgery including tooth extraction – daily for at least 1 day, until healing is achievedand 80-100 (pre- and post-operative) in major surgery every 8 to 24 hours as necessary until adequate wound healing, then therapy at least for another 7 days to maintain a factor VIII activity of 30% to 60% (IU/dL).

For children below the age of 12, more frequent or higher doses may be required (see Clinical efficacy). For adolescents of 12 years of age and above, the dose recommendations are the same as for adults.

Appropriate treatment monitoring by determination of factor VIII levels (by one-stage clotting or chromogenic assays) is advised to guide the dose to be administered and the frequency of repeated injections (see SmPC section 4.4).

A warning statement is included in the SmPC section 4.4 to inform that when using an in vitro thromboplastin time (aPTT)-based one stage clotting assay for determining factor VIII activity in patients' blood samples, plasma factor VIII activity results can be significantly affected by both the type of the aPTT reagent and the reference standard used in the assay. This is of importance particularly when changing the laboratory and/or reagent used in the assay.

There is limited experience in patients ≥ 65 years.

As the Phase 3 study programme was initiated before the final EMA guideline was issued and the requirement to evaluate PK of the highest and lowest product strengths was not included in the published draft guideline, a clinical study to compare the PK of the rFVIIIFc 1000 IU and 3000 IU vial strengths (Study 997HA307) was initiated. Updated data of the PK part of Study 997HA307, as the final analysis, were provided and only minor changes to the preliminary results presented. Comparability of the highest rFVIIIFc strength of 3000 IU to the strength of 1000 IU is demonstrated and approval of the 3000 IU vial is supported by the PK data of Study 997HA307.

2.4.5. Conclusions on clinical pharmacology

Overall PK evaluation of rFVIIIFc shows adequate results and compared to Advate where applicable, a prolongation of half-life and reduction of clearance of rFVIIIFc can be noted. The overall PK evaluation of rFVIIIFc shows adequate results for all age groups investigated.

Posology recommendations are agreed and appropriately reflected in the SmPC – also in the light of clinical efficacy and safety (see later sections).

2.5. Clinical efficacy

2.5.1. Dose response study(ies)

2.5.2. Main studies

Study 997HA301

An Open-label, Multicenter Evaluation of the Safety, Pharmacokinetics, and Efficacy of Recombinant Factor VIII Fc Fusion Protein (rFVIIIFc) in the Prevention and Treatment of Bleeding in Previously Treated Subjects With Severe Hemophilia A

Methods

Study Participants
Inclusion criteria

Subjects must meet the following criteria at screening and prior to dosing Day 0 (rFVIIIFc or Advate) to be eligible for the study:

-Male, ≥12 years of age and weighing at least 40 kg

-Severe hemophilia A defined as <1 IU/dL (<1%) endogenous FVIII as determined by one-stage clotting assay from the central laboratory at the time of screening. If the screening result is ≥1%, then the severity of hemophilia A may be confirmed by documented historical evidence from a certified clinical laboratory demonstrating <1% FVIII:C as determined by the one-stage clotting assay from the medical record or from a documented genotype known to produce severe hemophilia A.

-Previously treated subject, defined as having at least 150 documented prior exposure days to any recombinant and/or plasma-derived FVIII and/or cryoprecipitate products at Day 0 (Advate or rFVIIIFc).

-No measurable inhibitor activity in 2 consecutive samples and absence of clinical signs or symptoms of decreased response to FVIII administration.

-History of bleeding events and/or treatment with FVIII during the prior 12 weeks, as documented in the subjects' medical records

-Willingness and ability of the subject or a surrogate (a caregiver or a family member ≥18 years of age) to complete training in the use of the study EPD and to use the EPD throughout the study

For subjects entering Arm 1: Currently on a prophylaxis regimen at least 2 times per week with a FVIII product or on an on-demand regimen with ≥12 bleeding episodes in the 12 months prior to Day 0 (Advate or rFVIIIFc)

For subjects entering Arms 2 or 3: Currently on an on-demand regimen with ≥12 bleeding\episodes in the 12 months prior to Day 0 (rFVIIIFc)

Inclusion Criteria for Perioperative Management (Surgery) Subgroup

Subjects from any of the 3 treatment arms were required to meet the following criteria in order to be eligible for the perioperative management subgroup:

1. Were to have major surgery (elective or emergent)

2. Had at least 12 rFVIIIFc EDs

3. Had a negative inhibitor test result following at least 12 rFVIIIFc EDs and within 4 weeks prior to surgery

4. Had completed, as a minimum, abbreviated PK sampling (up to 96 hours) obtained with rFVIIIFc at a dose of 50 or 65 IU/kg

In addition:

Subjects who required emergency major surgery were eligible to receive rFVIIIFc if: The surgery occurred within the same institution with which the Investigator was affiliated or a study specific contract/agreement

was in place with the separate institution, and The Investigator was available for consultancy through the intra-operative period.

Subjects with planned surgery and participating in the sequential PK subgroup were not to enter the perioperative management subgroup until repeat PK sampling was completed 12 to 24 weeks following the rFVIIIFc Day 0 PK profiling.

Exclusion Criteria

1. History of, or currently detectable inhibitor. A positive inhibitor value is ≥0.6 BU/mL (or any value greater than or equal to the lower sensitivity cut-off for laboratories with cut-offs for inhibitor detection between 0.7 and 1.0 BU/mL). In addition, the following documentation should be provided:

-at least 2 negative inhibitor tests prior to the screening test AND

-within the past 5 years (or since the start of treatment with FVIII or cryoprecipitate, if available) absence of clinical suspicion of inhibitors (from medical records and patient history- no evidence of decreased therapeutic response due to inhibitor and normal FVIII recovery, as available).

Family history of inhibitors will not exclude the subject.2. Other coagulation disorder(s) in addition to hemophilia A

3. History of hypersensitivity or anaphylaxis associated with any FVIII or IV immunoglobulin administration

4. For the PK subgroup only: known hypersensitivity to mouse or hamster proteins

5. Currently taking (or likely to require during the study) acetylsalicylic acid (ASA) or ibuprofen (other non-steroidal anti-inflammatory drugs are permitted)

6. Concurrent systemic treatment with immunosuppressive drugs 12 weeks prior to Day 0 (Advate or rFVIIIFc). (Exceptions: ribavirin, treatment of hepatitis C virus [HCV] and HIV and/or systemic steroids [a total of 2 courses of pulse treatments within 7 days ≤1 mg/kg] and/or inhaled steroids)

7. Major surgery within the previous 8 weeks

8. Unable to enter accurate and timely information regarding injections and bleeding episodes into an EPD and without adequate parental/caregiver support to manage this (per the Investigator's judgment)

9. Unable or unwilling to refrain from taking additional prophylactic doses of rFVIII prior to sports activities or an increase in physical activity

10. Current enrollment or enrollment within the past 30 days in any other clinical trial involving investigational drugs

11. Any concurrent clinically significant major disease or other unspecified reasons that, in the opinion of the Investigator, makes the subject unsuitable for participation in the study

12. Abnormal renal function (serum creatinine >2.0 mg/dL)

13. Serum alanine transaminase (ALT) or aspartate aminotransferase (AST) >5 upper limit of normal (ULN)

14. Serum bilirubin >3 ULN

Treatments

For subjects in the sequential PK subgroup, the 50 IU/kg dose for rFVIIIFc Day 0 and for rFVIIIFc at Week 14, or 12 to 24 weeks after rFVIIIFc Day 0, were slowly administered to the subject IV by hand over 5 (±2) minutes. For all other clinic administrations and at-home administration (i.e., self-administration), rFVIIIFc was to be injected IV over several minutes.

Arm 1, Individualized (Tailored) Prophylaxis

Initial twice weekly dosing with 25 IU/kg of rFVIIIFc on Day 1 and 50 IU/kg on Day 4, followed by individualized dose and interval modification within the range of 25 to 65 IU/kg every 3 to 5 days to maintain a trough level of 1% to 3% (or higher, as clinically indicated) rFVIIIFc activity; further increases to target trough level up to 5% as required for bleeding.

Sequential PK subgroup, at selected sites, for full PK profiling at Day 0 and 12 to 24 weeks after Day 0

Sequential PK: single dose of 50 IU/kg Advate (Advate Day 0) prior to the first dose of rFVIIIFc, followed by single dose of 50 IU rFVIIIFc (rFVIIIFc Day 0) within 8 weeks of Advate dose and following at least 96 hours washout from Advate or any other FVIII product. Second single dose of 50 IU rFVIIIFc at Week 14 or 12 to 24 weeks after rFVIIIFc Day 0 Prophylaxis

Arm 2, Weekly Prophylaxis

65 IU/kg rFVIIIFc every 7 days

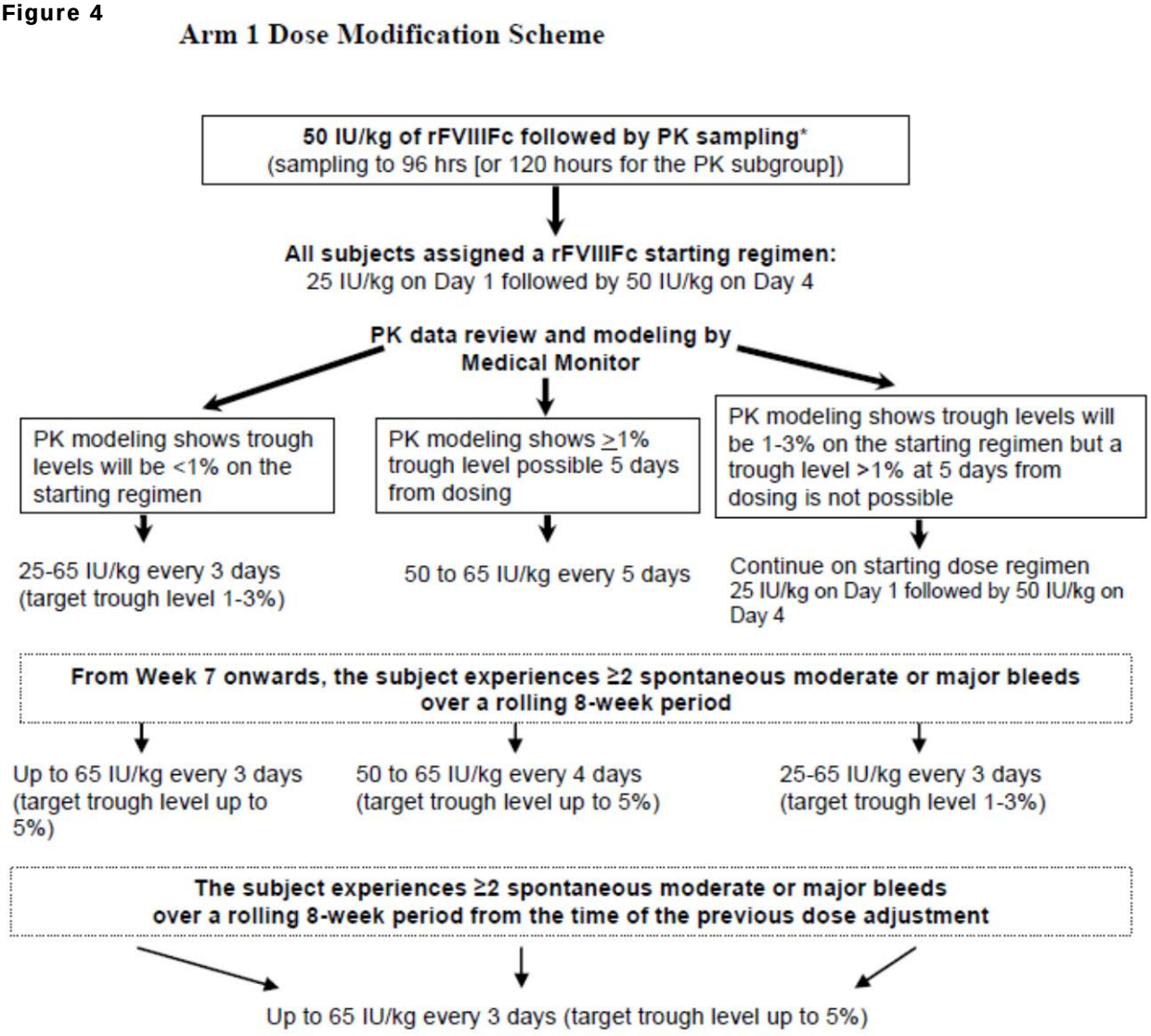
Arm 3, Episodic (On-Demand) Dosing

Initial single dose of 50 IU/kg rFVIIIFc followed by 10 to 50 IU/kg rFVIIIFc, as required to treat a bleeding episode

Modification of Dose and/or Dosing Interval for Subjects in Arm 1

For subjects in Arm 1 (individualized prophylaxis), PK data from samples collected following the first dose of rFVIIIFc at Day 0 were to be used to estimate the subject's PK parameters and to guide the appropriate dose or interval of dosing.

Figure 4



Bleeding episodes

From screening to first dose of rFVIIIFc, bleeding episodes were to be treated with the subject's previous FVIII product. After the first dose of rFVIIIFc, if a subject experienced bleeding of any kind (spontaneous or traumatic), rFVIIIFc was to be given at 10 to 50 IU/kg.

Treatment of Subjects in Perioperative Management (Surgery) Subgroup

In the case of minor surgery, subjects were to be treated with rFVIIIFc, according to local standard treatment guidelines for FVIII. Doses higher than 65 IU/kg were allowed in this study in cases of surgery or severe bleeding to achieve the required FVIII levels to control and prevent bleeding, while the maximum number of daily or every other day doses was not to exceed the Cmax of approximately 150% of normal (normal ranges are 50% to 150% FVIII activity).

Objectives

Primary Objectives

- To evaluate the safety and tolerability of rFVIIIFc administered as a prophylaxis, weekly, on-demand, and surgical treatment regimen
- To evaluate the efficacy of the rFVIIIFc tailored-prophylaxis regimen (Arm 1) To evaluate the efficacy of rFVIIIFc administered as an on-demand (Arm 3) and surgical treatment regimen

Secondary Objectives

- To characterize the PK profile of rFVIIIFc and compare the PK of rFVIIIFc with the currently marketed product, Advate
- To characterize the range of dose and schedules required to adequately prevent bleeding in a prophylaxis regimen (i.e., individualized prophylaxis and weekly prophylaxis); maintain hemostasis in a surgical setting (i.e., perioperative management); or to treat bleeding episodes in an on-demand, weekly treatment, or prophylaxis setting (i.e., episodic dosing, weekly prophylaxis, or individualized prophylaxis)

Outcomes/endpoints

Primary Endpoints

- Efficacy: Annualized number of bleeding episodes (spontaneous and traumatic) Arm 1 versus Arm 3
- Primary PK parameters were the following assessments of FVIII activity: dose-normalized area under the curve (DNAUC), half-life (t1/2), MRT, CL, and incremental recovery based on the one-stage clotting assay.
- *For* Safety and Tolerability: Clinically notable changes from baseline in physical examinations and vital signs Incidence of AEs, including clinically significant abnormal laboratory values Incidence of inhibitor development using the Nijmegen-modified Bethesda assay

Secondary Endpoints

- Annualized number of bleeding episodes (spontaneous and traumatic) Arm 2 versus Arm 3
- Total annualized rFVIIIFc consumption per subject
- Subjects' individual assessments of response to treatment with rFVIIIFc for bleeding episodes, using a bleeding response scale
- Investigators' assessment of subjects' response to treatment with rFVIIIFc for bleeding episodes treated in the clinic, using a bleeding response scale
- Annualized number of spontaneous bleeding episodes (joint, soft tissue, and muscle) per subject
- Annualized number of joint bleeding episodes (spontaneous and traumatic) per subject
- Time from last injection of rFVIIIFc to a bleeding episode
- Number of injections and dose per injection of rFVIIIFc required to resolve a bleeding episode (joint, soft tissue, and muscle)
- Additional parameters for PK assessments were to include but not be limited to: DNAUC, half-life, MRT, CL, and incremental recovery based on the two-stage chromogenic assay; volume of distribution (Vd), time at maximum activity (Tmax); and percent recovery for FVIII activity based on both the one-stage clotting assay and the two-stage chromogenic assay.

- QoL via hemophilia-specific health-related quality of life (HRQoL) questionnaire for children and parents (Haemo-QoL; for ages 13 to 16 years) or hemophilia-specific HRQoL questionnaire for adults (Haem-A-QoL; for ages 17 years and above)

Assessment of response was recorded using the following 4-point scale:

Excellent: bleeding episodes responded to less than or the usual number of injections or less than or the usual dose of rFVIIIFc, or the rate of breakthrough bleeding during prophylaxis was less than or equal to that usually observed.

Effective: most bleeding episodes responded to the same number of injections and dose, but some required more injections or higher doses, or there was a minor increase in the rate of breakthrough bleeding.

Partially Effective: bleeding episodes most often required more injections and/or higher doses than expected, or adequate breakthrough bleeding prevention during prophylaxis required more frequent injections and/or higher doses.

Ineffective: routine failure to control hemostasis or hemostatic control required additional agents.

Surgery Subgroup:

- Investigators'/Surgeons' assessments of subjects' response to surgery with rFVIIIFc, using a bleeding response scale.
- Number of injections and dose per injection required to maintain hemostasis during the surgical period
- Estimated blood loss during surgery
- Number and type of blood component transfusions required during surgery

Assessment of Clinical Response to rFVIIIFc Treatment for Bleeding

The following 4-point scale was used throughout the study for subjects' self-assessment of response to treatment with rFVIIIFc for bleeding episodes: Excellent, Good, Moderate, and No Response.

Excellent: abrupt pain relief and/or improvement in signs of bleeding within approximately 8 hours after the initial injection

Good: definite pain relief and/or improvement in signs of bleeding within approximately 8 hours after a single injection, but possibly requiring more than one injection after 24 to 48 hours for complete resolution

Moderate: probable or slight beneficial effect within approximately 8 hours after the initial injection and requires more than one injection

No response: no improvement, or condition worsens, within approximately 8 hours after the initial injection

Assessment of Response to Surgery

The Investigator/Surgeon who completed the surgical procedures was to assess the subject's response to surgery with rFVIIIFc treatment using a 4-point clinical scale as follows:

Excellent: Intraoperative and postoperative blood loss similar to (or less than) the nonhemophilic patient.

No extra doses of rFVIIIFc needed and Blood component transfusions required are similar to nonhemophilic patient

Good: Intraoperative and/or postoperative bleeding slightly increased over expectations for the nonhemophilic patient, but the difference was not clinically significant.

Intraoperative blood loss no more than 250 mL greater than expected for a nonhemophilic patient and

No extra doses of rFVIIIFc needed and Blood component transfusions required are similar to nonhemophilic patient

Fair: Intraoperative and/or postoperative blood loss is increased over expectation for the nonhemophilic patient and additional treatment was needed.

Intraoperative blood loss 250 to 500 mL greater than expected for person without hemophilia or

Extra dose of rFVIIIFc factor needed or Increased blood component transfusion requirement

Poor/none: Significant intraoperative and/or postoperative bleeding that was substantially increased over expectations for the nonhemophilic patient, required intervention, and was not explained by a surgical/medical issue other than hemophilia Intraoperative blood loss >500 mL greater than for the nonhemophilic patient or Unexpected hypotension or unexpected transfer to intensive care unit due to

bleeding or Substantially increased blood component transfusion requirement

Sample size

A sufficient number of subjects to assess the efficacy and safety of rFVIIIFc, would be approximately 144 subjects to be enrolled into 3 treatment arms per the designed allocation.

A key safety objective for any study of a new FVIII product is the evaluation of inhibitor development. Assuming that 2 or fewer subjects experience an inhibitor during the study (i.e., the observed incidence is less than or equal to 1.9% when using only the 104 subjects with at least 50 EDs in the denominator), then the upper bound of an exact (Clopper-Pearson) 2-sided, 95% CI would exclude 6.8%. Assuming that the true inhibitor incidence for the population eligible for this study is no greater than 1.0%, then there is at least 80% probability of no more than 2 subjects out of 144 developing an inhibitor.

The hypothesis test to compare the annualized bleeding rate between Arm 1 (individualized prophylaxis) and Arm 3 (episodic dosing) has greater than 90% power to detect a 60% reduction in annualized bleeding episodes (for example, from 10 to 4 bleeding episodes per subject per year) under the following conditions:

-The hypothesis test is conducted at the 2-sided 0.05 level of significance.

-A minimum of 1320 and 400 subject-weeks of follow-up are observed in Arm 1 and

-Arm 3, respectively. This would be surpassed if, for example, 104 subjects in Arm 1 and 20 subjects in Arm 3 are followed for bleeding episodes for at least 26 weeks.

-The true annualized bleeding rate for the population of subjects using episodic treatment is 10 bleeding episodes per subject per year or greater.

-To be considered of clinical importance, there must be at least a 50% reduction in the annualized bleeding rate.

Assuming the standard deviation of differences (rFVIIIFc – Advate) for the primary PK endpoints is no more than 0.45, then a comparison of log-transformed endpoints using an ANOVA model with factors for study treatment and subject will have at least 90% power to detect a 1.5-fold increase (rFVIIIFc over Advate) at the 2-sided, 0.05 level of significance.

Randomisation

Subjects presenting on an on-demand schedule who do not opt to enter Arm 1 will be randomized on enrollment into either Arm 2 or Arm 3. Randomization will be stratified according to the subject's annualized bleeding frequency, calculated based on bleeding episodes reported during the 12 months prior to screening:

1. 12 to 20 bleeding episodes per year

2. 21 to 50 bleeding episodes per year

3. >50 bleeding episodes per year

Blinding (masking)

This is an open-label study.

Statistical methods

Analysis Populations

The All-Enrolled Analysis Set was defined as subjects who were registered as enrolled by IXRS and assigned a unique subject identification number.

The Full Analysis Set (FAS) was defined as all subjects who received at least 1 dose of rFVIIIFc. The analysis of efficacy was performed in this population. Subjects who received a dose of Advate, but did not receive any rFVIIIFc, were not included in this population.

The Safety Analysis Set was defined as all subjects who received at least 1 dose of Advate or at least 1 dose of rFVIIIFc. The analysis of safety was performed in this population.

The Pharmacokinetic Analysis Set (PKAS) was defined as all subjects in Arms 1, 2, or 3 who had completed evaluable sampling timepoints (through at least the 48-hour timepoint for the Advate profile or the 72-hour timepoint for the rFVIIIFc PK profiling) to allow the acceptable determination of the terminal half-life.

The Sequential PK Subgroup was defined as subjects who had evaluable PK profiles for both Advate and baseline rFVIIIFc and/or evaluable PK profiles for both baseline rFVIIIFc and the repeat rFVIIIFc profile.

Annualized Measurements

The number of bleeding episodes was annualized for each subject using the following formula:

Annualized bleeding rate =Number of bleeding episodes during the efficacy period /Total number of days during the efficacy period × 365.25

Consumption

The total annualized rFVIIIFc consumption (IU/kg) was calculated for each subject using the following formula:

Annualized consumption = Total IU/kg of study drug received during the efficacy period/ total number of days during the efficacy period × 365.25

The total amount of rFVIIIFc received was the sum of the nominal IU/kg administered for each injection based on the units of rFVIIIFc as recorded from the subject's EPD and eCRF and his most recent weight.

Total annualized rFVIIIFc consumption was determined for the efficacy period (i.e., excluding the PK period, surgery/rehabilitation periods, minor surgeries, and procedures). Consumption for surgery/rehabilitation and minor surgeries or procedures was analyzed separately.

Handling of Missing Data

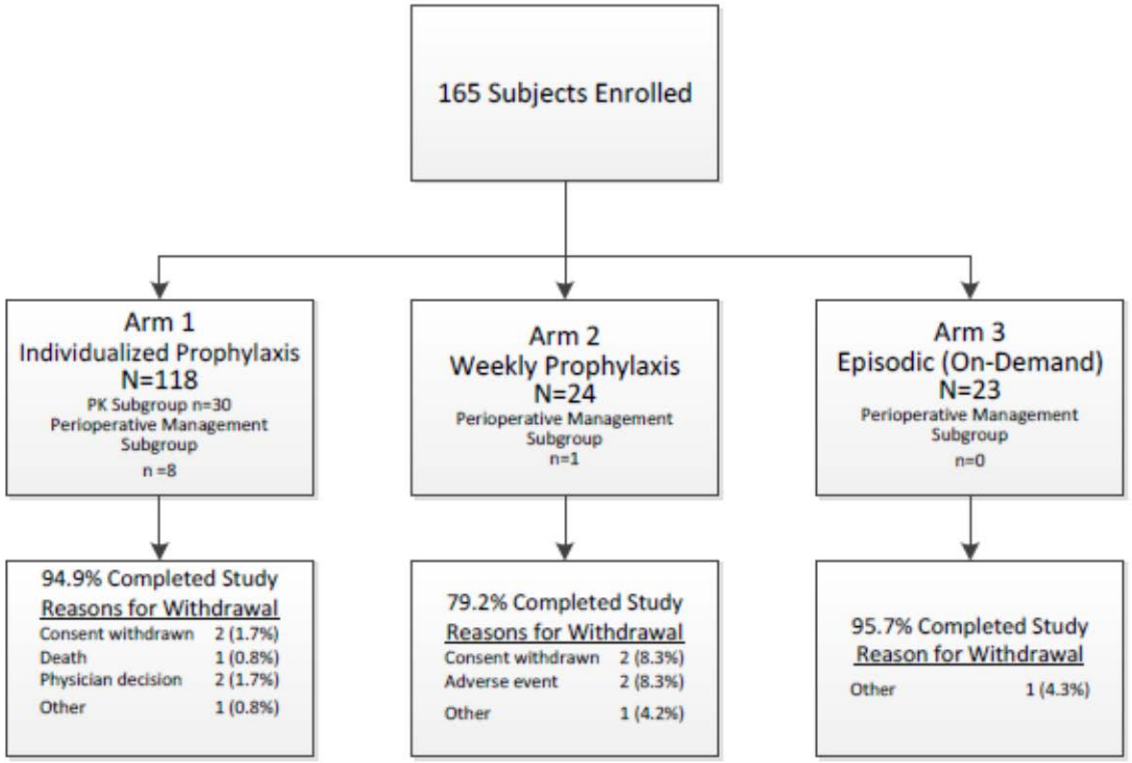
No imputation for missing data was applied for analyses of efficacy endpoints.

Primary efficacy endpoint; annualized number of breakthrough bleeding episodes (spontaneous and traumatic) during the efficacy period, referred to as an annualized bleeding rate.

Bleeding episodes classified as unknown were also included in the determination of the annualized bleeding rate. The comparison of annualized bleeding rates between Arm 1 (individualized [tailored] prophylaxis) and Arm 3 (episodic [on-demand] dosing) was assessed using a Poisson regression model with treatment arm as covariate. If the treatment factor in the Poisson regression model failed to show statistical significance at the 2-sided 5% level, then the study would have failed to demonstrate a difference between the individualized prophylaxis regimen and the episodic regimen. If the estimated ratio of annualized bleeding rates (individualized prophylaxis:episodic) is less than 0.5 (i.e., greater than a 50% reduction) clinical importance of the individualized prophylaxis regimen will have been demonstrated. If no overdispersion was detected at the 2-sided 5% level of significance (using the method of Wetherill and Brown [Wetherill and Brown 1991]), results from the Poisson regression model were to be used. Otherwise, a negative binomial model, which accounts for overdispersion, was to be used. Test results were tabulated by treatment arm along with the bleeding rate ratios and their 95% CI.

Results

Participant flow



Source: **Table 15**

Recruitment

A total of 165 male subjects were enrolled at 60 investigational sites in 19 countries worldwide.

The highest enrolling countries were the United States (54 subjects), United Kingdom (20 subjects), South Africa (17 subjects), India (15 subjects), and Japan (14 subjects)

Table 15 **Disposition**

Disposition
All-enrolled analysis set

	Arm 1 (N=118)	Arm 2 (N=24)	Arm 3 (N=23)	Total (N=165)
Number of subjects in each analysis set				
All enrolled	118	24	23	165
Full analysis set (a)	117 (99.2%)	24 (100.0%)	23 (100.0%)	164 (99.4%)
Subjects in the efficacy periods (b)	117 (99.2%)	23 (95.8%)	23 (100.0%)	163 (98.8%)
Safety analysis set (c)	118 (100.0%)	24 (100.0%)	23 (100.0%)	165 (100.0%)
PK analysis set (d)	110 (93.2%)	23 (95.8%)	22 (95.7%)	155 (93.9%)
Number of subjects enrolled in the sequential PK subgroup	30			30
Number of subjects evaluable for sequential PK subgroup (e)	29 (96.7%)			29 (96.7%)
Number of subjects who participated in surgery sub-group (f)	8 (6.8%)	1 (4.2%)	0	9 (5.5%)
Completion status				
Completed (g)	112 (94.9%)	19 (79.2%)	22 (95.7%)	153 (92.7%)
Discontinued prematurely	6 (5.1%)	5 (20.8%)	1 (4.3%)	12 (7.3%)
ADVERSE EVENT	0	2 (8.3%)	0	2 (1.2%)
DEATH	1 (0.8%)	0	0	1 (0.6%)
OTHER	1 (0.8%)	1 (4.2%)	1 (4.3%)	3 (1.8%)
PHYSICIAN DECISION	2 (1.7%)	0	0	2 (1.2%)
WITHDRAWAL BY SUBJECT (h)	2 (1.7%)	2 (8.3%)	0	4 (2.4%)

Footnotes are listed on the final page.

Source: Study 997HA301 Tables\T_DIS_ALL_IN_TEXT.SAS Date: 24JAN2013

A total of 153 subjects (92.7%) completed the study, and 12 subjects (7.3%) discontinued the study prematurely. The reasons for premature discontinuation were consent withdrawn (4 subjects, 2.4%), other (3 subjects, 1.8%), AEs (2 subjects, 1.2%), physician decision (due to concerns about patient compliance) [2 subjects, 1.2%], and death (1 subject, 0.6%)

Of the 3 subjects who discontinued for other reasons, 1 subject was incarcerated, 1 subject was traveling and could not ensure proper temperature conditions for study treatment, and 1 subject was not willing to reveal the reason for wanting to complete the early termination visit.

Of the 2 subjects who discontinued as a result of AEs, 1 subject experienced rash and 1 subject experienced a femur fracture. One additional subject experienced an AE (arthralgia) that resulted in discontinuation of study treatment; however, the reason for discontinuation was recorded as withdrawal of consent. Another subject experienced AEs that may have contributed to the subject's decision to withdraw consent.

Conduct of the study

Protocol Amendment 1 mainly introduced an increase to the sample size of Arm 1 from 66 to 104 subjects to ensure an adequate number of subjects with 50 EDs to support the evaluation of inhibitor development assuming that 2 or fewer subjects experience an inhibitor during the study (i.e., the observed incidence is less than or equal to 1.9%). The number of investigational sites was increased from 65 to approximately 75. The number of subjects who could be replaced was increased from 30 to 36.

Protocol Amendment 2 was made to reduce the required washout period from any FVIII product before collecting blood samples for PK assessment from 96 hours to 72 hours for adolescent subjects.

Protocol Amendment 3, introduced clarifications on end-of-study definition and criteria for recommending a modification of dose or dosing interval for subjects in Arm 1.

Baseline data

Table 16 **Demographics and Baseline Characteristics**

Demographics and baseline characteristic
Safety analysis set

	Arm 1 (N=118)	Arm 2 (N=24)	Arm 3 (N=23)	Surgery subgroup (N=9)	Total (N=165)
Age (years)					
n	118	24	23	9	165
Median	29.0	31.5	34.0	36.0	30.0
Min, Max	12, 65	18, 59	13, 62	26, 56	12, 65
Weight (kg)					
n	118	24	23	9	165
Median	71.65	75.85	70.00	77.20	71.60
Min, Max	42.0, 127.4	50.0, 105.0	48.0, 110.4	52.0, 104.0	42.0, 127.4
BMI (kg/m^2)					
n	118	24	23	9	165
Median	23.90	24.60	22.80	21.60	23.90
Min, Max	15.3, 37.1	18.8, 37.4	17.2, 35.6	17.0, 32.6	15.3, 37.4
Race					
White	79 (66.9%)	12 (50.0%)	16 (69.6%)	7 (77.8%)	107 (64.8%)
Black	7 (5.9%)	1 (4.2%)	2 (8.7%)	1 (11.1%)	10 (6.1%)
Asian	27 (22.9%)	11 (45.8%)	5 (21.7%)	1 (11.1%)	43 (26.1%)
Other	5 (4.2%)	0	0	0	5 (3.0%)
Geographic location					
Europe	34 (28.8%)	3 (12.5%)	4 (17.4%)	4 (44.4%)	41 (24.8%)
North America	44 (37.3%)	5 (20.8%)	7 (30.4%)	2 (22.2%)	56 (33.9%)
Other	40 (33.9%)	16 (66.7%)	12 (52.2%)	3 (33.3%)	68 (41.2%)

Footnotes are listed on the final page.

Source: Study 997HA301 Tables\T_DEM_SAF_IN_TEXT.SAS Date: 24JAN2013

A total of 153 subjects had a measured FVIII activity of <1% at either screening or baseline. Two additional subjects had a measured FVIII activity of <1% during the study period. All other subjects had either a genotype associated with severe haemophilia or a documented history of FVIII activity of <1% measured at the site. Ten subjects didn't have on-study FVIII activity of <1%; 2 were in Arm 2, and 8 were in Arm 1.

At study entry, 78 subjects (47.3%) were on a prior episodic regimen. The median number of bleeding episodes reported in the prior 12 months in the subjects on a prior episodic regimen in Arms 1 and 2 was similar to the median number of bleeding episodes reported in subjects in Arm 3. Within Arm 1, the median number of bleeding episodes reported in subjects on a prior episodic regimen was greater than the median number on prior prophylaxis (Table 17).

Table 17 Number of Bleeding Episodes in the Prior 12 Months

Prestudy FVIII Regimen	Arm 1 Individualized Prophylaxis (N=118)		Arm 2 Weekly Prophylaxis (N=24)		Arm 3 Episodic Dosing (N=23)	
	n	Median	n	Median	n	Median
Prophylaxis	86	6.0	0	--	0	--
Episodic	31	27.0	24	29.5	23	24.0

Note: The number of bleeding episodes in the prior 12 months was unknown for one subject in Arm 1.
Source: Table 58

There were fewer subjects with at least 1 target joint in Arm 1 (61.9%) than in Arms 2 and 3 (91.7% and 78.3%, respectively).

Table 18 Summary of Hemophilia History

Summary of hemophilia history
Safety analysis set

	Arm 1 (N=118)	Arm 2 (N=24)	Arm 3 (N=23)	Surgery subgroup (N=9)	Total (N=165)
Genotype (a)					
Intron 22 inversion	41/117 (35.0%)	7/ 21 (33.3%)	9/ 23 (39.1%)	2/ 9 (22.2%)	57/161 (35.4%)
Frameshift	24/117 (20.5%)	4/ 21 (19.0%)	6/ 23 (26.1%)	2/ 9 (22.2%)	34/161 (21.1%)
Missense	22/117 (18.8%)	4/ 21 (19.0%)	1/ 23 (4.3%)	3/ 9 (33.3%)	27/161 (16.8%)
Nonsense	19/117 (16.2%)	6/ 21 (28.6%)	1/ 23 (4.3%)	1/ 9 (11.1%)	26/161 (16.1%)
Splice site change	7/117 (6.0%)	0	4/ 23 (17.4%)	1/ 9 (11.1%)	11/161 (6.8%)
Intron 1 inversion	3/117 (2.6%)	0	1/ 23 (4.3%)	0	4/161 (2.5%)
Duplication	1/117 (0.9%)	0	0	0	1/161 (0.6%)
N/A	0	0	1/ 23 (4.3%)	0	1/161 (0.6%)
Von Willebrand factor (b)	118.0 (10, 327)	129.0 (48, 274)	131.0 (55, 380)	104.0 (10, 161)	118.0 (10, 380)
Blood type O (a)	46/118 (39.0%)	7/ 24 (29.2%)	10/ 23 (43.5%)	3/ 9 (33.3%)	63/165 (38.2%)
Est. bleeds prior 12 mths (b)	12.0 (0, 120)	29.5 (12, 59)	24.0 (12, 100)	17.0 (0, 120)	16.0 (0, 120)
Pre-study FVIII regimen (a)					
Prophylaxis	87/118 (73.7%)	0	0	4/ 9 (44.4%)	87/165 (52.7%)
On-demand	31/118 (26.3%)	24/ 24 (100.0%)	23/ 23 (100.0%)	5/ 9 (55.6%)	78/165 (47.3%)
>=1 target joints (a)	73/118 (61.9%)	22/ 24 (91.7%)	18/ 23 (78.3%)	5/ 9 (55.6%)	113/165 (68.5%)
Family history of inhibitor (a)	4/118 (3.4%)	1/ 24 (4.2%)	2/ 23 (8.7%)	0	7/165 (4.2%)
HIV positive (a)	25/118 (21.2%)	4/ 24 (16.7%)	7/ 23 (30.4%)	3/ 9 (33.3%)	36/165 (21.8%)
HCV positive (a)	55/118 (46.6%)	14/ 24 (58.3%)	13/ 23 (56.5%)	4/ 9 (44.4%)	82/165 (49.7%)

NOTE 1: Subjects in the surgery subgroup are also counted in the other arm in which they participated.
Each subject is counted once in the total column.
(a) Statistics are n/m (%) where m is the number of subjects with non-missing data.
(b) Statistics are median (minimum, maximum).

Source: Study 997HA301 Tables\T_HEM_HIST_SAF_IN_TEXT.SAS Date: 24JAN2013

At study entry, HIV status was positive in 36 subjects (21.8%) and HCV status was positive in 82 subjects (49.7%). Abnormalities of extremities/joints were reported in 98 subjects (60.1%). The other most frequent findings noted during the baseline physical examinations were musculoskeletal abnormalities, reported in 59 subjects (36.2%) and skin abnormalities, reported in 17 subjects (10.4%).

Protocol Deviations

Of the 67 subjects with major protocol deviations, 12 subjects (8.5%) were identified as having deviations that were considered to have a potential impact on the primary efficacy endpoint

Numbers analysed

Of the 164 subjects in the FAS, 1 subject in Arm 2 did not contribute data for the efficacy period since this subject withdrew after the PK evaluation and no efficacy evaluations could be made.

Therefore, efficacy endpoints were analyzed for 163 subjects: 117 in the individualized (tailored) prophylaxis (Arm 1), 23 in the weekly prophylaxis (Arm 2), and 23 in the episodic (on-demand) dosing (Arm 3).

The comparison of PK parameters between Advate and rFVIIIFc was performed using the sequential PK subgroup of Arm 1, which contained 29 evaluable subjects.

PK endpoints were analyzed using the PK Analysis Set, which included 155 subjects: 110 in Arm 1, 23 in Arm 2, and 22 in Arm 3.

Outcomes and estimation

Primary efficacy endpoints

Annualized Bleeding Rate per Subject and Comparison Between the Prophylaxis and Episodic Regimens Primary Endpoint: Arm 1 Versus Arm 3; Secondary Endpoint: Arm 2 Versus Arm 3

Table 19 **Annualized Bleeding Rates**

Annualized Bleeding Rate (Episodes/Year)	Arm 1 (N = 117) n (%)	Arm 2 (N = 24) n (%)	Arm 3 (N = 23) n (%)
0	53 (45.3%)	4 (17.4%)	0
>0-5	36 (30.8%)	11 (47.8%)	0
>5-10	21 (17.9%)	3 (13.0%)	1 (4.3%)
>10-20	7 (6.0%)	1 (4.3%)	2 (8.7%)
>20-30	0	2 (8.7%)	6 (26.1%)
>30-40	0	1 (4.3%)	7 (30.4%)
>40-50	0	0	2 (8.7%)
>50	0	1 (4.3%)	5 (21.7%)

Note: Efficacy endpoints were analyzed for 23 subjects in Arm 2; Subject 360-001 withdrew after the PK evaluations (no efficacy evaluations could be made).
Source: Table 81.

The annualized bleeding rate estimated from the negative binomial model was 2.91 (95% CI, 2.30, 3.68) in Arm 1, 8.92 (95% CI, 5.48, 14.51) in Arm 2, and 37.25 (95% CI, 24.03, 57.74) in Arm 3

The bleeding rate ratios obtained from the model were 0.08 ($p<0.001$) for Arm 1 versus Arm 3, and 0.24 ($p<0.001$) for Arm 2 versus Arm 3, indicating that the annualized bleeding rate was significantly reduced by 92% (Arm 1) and 76% (Arm 2) by using either the individualized prophylaxis or weekly prophylaxis compared with episodic treatment

Table 20 **Summary of Annualized Bleeding Episodes**

Summary of annualized bleeding episodes
Full analysis set
Page 1 of 3

	Arm 1 - Tailored prophylaxis (N=117)	Arm 2 - Weekly dosing (N=24)	Arm 3 - On demand (N=23)	Total (N=164)
Annualized bleeding episodes per subject (a)				
n	117	23	23	163
Mean (SD)	2.91 (3.925)	8.81 (13.690)	37.23 (20.208)	8.59 (15.222)
Median	1.60	3.59	33.57	2.76
25th, 75th percentile	0.00, 4.69	1.86, 8.36	21.14, 48.69	0.00, 7.62
Min, Max	0.0, 18.2	0.0, 58.0	9.8, 82.6	0.0, 82.6
Annualized bleeding episodes per subject based on last 6 months on study (subjects with >= 9 months on study)				
n	23	0	0	23
Mean (SD)	1.68 (4.061)			1.68 (4.061)
Median	0.00			0.00
25th, 75th percentile	0.00, 2.00			0.00, 2.00
Min, Max	0.0, 18.0			0.0, 18.0

Footnotes are listed on the final page.

Source: Study 997HA301 Tables\T_ANNUAL_BLEED_FAS.SAS Date: 24JAN2013

Secondary Efficacy Endpoints

Subjects' Assessments of Response to Treatment with rFVIIIFc for Bleeding Episodes

Overall, 77.6% of rFVIIIFc injections were rated by subjects as producing an excellent or good response. Responses were similar whether treatment occurred within 8 hours or after 8 hours from the onset of the bleeding episode.

Of a total of 880 injections for a bleeding episode in Arms 1, 2, and 3 during the study, 860 were evaluated for response ; 667 (77.6%) injections were rated by subjects as an excellent or good response, 187 (21.7%) were rated as moderate, and 6 (0.7%) were rated as no response

Table 21: Subject's Assessment of Response to rFVIIIFc Injections

Subject's assessment of response to rFVIIIFc injections
Full analysis set
Page 1 of 2

	Arm 1 - Tailored prophylaxis (N=117)		Arm 2 - Weekly dosing (N=24)		Arm 3 - On demand (N=23)		Total (N=164)	
To each injection for a bleeding episode								
Total number of injections	251		113		516		880	
Total number of injections evaluated	240		108		512		860	
Excellent or Good	189	(78.8%)	70	(64.8%)	408	(79.7%)	667	(77.6%)
Excellent	75	(31.3%)	17	(15.7%)	150	(29.3%)	242	(28.1%)
Good	114	(47.5%)	53	(49.1%)	258	(50.4%)	425	(49.4%)
Moderate	48	(20.0%)	37	(34.3%)	102	(19.9%)	187	(21.7%)
No response	3	(1.3%)	1	(0.9%)	2	(0.4%)	6	(0.7%)
To the first injection for each bleeding episode								
Total number of bleeds	209		92		456		757	
Total number of bleeds evaluated	202		89		454		745	

NOTE 1: Percentages are based on total number of injections evaluated (or bleeding episodes as appropriate) with a response within each arm or overall.
2: Subjects 500-003 (Arm 1) and 924-001 (Arm 3) had bleeds that were treated with non-study medication that are not evaluable for this analysis.

Source: Study 997HA301 Tables\T_SUBJ_ASSS_FAS.SAS Date: 24JAN2013

Annualized Bleeding Rates by Type and Location of Bleed

A low annualized bleeding rate was observed for spontaneous, joint, and spontaneous joint bleeding episodes in subjects on a prophylaxis regimen.

Consistent with the overall bleeding rate, the rate of both spontaneous and traumatic bleeding episodes was lower in the prophylactic arms compared to the episodic arm. A median of 0.00, 1.93, and 20.24 spontaneous bleeding episodes (mean of 1.70, 5.23, and 26.17) and a median of 0.00, 1.69, and 9.25 traumatic bleeding episodes (mean of 1.17, 3.58, and 10.84) were reported by subjects in Arms 1, 2, and 3, respectively. When summarized by location and type, the rate of spontaneous joint bleeding episodes was very low in the prophylactic arms, with a median of 0.00, 0.00, and 18.59 spontaneous bleeding episodes located in a joint (mean of 1.33, 4.15, and 21.10) reported by subjects in Arms 1, 2, and 3, respectively (Table 22).

Table 22: Summary of Annualized Bleeding Episodes Overall and by Location and Type of Bleeding Episode

Summary of annualized bleeding episodes overall and by location and type of bleeding episode
Full analysis set

	Arm 1 (N=117)	Arm 2 (N=24)	Arm 3 (N=23)
Number of subjects	117	23	23
Overall	1.60 (0.0, 18.2)	3.59 (0.0, 58.0)	33.57 (9.8, 82.6)
Joint	0.00 (0.0, 16.7)	1.93 (0.0, 50.2)	22.76 (5.9, 72.9)
Spontaneous	0.00 (0.0, 15.2)	0.00 (0.0, 30.9)	18.59 (1.7, 65.9)
Traumatic	0.00 (0.0, 7.5)	0.00 (0.0, 19.3)	3.93 (0.0, 45.3)
Muscle	0.00 (0.0, 6.6)	0.00 (0.0, 20.9)	5.57 (0.0, 27.6)
Spontaneous	0.00 (0.0, 6.6)	0.00 (0.0, 13.3)	5.13 (0.0, 16.6)
Traumatic	0.00 (0.0, 3.7)	0.00 (0.0, 7.6)	0.00 (0.0, 17.5)
Internal	0.00 (0.0, 2.0)	0.00 (0.0, 1.8)	0.00 (0.0, 7.5)
Spontaneous	0.00 (0.0, 2.0)	0.00 (0.0, 1.8)	0.00 (0.0, 7.5)
Traumatic	0.00 (0.0, 1.1)	0.00 (0.0, 1.7)	0.00 (0.0, 0.0)
Soft Tissue	0.00 (0.0, 5.2)	0.00 (0.0, 10.9)	0.00 (0.0, 12.9)
Spontaneous	0.00 (0.0, 3.5)	0.00 (0.0, 1.9)	0.00 (0.0, 9.2)
Traumatic	0.00 (0.0, 3.4)	0.00 (0.0, 10.9)	0.00 (0.0, 3.7)
Skin/mucosa	0.00 (0.0, 3.8)	0.00 (0.0, 5.7)	0.00 (0.0, 5.6)
Spontaneous	0.00 (0.0, 3.8)	0.00 (0.0, 5.7)	0.00 (0.0, 3.7)
Traumatic	0.00 (0.0, 2.4)	0.00 (0.0, 3.3)	0.00 (0.0, 3.5)

NOTE: Summary statistics are median (minimum, maximum)

Source: Study 997HA301 Tables\T_ANNUAL_BLEED_LOCTYP_FAS_IN_TEXT.SAS Date: 24JAN2013

Number of Injections and Dose per Injection for Resolution of a Bleeding Episode

Overall, 97.8% of bleeding episodes were controlled with ≤2 injections of rFVIIIFc, with 87.3% controlled by 1 injection. Per bleeding episode, the median dose per injection required for resolution of bleeding was 27.35 IU/kg, and the median total dose required was 28.23 IU/kg.

For resolution of each bleeding episode in Arms 1, 2, and 3, the median dose per injection was 29.94, 21.65, and 26.46 IU/kg, respectively, and the median total dose was 32.63, 30.26, and 27.35 IU/kg, respectively

The number of bleeding episodes requiring a second injection was small (96 bleeding episodes overall for 46 subjects), with the median interval per bleeding episode of 30.9 hours overall and 27.5, 27.5, and 36.0 hours for Arms 1, 2, and 3, respectively

Table 23: Summary of Number of Injections Required for Resolution of a Bleeding Episode

Summary of number of injections required for resolution of a bleeding episode
Full analysis set
Page 1 of 3

Method of analysis	Arm 1 - Tailored prophylaxis (N=117)	Arm 2 - Weekly dosing (N=24)	Arm 3 - On demand (N=23)	Total (N=164)
Per bleeding episode (a)				
1	179 (85.6%)	74 (80.4%)	408 (89.5%)	661 (87.3%)
2	23 (11.0%)	15 (16.3%)	41 (9.0%)	79 (10.4%)
3	5 (2.4%)	3 (3.3%)	5 (1.1%)	13 (1.7%)
4	0	0	0	0
>4	2 (1.0%)	0	2 (0.4%)	4 (0.5%)
1	179 (85.6%)	74 (80.4%)	408 (89.5%)	661 (87.3%)
>1	30 (14.4%)	18 (19.6%)	48 (10.5%)	96 (12.7%)
<=2	202 (96.7%)	89 (96.7%)	449 (98.5%)	740 (97.8%)
>2	7 (3.3%)	3 (3.3%)	7 (1.5%)	17 (2.2%)
n (b)	209	92	456	757
Mean (SD)	1.2 (0.60)	1.2 (0.49)	1.1 (0.45)	1.2 (0.51)
Median	1.0	1.0	1.0	1.0
25th, 75th percentile	1.0, 1.0	1.0, 1.0	1.0, 1.0	1.0, 1.0
Min, Max	1, 6	1, 3	1, 6	1, 6

Footnotes are listed on the final page.

Source: Study 997HA301 Tables\T_INJECT_RESOL_FAS.SAS Date: 24JAN2013

Table 24: Summary of Dose (IU/kg) of rFVIIIFc for Resolution of Bleeds

Summary of dose (IU/kg) of rFVIIIFc for resolution of bleeds
Full analysis set
Page 1 of 3

Method of analysis Dose calculation	Arm 1 - Tailored prophylaxis (N=117)	Arm 2 - Weekly dosing (N=24)	Arm 3 - On demand (N=23)	Total (N=164)
Per bleeding episode				
Average dose per injection				
n (a)	208	92	455	755
Mean (SD)	36.70 (14.141)	30.11 (15.950)	28.64 (9.914)	31.04 (12.538)
Median	29.94	21.65	26.46	27.35
25th, 75th percentile	24.49, 50.93	19.84, 32.47	21.51, 31.45	22.73, 32.71
Min, Max	11.5, 68.3	6.4, 69.2	2.7, 69.8	2.7, 69.8
Total dose (b)				
n (a)	208	92	455	755
Mean (SD)	44.53 (28.331)	36.02 (22.916)	32.63 (18.454)	36.33 (22.707)
Median	32.63	30.26	27.35	28.23
25th, 75th percentile	25.30, 53.11	20.16, 42.34	22.59, 32.71	23.26, 46.88
Min, Max	11.5, 223.1	6.4, 138.5	2.7, 184.6	2.7, 223.1

Footnotes are listed on the final page.

Source: Study 997HA301 Tables\T_MEAN_DOSE_FAS.SAS Date: 24JAN2013

QoL Questionnaires

For subjects from Arm 1 aged 17 years and older The median change from baseline to Week 28 suggests that subjects on a prior episodic regimen reported an improvement in their QoL in the domains of physical health (-25.00), feelings (-6.25), and work and school (-6.25) . There was no change in QoL for subjects switching from a prior prophylaxis regimen.

For subjects from Arm 2 and 3 aged 17 years and older

At Week 14 there was an improvement in QoL for subjects in Arm 2 in the domains of physical health (-10.00), feelings (-6.25), and sports and leisure (-10.00). These changes were also evident at Week 28, although there were fewer subjects who completed the questionnaire at this timepoint. For subjects in Arm 3, there was an improvement in the domain of feelings at Week 14 (-6.25) that was not evident at Week 28

EQ-5D Questionnaire

The EQ-5D visual analogue scale recorded a response from 0 to 100 representing a subject's overall self-rated health state with high scores indicating better QoL. The EQ-5D visual analogue scale was performed at Screening and Weeks 14, 28, 38, and 52.

Across all arms, there was a small increase from baseline in the EQ-5D visual analogue scale that ranged from 1.6 to 4.4. Results were similar when summarized by prior regimen. The small magnitude of the change across all arms indicates that QoL as recorded by the EQ-5D visual analogue scale remained stable over the

course of the study. These results are consistent with expectations given the short timeframe between baseline and end-of-study assessments for most subjects and the fact that the EQ-5D is a general instrument and not designed specifically for patients with hemophilia.

Perioperative Management (Surgery) Subgroup

Major Surgery

A total of 9 major surgeries were performed in 9 subjects.

Hemostasis was rated as excellent or good by the Investigators/Surgeons for 9 major surgeries, indicating that intraoperative and postoperative blood loss was comparable to what would be expected for a subject who does not have hemophilia. Assessment of hemostasis was to be recorded by Investigators/Surgeons approximately 24 hours postoperatively

Blood loss was estimated for 7 of the 9 surgeries. The median estimated blood loss was 15.0 mL during major surgery and 0.0 mL postoperatively (i.e., from the day following the day of surgery until discharge from the hospital); the mean estimated blood loss was 166.7 mL during major surgery and 214.3 mL postoperatively. A single subject required transfusion during the surgical period.

Overall, 100% of major surgeries required a single injection of rFVIIIFc to maintain hemostasis, and the median dose per injection was 51.4 IU/kg. On the day of surgery, most subjects received 2 injections with the total dose ranging from 65.8 to 115.4 IU/kg/day.

The median rFVIIIFc consumption was 80.55 IU/kg on the day of major surgery, 161.29 IU/kg for the first 3 days following the day of surgery, 387.10 IU/kg for Days 4 through 14 following surgery, and 539.03 IU/kg for the first 14 days following the day of surgery. No subject reported a bleeding episode during the postoperative/rehabilitation period

Table 25 **Listing of Major Surgery Information – Hemostatic Response to Treatment and Consumption**

Listing of major surgery information - hemostatic response to treatment and consumption
Surgery subgroup

Subject number/ Country	Surgical procedure	Response (b)	Days subject spent in the time interval: Days 1-3 post	Days subject spent in the time interval: Days 4-14 post	rFVIIIFc administered (IU/kg/day) (a) (total number of injections): Day of surgery (c)	rFVIIIFc administered (IU/kg/day) (a) (total number of injections): Days 1-3 post	rFVIIIFc administered (IU/kg/day) (a) (total number of injections): Days 4-14 post
300-002/ DEU	Laparoscopic inguinal hernia repair right	Excellent	3	3	68.8 (2)	29.2 (3)	9.4 (1)
301-002/ DEU	Laparoscopic inguinal hernia (right) surgery	Good	3	11	86.0 (2)	53.8 (6)	35.2 (14)
340-005/ IND	Bilateral knee joint replacement under genral anesthesia.	Excellent	3	11	77.6 (2)	37.4 (6)	36.1 (22)
401-001/ ITA	Toral right knee replacement. for this surgical procedure of total right knee replacement anesthetic was used as cm	Excellent	3	11	115.4 (2)	76.9 (6)	55.9 (16)
500-001/ ZAF	Knee replacement	Excellent	3	11	83.1 (2)	44.8 (4)	38.5 (18)

Footnotes are listed on the final page.

Source: Study 997HA301 Listings\L_SURG_HEMO_RESP_SUBGRP_IN_TEXT.SAS Date: 05FEB2013

Listing of major surgery information - hemostatic response to treatment and consumption
Surgery subgroup

Subject number/ Country	Surgical procedure	Response (b)	Days subject spent in the time interval: Days 1-3 post	Days subject spent in the time interval: Days 4-14 post	rFVIIIFc administered (IU/kg/day) (a) (total number of injections): Day of surgery (c)	rFVIIIFc administered (IU/kg/day) (a) (total number of injections): Days 1-3 post	rFVIIIFc administered (IU/kg/day) (a) (total number of injections): Days 4-14 post
500-013/ ZAF	Appendicectomy	Excellent	3	11	65.8 (1)	15.3 (2)	10.7 (3)
520-001/ ESP	Arthroscopy	Excellent	3	9	77.5 (2)	56.5 (4)	21.3 (7)
900-005/ USA	Total right knee replacement	Excellent	3	11	101.7 (2)	79.1 (5)	66.3 (13)
900-009/ USA	Right total knee revision	Excellent	3	11	80.5 (2)	59.9 (4)	32.7 (11)

NOTE: 1: DEU=Germany, ESP=Spain, IND=India, ITA=Italy, USA=United States, ZAF=South Africa.
(a) Total dose administered for any reason during this interval of time divided by the number of days the subject was in the surgical/rehabilitation period for this interval of time.
(b) The first post-surgery assessment of hemostasis by the surgeon/investigator.
(c) The day of surgery includes pre-surgery injections of rFVIIIFc even if administered on the previous day.

Source: Listings\L_SURG_HEMO_RESP_SUBGRP_IN_TEXT.SAS Date: 05FEB2013

Minor Surgeries

A total of 17 minor surgeries were performed in 15 subjects during the study: 7 surgeries in Arm 1, 5 in Arm 2, and 5 in Arm 3. Twelve subjects received rFVIIIFc for perioperative management (surgical prophylaxis) in 14 minor surgical procedures; the remaining 3 minor procedures were performed prior to the first dose of rFVIIIFc. Surgeons' assessments of hemostasis were collected at least 24 hours following the procedure for 12 minor surgeries. Hemostasis was rated as excellent for 11 minor surgeries and as good for 1 minor surgery.

Subject Number	Description of Surgery	Response
Arm 1		
300-002	Tooth extraction	
343-001	Tooth extraction	Excellent
423-001	Tooth extraction	Excellent
424-001	Tooth extraction	Excellent
501-001	Surgical removal of wisdom teeth	Excellent
520-001	Tooth extraction	Excellent
907-005	Surgical extraction of complete bony impacted tooth	Good
Arm 2		
120-001	Steristrips applied for wound closure after stabbing base of thumb with knife	
120-002	Cytoscopy, left retrograde pyelogram	Excellent
	Cytoscopy, removal left uretic stent	Excellent
	Cytoscopy, removal left uretic stent	Excellent
500-014	Yttrium synoviothesis*	
Arm 3		
122-002	Dental procedure with deep injection	Excellent
140-002	Gastroscopy and colonoscopy	Excellent
360-004	Tooth 15 extraction	Excellent
500-011	Yttrium synoviothesis*	
500-015	Yttrium synoviothesis*	

*Surgery occurred before the subject received a dose of rFVIIIFc.
Source: Table 13, Appendix 16.2.6.

Exploratory Endpoints

Investigators' Global Assessment of Subjects' Response to rFVIIIFc

The Investigators' global assessment of the subjects' response to their rFVIIIFc regimen was excellent or effective for 99.3% of the subjects' visits.

During the 5 visits in which data were collected, the Investigators' global assessment of the subjects' response to their rFVIIIFc regimen was excellent for 69.5% of the visits, effective for 29.8% of the visits, and partially effective for 0.7% of the visits. There were no subjects whose response to the rFVIIIFc regimen was assessed as ineffective at any visits The assessments remained consistent over the course of the study. The global response to the rFVIIIFc regimen was assessed as excellent or effective for 99.4% of subjects (154 of 155 subjects) at Week 7, for 98.7% of subjects (152 of 154 subjects) at Week 14, for 100.0% of subjects (90 of 90 subjects) at Week 28, for 100.0% of subjects (19 of 19 subjects) at Week 38, and for 100.0% of subjects (12 of 12 subjects) at Week 52.

Ancillary analyses

Summary of Annualized Bleeding Rates by Hemophilia Characteristics

Subjects were grouped by frequency of prior bleeding episodes, and for all groups there was a lower annualized bleeding rate for subjects on a prophylaxis regimen, relative to episodic treatment . Distribution of subjects within categories of the number of bleeding episodes was variable across arms. The percentage of subjects in Arms 1, 2, and 3 who had the highest pre-study bleeding frequency (>50 bleeding episodes) was 6%, 13%, and 17%, respectively, and their median annualized bleeding rates were 5.89, 1.93, and 52.09 (mean rates of 6.13, 3.43, and 51.49), respectively.

Because the number of bleeding episodes in Arms 1 and 2 in the prior 12 months is dependent on the subjects' previous treatment regimen, change in annualized bleeding rates was evaluated separately for prior prophylaxis and episodic treatment. When compared with the number of bleeding episodes in the 12 months prior to study start, based on subject-reported historical data, the observed annualized bleeding rates for subjects on a prior prophylaxis regimen showed a decrease in their annualized bleeding rates from their prior frequency of bleeding. Subjects on a prior episodic regimen had a decrease in their annualized bleeding rate when treated with a prophylaxis regimen on study (Table 26).

Table 26 Number of Bleeding Episodes in the Prior 12 Months Compared With the On-Study Annualized Bleeding Rate by Prestudy FVIII Regimen

Prestudy FVIII Regimen	Arm 1 (N = 117)	Arm 2 (N = 24)	Arm 3 (N= 23)
Prophylaxis			
n	85		
Baseline median	6.00		
On-study median	2.32		
Median difference	-3.00		
Episodic			
n	31	23	23
Baseline median	27.0	29.00	24.00
On-study median	0.00	3.59	33.57
Median difference	-27.00	-22.38	0.62

Note: One subject in Arm 1 had missing information regarding the bleeds in the 12 months prior to study; and 1 subject in Arm 2 withdrew after the PK evaluations and no efficacy assessments could be made.
Source: Table 91.

Among the subjects who participated in the efficacy period, there were 111 with target joints at Screening (61.5% of Arm 1, 91.3% of Arm 2, and 78.3% of Arm 3) and 52 with no target joints at Screening (38.5% of Arm 1, 8.7% of Arm 2, and 21.7% of Arm 3). The median annualized bleeding rates for subjects with no target joints present were 0.00, 20.32, and 28.45 (means of 1.85, 20.32, and 27.04) in Arms 1, 2, and 3, respectively. Out of 111 subjects with target joints, 69 subjects had less than or equal to the median number (38% of Arm 1, 61% of Arm 2, and 48% of Arm 3), and 42 subjects had greater than the median number (24% of Arm 1, 30% of Arm 2, and 30% of Arm 3). The median annualized bleeding rates in Arms 1, 2, and 3 for subjects with less than or equal to the median number of target joints were 1.50, 3.64, and 45.42 (means of 2.96, 9.84, and 44.18), respectively; the median annualized bleeding rates for subjects with greater than the median number of target joints were 3.68, 2.01, and 32.04 (means of 4.55, 3.48, and 33.60), respectively.

Summary of Annualized Bleeding Rates by Age

Thirteen subjects aged 12 through 17 years (9% of Arm 1 and 9% of Arm 3),149 subjects aged 18 through 64 years (90% of Arm 1, 96% of Arm 2, and 91% of Arm 3), and 1 subject aged ≥65 years (1% in Arm 1) contributed data in the efficacy period. For subjects aged 12 through 17 years, the median annualized bleeding rates were 1.92 and 28.85 (mean rates of 2.63 and 28.85) in Arms 1 and 3, respectively. For subjects aged 18 through 64 years, the median annualized bleeding rates were 1.44, 3.59, and 33.57 (mean rates of 2.88, 8.81, and 38.03) in Arms 1, 2, and 3, respectively

Summary of main study

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 27 Summary of Efficacy for trial 997HA301

Title: Safety, PK and Efficacy of Recombinant Factor VIII Fc Fusion Protein (rFVIIIFc) in the Prevention and Treatment of Bleeding in Previously Treated Subjects With Severe Hemophilia A		
Study identifier	997HA301	
Design	An Open-label, Multicenter, partially randomized study; uncontrolled, overall active comparator Advate for PK only	
	Duration of main phase: Duration of Run-in phase: Duration of Extension phase:	Up to 75 weeks for patients in the PK subgroup Up to 67 weeks for all other patients not applicable
Hypothesis	Efficacy of efmoroctocog alfa in individualised, routine weekly prophylaxis, on-demand prophylaxis	
Treatments groups	Arm 1 Individualised prophylaxis -and PK subgroup	In the PK subgroup 50 IU/kg dose of rFVIIIFc Individualised (tailored) prophylaxis: Initial twice weekly dosing with 25 IU/kg of rFVIIIFc on day 1 and 50 IU/kg of rFVIIIFc on day 4 followed by individualised dose in the range of 25 – 65 IU/kg every 3-5 days

	Arm 2 Weekly prophylaxis		65 IU/kg rFVIIIFc every 7 days
	Arm 3 Episodic (on-demand) prophylaxis		Initial single dose of 50 IU/kg rFVIIIFc followed by 10 to 50 IU/kg rFVIIIFc, as required to treat a bleeding episode
Endpoints and definitions	Primary endpoint	Efficacy PK Safety	Annualized number of bleeding episodes (spontaneous and traumatic) Arm 1 vs Arm 3 Dose-normalized area under the curve (DNAUC), half-life (t1/2), MRT, CL, and incremental recovery based on the one-stage clotting assay. Clinically notable changes from baseline in physical examinations and vital signs Incidence of AEs, including clinically significant abnormal laboratory values Incidence of inhibitor development using the Nijmegen-modified Bethesda assay
	Secondary endpoint	Efficacy PK	Annualized number of bleeding episodes (spontaneous and traumatic) Arm 2 vs Arm 3 -Total annualized rFVIIIFc consumption per subject -Subjects' assessment of response to treatment for bleeding episodes using a response scale -Investigators' assessment of subjects' response to treatment for bleeding episodes using a bleeding response scale -Annualized number of spontaneous bleeding episodes (joint, soft tissue, and muscle) per subject -Annualized number of joint bleeding episodes (spontaneous and traumatic) per subject -Time from last injection of rFVIIIFc to a bleeding episode -Number of injections and dose per injection of rFVIIIFc required to resolve a bleeding episode (joint, soft tissue, and muscle) - DNAUC, half-life, MRT, CL, and incremental recovery based on the two-stage chromogenic assay; volume of distribution (Vd), time at maximum activity (Tmax); % recovery for FVIII activity based on both the one-stage clotting assay and the two-stage chromogenic assay.

	Secondary endpoint	Efficacy / QoL	QoL via hemophilia-specific health-related quality of life (HRQoL) questionnaire for children and parents (Haemo-QoL; for ages 13 to 16 years) or hemophilia-specific HRQoL questionnaire for adults (Haem-A-QoL; for ages 17 years and above)
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Results and Analysis

Analysis description	**Primary Analysis**			
Analysis population and time point description	FAS			
Descriptive statistics and estimate variability	Treatment group	Arm 1	Arm 2	Arm 3
	Number of subject	117	24	23
	Annualised bleeding rate [negative binomial model] Mean (SD)	2.91 (3.92)	8.92 (13.69)	37.25 (20.21)
	95% CI	(2.30, 3.68)	(5.48, 14.51)	(2.30, 3.68)

Effect estimate per comparison	PK	Comparison groups	rFVIIIFc vs Advate
		Cmax (IU/dL), mean ratio	0.95
		95% CI	(0.73, 1.24)
		DNAUC (IU*h/dl per IU/kg) mean ratio	1.69
		95% CI	(1.54, 1.85)
	,	half-life (t1/2), Mean ratio	1.53 (1.34, 1.74)
		MRT, mean ratio 95% CI	1.57 (1.47, 1.67)
		CL, Mean ratio 95% CI	0.59 (0.54, 0.65)
		IV Mean ratio 95% CI	0.97 (0.90, 1.05)
	treatment of bleeds tailored prophylaxis	response was assessed as “excellent” or “good” for more than 80% of first rFVIIIFc injections in the treatment arms More than 80% of the occurred bleeds were treated with one injection with a median dose of ~25-30 IU/kg in subjects ≥12 years	

	Treatment of bleeds – surgical	Median surgical rFVIIIFc consumption 763.99 IU/kg 22 major surgeries; haemostasis “excellent” or “good”
Notes	<free text>	
Analysis description	**<Secondary analysis> <Co-primary Analysis> <Other, specify: >**	

Clinical study 8HA02PED

An Open-Label, Multicenter Evaluation of Safety, Pharmacokinetics, and Efficacy of Recombinant Coagulation Factor VIII Fc Fusion Protein, BIIB031, in the Prevention and Treatment of Bleeding Episodes in Pediatric Subjects With Hemophilia A This study was conducted to assess the PK, efficacy, and safety of rFVIIIFc in previously treated pediatric patients <12 years of age with hemophilia A.

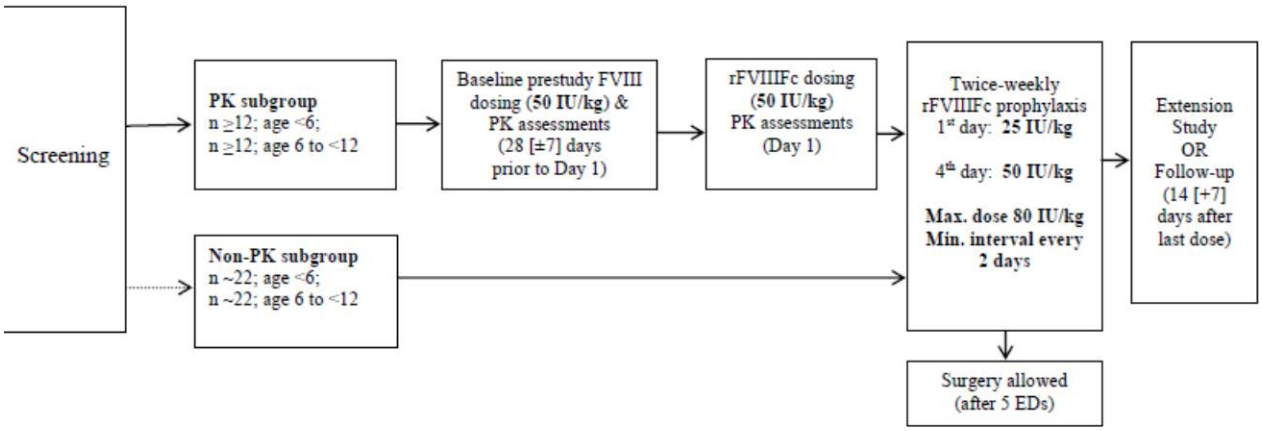
Methods

Inhibitor History and Testing

Subjects were tested for inhibitor formation at each clinic visit prior to dosing.

Testing for inhibitors was conducted within the first 10 to 15 EDs to rFVIIIFc. A Washout Period of at least 48 hours was required prior to inhibitor testing. A positive result for inhibitor development is any inhibitor (≥0.6 Bethesda units [BU]/mL) identified and confirmed on 2 separate samples drawn approximately 2 to 4 weeks apart. A low-titer inhibitor is defined as ≥0.6 but <5.0 BU/mL that was identified and confirmed on 2 separate samples drawn approximately 2 to 4 weeks apart. A high-titer inhibitor is defined as ≥5.0 BU/mL that was identified and confirmed on 2 separate samples drawn approximately 2 to 4 weeks apart.

Figure 5 Study Design



Source: Study 8HA02PED Protocol Version 3
ED = exposure day; FVIII = factor VIII; max. = maximum; min. = minimum; PK = pharmacokinetic; rFVIIIFc = recombinant coagulations factor VIII Fc fusion protein.

Bleeding and Treatment for Bleeding Episodes

The occurrence of bleeding in this study was obtained from EPDs and any medical records while the subject was receiving study treatment. The clinical sites and monitors ensured that there was consistency between the subject's medical record, source documents, EPDs, and eCRFs. During the clinical visits and telephone calls with the subject's caregiver once a month, the Investigator verified whether or not a bleeding episode had occurred and, if so, whether the bleed was "spontaneous" or "traumatic." If, following this discussion, the Investigator judged that the subject's caregiver classification was incorrect, the Investigator documented it in (1) the subject's medical notes with the rationale for the new classification and (2) the eCRF, documenting the new classification of the bleeding episode according to the Investigator and whether or not the subject's caregiver agreed with this new classification. With regard to dose changes, the Investigator's classification of "spontaneous" or "traumatic" was used (if different from the classification recorded in the EPD by the caregiver). Data from both spontaneous bleeding episodes and traumatic bleeding episodes were collected.

Each subject's caregiver rated the treatment response to rFVIIIFc to any bleeding episodes using the following 4-point scale:

- Excellent: abrupt pain relief and/or improvement in signs of bleeding within approximately 8 hours after the initial injection

- Good: definite pain relief and/or improvement in signs of bleeding within approximately 8 hours after a single injection but possibly requiring more than 1 injection after 24 to 48 hours for complete resolution

-Moderate: probable or slight beneficial effect within approximately 8 hours after the initial injection and required more than 1 injection

- None: no improvement or condition worsened within approximately 8 hours after the initial injection

Response could have also been assessed by the Physician/Investigator for those subjects who were treated in the clinic or hospital with rFVIIIFc for major bleeding episodes or postsurgery until discharge from the hospital.

Physician's Global Assessment

Investigators recorded assessments of each subject's response to his assigned rFVIIIFc regimen using the following 4-point scale:

- Excellent: Bleeding episodes responded to less than or equal to the usual number of injections or less than or equal to the usual dose of rFVIIIFc or the rate of breakthrough bleeding during prophylaxis was less than or equal to that usually observed.

- Effective: Most bleeding episodes responded to the same number of injections and dose, but some required more injections or higher doses, or there was a minor increase in the rate of breakthrough bleeding.

-Partially Effective: Bleeding episodes most often required more injections and/or higher doses than expected, or adequate breakthrough bleeding prevention during prophylaxis required more frequent injections and/or higher doses.

-Ineffective: Routine failure to control hemostasis or hemostatic control required additional agents

Study participants

Inclusion Criteria at the time of screening were:

1. Ability of parent or legal guardian to understand the purpose and risks of the study and provide signed and dated informed consent and authorization to use protected health information in accordance with national and local subject privacy regulations. Subjects may have provided assent in addition to the parental/guardian consent, if appropriate.

2. Male, <12 years of age, and weight ≥13 kg.

3. Severe hemophilia A defined as <1 IU/dL (<1%) endogenous FVIII as documented in medical records from a local clinical laboratory demonstrating <1% FVIII:C or a documented genotype known to produce severe hemophilia A.

Previously treated subject, defined as having at least 50 EDs to any recombinant or plasma-derived FVIII product including cryoprecipitate (blood products including fresh frozen plasma treatment was not considered in the count of the documented EDs).

5. If known to be human immunodeficiency virus (HIV) positive, the following laboratory values were required, based on results within last 6 months:

- platelet count ≥100,000 plts/μL
- CD4 count ≥200 cells/μL
- viral load of <400 copies/mL

6. No history of, or currently detectable, inhibitor. This included the following:

- at least 2 negative inhibitor tests from the reporting laboratory AND/OR normal recovery tests within the first 50 EDs to FVIII products
  AND
- absence of clinical signs of decreased response to FVIII administrations Historical positive inhibitor test was defined as per local laboratory Bethesda value for positive inhibitor test (i.e., equal to or above lower level of detection). Family history of inhibitors would not exclude the subject.

7. No measurable inhibitor activity using the Nijmegen-modified Bethesda assay (≥0.6 BU/mL is considered positive) at Screening.

8. Willingness and ability of the subject's parent or legal guardian to complete training in the use of the study electronic patient diary (EPD) and to use the EPD throughout the study.

Exclusion Criteria were:

1. Other coagulation disorder(s) in addition to hemophilia A.
2. History of anaphylaxis associated with any FVIII or IV immunoglobulin administration.
3. Active renal disease (per the discretion of the Investigator and medical records).
4. Active hepatic disease (per the discretion of the Investigator and medical records).
5. Any concurrent clinically significant major disease that, in the opinion of the Investigator, would have made the subject unsuitable for enrollment.
6. Current systemic treatment with chemotherapy and/or other immunosuppressant drugs, with the following exceptions: use of steroids for treatment of asthma or management of acute allergic episodes, and routine immunizations.
7. Participation within the past 30 days in any other clinical study involving investigational drugs.
8. Surgery within 30 days prior to the Screening Visit (visit could be rescheduled and subject screened).

Treatments

The starting dose regimen for this study was 25 IU/kg on Day 1 and 50 IU/kg on Day 4 rFVIIIFc administered twice weekly and was selected based on data from adult subjects who participated in the rFVIIIFc Phase 1 studyProphylactic dose and interval adjustments were made as follows:

-The dose was increased or decreased in increments of at least 5 IU/kg.

-The maximum prophylactic dose that was given was 80 IU/kg/injection.

-The dosing interval was shortened based on the subject's rFVIIIFc PK results, FVIII trough level, and clinical bleeding profile. The shortest dosing interval allowed was every 2 days if it was necessary in order to maintain adequate FVIII activity trough levels and to prevent spontaneous bleeding events.

The maximum dose used for treatment of bleeding and surgery was expected to be 100 IU/kg.

In the case of minor surgery, subjects were treated with rFVIIIFc during the minor intervention, according to local standard treatment guidelines for FVIII.

Subjects who underwent major surgery within 2 weeks before the end of study had their End-of-Study Visit performed no earlier than 14 days after surgery.

For any major surgery, blood draws were taken at least daily while the subject was hospitalized.

A blood sample for daily FVIII levels was taken while the subject remained in the hospital. The sample was tested at the local laboratory so that monitoring of the subject occurred in real time.

A duplicate plasma sample was prepared by making a separate aliquot for each blood sample drawn so that subsequent analysis at the central laboratory could be performed. Doses up to 100 IU/kg were allowed in this study in cases of surgery or severe bleeding to achieve the required FVIII levels to control and prevent bleeding.

Objectives

Primary Objective

The primary objective of the study was to evaluate the safety of rFVIIIFc in previously treated pediatric subjects with hemophilia A.

Secondary Objectives

Secondary objectives of this study were as follows:

- To evaluate the efficacy of rFVIIIFc for prevention and treatment of bleeding episodes.
- To evaluate and assess the PK of rFVIIIFc.
- To evaluate rFVIIIFc consumption for prevention and treatment of bleeding episodes.

Several PK endpoints have been discussed above

Outcomes/endpoints

Primary Endpoint

The primary endpoint was the occurrence of inhibitor development.

Secondary Endpoints

The secondary efficacy endpoints included the following:

- annualized number of bleeding episodes (spontaneous and traumatic) per subject
- annualized number of spontaneous joint bleeding episodes per subject
- assessments of response to treatment with rFVIIIFc for bleeding episodes, using the
- 4-point bleeding response scale
- total annualized rFVIIIFc consumption per subject for the prevention and treatment of bleeding episodes
- time from the last injection of rFVIIIFc to the bleeding episode
- number of injections and dose per injection of rFVIIIFc required to resolve a bleeding episode

Randomisation

This was an open-label trial.

Blinding (masking)

This was an open-label trial

Statistical methods

The Full Analysis Set was defined as all subjects who received at least 1 dose of rFVIIIFc. Analyses of efficacy, patient-reported outcomes, and health outcomes were performed in this population.

The Safety Analysis Set was defined as all subjects who received at least 1 dose of their prestudy FVIII treatment for the purpose of evaluating PK or at least 1 dose of rFVIIIFc.

Sample size

The determination of the number of subjects was based on clinical rather than statistical considerations. Taking into account recommendations from the Committee for Medicinal Products for Human Use [EMA (EMA/CHMP/BPWP/144533/2009) 2011], approximately 68 subjects (approximately 34 in each age cohort) were dosed with rFVIIIFc to achieve a minimum of 25 subjects with at least 50 EDs in each age cohort (<6 and 6 to <12 years of age). This allowed for a 25% drop-out rate.

Results

Recruitment

A total of 71 male subjects were enrolled in the study, and 69 of those subjects were treated with rFVIIIFc. A subject was considered enrolled if he received a PK baseline dose of prestudy FVIII or the study drug rFVIIIFc. The first subject was enrolled in the PK subgroup on 09 October 2012. The first PK dose of rFVIIIFc was administered on 01 November 2012.

Subjects were assigned to the appropriate age cohort (<6 years of age or 6 to <12 years of age) at the time of screening. The age cohort assigned at Screening was used in all analyses unless otherwise stated.

Of the 71 enrolled subjects, 36 subjects were assigned to the <6 years of age cohort, and 35 subjects were assigned to the 6 to <12 years of age cohort. The study was conducted at 23 investigational sites in 8 countries and represented a broad global sampling. The countries with the greatest number of enrolled subjects were United Kingdom (20 subjects), US (20 subjects), and South Africa (11 subjects)

Conduct of the study

Protocol Deviations

Of the 38 subjects with major protocol deviations, 2 subjects were identified as having deviations that were considered to have a potential impact on the annualized bleeding rate. The first subject took Advate during the Efficacy Period; use of any FVIII product except the study drug, rFVIIIFc, was forbidden in the study. The

second subject had >80% of his prophylactic dosing intervals noncompliant with his prescribed prophylactic dosing regimen.

There were 38 subjects (55.1%) with deviations that were considered major; 24 subjects (34.8%) had informed consent issues, 2 subjects (2.9%) took excluded medication, and 22 subjects (31.9%) had deviations based on other criteria. Every deviation associated with the completion of the ICF or the process of consent was considered major, regardless of whether the deviation was considered to be clinically meaningful. The majority of informed consent issues were administrative in nature, such as missing initials on individual pages or errors that were corrected prior to any study-specific procedures being performed.

The major deviations characterized as “other” were cited based on IP compliance criteria, administrative criteria, study procedures criteria, Regulatory Agency or Clinical Events Committee approval criteria, or other criteria; and included such issues as study-related tasks being performed by staff members not listed as delegates, IP shipments improperly documented by the receiving pharmacy, missing PI signature on physical examination assessment, incomplete physical examination or physical examination not performed during the Screening Visit, and noncompliance with the prescribed dose and/or regimen.

Baseline data

All subjects were male. The median overall age was 5.0 years (range, 1 to 11 years); in the <6 years of age cohort, the median age was 4.0 years (range, 1 to 5 years), and in the 6 to <12 years of age cohort, the median age was 8.0 years (range, 6 to 11 years). The median weight was 17.25 kg (range, 13.0 to 23.8 kg) for subjects <6 years of age and 31.35 kg (range, 19.1 to 59.6 kg) for subjects in the 6 to <12 years of age cohort. The predominant races represented in the study were white (67.6%) and black or African American (12.7%).

A total of 65 subjects (91.5%) had a measured FVIII activity of <1% at Baseline Screening. In accordance with the Study 8HA02PED protocol, FVIII levels of <1% were verified in the medical records of the other 6 subjects (8.5%).

Table 28 **Hemophilia History**

Hemophilia history
Safety Analysis Set
Page 1 of 3

	Age cohort		
	<6 years old (N=36)	6 to <12 years old (N=35)	Total (N=71)
Prestudy FVIII level (a)			
n	36	35	71
<1%	34 (94.4%)	31 (88.6%)	65 (91.5%)
>=1%	2 (5.6%)	4 (11.4%)	6 (8.5%)
F8 genotype (b)			
n	36	35	71
FRAMESHIFT	9 (25.0%)	7 (20.0%)	16 (22.5%)
INTRON 1 INVERSION	1 (2.8%)	2 (5.7%)	3 (4.2%)
INTRON 22 INVERSION	17 (47.2%)	9 (25.7%)	26 (36.6%)
MISSENSE	5 (13.9%)	7 (20.0%)	12 (16.9%)
NONSENSE	2 (5.6%)	7 (20.0%)	9 (12.7%)
NOT FOUND	1 (2.8%)	1 (2.9%)	2 (2.8%)
UNKNOWN	1 (2.8%)	2 (5.7%)	3 (4.2%)
Blood type O (c)	15/36 (41.7%)	7/35 (20.0%)	22/71 (31.0%)

	Age cohort		
	<6 years old (N=36)	6 to <12 years old (N=35)	Total (N=71)
HCV status at study entry			
Positive	0	0	0
Negative	18/36 (50.0%)	25/35 (71.4%)	43/71 (60.6%)
Unknown	18/36 (50.0%)	10/35 (28.6%)	28/71 (39.4%)
Est. bleeds prior 12 mths (c)	2 (0, 16)	4 (0, 36)	2 (0, 36)
Prestudy FVIII regimen (d)			
Prophylaxis	33/36 (91.7%)	30/35 (85.7%)	63/71 (88.7%)
Episodic	3/36 (8.3%)	5/35 (14.3%)	8/71 (11.3%)
>=1 target joints (d)	6/36 (16.7%)	7/35 (20.0%)	13/71 (18.3%)
Family history of inhibitors (d)	3/36 (8.3%)	3/35 (8.6%)	6/71 (8.5%)

Table 29 **Number of Bleeding Episodes in the Prior 12 Months**

Number of bleeding episodes in the prior 12 months
Safety Analysis Set

	Age cohort	
Most recent prestudy regimen	<6 years old (N=36)	6 to <12 years old (N=35)
Prophylaxis		
n	33	30
Median (min, max)	1.0 (0, 8)	2.5 (0, 36)
Episodic		
n	3	5
Median (min, max)	10.0 (10, 16)	12.0 (11, 19)

SOURCE: FACTOR8HA/8HA02PED/CSR/IN-T-BLD-PRIOR.SAS DATE: 09MAY2014

Baseline physical examination findings were consistent with those expected in a pediatric population with severe hemophilia, with abnormalities of extremities/joints reported in 13 subjects (18.3%). The other most frequent findings noted during the baseline physical examination were musculoskeletal abnormalities, reported in 9 subjects (12.7%), and skin abnormalities, predominantly bruising and ecchymosis, reported in 9 subjects (12.7%)

Collectively, the study population demonstrated good joint health, as reflected in the results of the HJHS, which was administered to all subjects 4 years of age and older at Screening. In the overall population, the median joint score, gait score, and total score were 0.0 (range: 0 to 19), 0.0 (range: 0 to 3), and 1.0 (range: 0 to 21), respectively

Prior FVIII Therapy

For the 63 subjects who were treated prophylactically with FVIII, 3 subjects (4.8%) reported a dosing frequency of 1 injection per week, 13 subjects (20.6%) reported 2 injections per week, and 47 subjects (74.6%) reported 3 or more injections per week (31 subjects were dosed 3 times per week, and 16 subjects were dosed every other day). The distribution of dosing frequencies was similar between both age cohorts.

Across the entire study population (71 subjects), the majority of subjects (55 subjects; 74.3%) used a recombinant FVIII product prior to study entry. The median dose typically used to treat bleeding episodes was 25.0 IU/kg (range: 13 to 72) for minor bleeding episodes, 40.0 IU/kg (range: 13 to 72) for moderate bleeding episodes, and 50.0 IU/kg (range: 13 to 100) for major bleeding episodes.

Numbers analysed

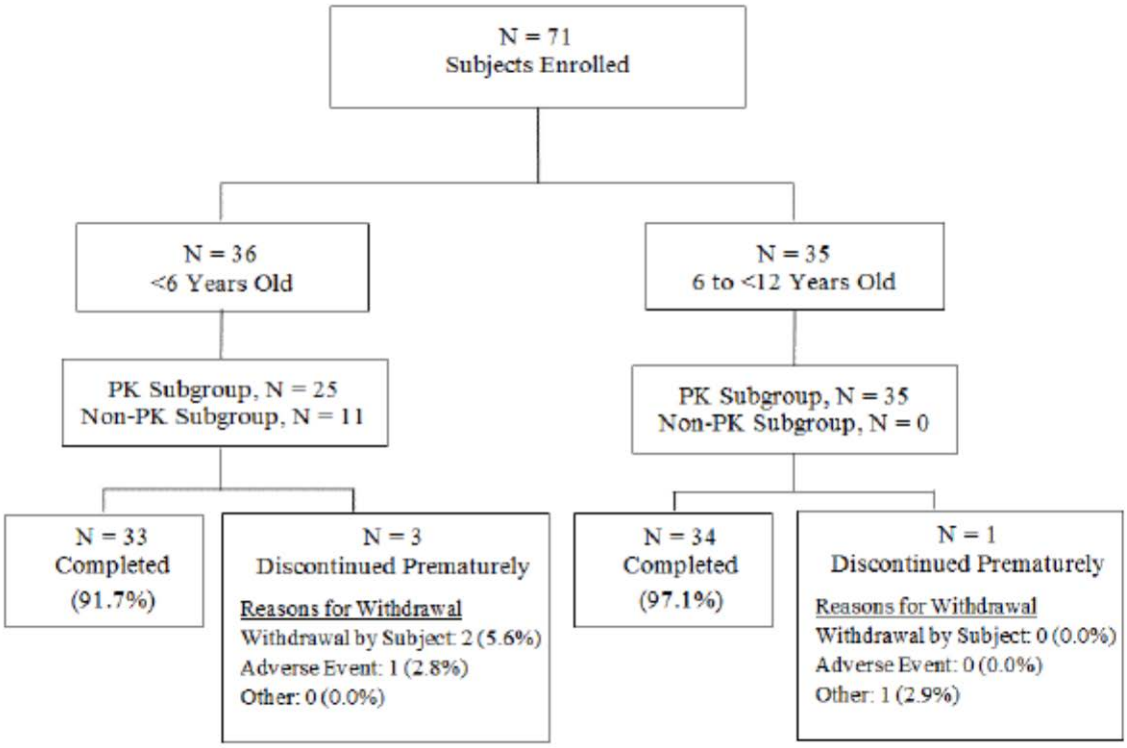
The Safety Analysis Set, including all enrolled subjects who received at least 1 dose of prestudy FVIII treatment for the purpose of evaluating PK or at least 1 dose of rFVIIIFc, was composed of 71 subjects (100%). The Full Analysis Set included only those 69 subjects who received rFVIIIFc; 2 subjects received

prestudy FVIII but were not treated with rFVIIIFc There were no subjects in the surgery subgroup, defined as subjects who have undergone major surgery after the first dose of study treatment

The majority of subjects (59 subjects; 85.5%) participated in the study for at least 24 weeks (<6 years of age: 74.3%; 6 to <12 years of age: 97.1%). The median time on the study was 26.3 weeks (range: 2 to 31 weeks) for the overall study population, 26.0 weeks (range: 2 to 28 weeks) for the <6 years of age cohort, and 26.3 weeks (range: 22 to 31 weeks) for the 6 to <12 years of age cohort

A total of 61 subjects (88.4%) had ≥50 EDs (27 subjects [77.1%] in the <6 years of age cohort and 34 subjects [100%] in the 6 to <12 years of age cohort), while 8 subjects (11.6%) had <50 EDs. All 61 subjects with ≥50 EDs had a valid inhibitor test after 50 EDs; therefore, the protocol requirement for assessment of inhibitor risk was met. The median number of EDs for the overall safety analysis set was 54.0 (range: 5 to 72)

Figure 6 **Overview of Subject Disposition**



Source Table 30 d Appendix 16.2.1, Table 1.
N = Number of subjects; PK = pharmacokinetics.

Table 30 Summary of Disposition

Summary of disposition
All-enrolled Analysis Set
Page 1 of 3

	Age cohort		
	<6 years old (N=36)	6 to <12 years old (N=35)	Total (N=71)
Number of subjects in the Full Analysis Set (a)	35 (97.2%)	34 (97.1%)	69 (97.2%)
Number of subjects with an efficacy period (b)	35 (97.2%)	34 (97.1%)	69 (97.2%)
Number of subjects in the Safety Analysis Set (c)	36 (100.0%)	35 (100.0%)	71 (100.0%)
Number of subjects in the surgery subgroup (d)	0	0	0
Number of subjects in the PK subgroup	25 (100.0%)	35 (100.0%)	60 (100.0%)
Number of subjects with a PK dose for (e):			
Prestudy FVIII	24 (96.0%)	31 (88.6%)	55 (91.7%)
Number of subjects exempted from Prestudy FVIII PK	1 (4.0%)	4 (11.4%)	5 (8.3%)
rFVIIIFc	24 (96.0%)	34 (97.1%)	58 (96.7%)
Both prestudy FVIII and rFVIIIFc	23 (92.0%)	30 (85.7%)	53 (88.3%)
Number of subjects with a complete and evaluable PK profile for (e,f):			
Prestudy FVIII	24 (96.0%)	31 (88.6%)	55 (91.7%)
rFVIIIFc (g)	24 (96.0%)	31 (88.6%)	55 (91.7%)
Both prestudy FVIII and rFVIIIFc	23 (92.0%)	28 (80.0%)	51 (85.0%)
Number of subjects in the non-PK subgroup	11 (30.6%)	0	11 (15.5%)

Footnotes are listed on the last page.

SOURCE: FACTOR8HA/8HA02PED/CSR/T-DISPOSITION.SAS DATE: 09MAY2014

Summary of disposition
All-enrolled Analysis Set
Page 2 of 3

	Age cohort		
	<6 years old (N=36)	6 to <12 years old (N=35)	Total (N=71)
Completion status			
Completed (h)	33 (91.7%)	34 (97.1%)	67 (94.4%)
Discontinued prematurely	3 (8.3%)	1 (2.9%)	4 (5.6%)
Adverse event	1 (2.8%)	0	1 (1.4%)
Other	0	1 (2.9%)	1 (1.4%)
Withdrawal by subject	2 (5.6%)	0	2 (2.8%)

Footnotes are listed on the last page.

SOURCE: FACTOR8HA/8HA02PED/CSR/T-DISPOSITION.SAS DATE: 09MAY2014

Outcomes and estimation

No development of inhibitor was detected in subjects of study 8HA02PED (See clinical safety).

The median annualized bleeding rate was 0.00 with 25th and 75th percentiles (interquartile range [IQR]) of 0.0, 3.96 in the <6 years of age cohort; 2.01 (IQR, 0.0, 4.04) in the 6 to <12 years of age cohort; and 1.96 (IQR, 0.0, 3.96) in the total. 32 subjects (46.4%) had no bleeding episodes reported during the Efficacy

Period: 18 subjects (51.4%) in the <6 years of age cohort and 14 subjects (41.2%) in the 6 to <12 years of age cohort.

Table 31 Summary of Annualized Bleeding Rates

Summary of annualized bleeding rates
Full Analysis Set
Page 1 of 3

	Age cohort		
	<6 years old (N=35)	6 to <12 years old (N=34)	Total (N=69)
Annualized bleeding rate (Episodes/Year)			
0	18 (51.4%)	14 (41.2%)	32 (46.4%)
>0-5	10 (28.6%)	13 (38.2%)	23 (33.3%)
>5-10	6 (17.1%)	6 (17.6%)	12 (17.4%)
>10-20	1 (2.9%)	0	1 (1.4%)
>20	0	1 (2.9%)	1 (1.4%)
Annualized bleeding rate per subject			
n	35	34	69
Mean	2.25	2.99	2.62
SD	2.976	5.022	4.100
Median	0.00	2.01	1.96
25th, 75th percentile	0.00, 3.96	0.00, 4.04	0.00, 3.96
Min, Max	0.0, 10.5	0.0, 27.2	0.0, 27.2

Footnotes are listed on the last page.

SOURCE: FACTOR8HA/8HA02PED/CSR/T-ABR.SAS DATE: 09MAY2014

Summary of Annualized Bleeding Rates by Prestudy Treatment

Of the 69 subjects who participated in the Efficacy Period, 7 subjects were on prior episodic dosing, and 62 subjects were on prior prophylaxis dosing. The median annualized bleeding rate during the study was 2.05 for subjects on prior episodic dosing and 1.96 for subjects on prior prophylaxis dosing

Summary of Annualized Bleeding Rates by Hemophilia Characteristics

Because the number of bleeding episodes in the prior 12 months was dependent on the subjects' previous treatment regimen, the change in annualized bleeding rates was evaluated separately for prior prophylaxis and episodic treatment. When compared with the number of bleeding episodes in the 12 months prior to study start based on subject-reported historical data, the observed annualized bleeding rates for subjects on a prior prophylaxis regimen showed a small decrease in annualized bleeding rates from prior frequency of bleeding (Table 32). Subjects on a prior episodic regimen also showed a decrease in their annualized bleeding rate when treated with a prophylaxis regimen on study (Table 32).

Table 32 **Number of Bleeding Episodes in the Prior 12 Months Compared With the On-Study Annualized Bleeding Rate by Prestudy FVIII Regimen**

Number of bleeding episodes in the prior 12 months compared with the on-study annualized bleeding rate by prestudy FVIII regimen
Full Analysis Set

	Age cohort			
	<6 years old (N=35)		6 to <12 years old (N=34)	
Prestudy regimen	Actual result	Difference (a)	Actual result	Difference (a)
Prophylaxis				
n	32	32	30	30
Baseline(b)				
Median	1.50		2.50	
Min, Max	0.0, 8.0		0.0, 36.0	
On-Study(c)				
Median	0.00	-0.41	2.01	-1.00
Min, Max	0.0, 10.5	-8.0, 6.2	0.0, 27.2	-34.0, 22.2
Episodic				
n	3	3	4	4
Baseline(b)				
Median	10.00		13.50	
Min, Max	10.0, 16.0		11.0, 19.0	
On-Study(c)				
Median	3.96	-6.11	0.00	-13.50
Min, Max	2.6, 9.9	-7.4, -6.0	0.0, 2.1	-16.9, -11.0

NOTE 1: The efficacy period begins with the first prophylactic dose of rFVIIIFc and ends with the last dose (regardless of the reason for dosing). Surgery/rehabilitation periods are not included in the efficacy period.
2: Prestudy FVIII regimen is the most recent regimen the subject was receiving prior to entering the study.
(a) The difference between the annualized bleeding rate and the estimated number of prior bleeds in the prior 12 months calculated for each subject. A negative number represents a decrease in bleeding.
(b) The baseline bleeds is the estimated bleeds in the 12 months prior to study. All bleeding events during the last 12 months are included in the 12-month total, whether or not they were experienced while on the most recent prestudy regimen.
(c) The on-study annualized bleeding rate is the total number of bleeding episodes during the efficacy period extrapolated to a 1-year interval of time.

SOURCE: FACTOR8HA/8HA02PED/CSR/IN-T-BLD-PRIOR-ONSTUDY.SAS
DATE: 09MAY2014

Overall Dosing

The median total number of injections per subject was 54.0 for both the <6 years of age cohort (range: 5 to 76) and the 6 to <12 years of age cohort (range: 52 to 64) . The median number of injections, per subject,

for prophylaxis treatment was 52.0 (range: 4 to 66). A median of 0.0 injections (range: 0 to 8), per subject, was required to treat spontaneous bleeding episodes

Prophylactic Dose and Dosing Interval

The median of the average dosing interval during the Efficacy Period was 3.49 days (range: 2.8 to 3.7 days), with no difference in median average dosing interval between cohorts.

The majority of subjects (62 subjects; 89.9%) made no changes to their prescribed dosing interval over the course of the study. The median number of prescribed interval adjustments was 0.0 (range: 0 to 1).

The median average weekly dose of rFVIIIFc for subjects <6 years of age was 91.63 IU/kg (range: 69.9 to 158.6 IU/kg) across the study and 101.86 IU/kg (range: 69.2 to 175.2 IU/kg) over the last 3 months of the study for those who were in the study for at least 24 weeks. For subjects in the 6 to <12 years of age cohort, the median average weekly dose was 86.88 IU/kg (range: 71.4 to 139.2 IU/kg) across the study and 88.97 IU/kg (range: 67.0 to 151.0 IU/kg) over the last 3 months of the study for those who were in the study at least 24 weeks.

Over half of subjects (53.6%) made no changes to their prescribed starting dose over the course of the study, and 30.4% only made 1 dose change during the study. The median number of prescribed dose changes per subject was 0.0 (range: 0 to 3).

Summary of prophylactic dosing interval
Full Analysis Set
Page 2 of 3

	Age cohort		
	<6 years old (N=35)	6 to <12 years old (N=34)	Total (N=69)
Total number of prescribed dosing interval changes per subject			
0	31 (88.6%)	31 (91.2%)	62 (89.9%)
1	4 (11.4%)	3 (8.8%)	7 (10.1%)
n	35	34	69
Mean	0.1	0.1	0.1
SD	0.32	0.29	0.30
Median	0.0	0.0	0.0
Min, Max	0, 1	0, 1	0, 1

Footnotes are listed on the last page.

SOURCE: FACTOR8HA/8HA02PED/CSR/T-PROPHY-DOSE-INT.SAS DATE: 09MAY2014

Summary of prophylactic dose
Full Analysis Set
Page 2 of 3

	Age cohort		
	<6 years old (N=35)	6 to <12 years old (N=34)	Total (N=69)
Total number of prescribed dose changes per subject			
0	20 (57.1%)	17 (50.0%)	37 (53.6%)
1	10 (28.6%)	11 (32.4%)	21 (30.4%)
2	4 (11.4%)	4 (11.8%)	8 (11.6%)
3	1 (2.9%)	2 (5.9%)	3 (4.3%)
n	35	34	69
Mean	0.6	0.7	0.7
SD	0.81	0.90	0.85
Median	0.0	0.5	0.0
Min, Max	0, 3	0, 3	0, 3

Footnotes are listed on the last page.

SOURCE: FACTOR8HA/8HA02PED/CSR/T-PROPHY-DOSE.SAS DATE: 09MAY2014

Annualized rFVIIIFc Consumption

The median annualized rFVIIIFc consumption during the Efficacy Period was 5146.3 IU/kg (range: 3695 to 8474 IU/kg) for subjects <6 years of age and 4699.6 IU/kg (range: 3819 to 8230 IU/kg) for subjects 6 to <12 years of age.

The median weekly dose and the annualized consumption are slightly higher and more variable in the <6 years of age cohort

Compliance

A total of 86 bleeding episodes were reported during the Efficacy Period (38 episodes in the <6 years of age cohort and 48 episodes in the 6 to <12 years of age cohort).

These bleeding episodes were experienced by 37 of the 69 subjects (53.6%) who received at least 1 dose of rFVIIIFc (17 subjects [48.5%] in the <6 years of age cohort and 20 subjects [58.8%] in the 6 to <12 years of age cohort) Overall, 67 of the 86 bleeding episodes (77.9%) were treated within

8 hours of the onset of bleeding. Of subjects <6 years of age, 58.8% were compliant by treating at least 80% of their bleeding episodes within 8 hours; this was true in 75.0% of subjects in the 6 to <12 years of age cohort

Prophylactic Dosing

Overall, the majority of subjects were compliant with prophylactic dosing. The median percentage of doses taken within 80% to 125% of the prescribed dose, per subject, was 90.38% (range: 35.8% to 100.0%) for subjects <6 years of age and 97.85% (range: 57.7% to 100.0%) for subjects 6 to <12 years of age.

A total of 21 subjects (60.0%) in the <6 years of age cohort and 31 subjects (91.2%) in the 6 to <12 years of age cohort had a dosing compliance rate of at least 80% during the Efficacy Period. The lower level of dose compliance in the <6 years of age cohort may be mostly attributable to the impact of the Directions for

Handling and Administration (DHA) instructions and the common medical practice of rounding up to the nearest vial size in lower weight subjects.

The median percentage of doses taken within 1 day of the prescribed interval, per subject, was 98.11% for subjects <6 years of age and 97.87% for subjects 6 to <12 years of age. A total of 31 subjects (88.6%) in the <6 years of age cohort and 33 subjects (97.1%) in the 6 to <12 years of age cohort had a dosing interval compliance rate of at least 80% during the Efficacy Period Overall, 48 subjects (69.6%) were compliant with both the prescribed dose (80% to 125% of the prescribed dose for at least 80% of their doses) and the prescribed dosing interval (within 1 day of prescribed interval for at least 80% of their dosing intervals). In the <6 years of age cohort, this was true for 18 subjects (51.4%), and in the 6 to <12 years of age cohort, this was true for 30 subjects (88.2%)

Secondary Efficacy Endpoints

Subjects' Assessments of Response to Treatment With rFVIIIFc Injections for Bleeding Episodes

Key results for the subjects' assessments of response to treatment with rFVIIIFc for a bleeding episode are as follows:

- Overall, 89.4% of rFVIIIFc injections were rated by subjects as producing an excellent or good response.

Of a total of 112 injections administered to treat the 86 bleeding episodes during the study, 104 were evaluated for response. Of the 104 injections, 93 injections (89.4%) were rated by subjects as producing an excellent or good response, 9 (8.7%) were rated as moderate, and 2 (1.9%) were rated as none (no improvement)

Summary of subject's assessment of response to rFVIIIFc injections for the treatment of bleeding episodes
Full Analysis Set
Page 2 of 3

	Age cohort		
	<6 years old (N=35)	6 to <12 years old (N=34)	Total (N=69)
First injection for each bleeding episode			
Based on injections with an evaluation			
n (a)	35	46	81
Excellent or Good	32 (91.4%)	43 (93.5%)	75 (92.6%)
Excellent	23 (65.7%)	22 (47.8%)	45 (55.6%)
Good	9 (25.7%)	21 (45.7%)	30 (37.0%)
Moderate	3 (8.6%)	1 (2.2%)	4 (4.9%)
None	0	2 (4.3%)	2 (2.5%)
Based on all injections			
n (b)	38	48	86
Excellent or Good	32 (84.2%)	43 (89.6%)	75 (87.2%)
Excellent	23 (60.5%)	22 (45.8%)	45 (52.3%)
Good	9 (23.7%)	21 (43.8%)	30 (34.9%)
Moderate	3 (7.9%)	1 (2.1%)	4 (4.7%)
None	0	2 (4.2%)	2 (2.3%)
Response not provided	3 (7.9%)	2 (4.2%)	5 (5.8%)

Footnotes are listed on the last page.

SOURCE: FACTOR8HA/8HA02PED/CSR/T-BLEED-RESPONSE.SAS DATE: 09MAY2014

Time From Last Injection of rFVIIIFc to Treatment of a Bleeding Episode

The median time from the last prophylaxis injection of rFVIIIFc to a spontaneous bleeding episode was similar when examined on a per subject basis (2.17, 2.55, and 2.27 for <6 years of age cohort, 6 to <12 years of age cohort, and total, respectively)

Number of Injections and Dose per Injection of rFVIIIFc Required to Resolve a Bleeding Episode

Overall, 93.0% of bleeding episodes were controlled with ≤2 injections of rFVIIIFc, with 81.4% controlled by 1 injection. Per bleeding episode, the median dose per injection required for resolution of bleeding was 49.69 IU/kg, and the median total dose required was 54.90 IU/kg.

Of the 86 bleeding episodes, analysis per bleeding episode showed that 1 injection of rFVIIIFc was adequate to resolve 76.3% of bleeding episodes in the <6 years of age cohort, 85.4% in the 6 to <12 years of age cohort, and 81.4% for the total.

For resolution of each bleeding episode in the <6 years of age cohort, 6 to <12 years of age cohort, and total, the median dose per injection was 51.35, 48.15, and 49.69 IU/kg, respectively, and the median total dose was 56.40, 53.49, and 54.90 IU/kg, respectively. The number of bleeding episodes requiring a second injection was small (16 bleeding episodes overall for 11 subjects), with the median time per bleeding episode of 23.88 hours overall and 23.77 hours in the <6 years of age cohort and 24.02 hours in the 6 to <12 years of age cohort.

Physician's Global Assessment of the Subject's Response to rFVIIIFc Regimen

During the visits in which data were collected, the Physician's global assessment of the subjects' response to their rFVIIIFc regimen was excellent for 92.8% of the visits, effective for 6.5% of the visits, and partially effective for 0.7% of the visits. There were no subjects whose response to the rFVIIIFc regimen was assessed as ineffective at any visits.

Change in Physical Activity

Overall, the majority of subjects reported similar or increased physical activity over the course of the study. Subjects in both age cohorts reported an increase in physical activity. Four subjects, 2 subjects in each age cohort, reported fewer/less physical activities at the end of the study.

Minor Surgeries

Although no specific objectives were specified for minor surgeries, information on the type of surgery and the hemostatic response was collected in the study. A total of 7 minor surgeries were performed in 7 subjects during the study: 2 surgeries in the <6 years of age cohort and 5 in the 6 to <12 years of age cohort Surgeons' assessments of hemostasis were collected at least 24 hours following the procedure. Hemostasis was rated as excellent for 5 minor surgeries and as good for 2 minor surgeries.

Patient-Reported Outcomes

The CHO-KLAT assessment was completed by subjects ≥5 years of age only and by the subjects' parent/proxy. The CHO-KLAT total score was also analyzed by the most recent prestudy regimen before entering the study. Subjects on a prophylaxis regimen before entry into the study remained stable when assessed by both the subject and the parent/proxy.

The Hemo-Sat Patient Satisfaction Scale questionnaire: Subjects maintained or slightly improved in these categories. The analysis was repeated for each prestudy regimen for which there were at least 10 subjects with a baseline and at least 1 postbaseline value. Subjects on a prestudy prophylaxis regimen also maintained or slightly improved EQ-5D-Y Questionnaire. The analyses were repeated for prestudy regimen when there were at least 10 subjects with a baseline and at least 1 postbaseline value. There was a small increase from baseline in the EQ-5D-Y visual analogue scale (median of 90.0 at baseline and 95.0 at End of Study)

Ancillary analyses

Summary of main study(ies)

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 33 Summary of Efficacy for trial 8HA02PED

Title: Study 8HA02PED: Evaluation of Safety, Pharmacokinetics, and Efficacy of Recombinant Coagulation Factor VIII Fc Fusion Protein, BIIB031, in the Prevention and Treatment of Bleeding Episodes in Pediatric Subjects With Hemophilia A

Study identifier	**8HA02PED**		
Design	An Open-Label, Multicenter		
	Duration of main phase: Duration of Run-in phase: Duration of Extension phase:	<time> <time> <not applicable> <time> <not applicable>	
Hypothesis	This study was conducted to assess the PK, efficacy, and safety of rFVIIIFc in previously treated pediatric patients <12 years of age with hemophilia A in accordance with guideline requirements.		
Treatments groups	Age cohort < 6 years Age cohort 6 to < 12 years		The starting prophylactic regimen consisted of 25 IU/kg on the first day followed by 50 IU/kg on the fourth day. Dosing of up to 80 IU/kg and a dosing interval as short as 2 days was allowed and used in a limited number of patients in the study.
Endpoints and definitions	Primary endpoint Safety	occurrence of inhibitor development any inhibitor (≥0.6 Bethesda units [BU]/mL)	A low-titer inhibitor is defined as ≥0.6 but <5.0 BU/mL that was identified and confirmed on 2 separate samples drawn approximately 2 to 4 weeks apart. A high-titer inhibitor is defined as ≥5.0 BU/mL that was identified and confirmed on 2 separate samples drawn approximately 2 to 4 weeks apart.
		Efficacy	Prophylaxis, treatment of bleeding episodes
		PK	PK parameters
Database lock	<date>		

Results and Analysis

Analysis description	**Primary Analysis**			
Analysis population and time point description	Study enrolled a total of 71 previously treated male paediatric patients with severe haemophilia A. Of the 71 enrolled subjects, 69 received at least 1 dose of ELOCTA and were evaluable for efficacy. Subjects were less than 12 years of age (35 were <6 years of age and 34 were 6 to <12 years of age).			
Descriptive statistics and estimate variability	Treatment group			
	Number of subject	69		
	Prophylaxis	Median dose interval	Median total weekly dose	Annualised bleeding rate
	Treatment of bleeding	%of patients controlled with 1 injection % of patients controlled with 2 or fewer injections		
	PK parameters	Incremental Recovery (IU/dL per IU/kg		

	<variability statistic>	AUC/Dose (IU*h/dL per IU/kg) $t_{½}$ (h) MRT (h) CL (mL/h/kg) V_{ss} (mL/kg)			
Effect estimate	Individualised prophylaxis	median dose interval		3.49 days (interquartile range 3.46-3.51)	
		median total weekly dose was IU/kg - for subjects <6 years of age		91.63 (interquartile range 84.72-104.56)	
		median total weekly dose was IU/kg - for subjects 6 to < 12 years		86.88 (interquartile range 79.12-103.08) IU/kg	
		overall annualised bleeding rate		1.96 (interquartile range 0.00-3.96)	
	Treatment of bleeding	% of patients controlled with 1 injection		81.4%	
		% of patients controlled with 2 or fewer injections		93.0%	
	Treatment of a bleeding episode	Median dose per injection		49.69 (interquartile range 29.41-56.82) IU/kg.	
		Median overall dose		54.90 IU/Kg (29.41, 71.09).	
	PK parameters	< 6 years		6 to < 12 years	
		N = 24	N= 23	N = 27	N=31
	Incremental Recovery (IU/dL per IU/kg	1.88 (1.73-2.05)	1.90 (1.79-2.02)	2.08 (1.91-2.25)	2.30 (2.04-2.59)
	AUC/Dose (IU*h/dL per IU/kg)	25.9 (23.4-28.7)	28.9 (25.6-32.7)	32.8 (28.2-38.2)	38.4 (33.2-44.4)
	$t_{½}$ (h)	14.3 (12.6-16.2)	12.3 (11.0-13.7)	15.9 (13.8-18.2)	13.5 (11.4-15.8)
	MRT (h)	17.2 (15.4-19.3)	16.8 (15.1-18.6)	20.7 (18.0-23.8)	19.0 (16.2-22.3)
	CL (mL/h/kg)	3.86 (3.48-4.28)	3.46 (3.06-3.91)	3.05 (2.62-3.55)	2.61 (2.26-3.01)
	V_{ss} (mL/kg)	66.5 (59.8-73.9)	57.9 (54.1-62.0)	63.1 (56.3-70.9)	49.5 (44.1-55.6)

Notes	A majority of patients (78.3%) remained on a treatment regimen with alternating doses (median of 31.73 IU/kg lower dose and 55.87 IU/kg higher dose). No bleeding episodes were experienced in 46.4% of paediatric subjects.
Analysis description	**Secondary analysis**

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

Summary tabulations across the two main studies are presented below.

Table 34: Summary of Efficacy in Treatment of Bleeding: Studies 8HA02PED and 997HA301, Full Analysis Set (FAS)

	Study 8HA02PED	Study 997HA301	
	Tailored Prophylaxis (N=69)	Prophylaxis (Arm 1 & Arm 2) (N=141)	Episodic (Arm 3) (N=23)
New bleeding episodes	86	301	456
Total injections to treat bleeding episodes	112	364	516
Number of injections to treat bleeding episodes (a)			
1 injection	70 (81.4%)	253 (84.1%)	408 (89.5%)
2 injections	10 (11.6%)	38 (12.6%)	41 (9.0%)
3 injections	3 (3.5%)	8 (2.7%)	5 (1.1%)
>=4 injections	3 (3.5%)	2 (0.7%)	2 (0.4%)
n (b)	86	300	455
Median dose per injection (IU/kg) to treat a bleeding episode (IQR)	49.69 (29.41, 56.82)	29.07 (23.32, 50.08)	26.46 (21.51, 31.45)
n (b)	86	300	455
Median total dose (IU/kg) to treat a bleeding episode (IQR)	54.90 (29.41, 71.09)	31.32 (23.53, 52.53)	27.35 (22.59, 32.71)
Response to first injection (c)	81	291	454
Excellent or good	75 (92.6%)	218 (74.9%)	364 (80.2%)
Moderate	4 (4.9%)	69 (23.7%)	89 (19.6%)
No response	2 (2.5%)	4 (1.4%)	1 (0.2%)

IQR = interquartile range

(a) Percentages are based on the number of bleeding episodes.

(b) n = total number of bleeding episodes with complete information on the dose(s) administered to treat a bleeding episode. 2 Subjects had incomplete information on the dose(s) administered to treat a bleeding episode so the average dose per injection and the total dose for the resolution of those bleeding episodes could not be determined.

(c) Percentages are based on the total number of bleeding episodes with a response to the first injection to treat the bleed.

rFVIIIFc **efficacy in routine prophylaxis** was mainly evaluated through assessment of (annualised) bleeding rates and rFVIIIFc consumption, as depicted in the following two tables below:

Table 35 Summary of Bleeding Episodes: Studies 8HA02PED and 997HA301, FAS

		Study 997HA301		
	Study 8HA02PED Tailored Prophylaxis (N=69)	Arm 1 Tailored Prophylaxis (N=117)	Arm 2 Weekly Prophylaxis (N=24)	Arm 3 Episodic (N=23)
Total bleeding episodes per subject, n (%)				
n	69	117	23	23
0 (a)	32 (46.4%)	53 (45.3%)	4 (17.4%)	0
1	17 (24.6%)	16 (13.7%)	8 (34.8%)	0
2	6 (8.7%)	16 (13.7%)	4 (17.4%)	0
3	9 (13.0%)	12 (10.3%)	0	0
4	1 (1.4%)	6 (5.1%)	4 (17.4%)	0
5	3 (4.3%)	5 (4.3%)	0	1 (4.3%)
>5	1 (1.4%)	9 (7.7%)	3 (13.0%)	22 (95.7%)
Total number of bleeding episodes	86	209	92	456
Total subject-years followed (b)	31.63	73.16	10.58	12.10
Mean subject-years followed	0.458	0.625	0.460	0.526
Annualized bleeding rate (c)				
Mean (SD)	2.62 (4.100)	2.91 (3.925)	8.81 (13.690)	37.23 (20.208)
Median	1.96	1.60	3.59	33.57
25th, 75th percentile	0.00, 3.96	0.00, 4.69	1.86, 8.36	21.14, 48.69
Min, Max	0.0, 27.2	0.0, 18.2	0.0, 58.0	9.8, 82.6
Annualized bleeding rate (negative bincmial model)	NA	2.91	8.92	37.25
95% confidence interval	NA	2.30, 3.68	5.48, 14.51	24.03, 57.74
Bleeding rate ratio (d) (percentage reduction)	NA	0.08 (92%)	0.24 (76%)	
95% confidence interval	NA	0.05, 0.13	0.12, 0.46	
P-value (d)	NA	<0.0001	<0.0001	

Note SD = standard deviation.

1: Percentages are based on the number of subjects in each arm whose efficacy period is of at least 1 day in duration.

(a) Represents the number of subjects with no bleeds.

(b) Total subject-years is the cumulative sum of time in years that subjects were followed during the efficacy period.

(c) Summary statistics are based on annualized bleeding rates for each subject.

(d) Rate ratio and p-values relate to pairwise comparisons of Arm 1 to Arm 3 and Arm 2 to Arm 3 in study 997HA301.

Table 36 rFVIIIFc Consumption: Studies 8HA02PED and 997HA301, FAS

	Study 8HA02PED		Study 997HA301		
	<6 years (N=35)	6 to <12 years (N=34)	Arm 1 Tailored Prophylaxis (N=117)	Arm 2 Weekly Prophylaxis (N=24)	Arm 3 Episodic Dosing (N=23)
No. of subjects with an efficacy period	35	34	117	23	23
Monthly rFVIIIFc consumption (IU/kg) (a)					
Overall					
n	35	34	117	23	23
Mean	444.32	414.46	386.00	333.64	108.70
SD	92.223	81.338	86.801	54.381	72.863
Median	428.86	391.63	350.98	317.06	86.60
25th, 75th pctl.	378.65, 507.40	353.63, 461.66	327.34, 411.85	297.55, 349.22	60.51, 152.37
Min, Max	307.9, 706.2	318.2, 685.8	239.8, 661.9	279.4, 516.4	23.4, 297.6
Prophylactic inj.					
n	35	34	117	23	23
Mean	431.86	400.11	374.75	306.05	0.00
SD	86.482	65.577	83.446	48.979	0.000
Median	410.03	378.26	342.87	294.99	0.00
25th, 75th pctl.	374.03, 483.00	350.33, 451.18	322.58, 403.47	288.36, 308.23	0.00, 0.00
Min, Max	307.9, 702.2	318.2, 601.7	233.3, 640.3	259.1, 516.4	0.0, 0.0
Monthly number of injections (b)					
Overall					
n	35	34	117	23	23
Mean	9.35	9.19	8.70	5.57	3.68
SD	0.707	0.596	1.379	1.643	2.198
Median	9.14	9.03	8.88	4.98	3.25
25th, 75th pctl.	8.87, 9.49	8.88, 9.25	7.27, 9.87	4.67, 5.57	2.05, 4.94
Min, Max	8.7, 11.8	8.6, 11.9	6.3, 11.6	4.4, 11.4	0.8, 9.3
Prophylactic inj.					
n	35	34	117	23	23
Mean	9.09	8.87	8.39	4.70	0.00
SD	0.569	0.238	1.291	0.887	0.000
Median	8.88	8.87	8.79	4.51	0.00
25th, 75th pctl.	8.83, 9.00	8.71, 8.92	7.03, 9.57	4.37, 4.60	0.00, 0.00
Min, Max	8.7, 11.1	8.5, 9.7	6.0, 10.3	4.2, 8.7	0.0, 0.0

Note 1: Consumption is calculated for the efficacy period. Periods of PK evaluations and surgery/rehabilitation are not included in the efficacy period.

2: Abbreviation: pctl. = percentile, inj. = injection

(a) Monthly consumptions are the total rFVIIIFc consumption (IU/kg) received during the efficacy period extrapolated to a 1-month interval of time.

(b) Monthly number of injections are the total number of rFVIIIFc injections received during the efficacy period extrapolated to a 1-month or interval of time.

Across the individualised/tailored prophylaxis arms of the Phase 3 study in adults and adolescents ≥12 years of age and both cohorts of the Phase 3 study in children <12 years of age, the median prophylactic dosing interval was approximately 3.5 days (IQR: 3.17, 4.43 for subjects ≥12 years and 3.46, 3.51 for subjects <12 years). The median weekly prophylactic dose for tailored prophylaxis was 91.63, 86.88, and 77.90 IU/kg for subjects <6 years of age, subjects 6 to <12 years of age, and subjects ≥12 years of age, respectively.

The final treatment regimen for the majority of subjects in Arm 1 (82/117 subjects) in Study 997HA301 was a regular dosing interval every 3 to 5 days. For these subjects, the median average single prophylactic

(tailored) dose was 50.41 IU/kg every 3 days, 47.85 IU/kg every 4 days, and 50.61 IU/kg every 5 days; please see also Table 37.

Table 37 **Summary of Prophylactic Dose for the Last Regular Prophylactic Regimen for Subjects in Arm 1 by Prescribed Frequency (997HA301)**

Summary of prophylactic dose for the last regular prophylactic regimen for subjects in Arm 1 by prescribed frequency (997HA301)
Full Analysis Set
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Dosing frequency	Arm 1 - Tailored prophylaxis (N=117)
Average single dose (IU/kg) (b)	
Every 3 Days	
n	40
Mean (SD)	51.08 (11.281)
Median	50.41
25th, 75th percentile	47.94, 58.01
Min, Max	25.0, 88.6
Every 4 Days	
n	3
Mean (SD)	49.93 (12.162)
Median	47.85
25th, 75th percentile	38.94, 62.99
Min, Max	38.9, 63.0
Every 5 Days	
n	39
Mean (SD)	51.85 (5.008)
Median	50.61
25th, 75th percentile	49.33, 52.13
Min, Max	46.8, 74.3

Of the 117 subjects in Study 997HA301, 35 subjects were on a treatment regimen (alternating dosing) with twice weekly dosing. 34 subjects were on 25 IU/kg on Day 1 and 50 IU/kg on Day 4, and 1 subject was on 30 IU/kg on Day 1 and 60 IU/kg on Day 4. The median average tailored prophylactic dose per week was 77.15 IU/kg, and the median average single dose was 38.83 IU/kg.

In Study 8HA02PED, for 15 out of 69 subjects the final treatment regimen was a regular treatment regimen. Most of these (10/15 subjects) had a dosing interval of twice weekly; the remaining subjects had intervals of every 2 or 3 days. The median average single prophylactic (tailored) dose was 57.63 IU/kg every 2 days, 56.57 IU/kg every 3 days, and 56.17 IU/kg twice weekly.

The majority of subjects (54/69 subjects) in Study 8HA02PED –remained on a treatment regimen with alternating doses. The median average tailored prophylactic dose per week was 87.13 IU/kg and the median average single dose was 37.56 IU/kg 3 times weekly (1 subject only) and 43.52 IU/kg twice weekly.

For **efficacy evaluation during perioperative management**, a total of 22 **major surgeries** were analysed, including 9 major surgeries in Study 997HA301 and 13 major surgeries in adults in Study 8HA01EXT. No major surgeries were conducted in Study 8HA02PED.

In all 22 evaluated major surgeries, haemostasis was assessed as excellent or good.

Blood loss for the major surgeries ranged from 0 to 1200 mL during the surgery and from 0 to 1100 mL postoperatively (i.e., from the day following the day of surgery until discharge from the hospital).

In total, three subjects (who all underwent joint replacement and/or amputation procedures) required transfusions during the surgical period; one of them 1, the other two of them 2 units of red blood cells each.

In Study 997HA301, in all 9 major surgeries, a single injection of rFVIIIFc (median dose 51.4 IU/kg) was administered to maintain haemostasis during surgery. Median rFVIIIFc consumption during the whole surgical/rehabilitation period was 763.99 IU/kg. In Study 8HA01EXT, one surgery required two injections of rFVIIIFc to maintain haemostatis during the procedure, all others required one (injection dose range: 45.3-101.6 IU/kg). Total consumption ranged from 132.8-569.6 IU/kg.

51 minor surgeries in 41 subjects have been performed while on rFVIIIFc treatment. Minor surgeries included dental procedures, wound closure, cystoscopy, port placement, port removal, and gastroscopy and colonoscopy. In all of the 32 minor surgeries with available assessment of haemostasis, haemostasis was assessed as excellent or good. Although no major surgeries were performed in subjects <12 years of age, a total of 7 of the 32 evaluable minor surgeries were performed in 7 subjects in Study 8HA02PED: 2 surgeries in the <6 age cohort and 5 in the 6 to <12 age cohort.

Furthermore, post hoc pre-study and on-study comparisons were conducted by the Applicant for those subjects, who had already been on prophylaxis before study.

In the Phase 3 study in adults and adolescents ≥12 years of age (997HA301) who were on prior prophylaxis (n = 85), the median annualised bleeding rate pre-study was 6.0 compared to a median annualised bleeding rate of 2.32 on-study. In the Phase 3 study in children <12 years of age (8HA02PED) on prior prophylaxis (n = 62), the overall median annualised bleeding rate pre-study was 2.0 compared to a median annualised bleeding rate of 1.96 on-study.

Supportive studies

Supportive efficacy data was provided from the currently ongoing extension study (8HA01EXT). Median dose per injection to treat a bleeding episode was in Study 997HA301 29.94 IU/kg in Arm 1 (tailored prophylaxis), 21.65 IU/kg in Arm 2 (weekly dosing) and 26.46 IU/kg in Arm 3 (episodic dosing) compared to 46.88 IU/kg (tailored prophylaxis), 33.19 (weekly dosing) and 26.88 IU/kg (episodic) in the extension study 8HA01EXT.

In Study 8HA02PED, the median dose per injection to treat a bleeding episode was 49.69 IU/kg compared to 43.86 and 49.27 IU/kg in the <6 years and 6 to <12 years of age cohorts, respectively, in the extension study.

Cumulative efficacy and safety data from the ongoing extension study (8HA01EXT).

All subjects that received a weekly dose were evaluated to determine the cumulative weekly dosing experience across Study 997HA301 and the extension study (8HA01EXT); 2 subgroups were analyzed:

- Subjects who received weekly dose any time (ever) in Studies 997HA301 and/or 8HA01EXT
- Subjects who only received weekly dosing in Studies 997HA301 and 8HA01EXT.

A total of 37 subjects received weekly dosing with rFVIIIFc at some point during Studies 997HA301 and/or 8HA01EXT. This included the 23 subjects who received weekly dosing in Study 997HA301 and the 14 subjects who switched from another regimen in Study 997HA301 to weekly dosing in the extension study.

The ABR for subjects who were on weekly dosing at any time (ever) in Studies 997HA301 and/or 8HA01EXT is provided in Table 38.

Table 38 **Summary of Annualized Bleeding Rate for Subjects Who Were Ever on Weekly Prophylaxis in Study 997HA301 and/or Study 8HA01EXT**

Summary of annualized bleeding rate for subjects who were ever on weekly prophylaxis in study 997HA301 and/or study 8HA01EXT
Full Analysis Set
Page 1 of 2

	Study 997HA301 (N=24)	Study 8HA01EXT (N=27)	Overall (a) (N=38)
Annualized bleeding episodes per subject			
n	23	27	37
Mean (SD)	8.81 (13.690)	3.70 (5.105)	5.94 (10.923)
Median	3.59	2.03	2.00
25, 75th percentile	1.86, 8.36	0.60, 4.39	0.72, 4.52
Min, Max	0.0, 58.0	0.0, 18.5	0.0, 58.0
Spontaneous annualized bleeding episodes per subject			
n	23	27	37
Mean (SD)	5.23 (9.023)	2.23 (3.681)	3.47 (6.971)
Median	1.93	0.76	1.00
25, 75th percentile	0.00, 4.78	0.00, 2.66	0.00, 2.66
Min, Max	0.0, 32.8	0.0, 16.5	0.0, 32.8

Note 1: Data cutoff for study 8HA01EXT was 6 January 2014.
2: The annualized bleeding rate is the total number of bleeding episodes during the efficacy period extrapolated to a 1-year interval of time.
3: The efficacy period begins with the first prophylactic dose of rFVIIIFc and ends with the last dose (regardless of the reason for dosing). Surgery/rehabilitation periods and large injection intervals are not included in the efficacy period.
4: Subject HA2116 in study 997HA301 withdrew after the PK evaluations (no efficacy assessments could be made).
(a) Presents the cumulative annualized bleeding rate from studies 997HA301 and 8HA01EXT.

For the 17 subjects who were only on weekly dosing, cumulative ABR across studies is presented in Table 39.

Table 39 **Summary of Annualized Bleeding Rate for Subjects Who Were Only on Weekly Prophylaxis in Study 997HA301 and study 8HA01EXT**

Summary of annualized bleeding rate for subjects who were only on weekly prophylaxis in study 997HA301 and study 8HA01EXT
Full Analysis Set
Page 1 of 2

	Study 997HA301 (N=18)	Study 8HA01EXT (N=13)	Overall (a) (N=18)
Annualized bleeding episodes per subject			
n	17	13	17
Mean (SD)	6.71 (8.458)	5.40 (6.835)	5.96 (7.448)
Median	4.02	2.03	2.00
25, 75th percentile	1.93, 7.62	0.67, 7.37	0.98, 7.43
Min, Max	0.0, 32.3	0.0, 18.5	0.0, 22.0
Spontaneous annualized bleeding episodes per subject			
n	17	13	17
Mean (SD)	3.67 (5.981)	2.95 (5.066)	2.85 (4.814)
Median	1.93	0.68	1.00
25, 75th percentile	0.00, 3.81	0.00, 2.30	0.49, 2.00
Min, Max	0.0, 24.7	0.0, 16.5	0.0, 18.6

Note 1: Data cutoff for study 8HA01EXT was 6 January 2014.
2: The annualized bleeding rate is the total number of bleeding episodes during the efficacy period extrapolated to a 1-year interval of time.
3: The efficacy period begins with the first prophylactic dose of rFVIIIFc and ends with the last dose (regardless of the reason for dosing). Surgery/rehabilitation periods and large injection intervals are not included in the efficacy period.
4: Subject HA2116 in study 997HA301 withdrew after the PK evaluations (no efficacy assessments could be made).
(a) Presents the cumulative annualized bleeding rate from studies 997HA301 and 8HA01EXT.

Clinical studies in special populations

	Age 65-74 (Older subjects number / total number)	Age 75-84 (Older subjects number / total number)	Age 85+ (Older subjects number / total number)
Controlled Trials	0	0	0
Non Controlled Trials	2/233	0	0

2.5.3. Discussion on clinical efficacy

The rFVIIIFc clinical development programme was designed to meet the requirements for pre-authorisation studies as set out in the guideline on the clinical investigation of recombinant and human plasma-derived FVIII products (EMA/CHMP/BPWP/144533/2009) such that comprehensive PK, efficacy, and safety data for rFVIIIFc were obtained to support approval. Data are provided from clinical studies 997HA301, 8HA02PED and 8HA01EXT in previously treated patients (PTPs) with haemophilia A.

Design and conduct of clinical studies

Conduct of the clinical investigation of rFVIIIFc follows the EMA Guideline on the clinical investigation of factor VIII products (EMA/CHMP/BPWP/144533/2009): A sufficient number of previously treated patients with severe haemophilia A out of the relevant age groups were followed for at least 50 EDs, with also a sufficient number of subjects ≥12 years who were followed for at least 6 months for assessment of rFVIIIFc efficacy in long-term prophylaxis. Likewise, the requested number of rFVIIIFc response assessments during (major) surgical procedures was satisfied.

Endpoints chosen are regarded appropriate for efficacy assessment of rFVIIIFc treatment and also in line with the current FVIII Guidance. rFVIIIFc efficacy was investigated in treatment of bleeds, routine prophylaxis and perioperative management by assessment of treatment response rating, rFVIIIFc consumption and determination of (annualised) bleeding rates. Presentation of results of response rating was done for all kinds of bleeding episodes. Because of the limited number of subjects with severe hemophilia A, the sample size was based on clinical rather than statistical considerations, this is in accordance to the guideline.

Efficacy data and additional analyses

For evaluation of rFVIIIFc efficacy in routine prophylaxis, annualised bleeding rates were determined. Specifically for Study 997HA301, also statistical comparisons of bleeding rates between the three different treatment arms of the trial were made. Comparisons between study arm 1 and arm 2, however, may be biased due to systematic differences between the respective patient populations. For patients in treatment arm 2 and 3, by contrast, the same eligibility criteria applied and subjects were randomised between these two arms. Assessment of differences between arm 2 and 3 show a significant reduction of the annualised bleeding rate for weekly rFVIIIFc prophylaxis compared to on-demand treatment.

When viewed separately for each of arm of Study 997HA301 as well as for Study 8HA02PED, for those subjects having received tailored prophylaxis regimen in these both studies, median annualised bleeding rates lie within an acceptable range.

For those subjects in Study 997HA301 with weekly prophylaxis, however, the bleeding rate achieved during this regimen cannot be regarded as sufficient, considering that prophylactic treatment would usually aim at a marked reduction in breakthrough bleeding frequency. In this context, it should also be noted, that for this

weekly dosing regimen, no bleeding episodes were reported for only 17.4% of subjects during the observation period (compared to 45.3% and 46.4% for tailored prophylaxis in Study 997HA301 and Study 8HA02PED, respectively, and 0% for on-demand treatment in Study 997HA301). New analyses of data from weekly prophylactic treatment with rFVIIIFc with cumulative ABRs show, that bleeding rates decreased during the extension study (8HA01EXT), where dosing changes were allowed (which was not allowed during the parent study 997HA301). From these cumulative ABRs it can be seen, that, after all, a highly selective patient population does exist, for whom weekly treatment with rFVIIIFc shows a sufficient level of efficacy at least over a limited period of time. However, only 37 of an overall of 233 subjects dosed with rFVIIIFc were ever - i.e. at any time during the clinical study programme - on weekly prophylaxis with the study product, and only 13 subjects remained on weekly prophylaxis during the whole period. This is not considered a relevant special population to be reflected in section 4.2 of the SmPC, as set out in EC Guideline on Summary of Product Characteristics. Weekly dosing as starting regimen is considered an option for all factor VIII products in current guidance of e.g. WFH or DHG. It is not deemed specific to rFVIIIFc, since neither clinical nor (population) PK data indicate, that a dosing interval >5 days would be a property of the product. It should further be taken into account that prophylaxis with FVIII as a therapeutic option is especially pertaining to paediatric patients with severe haemophilia A. In paediatric patients <12 years of age, though, weekly prophylaxis was not utilised at all. Therefore, a statement in the SmPC regarding a weekly treatment regimen, as initially proposed by the applicant, could not be endorsed (See also discussion in Clinical pharmacology).

For the tailored prophylaxis arms of both Phase 3 studies, median prophylactic dosing interval (3.5 days) and median weekly prophylactic dose (91.63, 86.88, and 77.90 IU/kg for subjects <6 years of age, subjects 6 to <12 years of age, and subjects ≥12 years of age, respectively) were presented by the MAA. Consumption data for overall and prophylactic rFVIIIFc consumption show, that for tailored prophylaxis, overall data and prophylactic data do not differ substantially, wherefore it can assumed, that for these treatment regimens, bleeding rates were mainly achieved by the regimen itself (and not to additional rFVIIIFc administration in the context of breakthrough bleeding).

Prophylactic dosing recommendations in section 4.2 of the SmPC of 50 IU/kg every 3 to 5 days could be established by clinical data of patients ≥12 years of age.

Patients <12 years of age, however, were mostly treated with alternating doses

As an additional analysis, post hoc pre-study and on-study comparisons are presented by the MAA. Comparisons between bleeding rates, number of injections and consumption before and during study treatment were only conducted for those subjects, who had already been on prophylaxis before study, which is considered appropriate. Nevertheless, it should be kept in mind that these comparisons were made to retrospective data and therefore have to be interpreted with caution. Considered, however, together with results of rFVIIIFc efficacy evaluation in prophylaxis, these analyses suggest that the prolonged dosing interval chosen during the clinical investigation of rFVIIIFc is paralleled by an increase of single doses, while overall consumption remains unchanged.

Overall efficacy of rFVIIIFc in the treatment of bleeding episodes could be shown with more than 80% of the occurred bleeding episodes having been treated with one injection of rFVIIIFc and median doses within an acceptable range in both Phase 3 studies across all treatment arms and age groups. However, in treatment arm 2 of Study 997HA301 (weekly dosing regimen), efficacy ratings are not fully consistent with the generally low number of infusions needed for the treatment of bleeds. This may suggest that symptom relief didn't manifest as unequivocally as expected by the subject and along with this, it is striking that median

dose per injection was lower in this study arm (21.65 IU/kg in Arm 2 vs 29.94 and 26.46 IU/kg in Arm 1 and Arm 3).

Regarding on-demand treatment in low-grade haemorrhage and minor surgery, a prolonged injection frequency was not sufficiently supported by the clinical data nor are prolonged dosing intervals considered reasonable in the treatment of acute bleeds, therefore the time interval for a repeated injection in on-demand treatment of low-grade haemorrhage was adjusted in accordance with the severity of the bleeding, a relevant guidance is given in the SmPC. The calculation of the required dose of recombinant factor VIII Fc is based on the empirical finding that 1 International Unit (IU) factor VIII per kg body weight raises the plasma factor VIII activity by 2 IU/dL so that the required dose is determined as: Required units = body weight (kg) x desired factor VIII rise (%) (IU/dL) x 0.5 (IU/kg per IU/dL). The amount to be administered and the frequency of administration should always be oriented to the clinical effectiveness in the individual case (see SmPC section 4.2 and 5.2). The time to peak activity is not expected to be delayed.

A sufficient number of major surgeries were evaluated for rFVIIFc efficacy in compliance with the EMA Guideline on clinical investigation of FVIII products. In paediatric patients, only minor surgeries were performed; however, evaluation of efficacy in major surgery in children is not explicitly requested by the current guidance. Assessments of haemostatic efficacy, blood loss, transfusion requirements and rFVIIIFc consumption show adequate results for rFVIIIFc efficacy during major surgical procedures.
In line with EMA guidance, a clinical study (8HA01EXT) has been initiated to collect long-term efficacy and safety data in order to extend the initial observations from pre-authorisation studies. Study 8HA01EXT is included as a post-marketing study in the Risk Management Plan; interim data from this study are provided in this MAA. Also in line with EMA guidance, a clinical study (997HA306) will be conducted to evaluate the efficacy and safety of rFVIIIFc in PUPs; as this study is planned for initiation in 2015 and data for PUPs are not required for initial marketing authorisation, data from this study are not included in this MAA.

2.5.4. Conclusions on the clinical efficacy

Efficacy of rFVIIIFc was adequately evaluated in the treatment of bleeds, routine prophylaxis and major surgeries showing positive results.

The CHMP considers the following measures necessary to address issues related to efficacy:

- Submission of the results from study 997HA306, An Open-Label, Multicentre Evaluation of the Safety and Efficacy of Recombinant Coagulation Factor VIII Fc Fusion Protein (rFVIIIFc; BIIB031) in the Prevention and Treatment of Bleeding in PUPs with Severe Haemophilia A (PUPs study).

2.6. Clinical safety

Safety data is derived from all five rFVIIIFc studies (Studies 998HA101, 997HA301, 8HA02PED, 8HA01EXT, and 997HA307).

The clinically relevant repeat-dose safety data in support of marketing authorisation are from the completed Phase 3 studies 997HA301 and 8HA02PED, and from the interim data (as of the cut-off of 06 January 2014) for the extension study 8HA01EXT. Data from these three studies were pooled for an integrated presentation.

Data from the Phase 1/2a study are discussed separately because of the relatively small number of subjects and study design differences, including single-dose exposure, different visit schedules, and shorter duration of observation.

Patient exposure

For studies 998HA101, 997HA301, 8HA02PED, patient exposure is presented in the following two tables:

Table 40 Cumulative Summary of Duration of Dosing with rFVIIIFc For All Subjects Enrolled in Studies 997HA301, 8HA02PED, and 8HA01EXT by Age, Safety Analysis Set (SAS)

	Age cohort (years old)				
	<6 (N=35)	6 to <12 (N=34)	12 to <18 (N=13)	>= 18 (N=151)	Total (N=233)
Cumulative number of weeks on rFVIIIFc (a)					
At least 13 weeks	31 (88.6%)	34 (100.0%)	13 (100.0%)	146 (96.7%)	224 (96.1%)
At least 26 weeks	28 (80.0%)	33 (97.1%)	13 (100.0%)	144 (95.4%)	218 (93.6%)
At least 39 weeks	15 (42.9%)	31 (91.2%)	12 (92.3%)	138 (91.4%)	196 (84.1%)
At least 52 weeks	5 (14.3%)	17 (50.0%)	11 (84.6%)	138 (91.4%)	171 (73.4%)
At least 65 weeks	0	0	10 (76.9%)	136 (90.1%)	146 (62.7%)
At least 78 weeks	0	0	10 (76.9%)	135 (89.4%)	145 (62.2%)
At least 91 weeks	0	0	10 (76.9%)	133 (88.1%)	143 (61.4%)
At least 104 weeks	0	0	9 (69.2%)	127 (84.1%)	136 (58.4%)
At least 117 weeks	0	0	4 (30.8%)	36 (23.8%)	40 (17.2%)
At least 130 weeks	0	0	0	11 (7.3%)	11 (4.7%)
At least 143 weeks	0	0	0	3 (2.0%)	3 (1.3%)
At least 156 weeks	0	0	0	1 (0.7%)	1 (0.4%)
Total weeks on rFVIIIFc					
n	35	34	13	151	233
Mean	34.86	50.87	99.34	104.89	86.18
SD	14.981	9.464	30.684	29.221	38.260
Median	33.92	53.38	109.94	111.08	108.50
Min, Max	2.0, 60.1	22.1, 61.7	35.2, 128.1	<1, 161.5	<1, 161.5

NOTE 1: Data cut-off for study 8HA01EXT was 6 January 2014.

2: Percentages are based on numbers of subjects dosed with rFVIIIFc in each age cohort or overall.

3: Time on rFVIIIFc refers to the length of time from the first rFVIIIFc dose in the parent study (997HA301 or 8HA02PED) through 6 January 2014 (date of data cut-off) for subjects ongoing in study 8HA01EXT, or the date of last rFVIIIFc dose or the date of the last non-safety follow-up study visit for subjects who withdrew from the study (997HA301, 8HA02PED or 8HA01EXT) and whose last treatment regimen was prophylactic or episodic, respectively. The time between the parent study and study 8HA01EXT was excluded if the gap was greater than 7 days for subjects originating from study 997HA301 or 4 days for subjects originating from study 8HA02PED, respectively.

(a) A subject can appear in more than one category of treatment duration.

Table 41 Cumulative Summary of Injections and Days of Exposure to rFVIIIFcFor All Subjects Enrolled in Studies 997HA301, 8HA02PED, and 8HA01EXT by Age, SAS

	Age cohort (years old)				
	<6 (N=35)	6 to <12 (N=34)	12 to <18 (N=13)	>= 18 (N=151)	Total (N=233)
Total exposure days (a)					
<50	7 (20.0%)	0	0	11 (7.3%)	18 (7.7%)
50-<100	19 (54.3%)	8 (23.5%)	2 (15.4%)	12 (7.9%)	41 (17.6%)
100-<150	9 (25.7%)	26 (76.5%)	1 (7.7%)	36 (23.8%)	72 (30.9%)
150-<200	0	0	3 (23.1%)	30 (19.9%)	33 (14.2%)
200-<250	0	0	4 (30.8%)	34 (22.5%)	38 (16.3%)
250-<300	0	0	3 (23.1%)	27 (17.9%)	30 (12.9%)
300-<350	0	0	0	1 (0.7%)	1 (0.4%)
n	35	34	13	151	233
Mean	72.8	104.7	194.0	173.0	149.1
SD	33.13	19.46	64.10	76.41	76.50
Median	69.0	109.0	220.0	180.0	129.0
Min, Max	5, 142	52, 142	77, 272	1, 326	1, 326
Total number of injections per subject					
n	35	34	13	151	233
Mean	73.8	106.6	195.9	175.4	151.3
SD	34.22	20.33	64.22	78.35	78.11
Median	70.0	110.0	221.0	185.0	136.0
Min, Max	5, 146	53, 145	77, 273	1, 328	1, 328

NOTE 1: Data cut-off for study 8HA01EXT was 6 January 2014.

2: Percentages are based on numbers of subjects dosed with rFVIIIFc in each age cohort or overall.

(a) An exposure day is a 24-hour period in which one or more rFVIIIFc injections are given. All injections over the study course are counted.

Exposure stratified **by dose** is presented as follows:

Table 42 Cumulative summary of duration of dosing and days of exposure with rFVIIIFc for all subjects enrolled in studies 997HA301, 8HA02PED, and 8HA01EXT by dose, SAS

	Dose group			
	<=50 IU/kg (N=231)	>50 to <65 IU/kg (N=216)	>=65 IU/kg (N=101)	Total (N=233)
Cumulative number of weeks on rFVIIIFc (a)				
At least 13 weeks	160 (69.3%)	155 (71.8%)	61 (60.4%)	224 (96.1%)
At least 26 weeks	105 (45.5%)	115 (53.2%)	43 (42.6%)	218 (93.6%)
At least 39 weeks	75 (32.5%)	80 (37.0%)	38 (37.6%)	196 (84.1%)
At least 52 weeks	59 (25.5%)	63 (29.2%)	34 (33.7%)	171 (73.4%)
At least 65 weeks	44 (19.0%)	46 (21.3%)	31 (30.7%)	146 (62.7%)
At least 78 weeks	37 (16.0%)	35 (16.2%)	22 (21.8%)	145 (62.2%)
At least 91 weeks	28 (12.1%)	23 (10.6%)	14 (13.9%)	143 (61.4%)
At least 104 weeks	17 (7.4%)	10 (4.6%)	5 (5.0%)	136 (58.4%)
At least 117 weeks	1 (0.4%)	2 (0.9%)	1 (1.0%)	40 (17.2%)
At least 130 weeks	0	1 (0.5%)	0	11 (4.7%)
At least 143 weeks	0	0	0	3 (1.3%)
At least 156 weeks	0	0	0	1 (0.4%)

NOTE 1: Data cutoff for study 8HA01EXT was 6 January 2014.
2: Percentages are based on numbers of subjects dosed with rFVIIIFc in each dose group or total for each age cohort or overall.
3: Time on rFVIIIFc refers to the length of time from the first rFVIIIFc dose in the parent study (997HA301 or 8HA02PED) through 6 January 2014 (date of data cutoff) for subjects ongoing in study 8HA01EXT, or the date of last rFVIIIFc dose or the date of the last non-safety follow-up study visit for subjects who withdrew from the study (997HA301, 8HA02PED or 8HA01EXT) and whose last treatment regimen was prophylactic or episodic, respectively. The time between the parent study and study 8HA01EXT was excluded if the gap was greater than 7 days for subjects originating from study 997HA301 or 4 days for subjects originating from study 8HA02PED, respectively.
4: Subjects are included in each dose group they participated in for the duration of time on that dose group and as such may appear in more than one dose groups.
5: Time on rFVIIIFc for injections with missing dose is included in the total column, but is not included in any dose group.
(a) A subject can appear in more than one category of treatment duration.

SOURCE: FACTOR8HA/EU/DAY120/T-DUR-DOSING-AGEDOSE-SCE.SAS DATE: 05MAY2015

	Dose group			
	<=50 IU/kg (N=231)	>50 to <65 IU/kg (N=216)	>=65 IU/kg (N=101)	Total (N=233)
Total exposure days (a)				
<50	117 (50.6%)	108 (50.0%)	62 (61.4%)	18 (7.7%)
50-<100	60 (26.0%)	57 (26.4%)	18 (17.8%)	41 (17.6%)
100-<150	20 (8.7%)	29 (13.4%)	15 (14.9%)	72 (30.9%)
150-<200	23 (10.0%)	11 (5.1%)	1 (1.0%)	33 (14.2%)
200-<250	8 (3.5%)	10 (4.6%)	4 (4.0%)	38 (16.3%)
250-<300	3 (1.3%)	1 (0.5%)	1 (1.0%)	30 (12.9%)
300-<350	0	0	0	1 (0.4%)

NOTE 1: Data cutoff for study 8HA01EXT was 6 January 2014.
2: Percentages are based on numbers of subjects dosed with rFVIIIFc in each dose group or total for each age cohort or overall.
3: Subjects are included in each dose group they participated in for the exposure days on that dose group and as such may appear in more than one dose groups.
4: Injections with missing dose are included in the total column, but are not included in any dose group.
(a) An exposure day is a 24-hour period in which one or more rFVIIIFc injections are given. All injections over the study course are counted. If multiple injections in different dose groups were given within an exposure day, the exposure day is included in each dose group.

SOURCE: FACTOR8HA/EU/DAY120/T-EXPOSURE-AGEDOSE-SCE.SAS DATE: 05MAY2015

Adverse events

The most frequently reported treatment-emergent adverse events (TEAEs; AEs emerging during treatment with rFVIIIFc but excluding AEs emerging during the perioperative management period for a major surgery) with an incidence ≥5% were nasopharyngitis (18.9%), upper respiratory tract infection (12.4%), arthralgia (11.6%), headache (10.7%), cough (10.3%), fall (7.7%), diarrhoea (6.0 %), pyrexia (5.6%), and influenza and vomiting (5.2% each).

Most subjects had TEAEs that were judged by the Investigator as unrelated to the rFVIIIFc treatment. After medical review, a total of 25 AEs were considered as related to study treatment and included as adverse drug reactions (ADRs): malaise, headache, arthralgia, and myalgia (2 subjects or 0.9% each), and bradycardia,

abdominal pain lower, chest pain, feeling cold, feeling hot, procedural hypotension, joint swelling, dizziness, dysgeusia, cough, rash, angiopathy (vascular pain after injection), hypertension, back pain, hot flush, and rash erythematous (1 subject or 0.4% each).

In the Phase 1/2a study 998HA101, 44 TEAEs were reported by 11 subjects (68.8%), including 4 subjects (66.7%) in the 25 IU/kg dose group and 7 subjects (70%) in the 65 IU/kg dose group. Most AEs were reported by 1 subject; back pain, dysgeusia, and myalgia were reported in 2 subjects each; nasopharyngitis and headache were reported in 3 subjects each. Two subjects in the 65 IU/kg dose group experienced AEs considered by the Investigator to be at least possibly related to study treatment. One subject reported muscle tightness, myalgia, and dizziness that were considered possibly related and reported dysgeusia that was considered related. The other subject reported tachycardia, hyperreflexia, malaise, and paraesthesia, all of which were considered possibly related.

Adverse drug reactions are listed in the table below with their respective frequencies.

Table 43: Adverse drug reactions and respective frequencies.

Adverse reactions	Number of patients (%), N=233
Headache Dizziness Dysgeusia	2 (0.9%) 1 (0.4%) 1 (0.4%)
Bradycardia	1 (0.4 %)
Hypertension Hot flush Angiopathy[1]	1 (0.4%) 1 (0.4%) 1 (0.4%)
Cough	1 (0.4%)
Abdominal pain, lower	1 (0.4%)
Rash Rash erythematous	1 (0.4%) 1 (0.4%)
Arthralgia Myalgia Back pain Joint swelling	2 (0.9%) 2 (0.9%) 1 (0.4%) 1 (0.4%)
Malaise Chest pain Feeling cold Feeling hot	2 (0.9%) 1 (0.4%) 1 (0.4%) 1 (0.4%)
Anti-Factor VIII antibody positive[2]	1 (0.4%)
Procedural hypotension	1 (0.4%)

[1] Investigator term*: vascular pain after injection of ELOCTA*

[2]One adult subject had a positive anti-Factor VIII antibody test result coincident with a single measurement of a neutralising antibody titre of 0.73 Bethesda Units/mL at Week 14. The neutralising antibody was not confirmed upon repeat testing 18 days later and was negative at subsequent visits. There was an increase in clearance (CL) at Week 14 that resolved with continued rFVIIIFc treatment.

[3]table reflected in the SmPC according to the MedDRA system organ classification (SOC and Preferred Term Level), where frequencies follow the convention: very common (≥1/10); common (≥1/100 to <1/10); uncommon (≥1/1,000 to <1/100); rare (≥1/10,000 to <1/1,000); very rare (<1/10,000), not known (cannot be estimated from the available data).

Serious adverse events and deaths

Of the total of 233 subjects treated with rFVIIIFc, 39 subjects (16.7%) experienced a total of 55 serious TEAEs. All of the 55 serious TEAEs were assessed by the Investigator as unrelated to rFVIIIFc treatment (none were missing an assessment of relationship), and all resolved.

Two serious TEAEs were associated with a fatal outcome, overdose (polysubstance overdose) and completed suicide in 1 subject with a history of depression, substance addiction, and substance overdose. The Investigator assessed the overdose and the completed suicide as unrelated to rFVIIIFc treatment.

A review of AEs of special interest revealed 12 non-serious AEs of allergic reactions, thereof 10 assessed as not related to rFVIIIFc and 1 non-serious AEs of thrombotic events, all assessed as not related.

Of the 22 subjects, who underwent 24 **major surgeries**, 8 experienced a total of 18 (S)AEs during the postoperative period, all assessed by the Investigator as unrelated to rFVIIIFc.

Most frequently reported were AEs related to postoperative fever/pyrexia (3 subjects) and anaemia/Hb decreased (2 subjects). 1 SAE of a post-procedural haemorrhage, following a major surgery of knee revision arthroplasty, was reported in 1 subject); it resolved 1 day after onset, and no action was taken with study treatment as a result of the event.

No deaths and no SAEs occurred during Study 998HA101.

Laboratory findings

There were no patterns or trends observed in abnormalities in haematology or blood chemistry parameters. However, some discrepant information needs clarification, as outlined in the list of questions.

Safety in special populations

The clinical data from the completed studies 997HA301 and 8HA02PED and the ongoing extension study 8HA01EXT as of the data cut off of 6 January 2014, includes two patients $\geq$ 65 years of age (2/233, 0.86%). Neither of the patients experienced a serious adverse event (SAE). In total, these patients experienced 12 non serious adverse events (AEs) throughout the study. None of these events led to study discontinuation. The AEs events reported included the following: Nervous systems disorders (1 event), cardiac disorders (1 event), infections and infestations (3 events), Injury poisoning and procedural complications (2 events), gastrointestinal disorders (3 events), renal and urinary disorders (1 event), and general disorders and administration site conditions (1 event).

Immunological events

Inhibitor development

One subject from Study 997HA301 had a low-titre positive neutralising anti-rFVIIIFc antibody test result at Week 14 during Study 997HA301, with negative results upon repeat testing of a separate sample taken 18 days later upon subsequent testing at Week 28 and End of Study (Week 34) during Study 997HA301, as well as at Months 6, 12, and 18 during the extension study.

Positive test results for Anti-rFVIIIFc binding antibody (ADA), which is distinguished from neutralising antibody (inhibitor), were observed both prior to and following initiation of treatment with rFVIIIFc. 12 subjects had ADA first detected prior to treatment with rFVIIIFc (5 subjects from Study 997HA301 and 7 subjects from Study 8HA02PED). 6 subjects with negative results prior to rFVIIIFc treatment had positive results during the study (all from Study 997HA301). One of these subjects from Study 997HA301 had a positive rFVIIIFc neutralising antibody test result (0.73 BU/mL) at the time he had an ADA-positive result at Week 14 without associated AEs.

Of those subjects, with ADA positive test results prior to initiation of treatment, 1 subject from Study 8HA02PED had increased clearance of 5.42 mL/h/kg accompanied by slightly higher than normal IR of 3.44 IU/dL per IU/kg by the one-stage assay.

Infection

There may be a theoretical concern that saturation of FcRn with rFVIIIFc might result in increased catabolism and reduced half-life of IgG (thereby increasing a subject's risk of infection). However, the level of rFVIIIFc in the circulation after administration is minimal compared with the level of endogenous IgG. Nonetheless, a comprehensive data collection and evaluation of total serum IgG and IgG subclass levels was performed in the Phase 3 study in adults and adolescents ≥12 years of age (997HA301) revealing no clinically meaningful changes.

Samples for testing of serum immunoglobulin were not collected in Study 8HA02PED or Study 8HA01EXT.

Furthermore, a comprehensive medical review of event terms relevant to infection was performed for Studies 997HA301, 8HA02PED, and 8HA01EXT. Of the total of 233 subjects treated with rFVIIIFc, 127 subjects (54.5%) experienced at least 1 TEAE in the infections and infestations SOC. The infection TEAEs reported by 12 or more subjects (≥5%) were nasopharyngitis in 44 subjects (18.9%), upper respiratory tract infection in 29 subjects (12.4%), and influenza in 12 subjects (5.2%). All of the TEAEs in the infections and infestations SOC were assessed by the Investigator as unrelated to rFVIIIFc treatment, including 8 serious TEAEs in the infections and infestations SOC, which were reported in 6 subjects (2.6%). The serious TEAEs in the infections and infestations SOC included Pericoronitis (wisdom tooth), Appendicitis, Influenza, Metapneumovirus infection, Viral Infection, Bacillus infection and Escherichia infection, Croup infectious.

Safety related to drug-drug interactions and other interactions

Not applicable

Discontinuation due to adverse events

A total of 5 subjects discontinued or withdrew due to a TEAE: related arthralgia, related rash, unrelated femur fracture, unrelated overdose and completed suicide with an outcome of death; blood creatinine increased, assessed as related by the Investigator, after medical review as unlikely related to study treatment. Additionally, for one subject with multiple related AEs, who discontinued the study, it is unknown whether the events contributed to the subject's decision to withdraw consent.

Post marketing experience

rFVIIIFc was approved in the US on 06 June 2014 and became commercially available on 14 July 2014. As of 31 August 2014, 1 SAE of a high-titre factor VIII inhibitor in an 11-month-old minimally treated patient with severe haemophilia A was reported.

2.6.1. Discussion on clinical safety

Patient exposure is in accordance with the requirements of the EMA FVIII Guideline for an application for marketing authorisation, with a sufficient number of patients out of the relevant age groups exposed over a sufficiently long period of time.

Compared to the current EMA factor VIII core SmPC, considerably higher doses (up to 65 IU/kg in patients ≥12 years and up to 80 IU/kg in patients <12 years) were proposed for prophylactic treatment. As FVIII core SmPC recommendations are based on longstanding clinical experience in haemophilia treatment, there is a limitation of the global factor VIII clinical safety database concerning long-term prophylactic treatment with such high doses. As already discussed under Pharmacokinetics, for these doses of 65 IU/kg, elevated factor VIII activity peak levels >150 IU/dl were observed during study 998HA101, which may constitute a risk factor for venous thromboembolism (Jenkins et al. 2012).

Additional data on rFVIIIFc exposure stratified by dose as well as dose-related AE data support dose recommendations in the SmPC up to 65 IU/kg for patients ≥12 years of age at this stage. For patients <12 years, although exposure to rFVIIIFc to doses ≥65 IU/kg was low, no specific restriction to doses <65 IU/kg are considered necessary either. However, the SmPC recommendation to treatment doses up to 80 IU/kg in the paediatric population below the age of 12 is not acceptable since not supported by clinical data.

The clinical safety database of rFVIIIFc is limited with regard to elderly patients, who are at higher risk for thromboembolism. None of the study subjects investigated within the rFVIIIFc clinical development programme was older than 65 years of age and thus also no dose-related data exist. Although their investigation is not strictly recommended by the current factor VIII guidance, this population is of increasing importance, since age composition of the haemophilic population has changed over the last years with a growing proportion of elderly patients. Individual case reports of elderly haemophilia A subjects experiencing thrombotic events under FVIII treatment exist (Lickfett et al. 1998). With regard to this patient population, concerns remain. According to the applicant, routine pharmacovigilance activities to assess the safety of rFVIIIFc for patients in the age category >65 years will be implemented. The safety profile in patients >65 years old is stated as missing information in the RMP. Possible dose-related implications in terms of an increased risk for TEE are however not addressed by post-marketing measures yet (See RMP).

As the most important safety aspect of a factor VIII product, inhibitor development has to be taken into account. Procedures and definitions regarding inhibitor testing, as conducted in the context of the clinical development programme of rFVIIIFc, meet the standards set out in the current EMA FVIII guidance. Furthermore, it was tested for anti-rFVIIIFc binding antibodies (ADA), which is considered adequate for a novel recombinant factor VIII product.

One subject from Study 997HA301 had a low-titre (0.73 BU/mL) positive inhibitory anti-rFVIIIFc antibody test result at Week 14 during Study 997HA301, with negative results upon multiple repeat testing from 18 days up to 18 months later. Together with a transiently reduced rFVIIIFc activity and recovery coinciding with the Week 14 positive inhibitor test result, this is suggestive of a transient low-titre inhibitor in this subject. Additionally, during the post-marketing period in the US, one case of a high-titre inhibitor development (37 BU/mL at first and 27 BU/mL upon repeat testing) in an 11-month-old minimally treated patient with severe haemophilia A was reported. Overall, these findings are not indicative of a higher than expected inhibitor incidence under treatment with rFVIIIFc.

ADA could be detected in a total of 18 subjects prior or during the study. There was no relationship with adverse events or problems with FVIII plasma exposure, except in the above mentioned subject who had an increase in CL and only one coincidental positive unconfirmed inhibitor test. According to the applicant, there was a possible temporal association of increased bleeding tendency and an increase in CL and Vss with the positive ADA results and the transient positive neutralizing antibody test result in this Subject. This is considered a justification to include this issue in the SmPC. The physicians should be informed of the detection of others antibodies, particularly if these can have PK consequences.

The theoretical concern, that a subject's risk of infection might be increased because of saturation of the neonatal Fc receptor by rFVIIIFc, was addressed by the applicant. Neither evaluation of serum IgG levels nor review of the respective infection event terms showed any results out of the expected ranges.

Previously untreated patients (PUPs) were not investigated yet. A respective statement, as required by the current EMA FVIII guidance, was included under section 4.2 of the SmPC.

Limitations of the clinical safety database for patients >65 years in view of the SmPC dose range are of importance, since the proposed unusual high factor VIII doses might be associated with an increased risk for thromboembolic events especially in this patient population. This is addressed in the RMP as additional data are expected through routine pharmacovigilance and ongoing studies in the PhV plan.

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

2.6.2. Conclusions on the clinical safety

The clinical safety data as presented by the applicant are not indicative of unexpected findings concerning the safety profile of rFVIIIFc and inhibitor incidence under rFVIIIFc treatment.

No safety concern precluding an approval has been identified, additional safety information will be obtained as post-authorisation

The CHMP considers the following measures necessary to address issues related to safety:

- Submission of the results from 8HA01EXT, An Open-Label, Multicentre Evaluation of the Long-Term Safety and Efficacy of Recombinant Human Coagulation Factor VIII Fusion Protein (rFVIIIFc) in the Prevention and Treatment of Bleeding Episodes in Previously Treated Subjects with Haemophilia A Long-term safety of rFVIIIFc in subjects with haemophilia A; Long-term safety evaluation Safety profile in patients ≥65 years old.
- Submission of the results from 997HA306, An Open-Label, Multicentre Evaluation of the Safety and Efficacy of Recombinant Coagulation Factor VIII Fc Fusion Protein (rFVIIIFc; BIIB031) in the Prevention and Treatment of Bleeding in PUPs with Severe Haemophilia A (PUPs study); to evaluate the safety of rFVIIIFc in PUPs with severe haemophilia; Safety profile in PUPs including patients <2 years old.
- Final results of the ongoing safety part of Study 997HA307 are expected by the March 2016.

2.7. Risk Management Plan

The CHMP received the following PRAC Advice on the submitted Risk Management Plan:

The PRAC considered that the risk management plan version 1.3 is acceptable. The PRAC endorsed PRAC

Rapporteur assessment report is attached.

The CHMP endorsed this advice without changes.

The CHMP endorsed the Risk Management Plan version 1.3 with the following content:

Safety concerns

Summary of safety concerns	
Important identified risks	Inhibitor development to FVIII
Important potential risks	Allergic reaction or anaphylaxis Medication errors Serious vascular thromboembolic events in patients with risk factors for thromboembolism
Missing information	Safety profile in patients <2 years old Safety profile in patients ≥ 65 years of age Safety profile in patients with renal insufficiency Safety profile in PUPs Use of rFVIIIFc for ITI therapy Use in female patients (including pregnant and breastfeeding)

Pharmacovigilance plan

Activity/Study title (type of activity, study title [if known] category 1-3)*	**Objectives**	**Safety concerns addressed**	**Status Planned, started,**	**Date for submission of interim or final reports (planned or actual)**
8HA01EXT, An Open-Label, Multicentre Evaluation of the Long-Term Safety and Efficacy of Recombinant Human Coagulation Factor VIII Fusion Protein (rFVIIIFc) in the Prevention and Treatment of Bleeding	The primary objective of the study is to evaluate the long-term safety of rFVIIIFc in subjects with haemophilia A.	Long-term safety evaluation. Safety profile in patients ≥65 years old	Ongoing	Submission date dependent on study finish dates. Study last patient last visit by March 2017 as per the agreed PIP (EMEA-001114-PIP01-10-M02)

Activity / Study title (type of activity, study title [if known] category 1-3)*	Objectives	Safety concerns addressed	Status Planned, started,	Date for submission of interim or final reports (planned or actual)
Episodes in Previously Treated Subjects with Haemophilia A (safety extension study, Category 3)				
997HA306, An Open-Label, Multicentre Evaluation of the Safety and Efficacy of Recombinant Coagulation Factor VIII Fc Fusion Protein (rFVIIIFc; BIIB031) in the Prevention and Treatment of Bleeding in PUPs with Severe Haemophilia A (PUPs study, Category 3)	The primary objective of the study is to evaluate the safety of rFVIIIFc in PUPs with severe haemophilia A	Safety profile in PUPs including patients <2 years old	Ongoing	Submission date dependent on study finish dates. Study last patient last visit by September 2019 as per agreed PIP (EMEA-001114-PIP01-10-M02)
997HA307, Crossover study to investigate the PK of the 1000 and 3000 IU/ vial strengths. Phase 3 (category 3)	The primary objective of the study is to characterize the PK of rFVIIIFc administered at vial strengths of 1000 and 3000 IU in subjects with severe hemophilia A.	Safety of rFVIIIFc beyond the PK assessment for up to 6 months	Ongoing	May 2016
Data collected from participation in the European Haemophilia Safety Surveillance System (EUHASS) registry to be provided on an ongoing basis (category 3)	Monitor the safety of treatments for people with haemophilia, including Elocta.	Inhibitor development Serious Allergic reactions or Anaphylaxis Serious vascular thrombotic events	Planned – will start upon product launch in the EU	N/A Data will be reviewed on an ongoing basis as a part of Pharmacovigilance signal detection and reported within the PSUR reports

*Category 1 are imposed activities considered key to the benefit risk of the product.
Category 2 are specific obligations
Category 3 are required additional PhV activity (to address specific safety concerns or to measure effectiveness of risk minimisation measures)

The PRAC, having considered the data submitted, was of the opinion that the proposed post-authorisation PhV development plan is sufficient to identify and characterise the risks of the product.

The PRAC also considered that the studies in the post-authorisation development plan and participation in the European Haemophilia Safety Surveillance System (EUHASS) registry are sufficient to monitor the effectiveness of the risk minimisation measures.

Risk minimisation measures

Safety concern	**Routine risk minimisation measures**	**Additional risk minimisation measures**
Inhibitor development to FVIII	Section 4.4 of SmPC: <u>Inhibitors</u> The formation of neutralising antibodies (inhibitors) to factor VIII is a known complication in the management of individuals with haemophilia A. These inhibitors are usually IgG immunoglobulins directed against the factor VIII procoagulant activity, which are quantified in Bethesda Units (BU) per mL of plasma using the modified assay. The risk of developing inhibitors is correlated to the exposure to factor VIII, this risk being highest within the first 20 exposure days. Rarely, inhibitors may develop after the first 100 exposure days. Cases of recurrent inhibitor (low titre) have been observed after switching from one factor VIII product to another in previously treated patients with more than 100 exposure days who have a previous history of inhibitor development. Therefore, it is recommended to monitor all patients carefully for inhibitor	No additional risk minimisation measures are proposed.

Safety concern	Routine risk minimisation measures	Additional risk minimisation measures
	occurrence following any product switch. In general, all patients treated with coagulation factor VIII products should be carefully monitored for the development of inhibitors by appropriate clinical observations and laboratory tests. If the expected factor VIII activity plasma levels are not attained, or if bleeding is not controlled with an appropriate dose, testing for factor VIII inhibitor presence should be performed. In patients with high levels of inhibitor, factor VIII therapy may not be effective and other therapeutic options should be considered. Management of such patients should be directed by physicians with experience in the care of haemophilia and factor VIII inhibitors. Section 4.8 of SmPC: Patients with haemophilia A may develop neutralising antibodies (inhibitors) to factor VIII. If such inhibitors occur, the condition will manifest itself as an insufficient clinical response. In such cases, it is recommended that a specialised haemophilia centre be contacted. <u>Post Marketing Experience</u> In post-marketing experience, FVIII inhibitor development has been observed. Package leaflet (warnings and	

Safety concern	Routine risk minimisation measures	Additional risk minimisation measures
	precautions): Talk to your doctor if you think that your bleeding is not being controlled with the dose you receive, as there can be several reasons for this. For example, the formation of antibodies (also known as inhibitors) to factor VIII is a known complication that can occur during the treatment of haemophilia A. The antibodies prevent the treatment from working properly. This would be checked by your doctor. Do not increase the total dose of ELOCTA to control your bleed without talking to your doctor.	
Allergic reaction or anaphylaxis	Section 4.4 of SmPC: <u>Hypersensitivity</u> Allergic type hypersensitivity reactions are possible with ELOCTA. If symptoms of hypersensitivity occur, patients should be advised to discontinue use of the medicinal product immediately and contact their physician. Patients should be informed of the signs of hypersensitivity reactions including, rash, hives, generalised urticaria, tightness of the chest, wheezing, hypotension and anaphylaxis. In case of anaphylactic shock, standard medical treatment for shock should be implemented. Section 4.8 of SmPC: Hypersensitivity or allergic	No additional risk minimisation measures are proposed.

Safety concern	Routine risk minimisation measures	Additional risk minimisation measures
	reactions (which may include swelling of the face, rash, hives, tightness of the chest and difficulty breathing, burning and stinging at the infusion site, chills, flushing, generalised urticaria, headache, hypotension, lethargy, nausea, restlessness, tachycardia) have been observed rarely and may in some cases progress to severe anaphylaxis (including shock). Package leaflet (warnings and precautions): There is a rare chance that you may experience an anaphylactic reaction (a severe, sudden allergic reaction) to ELOCTA. Signs of allergic reactions may include swelling of the face, rash, generalised itching, hives, tightness of the chest, difficulty breathing and low blood pressure. If any of these symptoms occur, stop the injection immediately and contact your doctor.	
Medication errors	Section 4.2 of SmPC: Treatment should be initiated under the supervision of a physician experienced in the treatment of haemophilia. <u>Treatment monitoring</u> When using an in vitro thromboplastin time (aPTT)- based one stage clotting assay for determining factor VIII activity in patients' blood samples, plasma factor VIII activity results can be significantly affected by both the	No additional risk minimisation measures are proposed.

Safety concern	Routine risk minimisation measures	Additional risk minimisation measures
	type of the aPTT reagent and the reference standard used in the assay. This is of importance particularly when changing the laboratory and/or reagent used in the assay. Package leaflet (warnings and precautions): Treatment with ELOCTA will be started by a doctor who is experienced in the care of patients with haemophilia. Always use this medicine exactly as your doctor has told you. Check with your doctor, pharmacist or nurse if you are not sure. Check the name and strength of the package, to make sure it contains the correct product.	
Serious vascular thromboembolic events in patients with risk factors for thromboembolism	Section 4.4 of SmPC: <u>Cardiovascular events</u> In patients with existing cardiovascular risk factors, substitution therapy with FVIII may increase the cardiovascular risk	No additional risk minimisation measures are proposed.
Safety profile in patients <2 years old	No additional risk minimisation measures, in addition to routine pharmacovigilance, are proposed.	No additional risk minimisation measures are proposed.
Safety profile in patients ≥ 65 years of age	Section 4.2 of SmPC: <u>Elderly</u> There is limited experience in patients ≥ 65 years.	No additional risk minimisation measures are proposed.
Safety profile in patients with renal insufficiency	No additional risk minimisation measures, in addition to routine pharmacovigilance, are proposed.	No additional risk minimisation measures are proposed.

Safety concern	Routine risk minimisation measures	Additional risk minimisation measures
Safety profile in PUPs	Section 4.2 of the SmPC: Previously untreated patients The safety and efficacy of ELOCTA in previously untreated patients have not yet been established. No data are available.	No additional risk minimisation measures are proposed.
Use of rFVIIIFc for ITI therapy	No additional risk minimisation measures, in addition to routine pharmacovigilance, are proposed.	No additional risk minimisation measures are proposed.
Use in female patients (including pregnant and breastfeeding)	Section 4.6 of the SmPC: Pregnancy and breast-feeding Animal reproduction studies have not been conducted with ELOCTA. A placental transfer study in mice was conducted (see section 5.3). Based on the rare occurrence of haemophilia A in women, experience regarding the use of factor VIII during pregnancy and breast-feeding is not available. Therefore, factor VIII should be used during pregnancy and lactation only if clearly indicated. Package leaflet (warnings and precautions): Pregnancy and breast-feeding If you are pregnant or breastfeeding, think you may be pregnant or are planning to have a baby, ask your doctor or pharmacist for advice before taking this medicine.	No additional risk minimisation measures are proposed.

2.8. Pharmacovigilance

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.

2.9. Product information

2.9.1. 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.*

The Applicant's proposal to implement a combined PL for all 7 strengths is in line with the "Guideline on Compilation of QRD decisions on stylistic matters in product information [EMA/25090/2002] Rev. 16, April 2014" and considered to be acceptable. The applicant's proposal to implement a combined SmPC is in line with the criteria as defined in the "Policy on combined Summaries of Product Characteristics (SmPCs)."

2.9.2. Additional monitoring

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

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

3. Benefit-Risk Balance

Benefits

Beneficial effects

Efmoroctocog alfa -rFVIIIFc, a recombinant human coagulation factor VIII Fc fusion protein- is efficient as a replacement therapy of patients with haemophilia A, as measured by treatment response assessments, factor VIII consumption, and, in surgical procedures, also by determination of blood loss/transfusion requirements (in line with the EMA clinical factor VIII guideline). Furthermore, annualised bleeding rates during prophylaxis can be determined and an every 3-5 day posology for prophylaxis is recommended. PK data serve as an important surrogate endpoint.

In the treatment of bleeds, response was assessed as "excellent" or "good" for more than 80% of first rFVIIIFc injections in the tailored prophylaxis treatment arms of both Phase 3 studies as well as the episodic treatment arm of the Phase 3 study in subjects ≥12 years of age. More than 80% of the occurred bleeds

were treated with one injection with a median dose of ~25-30 IU/kg in subjects ≥12 years and ~50 IU/kg in subjects <12 years of age. Median annualised bleeding rates during tailored prophylaxis are below 2 and overall rFVIIIFc consumption does not markedly exceed prophylactic rFVIIIFc consumption. Heamostasis achieved in 22 major surgeries was assessed as “excellent” or “good” in all of them. Three subjects required transfusions, all underwent joint replacement and/or amputation procedures. Median surgical rFVIIIFc consumption was 763.99 IU/kg in the Phase 3 study in subjects ≥12 years; in the extension study, consumption ranged from 132.8-569.6 IU/kg.

In a Study in the of 69 evaluable previously treated male paediatric patients <12 years of age, the median dose interval of the individualised prophylaxis regimen was 3.49 (interquartile range 3.46-3.51) days and the median total weekly dose was 91.63 (interquartile range 84.72-104.56) IU/kg for subjects <6 years of age and 86.88 (interquartile range 79.12-103.08) IU/kg for subjects 6 to <12 years of age. The median overall annualised bleeding rate was 1.96 (interquartile range 0.00-3.96). No bleeding episodes were experienced in 46.4% of paediatric subjects. Of the 86 bleeding events observed, 81.4% were controlled with 1 injection, and overall 93.0% of bleedings episodes were controlled with 2 or fewer injections. The median dose per injection to treat a bleeding episode was 49.69 (interquartile range 29.41-56.82) IU/kg. The median overall dose to treat a bleeding episode was 54.90 IU/Kg (29.41, 71.09).

Uncertainty in the knowledge about the beneficial effects.

In addition to an every 3-5 day posology, Efmoroctocog alfa was also developed with the intention to explore a once weekly posology for prophylactic use. Although there is evidence from the PK evaluation for a prolonged half-life, posology may not solely be based thereon, and is PK evaluation not considered suitable to constitute a generalisable multiplication factor for rFVIIIFc dosing intervals. In on-demand treatment of bleeding episodes, broad prolongation of time intervals between repeated injections is not endorsed. In prophylactic treatment, dosing intervals >5 days are neither supported by PK nor by clinical data. Therefore such considerations could not be made and final SmPC recommendations are appropriately reflecting posology recommendations.

No data are available for previously untreated patients, a trial investigating the safety and efficacy of efmoroctocog alfa in PUPs is however currently under way (997HA306).

Risks

Unfavourable effects

The nature and frequency of the reported adverse events do not give rise to concern and do not reveal unexpected safety signals. Most of the ADRs reported (headache, back pain, dizziness, hypertension, bradycardia, hot flush, abdominal pain, rash, arthralgia, malaise, chest pain) occurred only once but as database consists of 233 patients, frequency was reported as uncommon.The size of the safety database available at the moment is in compliance with guideline requirements.

Apart from that, the presented data are not indicative of unfavourable effects that go beyond what would be expected for a factor VIII product. One adult subject had a positive anti-Factor VIII antibody test result coincident with a single measurement of a neutralising antibody titre of 0.73 Bethesda Units/mL at Week 14. The neutralising antibody was not confirmed upon repeat testing 18 days later and was negative at subsequent visits. There was an increase in clearance (CL) at Week 14 that resolved with continued rFVIIIFc

treatment. Therefore, it can be considered that there was no higher than expected incidence of inhibitor development from the results of the clinical studies.

As the product is approved in the US, from the post-marketing setting 1 SAE of a high-titre factor VIII inhibitor in an 11-month-old minimally treated patient with severe haemophilia A was reported.

Uncertainty in the knowledge about the unfavourable effects

The clinical safety database is limited with regard to elderly patients >65 years of age, who are at higher risk for thromboembolism and therefore considered a critical population especially when treated with higher doses >50 IU/kg. Due to the rareness of the disease the safety database is relatively small although in line with guideline requirements. Data on long-term safety will be obtained in the post-marketing phase as foreseen by the relevant guideline.

In the PK evaluation, median rFVIIIFc peak levels of 182 IU/dl were observed for single doses of 65 IU/kg; however, it could not be ruled out that repeated long term administration of doses up to 65 mg/dl and for children even doses up to 80 mg/dl for rFVIIIFc long term prophylactic treatment with consecutive repeatedly elevated factor VIII peak levels would put patients at an increased risk for thromboembolic events. This is addressed in the RMP.

A Clinical trial planned as extension study to one of the pivotal trials (8HA01EXT) and a clinical study in PUPs (997HA306), post marketing study and the data from a registry (EUHASS) are expected to bring more information on the safety in PUPs, occurrence of adverse events of special interest, i.e. development of inhibitors, thromboembolic events or hypersensitivity, anaphylactic or allergic reactions and are included in the pharmacovigilance plan. Final safety analyses from study 997HA307 will be submitted post authorisation and are expected to provide more information on safety aspects such as inhibitor development to FVIII and allergic reactions.

Effects table

Table 44. Effects Table for Elocta.

Effects table

	Effect	Short Description	Unit	Comparator	rFVIIIFc	Uncertainties/ Strength of evidence	References
Favourable	PK	basic PK parameters; half-life, clearance, IR	Half-life: h CL: mL/h/kg IR: IU/dL /IU/kg	subjects ≥12y: Advate	comparable IR prolonged half-life (~19-20h) and reduced clearance	PK data serve as surrogate endpoints for FVIII efficacy sufficient robustness of PK analysis could be shown	Ph. 1/2a (PK) study both Ph. 3 studies
	Efficacy in treatment of bleeding	rFVIIIFc consumption per bleeding episode	number of injections dose per injection total dose per bleed	none	>80% of bleeds treated with 1 injection dose per injection ~20-50 IU/kg *(IQR)* per bleed ~20-70 IU/kg *(IQR)*	results comparable to marketed FVIII (reduced injection frequency for on demand treatment) not fully supported	both Ph. 3 studies (≥12y and <12y)
		response to first injection	rating scale	none	~80-90% of first injections "excellent" or "good" (except arm 2 of study 997HA301: dose per injection was lower in this arm)		
	Efficacy in routine prophylaxis	annualised bleeding rate (ABR)	median number of bleeds/year	none	tailored prophylaxis: 1.6 (≥12y) 1.96 (<12y) weekly prophylaxis: 3.59 >20 in 4 patients (17.3%) >50 in 1 patient	ABR<2 comparable to marketed FVIII prophylactic dosing recommendations in SmPC (50 IU/kg every 3-5d) supported weekly prophylaxis not supported	both Ph. 3 studies
		overall and prophylactic consumption	IU/kg per month	none	overall consumption does not markedly exceed prophylactic consumption	(prophylactic) bleeding rates were mainly achieved by the regimen itself	
	Efficacy during surgery	assessment of haemostasis, blood loss, consumption	rating scale blood loss in ml IU/kg/surgery	none	all 22 major surgeries "excellent" or "good" blood loss, transfusion requirements, consumption within acceptable range also for minor surgery appropriate results	results for major & minor surgery comparable to marketed FVIII reduced injection frequency in surgery not supported by data	both Ph. 3 studies extension study
Unfavourable	PK	Cmax/ peak levels	IU/dl	subjects ≥12y: Advate	after dosing of 65 IU/kg, median rFVIIIFc activity peak levels 182 IU/dl	FVIII activity levels >150 IU/dl may constitute a risk factor for TEE, high risk subjects >65y not exposed: to be addressed in RMP prophylactic dosing recommendations in SmPC -65 IU/kg supported	Ph. 1/2a (PK) study
	FVIII inhibitor	development of inhibitory antibodies to FVIII	BU/ml	none	1 transient low-titre (0.73 BU/ml) inhibitor during Study 997HA301 1 high-titre (37 BU/ml at first and 27 BU/ml upon repeat testing) inhibitor during post-marketing period in US	no evidence of a higher than expected inhibitor incidence	both Ph. 3 studies post-marketing (US)

Benefit-risk balance

Importance of favourable and unfavourable effects

Available clinical efficacy data from efmoroctocog alfa, support that it is an efficacious new FVIII product for the prevention and treatment of bleeds in previously treated patients with haemophilia A. Beneficial effects arising from maintaining of haemostasis in haemophilia A are of obvious importance, since they results in an improvement of the quality of life and increased life-expectancy. This could adequately be shown for rFVIIIFc.

The number of included patients across all clinical trials is in accordance with guideline requirements and the safety database is considered sufficient to evaluate the tolerability of efmoroctocog alfa before marketing authorisation. The observed adverse event profile is considered similar to that of other licensed FVIII products. Inhibitor development has to be regarded as the most important unfavourable effect of factor VIII products in general. Importantly, apart from a case of a transient low titre inhibitor, no patients developed FVIII inhibitors and no thromboembolic events occurred in the clinical trials; however one case of inhibitor development was reported from postmarketing data..

Benefit-risk balance

Overall, efficacy has been established by the provided clinical data as per the requirements of relevant Guidelines. Safety-profile of Elocta is in line with what is expected. The benefits of rFVIIIFc outweigh the risks.

The benefit-risk balance in the indication of the treatment and prophylaxis of bleeding in paediatric and adult patients with haemophilia A (congenital factor VIII deficiency) is considered to be positive.

Discussion on the benefit-risk balance

In view of the proposed high treatment doses, doses up to 80 IU/kg in patients <12 years should not be recommended in the SmPC either. The possible risk for TEE in elderly patients under high treatment doses >50 IU/kg should be addressed in the context of post marketing measures (see RMP).

Overall, efficacy of efmoroctocog alfa in adult and paediatric patients with haemophilia A covering treatment of bleeding episodes, prophylaxis of bleeds and prophylaxis in surgical procedures is adequately supported by submitted clinical data according to the currently valid Clinical Guideline. Furthermore, the documented safety profile is within the expected range for factor VIII products. Studies detailed in the pharmacovigilance plan are expected to update the knowledge on issues of special interest in this class (development of inhibitors, hypersensitivity, anaphylactic or allergic reactions, safety in previously untreated patients).

4. Recommendations

Outcome

Based on the CHMP review of data on quality, safety and efficacy, the CHMP considers by consensus that the risk-benefit balance of ELOCTA in the

"treatment and prophylaxis of bleeding in patients with haemophilia A (congenital factor VIII deficiency).

ELOCTA can be used for all age groups."

is favourable and therefore recommends the granting of the marketing authorisation subject to the following conditions:

Conditions or restrictions regarding supply and use

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

Conditions and requirements of the Marketing Authorisation

- **Periodic Safety Update Reports**

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

The marketing authorisation holder shall submit the first periodic safety update report for this product within 6 months following authorisation.

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

- **Risk Management Plan (RMP)**

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

An updated RMP should be submitted:

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

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

Not applicable.

New Active Substance Status

Based on the CHMP review of data on the quality properties of the active substance, the CHMP considers that efmoroctocog alfa is qualified as a new active substance.

Paediatric Data

Furthermore, the CHMP reviewed the available paediatric data of studies subject to the agreed Paediatric Investigation Plan P/0077/2014 and the results of these studies are reflected in the Summary of Product Characteristics (SmPC) and, as appropriate, the Package Leaflet.