25 April 2024
EMA/459190/2024 Corr.1*[1]
Committee for Medicinal Products for Human Use (CHMP)

Assessment report

Altuvoct

International non-proprietary name: efanesoctocog alfa

Procedure No. EMEA/H/C/005968/0000

Note

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

[1] *Correction dated 16 December 2024 to add additional information on BMI in the discussion on clinical pharmacology section and additional information has been added in the safety section.*

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List of abbreviations

AAV	Adeno-associated virus
ABR	Annualised bleeding rate
ADA	Anti-drug antibody (against BIVV001)
ADR	Adverse drug reaction
AESI	Adverse event of special interest
ALT	Alanine aminotransferase
aPCC	Activated prothrombin complex concentrate
aPTT	Activated partial thromboplastin time
AST	Aspartate aminotransferase
ATC	Anatomical Therapeutic Chemical
BDD	B-domain deleted
$AUC_{0\text{-}tau}$	Area under the activity-time curve over the dosing interval
BMI	Body mass index
CFC	Clotting factor concentrates
CHMP	Committee for Medicinal Products for Human Use
CI	Confidence interval
C_{max}	Maximum activity
C_{maxss}	Maximum FVIII activity at steady state
CNS	central nervous system
CPV	Continued process verification
CS	Chromogenic substrate assay
CSR	Clinical study report
DLP	Data lock point
DNA	Deoxyribonucleic acid
DP	Drug product
DS	Drug substance
eCTD	electronic common technical document
ECG	Electrocardiogram
EEA	European economic area
ED	Exposure day
EHL	Extended half-life
EMA	European Medicines Agency
EU	European Union

Fc	Fragment crystallisable region of IgG1
FcRn	Neonatal Fc receptor
FDA	Food and Drug Administration (United States)
FVIII	Coagulation factor VIII
GCP	Good clinical practice
GLP	Good laboratory practice
GMP	Good manufacturing practice
Haem-A-QoL	Haemophilia-Specific Health-Related Quality of Life Questionnaire for adults
HCC	Hepatocellular carcinoma
HCP	Host cell protein
HCV	Hepatitis C virus
HemA	Haemophilia A
HIV	Human immunodeficiency virus
HJHS	Haemophilia Joint Health Score
ICF	Informed consent form
ICH	International Council for Harmonisation
IgG	Immunoglobulin G
IgG1	Immunoglobulin G1
INN	International non-proprietary name
IIV	Interindividual variability
ISI	Integrated summary of immunogenicity
IU	International unit
IV	Intravenous
IVIG	Intravenous immunoglobulin
kg	Kilogram
MASAC	Medical and Scientific Advisory Council
MRI	Magnetic resonance imaging
MWGC	Meaningful within group change
NCA	Noncompartmental analysis
NHF	National Haemophilia Foundation
NSAID	Non-steroidal anti-inflammatory drug
OSC	One-stage clotting assay
PACMP	Post-approval change management protocol
PD	Pharmacodynamic

PK	Pharmacokinetic
PPQ	Process performance qualification
PROMIS	Patient-Reported Outcomes Measurement Information System
PT	Preferred term
PTP	Previously treated patient
PUP	Previously untreated patient
PVP	Process validation plan
PWH	People with haemophilia
QPPV	Qualified person responsible for pharmacovigilance
rFVIII	Recombinant FVIII
RMP	Risk management plan
ROTEM	rotational thromboelastometry
RTTE	Repeated time to event
SAP	Statistical analysis plan
SD	Standard deviation
SHL	Standard half-life
SmPC	Summary of product characteristics
SMR	Standardised mortality ratio
SOC	System organ class
sWFI	Sterile water for injections
TEAE	Treatment-emergent adverse event
TEAESI	Treatment-emergent adverse event of special interest
TESAE	Treatment-emergent serious adverse event
TGA	Thrombin generation assay
TK	Toxicokinetics
TVT	Tail vein transection
ULN	Upper limit of normal
US	United States
Vss	Volume of distribution at steady state
VWD	von Willebrand disease
VWF	von Willebrand factor
WFH	World Federation of Haemophilia
WT	wildtype
XTEN polypeptide	Unstructured hydrophilic polypeptides, composed of repeating motifs of 6 natural amino acids (G, A, P, E, S, T)

1. Background information on the procedure

1.1. Submission of the dossier

The applicant Swedish Orphan Biovitrum AB (publ) submitted on 25 April 2023 an application for marketing authorisation to the European Medicines Agency (EMA) for Altuvoct, 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 22 July 2021.

Altuvoct was designated as an orphan medicinal product EU/3/19/2176 on 28 June 2019 in the following condition: Haemophilia A.

Following the CHMP positive opinion on this marketing authorisation, the Committee for Orphan Medicinal Products (COMP) reviewed the designation of Altuvoct as an orphan medicinal product in the approved indication. More information on the COMP's review can be found in the orphan maintenance assessment report published under the 'Assessment history' tab on the Agency's website: https://www.ema.europa.eu/en/medicines/human/EPAR/altuvoct.

The applicant applied for the following indication: Treatment and prophylaxis of bleeding in patients with haemophilia A (congenital factor VIII deficiency). Altuvoct can be used for all age groups.

1.2. Legal basis, dossier content

The legal basis for this application refers to:

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

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

1.3. Information on Paediatric requirements

Pursuant to Article 7 of Regulation (EC) No 1901/2006, the application included an EMA Decision P/0382/2022 on the agreement of a paediatric investigation plan (PIP).

At the time of submission of the application, the PIP P/0382/2022 was completed.

The PDCO issued an opinion on compliance for the PIP P/0382/2022

1.4. Information relating to orphan market exclusivity

1.4.1. Similarity

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

1.5. Applicant's request for consideration

1.5.1. New active substance status

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

1.6. Protocol assistance

The applicant received the following protocol assistance on the development relevant for the indication subject to the present application:

Date	Reference
28 March 2019	EMEA/H/SA/4066/1/2019/III
27 June 2019	EMEA/H/SA/4066/1/FU/1/2019/II
14 October 2021	EMA/SA/0000067195
16 December 2021	EMA/SA/0000070828
15 September 2022	EMA/SA/0000096483

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

EMEA/H/SA/4066/1/2019/III - Quality, non-clinical and clinical development

- The proposed assay to assign potency of the product for product release and for stability monitoring.
- Adequacy of the non-clinical programme to support a marketing authorisation application (MAA).
- The rationale for initiation of phase 3 studies based on the phase 1/2a studies; the design of the phase 3 study in PTPs ≥12 years of age (study 242HA301) and, in particular, the proposed primary/secondary endpoints and dose regimen; the proposed timing for initiation of the phase 3 study in PTPs <12 years of age (study 242HA302); the proposed data package for an MAA.

EMEA/H/SA/4066/1/FU/1/2019/II - Clinical development

- The overall study design, inclusive of an on-demand arm, revised primary endpoint, and dose regimen in the planned phase 3 study in PTPs ≥12 years of age (study 242HA301).

EMA/SA/0000067195 - Clinical development

- Adequacy of the proposed interim paediatric data to support an initial MAA for the treatment of haemophilia A in all age groups; the clinical relevance of the proposed PROs in patients with haemophilia; the proposed assay to be used as a primary assay for potency assignment, assessment of clinical PK endpoints and clinical laboratory testing at the MAA submission; the proposed strategy to assess immunogenicity; the approach to use a repeated time to event (RTTE) model-based PK/PD analysis to support the evaluation of clinical benefit.

EMA/SA/0000070828 – Quality development

- The proposed strategy for drug product PPQ runs, based on the leveraging of the clinical batches; the stability data package supporting the storage condition and shelf life of the commercial DP.

EMA/SA/0000096483 - Quality development

- The proposed filing approach to combine within the MAA Post-Approval Change Management Protocols (PACMPs) for a drug substance manufacturing site transfer and for a drug product manufacturing site transfer; adequacy of the proposed dataset for type IB variations following the PACMPs.

1.7. Steps taken for the assessment of the product

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

Rapporteur: Jan Mueller-Berghaus Co-Rapporteur: Daniela Philadelphy

The application was received by the EMA on	25 April 2023
The procedure started on	18 May 2023
The CHMP Rapporteur's first Assessment Report was circulated to all CHMP and PRAC members on	7 August 2023
The CHMP Co-Rapporteur's critique was circulated to all CHMP and PRAC members on	23 August 2023
The PRAC Rapporteur's first Assessment Report was circulated to all PRAC and CHMP members on	22 August 2023
The PRAC Rapporteur's updated Assessment Report was circulated to all PRAC and CHMP members on	31 August 2023
The CHMP agreed on the consolidated List of Questions to be sent to the applicant during the meeting on	14 September 2023
The applicant submitted the responses to the CHMP consolidated List of Questions on	23 November 2023
The CHMP Rapporteurs circulated the CHMP and PRAC Rapporteurs Joint Assessment Report on the responses to the List of Questions to all CHMP and PRAC members on	3 January 2024
The PRAC agreed on the PRAC Assessment Overview and Advice to CHMP during the meeting on	11 January 2024
The CHMP agreed on a list of outstanding issues to be sent to the applicant on	25 January 2024

The applicant submitted the responses to the CHMP List of Outstanding Issues on	19 February 2024
The CHMP Rapporteurs circulated the CHMP and PRAC Rapporteurs Joint Assessment Report on the responses to the List of Outstanding Issues to all CHMP and PRAC members on	3 March 2024
The CHMP Rapporteurs circulated the CHMP and PRAC Rapporteurs Joint Updated Assessment Report on the responses to the List of Outstanding Issues to all CHMP and PRAC members on	14 March 2024
The CHMP agreed on a 2nd list of outstanding issues to be sent to the applicant on	21 March 2024
The applicant submitted the responses to the CHMP List of Outstanding Issues on	27 March 2024
The CHMP Rapporteurs circulated the CHMP and PRAC Rapporteurs Joint Assessment Report on the responses to the List of Outstanding Issues to all CHMP and PRAC members on	10 April 2024
The CHMP Rapporteurs circulated the CHMP and PRAC updated Rapporteurs Joint Assessment Report on the responses to the List of Outstanding Issues to all CHMP and PRAC members on	18 April 2024
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 Altuvoct on	25 April 2024
The CHMP adopted a report on similarity of Altuvoct with Roctavian on	25 April 2024
Furthermore, the CHMP adopted a report on new active substance (NAS) status of the active substance contained in the medicinal product	25 April 2024

2. Scientific discussion

2.1. Problem statement

2.1.1. Disease or condition

Haemophilia A is a rare X chromosome-linked bleeding disorder that occurs predominantly in males and is characterised by deficiency of functional coagulation FVIII leading to potentially life-threatening bleeding in response to trauma and recurrent bleeding into soft tissue and joints (Mannucci *et al.* 2001, Berntorp *et al.* 2021). It is caused by any of a variety of mutations in the F8 gene, which number over 3000, including missense or nonsense mutations, gene deletions, inversions, and splice junction mutations (Furie *et al.* 1990, Graw *et al.* 2005, EAHAD 2023).

2.1.2. Epidemiology

The worldwide prevalence of haemophilia A, based on pooling across all available national registries, has been estimated to be 17.1 cases per 100 000 males (Iorio *et al.* 2019). As of its most recent survey (2020), at least 165 379 cases of haemophilia A are known to the World Federation of Haemophilia (WFH), but the actual number of cases may be up to 4 times higher because the majority of mild and moderate cases, especially in developing countries, remains undiagnosed (Skinner 2012, Iorio *et al.* 2019, World Federation of Haemophilia 2021). Although haemophilia A is expected to be equally distributed across the world (Skinner 2012, World Federation of Haemophilia 2021), differences in the observed prevalence reflect differences in diagnostic capability, in the reporting efficiency and effectiveness of national registries, and in economic capacity (Stonebraker *et al.* 2003, Stonebraker *et al.* 2010).

2.1.3. Biologic features

The severity of disease is characterised by the level of endogenous FVIII activity measured in the plasma. Severe haemophilia A (<1% endogenous FVIII activity level, i.e. <1 IU/dL) accounts for approximately 30% to 50% of all cases of haemophilia A (Aznar *et al.* 2009, Iorio *et al.* 2019, WFH 2021).

2.1.4. Clinical presentation, diagnosis

Severe haemophilia is a life-long disease for which there is no available cure. Individuals with severe haemophilia A experience frequent bleeding episodes into major joints, soft tissue, and muscle, either spontaneously or following even minor trauma. Repeated bleeding can lead to debilitating long-term complications, including haemophilic arthropathy from bleeding into the joints. Intracranial haemorrhage can result in disability and death and is one of the leading causes of haemorrhagic death in individuals with haemophilia (Witmer *et al.* 2011, Loomans *et al.* 2017). Significant effects on physical and psychosocial well-being and quality of life and substantial financial burden have been reported in patients with severe haemophilia (Mazza 2016, Thorat *et al.* 2018). Despite significant advances in treatment options, individuals with severe haemophilia A, even in high-income countries, still have significant quality of life limitations and life expectancy disadvantages relative to the general population (Iorio *et al.* 2019, Hassan *et al.* 2021, Hay *et al.* 2021).

2.1.5. Management

Per the current recommendations of the WFH Guidelines for the Management of Haemophilia as well as of many national and international haemophilia organisations, the standard of care for all patients with severe haemophilia A is primary prophylaxis, defined as regular therapy with FVIII replacement products or other haemostasis products to prevent spontaneous bleeding. Primary prophylaxis should be initiated early in life prior to the onset of joint disease, before the second clinically evident joint bleed and before 3 years of age to prevent musculoskeletal complications from recurrent joint and muscle bleeds (Srivastava *et al.* 2020). Hemlibra (emicizumab) is indicated for routine prophylaxis of bleeding episodes in patients with haemophilia A (congenital factor VIII deficiency) with or without factor VIII inhibitors. Another treatment option is gene therapy of haemophilia A, Valoctocogene roxaparvovec, an adeno-associated viral serotype 5 (AAV5) vector containing a B-domain-deleted variant of human FVIII, has the potential to provide sustained FVIII activity levels and recently received a conditional marketing authorisation in the EU. Episodic or on-demand FVIII treatment, i.e., treating bleeds when they occur, is no longer considered the standard of care for the management of haemophilia as it does not alter the natural history of frequent and recurrent bleeding and related complications.

Patients suffering from severe haemophilia A usually receive prophylactic treatment with FVIII products, which requires regular infusion every 2 to 3 days. Another option for bleeding prophylaxis is the subcutaneous administration of Hemlibra, which needs to be given only once a week to once every four weeks.

2.2. About the product

Efanesoctocog alfa (BIVV001) is a recombinant fusion protein consisting of a single chain B domain- deleted human FVIII covalently linked to the D'D3 domain of human VWF via the Fc domain of human immunoglobulin G1 (IgG1) and 2 XTEN polypeptides. The D'D3 domain prevents interaction of BIVV001 with natural vWF, the XTEN domains increase the hydrodynamic range of the molecule protecting from proteolytic degradation and rapid clearance. Binding of the Fc chain to the neonatal Fc receptor (FcRn) delays lysosomal clearance and is important for the longer circulating half-life. BIVV001 has been developed as a long-acting version of recombinant FVIII for the control and prevention of bleeding episodes in individuals with haemophilia A.

Efanesoctocog alfa is formulated as a sterile, non-pyrogenic, preservative-free, lyophilised, white to off-white powder for intravenous administration in a single-use vial. Each single-use vial contains nominally 250, 500, 750, 1000, 2000, 3000 or 4000 International Units (IU) of BIVV1001 for reconstitution with the diluent–Sterile Water for Injection (sWFI), which is provided in a pre-filled syringe.

The prolonged half-life of Altuvoct allows an extended dosing interval of 7 days, which will to some extent decrease the burden of the regular prophylactic infusion for patients with severe haemophilia A, compared to the currently available extended half-life products. The compliance during the pivotal phase 3 study was very high. It is considered likely that the necessity of less frequent administrations could also increase the treatment compliance outside the scenario of a clinical trial.

2.3. Type of application and aspects on development

The applicant applied for the following indication:

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

The clinical programme comprises 7 clinical studies, 6 of which enrolled previously treated patients (PTPs) with severe haemophilia A. Four of the 6 studies in PTPs with severe haemophilia A are completed: the pivotal Phase 3 study in adult and adolescent patients (EFC16293) and 3 Phase 1 and Phase 1/2a studies. The results of these studies are included in this dossier.

As of the 24 January 2022 data cut-off date, which coincided with the closure of Study EFC16293 (pivotal study), 2 studies in severe haemophilia A were ongoing: a Phase 3 efficacy and safety study in paediatric PTPs (EFC16295) and a Phase 3 long-term extension study in PTPs of all ages (LTS16294). Study EFC16295 is still ongoing, although last patient last visit (LPLV) has since been achieved (18 January 2023).

Important aspects for MA addressed during Scientific Advice procedures:

The proposal to use the one-stage aPTT-based clotting assay to assign potency of BIVV001 for purposes of product release and for stability monitoring has been discussed in the scientific advice EMA/CHMP/SAWP/182022/2019. Although the Ph. Eur. requires a chromogenic assay for potency determination of Factor VIII products, the alternative use of a one stage clotting assay (instead of a chromogenic assay) was in principle agreed. The applicant reassured the use of the proposed clotting method by comparing data of the 1-stage clotting and the chromogenic assay in in vitro test systems like TGA, ROTEM and fibrin generation or the in vivo HemA mouse model (with Advate as comparator).

The strategy for drug product PPQ runs, based on the leveraging of the clinical batches and the stability data package supporting the storage condition and shelf life of the commercial DP were discussed and agreed in the protocol assistance EMADOC-360526170-753945.

2.4. Quality aspects

2.4.1. Introduction

Efanesoctocog alfa finished product (FP) is a sterile, lyophilised powder for solution for injection for intravenous administration. It is supplied in aseptically filled single-use vials in seven nominal strengths 250 IU, 500 IU, 750 IU, 1000 IU, 2000 IU, 3000 IU and 4000 IU/vial. The excipients comprise histidine, arginine hydrochloride, sucrose, calcium chloride dihydrate and polysorbate 80. Water for injections (WFI) is provided as solvent in a co-packaged pre-filled syringe. The composition of the formulation excipients is the same for all dosage strengths; only the quantity of efanesoctocog alfa varies. The same fill volumes the same reconstitution volume of 3 ml is used for all strengths. The efanesoctocog finished product vial and the WFI (pre-filled syringe) are packaged together in a product pack with a plunger rod, a vial adaptor for reconstitution and infusion set, which are all CE-certified.

2.4.2. Active Substance

2.4.2.1. General Information

Efanesoctocog alfa (BIVV001), is the active ingredient of Altuvoct, a human coagulation factor VIII (FVIII) replacement product that is designed to be independent of endogenous Von Willebrand Factor (VWF) in order to overcome the half-life limit imposed by FVIII and VWF interactions. Altuvoct is administered by intravenous injection. The commercial formulation is a sterile, non-pyrogenic, lyophilised white to off-white cake powder for reconstitution for intravenous injection and is supplied in a single-use vial. Each vial contains nominally 250 through 4000 IU/vial of BIVV001. Each pack contains a powder vial (Type 1 glass) with chlorobutyl rubber stopper and 3 mL sterile water for injection in a pre-filled syringe (Type 1 glass), with a bromobutyl rubber plunger stopper and a tamper proof tip-cap, and a sterile vial adapter reconstitution device.

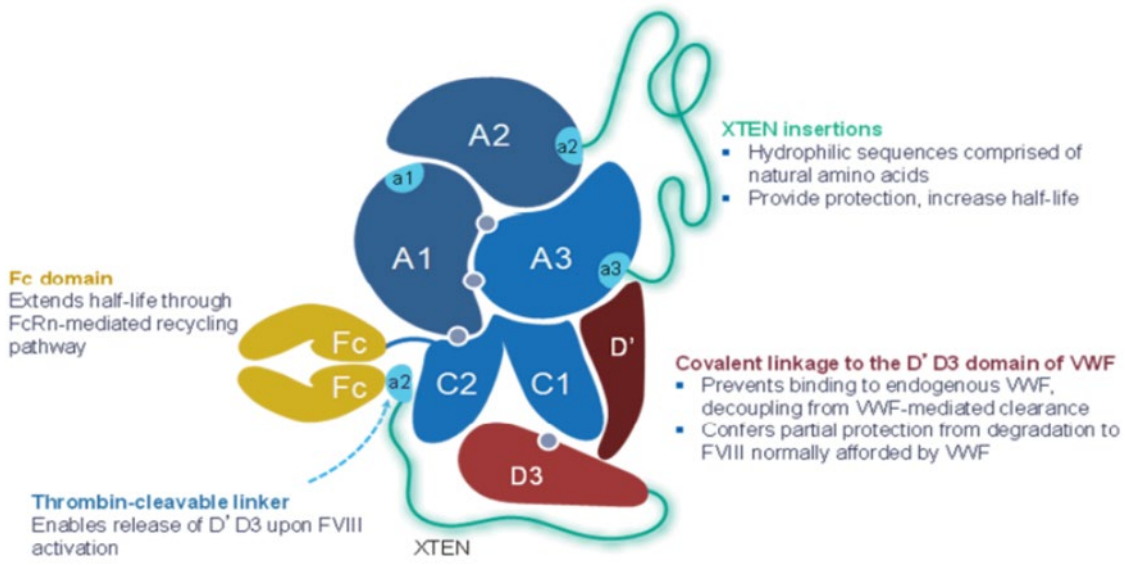
BIVV001 is a recombinant fusion protein consisting of a single-chain B domain deleted human FVIII covalently linked to the D'D3 domain of human VWF via the Fc domain of human immunoglobulin G1 (IgG1) and 2 XTEN polypeptides (unstructured hydrophilic polypeptides, composed of repeating motifs of 6 natural amino acids, Gly, Ala, Pro, Glu, Ser and Thr).

The D'D3 domain prevents interaction of BIVV001 with natural VWF and thus from the half-life ceiling imposed by VWF, but retained the stability ordinarily conferred by endogenous VWF. The XTEN domains increase the hydrodynamic range of the molecule protecting from proteolytic degradation and rapid clearance. Binding of the Fc chain to the neonatal Fc receptor, FcRn, delays lysosomal clearance and is important for the longer circulating half-life.

In BIVV001, the first XTEN polypeptide is inserted between N745 and E1649 amino acid residues, replacing the natural B domain in FVIII. Thus, it is flanked by natural FVIII thrombin cleavage sites, resulting in its release upon thrombin activation. The second XTEN polypeptide is inserted between the D'D3 and Fc (fragment of IgG1). An additional FVIII a2 thrombin cleavage site was introduced between D'D3-XTEN and Fc to enable efficient release of D'D3-XTEN from the rFVIII-Fc fusion protein upon activation by thrombin.

The efanesoctocog alfa protein has a molecular weight of approximately 312 kDa and is synthesised as 2 polypeptide chains: 1) FVIII-XTEN-Fc polypeptide chain (216.3 kDa, 1946 amino acids); 2) VWF-XTEN-a2-Fc polypeptide chain (after intracellular processing: 95.3 kDa, 883 amino acids). The 2 polypeptide chains are covalently linked by 2 Fc hinge disulfide bonds, similar to the native intact IgG1 heavy chains, as well as through extensive noncovalent interactions.

Figure 1 Molecular structure of efanesoctocog alfa



Abbreviations: Fc: fragment crystallizable region of IgG1; FcRn: neonatal Fc receptor; FVIII: factor VIII; VWF: von Willebrand factor; a1, a2 and a3: FVIII acidic region 1, 2 and 3;
XTEN polypeptides: unstructured polypeptides and consist of 6 amino acids (Gly, Ala, Pro, Thr, Ser, Glu or G,A,P,T,S,E)
Note: Green lines: XTEN polypeptides

2.4.2.2. Manufacture, characterisation and process controls

The manufacturing process of the active substance (AS) (upstream cell culture, downstream purification and QC) is performed at a facility which is routinely GMP inspected and operates under GMP compliant conditions.

Satisfactory GMP documents were provided for additional active substance sites:

Cell banking sites have been detailed and GMP confirmed.

The commercial manufacturing process is described in detailed flowcharts and written procedures in a way to sufficiently understand all process steps. Tabular flow diagrams provide a comprehensive overview of the individual process steps, their established in-process controls (IPCs) with acceptance limits and acceptance criteria, as well as process parameters that control the process, including their criticality. Production starts from working cell bank (WCB) vial thaw.

Microbial control is achieved throughout the manufacturing process, and a flowchart of microbial control sampling is provided in the dossier.

Control of materials

The details presented on compendial and non-compendial raw materials are sufficient to assure that these are of adequate quality and purity for the intended use. Specifications for chromatography resins are provided. Materials used for filters, and disposable containers are listed. QC control includes at least vendor certificate of analysis and identity check. Solutions and media used employed during the upstream and

downstream manufacturing processes are listed, including the manufacturing stage and the acceptance range.

No raw materials of animal or biologic origin are used during the production of efanesoctocog alfa AS. For non-compendial raw materials, certificates of analysis were provided. Acceptance criteria for some non-compendial raw materials during in house testing have still to be established after sufficient AS lots are produced. For a cell culture media component, confidential details on its composition are provided.

Manufacturing process development

Process validation and evaluation

Shipping has been properly qualified.

Viral clearance studies confirmed that the purification process is considered able to clear viruses in the unlikely event they are introduced.

As part of an enhanced validation approach, continued process verification (CPV) will be applied to assure that the process operates under a state of control. As part of a life cycle management, potential trending will be regularly reviewed and the impact of deviations, changes and CAPAs will be assessed annually.

The AS process is considered adequately validated.

Characterisation

The physico-chemical characterisation of AS lots included purity, post-translational modifications PTM, charge heterogeneity, glycosylation. Mostly consistent results are found between the Process B PPQ batches, and the batches used in clinical trials. Minor different results are considered by the applicant to be attributable to assay variability, which appears reasonable. Hence, consistent physico-chemical properties among the tested AS lots is demonstrated. The characterisation data support the conclusion that, irrespective of the origin of the starting material, AS of comparable quality and safety is obtained.

Molecular size distribution confirms the presence of heterogeneous HMW species size variants.

Secondary and higher order structure were determined for all PPQ batches. In summary, mostly a relatively good consistency in secondary and higher order structures could be shown for the tested AS lots.

Potency was measured in a one-stage clotting assay (OSA), based on an Actin FSL-triggered aPTT assay and in a chromogenic substrate assay (CSA)The discrepancy observed between the chromogenic and the clotting assay results is discussed and appears reasonable.

Furthermore, investigating the integrity of the Fc domain comparable results were obtained among tested AS lots.

During analysis of the kinetic of cleavage of efanesoctocog alfa, lower potency results in the OSA may be partially attributable to a delayed cleavage/activation of efanesoctocog alfa by thrombin. It has been shown that different aPTT reagents influence the potency results in the OSA, with Actin FS substantially over-estimating and SynthASil underestimating FVIII activity, compared to the aPTT reagent Actin FSL.

Impurities

The applicant performed an investigation on product- and process-related impurities in accordance with ICH Q3 recommendations. Reduction of impurities was evaluated at different stages of the process during PPQHMW species are present at low level and also show decreased activity.

A safety assessment provides a high level of assurance that all process-related impurities are well below any permitted daily exposure safety limits, with an at least 1000-fold safety margin.

There are no container closure related impurities for efanesoctocog alfa active substance.

Host Cell Protein (HCP) levels are reduced during purification and are monitored. The method description for the platform HCP as well as the validation of the HCP assay were included into the dossier. More detailed information was provided regarding the minor HCP impurities and a respective risk assessment was included for both minor and major HCP impurities. No immunogenicity risks were detected.

A validated platform was implemented for testing. The validation is in accordance with ICH Q2(R1) guideline and the E.P. general chapter 2.6.34.

The HCP is implemented as a routine AS release test and the chosen acceptance criterion was tightened to reflect the commercial batch analysis data available.

2.4.2.3. Specification

The AS release and stability testing parameters were established in line with ICH Q6B to control AS potency, purity, impurities and safety. Pharmacopeial procedures requiring specific information for conduct of analysis are followed. For each of the non-pharmacopoeial methods, sufficiently detailed descriptions are provided. All non-compendial analytical methods used in release testing of AS (and FP, where applicable) have been validated in accordance with ICH Q2(R1). The established acceptance limits for each test parameter are mostly sufficiently supported and justified by available data at this stage of product history but should be re-evaluated after the analysis of more batches. AS and FP test methods are identified by unique method identification numbers, in line with the recommendation in the Q&A document for biological medicinal products published on the EMA website.

Non-compliance of the specific activity of AS to Ph. Eur. monograph for rFVIII has been justified by the applicant. Hence, the currently proposed acceptance range can be accepted.

A major objection (MO) was raised in respect to the assay used for potency determination. Potency testing using the Actin FSL-triggered OSA is not in line with Ph. Eur. recommendation for rFVIII. The applicant presented a justification why the clotting assay is more suitable as release test for efanesoctocog alfa AS and FP and the Major Objection is solved. However, considering the low recovery of FVIII in the, the compendial assay will be added as a separate AS and FP monitoring test, since a correction factor between the assay results is stated in the product information. Consistency of the ratio will be further evaluated and if no consistent ratio is observed, the chromogenic assay has to be implemented as additional AS and FP release test. Based on evaluation of potency data according Ph. Eur. chapter 5.3, efanesoctocog alfa FVIII activity is traceable to the WHO international standard (IS) and calibration of efanesoctocog alfa in International Units (IU) is justified.

Batch analysis data are presented for all AS lots, including those manufactured until 2023.

Reference materials

The reference material, a primary and a working standard (PS and WS, respectively) used in the testing of AS and FP has been adequately characterised and equivalency of the PS and the WS is demonstrated. The current reference material is representative of commercial material. The standards have been calibrated against the latest WHO IS FVIII Concentrate. For a more complete characterisation of the in-house reference materials, the potency and the specific activity based on the assay will be provided in case this assay is implemented as additional release test for FVIII potency. The CHMP recommends evaluating the behaviour of the in-house PS or WS relative to the WHO IS FVIII Concentrate in the potency assay.

The history of reference material used during development is outlined as well. Similar to AS from the different stages of development, differences exist between previous and current reference material. At any time, reference material was representative of material used in clinical trials at that time. A protocol how new reference material will be qualified or how existing PS and WS will be recalibrated in case of release of a new WHO IS for FVIII is in line with ICH Q6B. The protocol, however, should include calibration of PS and WS with both the clotting assay and the chromogenic assay, if necessary. Currently, only OSA data are available.

Container Closure System

Based on details provided in sections *3.2.S.2.6 Manufacturing process development*, section 3*.2.S.6 Container Closure System* and *3.2.S.7 Stability* the suitability of the primary packaging material is sufficiently demonstrated. The material of the bottle is in accordance with EU Commission Regulation No.10/2011, Amended No. 1183/2012, the screw caps are of Ph. Eur. quality. Qualification studies following EMEA/CVMP/205/04 (Guideline on plastic immediate packaging materials) support the applicant's conclusion that there is no risk for patients due to long-term storage of AS in the container.

2.4.2.4. Stability

The applicant has investigated the stability of the AS in accordance with ICH Q5C on a set of in total ~~9~~ Process B AS batches. Current data on all ~~3~~ primary stability lots, for all supportive AS batches and data for confirmatory lots support the long-term storage of efanesoctocog alfa AS.

Stress studies indicate that efanesoctocog alfa is sensitive to elevated temperature and light and has to be stored under controlled temperature and protected from light.

The post-approval stability protocol and stability commitment are considered adequate to assure completion of ongoing stability studies, to monitor the stability profile of the AS during CPV and to comply with ICH Q7 regarding handling of deviations during ongoing stability studies.

2.4.3. Finished Medicinal Product

2.4.3.1. Description of the product and pharmaceutical development

Efanesoctocog alfa finished product is a sterile, lyophilised powder for solution for injection for intravenous administration. It is supplied in aseptically filled single-use vials in seven nominal strengths 250 IU, 500 IU, 750 IU, 1000 IU, 2000 IU, 3000 IU and 4000 IU/vial. The composition of the formulation excipients is the same for all dosage strengths; only the quantity of efanesoctocog alfa varies.

The powder for solution for injection is reconstituted in ~~sterile~~ WFI supplied in a prefilled syringe at a nominal volume of 3 mL (target volume 3.367 ml to ensure withdrawal of 3 mL). A vial adapter is also provided with the finished product vial and the sterile WFI pre-filled syringe to help in the administration. The efanesoctocog finished product vial and the diluent WFI (pre-filled syringe) are packaged together in a product pack with a plunger rod, a vial adaptor for reconstitution, an infusion set, which are all CE-certified. Separately, alcohol swabs, plasters and gauze pads are required for administration. Suitable information has been provided on the finished product composition.

Since the prefilled syringe containing the WFI is considered as an integral medical device, a notified body opinion confirming full compliance with the relevant General Safety and Performance Requirements (GSPRs) in Annex I of Regulation (EU) 2017/745 was provided as Appendix in the dossier section 3.2.R.3.2.

Efanesoctocog alfa was developed as a FP suitable for parenteral delivery. The formulation components and pH were based on development studies and these components are commonly used excipients in parenteral protein formulations.

The FP manufacturing was implemented at seven strengths of FP (250, 500, 750, 1000, 2000, 3000, and 4000 IU/vial) which were manufactured from frozen AS to support Phase 2 and Phase 3 clinical trials and to increase production to commercial scale.

To ensure consistent manufacturing and that the quality of efanesoctocog finished product meets its critical quality attributes, a risk control strategy was developed. The commercial control strategy for the FP manufacture was kept unchanged when compared to the control strategy put in place for PPQ manufacturing.

More detailed information was presented on the development of the risk control strategy (ICH Q8, Q9, Q10) including the calculation of the Risk Priority Number (RPN) for each input and output. These scores were be used to identify and justify the potential high-risk parameters that need specific focus in validation studies.

The formulation buffer developed is free of development studies on the process have led to a robust commercial process which yields a product with consistent quality attributes. Since identical the fill volumes for all strengths (250 IU – 4000 IU) are used, the same cycle applies for all strengths.

During manufacturing, no overages are applied and no reprocessing is performed.

The container closure system for efanesoctocog alfa powder for solution for injection consists of a glass vial closed with a rubber stopper and sealed with a seal with a polypropylene cap. Each seal for the seven finished product strengths (250 IU, 500 IU, 750 IU, 1000 IU, 2000 IU, 3000 IU and 4000 IU) has a different colour. The materials are in accordance with the respective international Pharmacopoeias (Ph. Eur., USP, JP). Extractable studies were performed for the container closure parts coming into direct contact with the finished product (glass vial and stopper). Based on the results from these extractable studies, the applicant concludes that the risk of leachables from the container closure system in the finished product is low and consequently no leachable study was, therefore, conducted. The studies on the conducted extractable studies for the vial and stopper were presented in the development section (for traceability a link should be included in the container closure section).

Integrity of the container/closure and physicochemical compatibility of the reconstituted finished product with solvent (WFI) and commonly used infusion components has been shown.

2.4.3.2. Manufacture of the product and process controls

Satisfactory GMP compliance has been demonstrated for these sites.

The manufacturing process of efanesoctocog alfa finished product consists of 10 steps, detailed in the process flow summary outlined below:

A finished product batch is manufactured using a batch in which formulated active substance batches can be pooled. A detailed flow-diagram of the finished product manufacturing process for efanesoctocog alfa (250 IU, 500 IU, 750 IU, 1000 IU, 2000 IU, 3000 IU and 4000 IU) is provided. It includes in-process controls, as well as process parameters controlled during the manufacturing process.

Finished product compounding starts with pooling of the AS. The final dilution to FP takes place in a compounding area under controlled conditions.

The classification of the parameters according to their criticality was explained in more detail using as support the calculation of the Risk Priority Numbers (RPNs).

All acceptance criteria and action limits for CPP/KPPs and IPCs have been provided in section *3.2*.P.3.4 Control of critical steps and intermediates.

The commercial production process was validated at full scale (PPQ) based on the results for the critical process parameters and parameters with elevated criticality (CCPs, KCPs, IPCs, IPTs, CIPTs). All the validation information was provided in an overall PPQ summary report.

During process validation, the commercial manufacturing process has been evaluated on commercial batches for process consistency, hold times and aseptic manufacturing conditions. The applicant has demonstrated that the manufacturing process of the finished product operates within established parameters and performs reproducibly under controlled conditions leading to a product that meets its quality attributes. Therefore, the data presented support that the commercial manufacturing process has been successfully validated.

The process validation activities and the PPQ are acceptable and a CPV approach as described in the relevant guidelines (ICH Q8-10) is in place.

The excipients chosen for formulation of efanesoctocog alfa are well-known and widely used in commercial formulations for intravenous injection. All excipients used in the manufacture of efanesoctocog alfa finished product are manufactured and tested per the appropriate compendial monographs. In summary sufficient information on the excipients is provided and no concern has been identified.

Batch analysis data have been provided for toxicological, clinical and process performance qualification (PPQ) batches of efanesoctocog alfa (BIVV001) product.

The manufacturing sites, the manufacturing scale, the active substance batches used for manufacturing, the date of manufacture and the batch use were indicated in tabular overviews.

The results were in accordance with the set acceptance criteria.

finished product batch results

All results are in accordance with the proposed release specifications.

2.4.3.3. Product specification

The efanesoctocog alfa finished product specification used for the release/shelf-life testing is considered appropriate including adequate tests for integrity, potency, purity and microbiological quality.

The test methods applied during batch release (and stability testing) are either compendial or were validated in line with the ICH Q2(R) guideline. Some of the analytical methods are applicable to both active substance and finished product release testing. The respective validations were then mainly performed for the active substance and only a few methods were partially revalidated for the finished product.

The acceptance criteria are based on data for process validation batches. The PPQ batches and the clinical batches are in accordance with the acceptance criteria. The specification parameters and their acceptance criteria and limits are mostly adequate and meet the requirements of guideline ICH Q6B.

In general, the proposed control strategy ensures that efanesoctocog alfa finished product of consistent quality is produced. The finished product is tested using pharmacopoeial and non-pharmacopoeial analytical methods. Brief method descriptions and brief validations summaries for non-pharmacopoeia test methods were provided.

During the procedure, the applicant presented more supporting data justifying use of the assay for FVIII specific activity of active substance and finished product. Most concerns related to the proposed use of the assay, which taken together left a considerable level of uncertainty, have been sufficiently addressed.

Several other concerns raised during assessment were addressed by the applicant:

Analytical methods for finished product release and stability testing were identified by unique method identification numbers. A clear link between specifications, methods and method validations is in place.

Release and stability acceptance criteria have been calculated based on release and stability data from GMP finished product batches from the commercial process. As requested for some impurities, the proposed acceptance criteria were tightened. In general, the acceptance criteria were set in accordance to ICH Q6B and are justified from a safety and efficacy point of view reflecting the commercial process.

Finished product impurities comprise process- and product-related impurities from the FP manufacturing process and the storage. The potential product- and process-related impurities and contaminants of the FP manufacturing process were described.

The potential introduction of elemental impurities in the finished product has been evaluated by a risk assessment considering the potential sources like process equipment with direct product contact, utilities used in the manufacturing process, WFI as raw material and the container closure parts. The risk of a potential release of elemental impurities caused by the manufacturing equipment used is evaluated as negligible and is in accordance with ICH Q3D, Guideline for Elemental Impurities.

The EMA document *"Questions and answers for marketing authorisation holders/applicants on the CHMP Opinion for the Article 5(3) of Regulation (EC) No 726/2004 referral on nitrosamine impurities in human medicinal products"* lists as risk factor under #12: *"Reaction of amines leaching from quaternary ammonium anion exchange resins (e.g. used for purification steps) with nitrosating agents present in the liquid phase"*. The purification of efanesoctocog alfa includes adequate process steps and the applicant provided a satisfactory nitrosamine risk assessment, concluding a negligible risk from amines leaching form quaternary ammonium exchange columns.

An appropriate description of the container closure system is included.

2.4.3.4. Stability of the product

The proposed shelf-life for all dosage strengths is four years when stored at 2-8°C including 6 months storage up to 30°C (after storage at room temperature, the medicinal product may not be returned to the refrigerator). Based on the stability data presented (primary, supportive and confirmatory stability data), the proposed shelf life is acceptable.

The proposed shelf life is supported by the primary stability data for 6 batches total comprising the 250 IU, 500 IU, 1000 IU, 2000 IU, 3000 IU and 4000 IU strengths. The long-term and accelerated stability studies are finalised. The results are within the defined acceptance criteria.

The long-term and accelerated stability studies are finalised. The results are within the defined acceptance criteria. Furthermore, a confirmatory stability study was started including the three PPQ batches at commercial scale (1x 250 IU, 1x 1000 IU and 1x 4000 IU).

Since, the supportive and the confirmatory studies are ongoing, the applicant commits to report confirmed OOS results immediately. Furthermore, the applicant commits to assess the ratio during stability studies to demonstrate consistency of the ratio over shelf life of the product. In addition, according to GMP requirements, annual follow-up stability studies will be initiated as indicated. In the SmPC, the indication of stability after reconstitution was removed due to the lack of appropriate stability data. The SmPC was revised accordingly.

Finished product – Solvent Water for Injections (WFI) in a pre-filled Syringe

The information provided in the dossier for the solvent shows that WFI is manufactured under GMP compliant conditions using a validated process. The container closure system consists of a glass barrel, a plunger, and a closure system composed of a tip cap with a Luer lock and a tamper-evident seal. The proposed shelf life conditions were supported by real time stability data.

The manufacture of WFI, which is used as solvent for reconstitution of efanesoctocog alfa, includes appropriate process steps. In both manufacturing steps post-use testing is classified as IPC.

2.4.3.5. Post approval change management protocol(s)

A post-approval change management protocol (PACMP) was included in the marketing authorisation application for efanesoctocog alfa.

A comparability protocol which is based on the biochemical properties of the finished product was presented to evaluate the possible impact of the proposed changes on product quality. Only a very brief description of the comparability approach was provided. Several studies were performed in order to de-risk the planned changes. The applicant provided only very brief summaries of these studies.

The comparability protocol includes based on clinical, PPQ and more recent batches manufactured at. The applicant justified the statistical approach taking into account the Reflection paper on Statistical methodology for the comparative assessment of quality attributes in drug development (EMA/CHMP/138502/2017).

In addition, a subset of analytical methods for release testing will be implemented at the site. Consequently, test method transfer validations will be considered for all applied methods.

The proposed PACMP is approvable and was updated incorporating the outstanding issues regarding the active substance and the finished product manufacture. Any remaining updates to the PACMP may be included in the closing sequence.

2.4.3.6. Medical device

The efanesoctocog alfa finished product vial and pre-filled solvent syringe containing water for injections co-packaged in a product pack with a plunger rod, a vial adapter for reconstitution, and an infusion set. For the CE-marked device components (vial adapter for reconstitution, infusion set) Declarations of Conformity and the EC certificates are provided. A notified body opinion for the syringe containing WFI confirming full compliance with the relevant General Safety and Performance Requirements (GSPRs) in Annex I of Regulation (EU) 2017/745 was provided during the procedure.

2.4.3.7. Adventitious agents

TSE compliance

Compliance with the TSE Guideline (EMEA/410/01 – rev. 3) has been sufficiently demonstrated. Therefore, the production of BIVV001 is in accordance with the regulatory requirements.

Virus safety

The virus safety of BIVV001 was sufficiently demonstrated. The deficiencies on virus testing as outlined initially were addressed appropriately.

2.4.4. Discussion on chemical, pharmaceutical and biological aspects

Active substance

Altuvoct (BIVV001, efanesoctocog alfa) is a novel, heterodimeric recombinant fusion protein consisting of a single chain B domain deleted human FVIII chain linked to the D'D3 domain of human VWF via the Fc domain of human immunoglobulin G1 (IgG1) and 2 XTEN polypeptides. The D'D3 domain prevents interaction of BIVV001 with natural vWF, the XTEN domains increase the hydrodynamic range of the molecule protecting from proteolytic degradation and rapid clearance. Binding of the Fc chain to the neonatal Fc receptor, FcRn, delays lysosomal clearance and is important for the longer circulating half-life.

Following process validation guidance (EMA/CHMP/BWP/187338/2014) the applicant has developed and characterised a commercial manufacturing process for efanesoctocog alfa, based on experience from other products.

After establishing appropriate process control parameters, the results of this process verification confirmed that the commercial process, operated at pre-established process parameters, performs consistently under routine manufacturing conditions. Only minor deviations were observed, which do not question the successful outcome of the process verification.

The commercial manufacturing process has been preceded by providing early material for phase 1and 2 clinical trials. Substantial changes were, however, made in the transition, resulting in significant differences in efanesoctocog alfa quality attributes and commercial lots can now be considered as comparable and the

major objection was resolved. Batches from different processes are well comparable to each other with respect to quality and safety.

In line with ICH Q5B a two-tiered cell banking system, a MCB and a WCB has been established, providing sufficient details on the origin of the transgenes and of the cell line as required by ICH Q5B and Q5D. The testing regime established for the MCB, the WCB and future cell banks is considered in line with ICH Q 5D.

A detailed, but not fully completed characterisation of efanesoctocog alfa and its impurity profile on multiple AS lots demonstrates consistent physico-chemical and functional characteristics of AS lots with respect to primary, secondary and higher order structures.

The AS release and stability testing parameters were established mostly in line with ICH Q6B to control AS potency, purity, impurities and safety. Tests are carried out using compendial analytical test procedures, where applicable, with exception of potency testing. All non-compendial analytical methods used in release testing of AS (and FP, where applicable) have been validated in accordance with ICH Q2(R1). The established acceptance limits for each test parameter are mostly sufficiently supported and justified by available data at this stage of product history.

It has been demonstrated by data that labelling of the product-specific in-house reference primary and working standards (and thus this product) in international units (IU) is justified based on the one-stage assay.

Finished product

The finished product is manufactured using a process that operates reproducibly within established parameters, leading to a product that meets preset quality attributes.

The PProcess Control Strategy (PCS) was described including the parameter classifications. The rationale for the parameter classifications was outlined in more detail and was supported by the calculation of risk priority numbers. A risk control strategy in accordance with the corresponding guidelines ICH Q8/9/10 was implemented and included into the dossier.

A process validation summary was provided covering the finished product manufacturing steps which is considered acceptable. The applicant indicates that no further specific process validation reports exist covering the single finished product manufacturing steps.

Regarding the quality control of the finished product, the implemented finished product specifications are suitable. An adequate set of parameters was established based on a risk analysis.

In conclusion, based on the review of the quality data provided, it is considered that the marketing authorisation application for Altuvoct is approvable from the quality point of view.

2.4.5. Conclusions on chemical, pharmaceutical and biological aspects

The overall quality of Altuvoct is considered acceptable when used in accordance with the conditions defined in the SmPC. The different aspects of the chemical, pharmaceutical and biological documentation comply with existing guidelines.

In conclusion, based on the review of the data provided, the MAA for Altuvoct is considered approvable from the quality point of view.

2.4.6. Recommendations for future quality development

In the context of the obligation of the MAHs to take due account of technical and scientific progress, the CHMP has made a number of recommendations.

2.5. Non-clinical aspects

2.5.1. Introduction

The non-clinical programme included *in vitro* and *in vivo* pharmacology studies, PK and toxicology studies. Pharmacology studies evaluated BIVV001 *in vitro* clotting activity and *in vivo* efficacy in prophylactic and acute bleeding models in Haemophilia A mice. In these studies, BIVV001 was compared to Advate (octocog alfa), i.e. an already authorised full-length recombinant factor VIII molecule. PK studies in Haemophilia A mice, rats, and monkeys evaluated the disposition of BIVV001, including its elimination half-life and confirmed its independence from VWF. Toxicology studies in rats and monkeys evaluated the safety and toxicokinetics of repeat dosing of BIVV001 at a range of dose levels (up to 750 IU/kg/dose) in order to provide sufficient safety margins for clinical trials and marketing authorisation.

EMA Scientific Advice concerning the non-clinical development of BIVV001 was received in 2019 (EMEA/H/SA/4066/1/2019/III, Letter dated 28 March 2019). Back then, CHMP considered the methods and extent of the non-clinical development programme principally appropriate to support marketing authorisation of BIVV001. However, issues e.g. regarding the potency assignment were noted, and the applicant was advised to further elaborate on the preference of using the 1-stage clotting assay over the chromogenic assay for the determination of BIVV001's FVIII activity.

In addition, a pre-submission meeting was held with the Rapporteur's and Co-Rapporteur's review teams on 16 February 2023 to discuss, *inter alia*, the requirement of additional non-clinical biodistribution studies. At that time, it was agreed with the applicant that the omission of such studies could be considered acceptable in principle, but attention was drawn to the need for adequate and thorough justification at the time of application. This justification has been provided in module 2.4 of the eCTD in this MAA.

2.5.2. Pharmacology

2.5.2.1. Primary pharmacodynamic studies

The non-clinical evaluation of the pharmacology of BIVV001 included *in vitro* characterisations of its FVIII activity (measured by different assay systems), its thrombin activation kinetics, and its behaviour in ROTEM,

TGA and fibrin generation assays. In addition, *in vivo* pharmacodynamics of BIVV001 were evaluated in two different bleeding models in Haemophilia A mice: Firstly, a tail clip bleeding model to assess acute efficacy and secondly, a tail vein transection (TVT) model to assess efficacy of prophylaxis.

In all of these studies, BIVV001 demonstrated dose-dependent effects. In the *in vitro* FVIII activity assays, BIVV001 was found to have a >2-fold lower specific FVIII activity when measured by the aPTT-based 1-stage clotting assay compared to the 2-stage chromogenic assay. Based on comparisons to Advate in the *in vitro* and *in vivo* functional studies, the applicant concludes that the physiological activity of BIVV001 is best described by the 1-stage clotting assay. Based on comparable results achieved with BIVV001 administered 72 hours and Advate administered 24 hours prior to the intervention in the TVT model, the applicant further concludes on a 3-fold prolongation of efficacy of BIVV001 compared to Advate.

2.5.2.2. Secondary pharmacodynamic studies

No secondary pharmacodynamic studies were performed which was considered acceptable (see section 2.5.6.).

2.5.2.3. Safety pharmacology programme

No separate safety pharmacology studies were performed which was considered acceptable (see section 2.5.6.).

2.5.2.4. Pharmacodynamic drug interactions

No PD drug interaction studies have been performed which was considered acceptable (see section 2.5.6.).

2.5.3. Pharmacokinetics

Non-clinical pharmacokinetics of BIVV001 were studied in Haemophilia A mice, wildtype Sprague-Dawley rats and wildtype *Cynomolgus* monkeys following intravenous administration. In rats and monkeys, PK/TK was further evaluated as part of the GLP toxicology studies. PK comparability of different production batches has been demonstrated in a separate study in Haemophilia A mice. PK parameters were determined by measuring plasma FVIII activity and concentration over time. In mice and rats, direct PK comparisons were made between BIVV001 versus Advate, whereas in monkeys BIVV001 PK was compared to previously published PK data for Advate.

In all species tested, BIVV001 displayed dose linearity over multiple dose levels (Haemophilia A mice: 25-100 IU (1-stage)/kg; WT rats: 75-750 IU (chromogenic)/kg and WT monkeys: 25-750 IU (chromogenic)/kg). PK profiles measured based on concentration overlapped with profiles measured using FVIII activity.

In all species tested, BIVV001 demonstrated an approx. 3-fold longer half-life compared to standard half-life FVIII molecules (i.e. Advate).

A non-FcRn binding variant of BIVV001 (IHH triple mutant) was shown to exhibit a 20% shorter half-life than the wild type molecule, confirming FcRn-mediated recycling as one of the contributors to the extended half-life of BIVV001. In addition, the successful decoupling of BIVV001 from endogenous VWF has been experimentally confirmed by comparative PK analyses of BIVV001 in HemA (FVIII-/-/VWF+/+), VWF heterozygous (FVIII-/-/VWF-/+) and double knockout (FVIII-/-/VWF-/-) mice.

2.5.4. Toxicology

2.5.4.1. Single dose toxicity

No single dose toxicity studies were performed which was considered acceptable (see section 2.5.6.).

2.5.4.2. Repeat dose toxicity

The toxicology programme for BIVV001 included two GLP-compliant repeat-dose toxicology studies of 4-week duration, which evaluated BIVV001 administered at 75, 250, and 750 IU/kg every 3 days in SD rats and at 25, 75, 250, 750 IU/kg every 4 days in *Cynomolgus* monkeys.

Overall, there were no adverse findings directly attributed to the pharmacologic activity of BIVV001. BIVV001 was well tolerated at the injection site in both species. For both species, the NOAEL was determined to be 750 IU/kg/dose, i.e. the highest dose level evaluated.

2.5.4.3. Genotoxicity

No genotoxicity studies were performed which was considered acceptable (see section 2.5.6.).

2.5.4.4. Carcinogenicity

No carcinogenicity studies were performed which was considered acceptable (see section 2.5.6.). A carcinogenicity risk assessment has been provided (section 2.6.6.5 of eCTD module 2.6.6).

2.5.4.5. Reproductive and developmental toxicity

No reproductive and developmental toxicity studies were performed which was considered acceptable (see section 2.5.6.).

2.5.4.6. Toxicokinetic data

Please refer to the Pharmacokinetic data.

2.5.4.7. Local tolerance

No classical local tolerance studies were performed which was considered acceptable (see section 2.5.6.).

2.5.4.8. Other toxicity studies

The toxicology programme for BIVV001 included an *in vitro* assessment of haemocompatibility. In this study, BIVV001 demonstrated no potential for haemolysis or plasma flocculation in whole blood samples collected from 3 healthy male and 3 healthy female human subjects with a 7.4-fold margin compared to steady state exposure in haemophilia A patients receiving 50 IU/kg.

2.5.5. Ecotoxicity/environmental risk assessment

In accordance with the guideline CHMP/SWP/4447/00 (1), efanesoctocog alfa as a protein is exempted from an environmental risk assessment since proteins are unlikely to result in a significant risk to the environment. Therefore, efanesoctocog alfa is not expected to pose a risk to the environment.

2.5.6. Discussion on non-clinical aspects

Pharmacology:

Primary pharmacodynamic studies

The assays and models chosen for the *in vitro* and *in vivo* characterisation of BIVV001 pharmacology are considered state-of-the-art. *In vivo* studies modelled the intended clinical use of BIVV001, i.e. the treatment and prophylaxis of bleeding in haemophilia A.

The use of Advate (i.e. an already authorised full-length recombinant factor VIII product) as a comparator is considered principally acceptable and supported by an extensive body of available data. Nevertheless, substantial differences between the FVIII moieties of both products (with BIVV001 being B-domain deleted and Fc-conjugated) are noted.

Overall, the types and amount of submitted PD studies are considered sufficient to support marketing authorisation. Although it is generally appreciated that PD studies are conducted in more than one species, the restriction to mouse models is considered acceptable as FVIII replacement therapy by rFVIII products is well understood and data was compared to the widely used rFVIII Advate. Data are considered sufficient in view of the fact that BIVV001 should replace endogenous factor VIII and no further pharmacodynamic properties are to be expected. This is also in accordance with the principles of the 3Rs.

Except for the tail clip model in HemA mice, for which a precursor molecule of BIVV001 was used (FVIIIFc-VWF-XTEN, differing from final BIVV001 by 2 extra amino acids in the 144 XTEN polypeptide), all PD studies were performed with final BIVV001

Importantly, BIVV001 was found to have a >2-fold lower specific FVIII activity when measured by the aPTT-based 1-stage clotting assay compared to the 2-stage chromogenic assay. Based on comparisons to Advate in the *in vitro* and *in vivo* efficacy studies, the applicant concludes that the physiological activity of BIVV001 is best described by the 1-stage clotting assay. In this context, it is considered noteworthy that the proposed assignment of potency using the 1-stage clotting assay results in 3- to 4-fold higher plasma levels of BIVV001 compared to alternative FVIII products. Consequently, a convincing pre-clinical demonstration that the results of the 1-stage rather than the 2-stage chromogenic assay more appropriately reflect the physiological activity of BIVV001 is considered important to minimise potential risks, particularly with regards to thromboembolic complications that may result from an excessive administration of Factor VIII.

Due to (1) uncertainties regarding the relevance of the material used in the preclinical PD studies for the material intended for commercialisation , and (2) a trend towards increased *in vivo* efficacy of BIVV001 compared to Advate when dosing was based on 1-stage FVIII activities, and a lack of similar comparisons with a dosing based on chromogenic FVIII activity, the applicant was requested to provide additional justification for the proposed 1-stage FVIII activity-based dosing of BIVV001.

Regarding the first point, the applicant provided additional information on the specific activities of the precursor material used in the tail-clip bleeding model and confirmed a similar degree of assay discrepancy compared to final BIVV001. Therefore, it is agreed that the material used in the tail-clip bleeding model can be considered representative of the final material. Furthermore, the applicant has provided additional support for the claimed comparability of materials from different manufacturing processes. Therefore, the omission of additional preclinical PD studies using commercial material is considered acceptable.

Regarding the second point, the applicant provided additional data allowing for a comparison of potency assignments using the 1-stage clotting assay vs. the chromogenic assay in the *in vitro* studies and in the *in vivo* tail-clip bleeding model. In view of these data — in particular, a comparison of successful bleeding protection in the tail-clip bleeding model (defined as a blood loss less than 0.175 mL, which was the mean + 2SD of the blood loss in WT mice) — it is agreed that approximately three times higher doses of BIVV001 appear to be required to achieve similar in vivo efficacy to Advate when dosing is based on chromogenic FVIII activity.

Hence, overall, it is agreed that the submitted preclinical PD data provide appropriate support for the intended dosing of BIVV001 based on its 1-stage FVIII activity (using Actin FSL).

Nevertheless, it is considered worth to note that the physiological relevance of the 1-stage FVIII activity of BIVV001 contrasts with alternative single-chain FVIII molecules (namely Afstyla and the single-chain variant of Elocta [SC rFVIII-Fc]), for which it has been concluded that not the results of the 1-stage clotting assay but that of the chromogenic activity assay most accurately reflect their clinical haemostatic potentials (cf. Buyue et al., 2014 and the Afstyla SmPC). However, even though the underlying reason(s) for the apparently different behaviour of BIVV001 remain unclear, it may well be explained by its increased structural complexity including additional elements (i.e. covalent attachment of the VWF D'D3 domain and XTEN modifications), which are considered likely to further affect the kinetics of thrombin-mediated activation.

Based on the results obtained in the TVT model in Haemophilia A mice, the applicant concludes on a 3-fold prolongation of efficacy of BIVV001 compared to Advate. Considering the improved PK behaviour of BIVV001, together with the well-established correlation between plasma factor VIII efficacy and bleeding protection, it is agreed that results obtained in this model point towards a prolonged efficacy of BIVV001 compared to Advate. However, since for each of the two products different administration time points were investigated (72 hours prior TVT for BIVV001 and 24 hours prior TVT for Advate), the conclusion of a 3-fold prolongation of efficacy compared to Advate remains indirect.

Secondary pharmacodynamic studies

Given the well characterised pharmacology of factor VIII, the absence of any known biological activity of the D'D3 fragment of VWF besides binding to FVIII, and the intended use of BIVV001 for replacement therapy, the absence of secondary pharmacodynamic studies is considered acceptable.

Safety pharmacology programme

No separate safety pharmacology studies were conducted, which is considered acceptable. Relevant safety pharmacology measurements (electrocardiograms and cage-side observation for signs of respiratory distress and abnormal CNS effects) were evaluated as part of the GLP repeat-dose toxicology study in *Cynomolgus* monkeys.

Pharmacodynamic drug interactions

No PD drug interaction studies have been conducted which is considered acceptable. Based on the pharmacology of BIVV001, no pharmacokinetic drug interactions are expected.

In summary, the submitted non-clinical pharmacology data are considered sufficient to support marketing authorisation of BIVV001 as a factor VIII replacement product for the treatment of haemophilia A.

Pharmacokinetics:

Non-clinical pharmacokinetics of BIVV001 were studied in Haemophilia A mice, wildtype rats and wildtype monkeys. Of note, wildtype animals will have a significant portion of circulating VWF pre-occupied with endogenous FVIII. In contrast, the endogenous VWF in Haemophilia A mice is free of FVIII and ready to bind the infused FVIII molecules immediately. As a result, Haemophilia A mice have been widely used for the PK assessment of FVIII products, and although theoretically less relevant for BIVV001 (which is claimed to be decoupled from VWF), PK characterisation using this disease model is considered appropriate.

For most of the PK studies, BIVV001 material derived from the manufacturing cell line clone was used. Deviations thereof (use of a precursor molecule or research grade material in studies R-BV001-11 and Rsch-2015-044) are not considered to affect the validity of the conclusions drawn from these studies (i.e. VWF-independent half-life and an approx. 20% contribution of its Fc domain to half-life extension).

The employed analytical methods do not raise concerns regarding the validity of the reported PK data. In the non-GLP studies, a commercially available FVIII chromogenic assay was used as per product insert. In the GLP toxicology studies validated assays were used to assess BIVV001 concentration (ELISA with anti-human FVIII capture and detection through a biotinylated anti-XTEN monoclonal antibody) and activity (modified chromogenic assay with anti-XTEN capture).

The use of only the chromogenic assay for the assessment of FVIII activity in most of the preclinical PK studies is considered sufficiently justified by the demonstration of assay-independent PK behaviour of BIVV001 in Haemophilia A mice (Study R-BV001-02).

Results of the non-clinical PK studies support the claim of a species-independent approx. 3-fold longer half-life compared to standard half-life FVIII molecules. In all species test, BIVV001 displayed dose linearity over multiple dose levels (Haemophilia A mice: 25-100 IU [1-stage]/kg; WT rats: 75-750 IU [chromogenic]/kg and WT monkeys: 25-750 IU [chromogenic]/kg). PK profiles measured based on concentration overlapped with profiles measured using FVIII activity. The volumes of distribution estimated in Haemophilia A mice (mean [SD]: 53 [8.35] ml/kg), and monkeys (mean: 76 [15.19] ml/kg in males and 68 [16.05] ml/kg in females) support the conclusion that BIVV001 is not extensively distributed beyond the vasculature.

The intended evaluation of repeat-dose PK/TK in the GLP toxicology studies was severely compromised by the development of ADAs. However, limited data from a few ADA-negative rats in the lowest dose group (75 IU/kg) of study P073-16-02 indicate largely comparable exposure on day 28 compared to day 1 with accumulation ratios ranging from 1.24 to 1.44 for C_{max} and from 1.56 to 1.58 for $AUC_{(0-t)}$.

The totality of available preclinical PK data do not argue for a clinically relevant gender-specific PK behaviour of BIVV001.

In summary, the submitted non-clinical PK data suggest that BIVV001, a new class of FVIII that uncouples rFVIII from VWF in the bloodstream, leads to a prolonged half-life and are considered sufficient to support marketing authorisation.

Toxicology:

Single-dose toxicology

No single-dose toxicology was performed which is considered acceptable. BIVV001 was well tolerated based on clinical observations in single dose non-GLP PK studies that evaluated BIVV001 at 150 IU/kg in Sprague-Dawley rats and 100 IU/kg or 300 IU/kg in cynomolgus monkeys. In addition, no adverse effects or clinical signs were noted on Day 1 of dosing in the GLP repeat-dose toxicology studies in rats and monkeys up to 750 IU/kg.

Repeat-dose toxicity

The species used in the GLP repeat-dose toxicology studies (SD rats and *Cynomolgus* monkeys) represent standard species used for non-clinical evaluation of potential toxicities. Although not used in the PD studies, both species can be considered pharmacologically relevant given the generally well-conserved coagulation cascade and available data confirming Fc binding to the FcRn of both species.

As noted by the applicant, although the intended patient population is predominantly male, female animals were included in the toxicology programme to support the potential use of BIVV001 in women with FVIII deficiency.

In the *in vivo* studies, BIVV001 was administered intravenously, which reflects the intended route of clinical use. Noteworthy, the material used in the toxicology studies differed from commercial material by a liquid instead of lyophilised formulation and was generated at non-GMP pilot scale. PK comparability of this material to the material intended for clinical use has been established in study R-BV001-14. Additional support for the relevance of the material used in the toxicology studies was provided by confirming the absence of any new species introduced with later changes of the manufacturing process and only small quantitative differences which can be considered well-covered by the established safety margins.

The nonclinical repeat-dose toxicology studies evaluated BIVV001 administered at 75, 250, and 750 IU/kg every 3 days in rats and at 25, 75, 250, 750 IU/kg every 4 days in monkeys. Importantly, dosing was based on 1-stage FVIII activity. As such, the highest dose applied in the toxicology studies (750 IU/kg/dose) provides a 15-fold safety margin (isometric scaling) to the clinical dosing proposed for routine prophylaxis (50 IU/kg). Systemic exposure was confirmed using validated detection methods of BIVV001 concentration and activity.

Overall, there were no adverse findings directly attributed to the pharmacologic activity of BIVV001. BIVV001 was well tolerated at the injection site in both species. For both species, the NOAEL was determined to be 750 IU/kg/dose, i.e. the highest dose level evaluated.

As expected, the conduct of the repeat-dose toxicology studies was strongly affected by immune reactions against the foreign material of human origin, with a high frequency of dose- and time-depended ADA development in both species. Of note, ADA-positive monkeys showed signs of acquired haemophilia (prolonged aPTT), which can be explained by cross-reactivity of ADAs with endogenous FVIII. This phenomenon also provides a plausible explanation for the reported death of one animal in the high-dose group due to haemorrhage (ADA Titre of 1280 and aPTT of 47.8 sec the day before). As pointed out by ICH S6, the induction of antibody formation in animals is not predictive of a potential for antibody formation in humans. However, the characterisation of the immune responses in the species used in the toxicology studies serves as an appropriate justification for the omission of longer-term studies and provides valuable information for the interpretation of the repeat-TK and safety data obtained in these studies.

In both species some reversible, minimal changes in clinical chemistry and haematology parameters were observed. However, in view of their minor magnitude, high variability and the lack of microscopic or organ weight correlates, it is agreed with the applicant that these observations can be considered non-adverse. Individual cases of increased plasma creatine kinase (CK) levels observed upon administration of BIVV001 may be explained by a potential impact of cross-reacting antibodies to endogenous FVIII, which in turn may have favoured events of minor intramuscular haemorrhage. Although the exact cause of this finding remains unclear, the absence of associations to macro- or microscopic correlates, an apparent lack of dose responsiveness, the absence of similar findings in rodents, and the absence of signals indicating muscle injury or disease in the clinical trials provide reassurance on a monkey-specific (and likely immunogenicity-related) phenomenon not raising concerns regarding the clinical use of BIVV001.

Genotoxicity

No genotoxicity studies were performed, which is considered acceptable. As pointed out by the applicant, given its size, BIVV001 is not expected to cross cellular and nuclear membranes or to directly interact with DNA or other chromosomal material.

Carcinogenicity

No carcinogenicity studies were performed, which is considered acceptable in accordance with ICH S6(R1) - Guidance for Industry. Preclinical Safety Evaluation of Biotechnology- derived Pharmaceuticals, stating that carcinogenicity testing of biological products is not required unless there is cause for concern. A carcinogenicity risk assessment has been provided (section 2.6.6.5 of eCTD module 2.6.6).

Reproductive and developmental toxicity

No reproductive and developmental toxicity studies were performed, which is considered acceptable. On the basis of a well-understood mechanism of action, FVIII replacement products are not expected to affect embryo-foetal development. Of note, histological evaluation of the reproductive organs in the GLP repeat-dose toxicology studies did not indicate any BIVV001-related toxicity in either sex.

Local tolerance

No classical local tolerance studies were performed, which is considered acceptable. Results of the two GLP repeat-dose toxicity studies (rats and monkeys) support the conclusion of a locally well tolerated intravenous administration of BIVV001. There were no BIVV001-related changes (macroscopic or microscopic) observed at the site of intravenous administration in any study.

Taken together, the presented toxicology data are considered appropriate to support marketing authorisation of BIVV001 in the treatment and prophylaxis of bleeding in patients with haemophilia A.

Ecotoxicity/environmental risk assessment

In accordance with the guideline CHMP/SWP/4447/00 (1), efanesoctocog alfa as a protein is exempted from an environmental risk assessment since proteins are unlikely to result in a significant risk to the environment.

Therefore, efanesoctocog alfa is not expected to pose a risk to the environment.

2.5.7. Conclusion on the non-clinical aspects

From a non-clinical perspective, the submitted data are considered appropriate to support marketing authorisation of BIVV001 as a factor VIII replacement product for the treatment of haemophilia A.

2.6. Clinical aspects

2.6.1. Introduction

GCP aspects

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

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

- **Tabular overview of clinical studies**

Table 1: Overview of clinical studies with Altuvoct in Haemophilia A

Study type	**Study code** **Phase**	**Number of participants enrolled**	**Treatment duration** **Dose**	**Trial status**
Pharmacokinetics and initial tolerability in patients with haemophilia A				
Single ascending dose	242HA101 (TDU16220) Phase 1/2a	16 (7 in the low dose cohort, 9 in the high dose cohort)	Single dose Low dose cohort: 25 IU/kg Advate, then 25 IU/kgBIVV001 High dose cohort: 65 IU/kg Advate, then 65 IU/kg BIVV001	Completed
Multiple ascending doses study	242HA102 (TDR16219) Phase 1/2a	24 (10 in the 50 IU/kg cohort, 14 in the 65 IU/kg cohort)	4 once-weekly doses Cohort 1: 50 IU/kg BIVV001 Cohort 2: 65 IU/kg BIVV001	Completed
Sequential single dose study	PKM17085 Phase 1	13	Single dose 50 IU/kg Advate, then 50 IU/kg Adynovi/Adynovate, then 50 IU/kg BIVV001	Completed
Efficacy and safety studies in patients with severe haemophilia A				
Safety, efficacy, and PK in patients ≥12 years of age	EFC16293 (XTEND-1) Phase 3	159 (133 in Arm A, 26 in Arm B)	Arm A (prophylaxis): 52 weeks 50 IU/kg BIVV001 once weekly Arm B: 26 weeks 50 IU/kg BIVV001 (on demand), then 26 weeks 50 IU/kg BIVV001 once weekly (prophylaxis)	Completed
Safety, efficacy, and PK in	EFC16295	74 (38 in <6 years of age	52 weeks	Completed

patients <12 years of age	(XTEND-kids) Phase 3	cohort, 36 in 6 to <12 years age cohort)	50 IU/kg BIVV001 once weekly	
Long-term safety and efficacy in patients ≥12 years of age	LTS16294 (XTEND-ed) Phase 3	218 (176 in Arm A, 37 in Arm B, 5 in Arm C)[a]	Up to 4 years 50 IU/kg BIVV001 once weekly	Ongoing[b]

Abbreviations: OSC = one-stage clotting (assay); PD = pharmacodynamic; PK = pharmacokinetic.
Advate is a full-length rFVIII, Adynovi/Adynovate is a PEGylated full length rFVIII.
[a.] Study ongoing. Number of participants enrolled as of cut-off date (30 June 2022).
[b.] FVIII activity listing is included only for Arm C in the current submission.
Source: adapted from Module 2.7.2 Table 1

2.6.2. Clinical pharmacology

2.6.2.1. Pharmacokinetics

Absorption

BIVV001 is administered intravenously, thus no specific data on absorption are presented. In the Phase 3 study EFC16293 the mean IR was approximately 2.6 IU/dL per IU/kg and remained consistent during the study for 52 weeks. Similar IR were obtained in the Phase 1, 1/2a PK studies.

Distribution

BIVV001 is distributed primarily in the circulatory system as illustrated by the limited volume of distribution ranging from 31.3 to 38.3 mL/kg for doses 25 to 65 IU/kg (Table 2).

Table 2: BIVV001 CL and Vss by dose in adult and adolescent patients with haemophilia A after a single (or first) dose

Day 1 Mean (SD)	25 IU/kg 242HA101 N=6	50 IU/kg-242HA102[a] N=9	50 IU/kg-EFC16293 N=153	50 IU/kg-PKM17085 N=13	65 IU/kg-242HA101 N=8	65 IU/kg-242HA102[a] N=14
CL (mL/h/kg)	0.590 (0.220)	0.610 (0.110)	0.508 (0.124)	0.503 (0.0974)	0.510 (0.100)	0.600 (0.140)
V_{ss} (mL/kg)	36.0 (9.87)	38.3 (8.31)	31.7 (7.44)	31.3 (3.44)	36.3 (7.58)	34.8 (6.95)

CL = clearance; SD = standard deviation; V_{ss} = volume of distribution at steady state.
[a] Values from Day 22 after 4 weekly doses
Source: Table 2.7.2 - 9; Table 2.7.2 - 13; 5.3.3.2 242HA101, 15.4 Pharmacokinetic data Table 3; 5.3.3.2 242HA102 Table 22.
A similar volume of distribution (38.6 mL/kg) was predicted based on population PK analysis in a typical patient (POH0731).

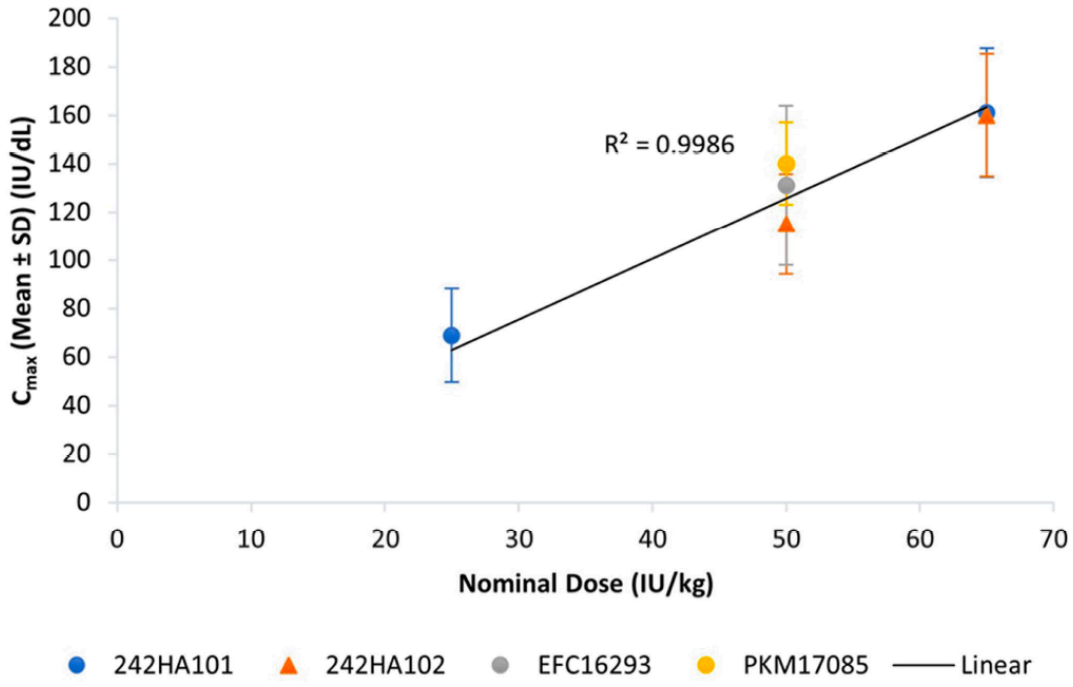
Elimination

Being an Fc fusion protein with D'D3 domain of VWF, its clearance is governed by 2 mechanisms: recycling through FcRn and VWF-independent clearance, both of which would reduce the clearance and prolong the half-life compared to other FVIII products. The presence of 2 XTEN polypeptides further reduces the clearance. Thus, BIVV001 clearance (0.503 mL/h/kg) was lower compared to Advate (3.26 mL/h/kg) (SHL product) and Adynovi (1.86 mL/h/kg) (EHL product), resulting in a half-life of BIVV001 (44.4 hours) that was markedly longer than that of Advate (3.94-fold) and Adynovi (2.82-fold). From the population PK model, the BIVV001 CL was 0.553 mL/h/kg and half-life was 48.4 hours in a typical patient (POH0731).

Dose proportionality and time dependencies

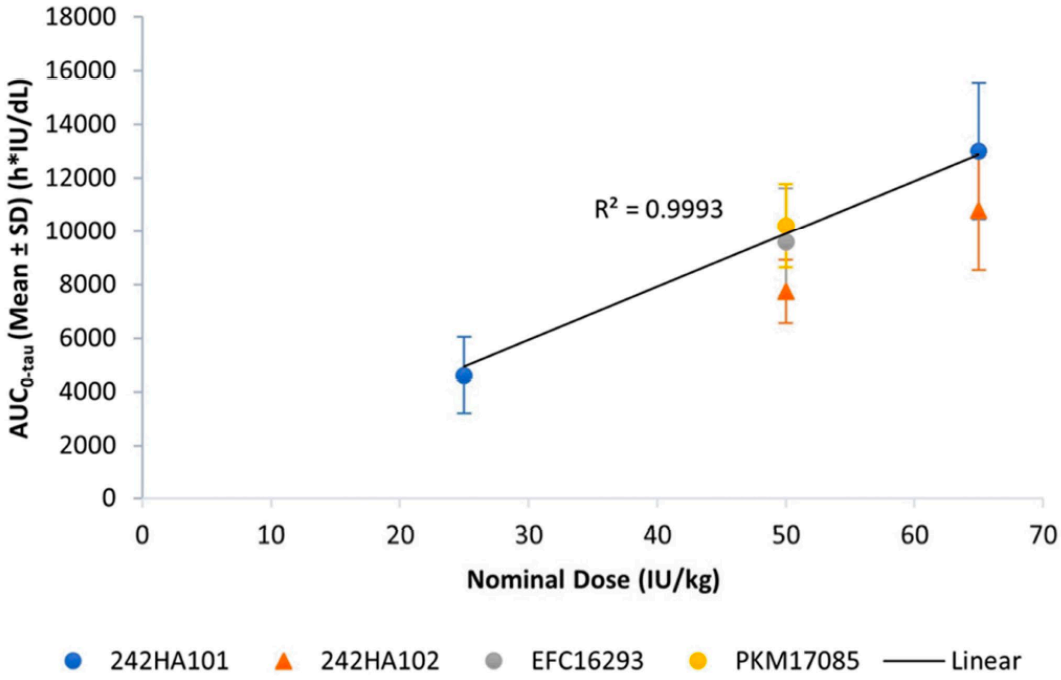
Following a single dose of BIVV001, the CL and Vss were independent of dose between 25 and 65 IU/kg BIVV001 (Table 4). Dose-proportionality was observed for C_{max} and $AUC_{0\text{-}tau}$ between 25 and 65 IU/kg of BIVV001 (Figure 1, Figure 2).

Figure 2: BIVV001 Cmax by dose in patients with haemophilia A after a single (or first) dose



Cmax = maximum FVIII activity at Day 1; SD = standard deviation.
Source: Table 2.7.2 - 9, Table 2.7.2 - 13; 5.3.3.2 242HA101, 15.4 Pharmacokinetic data Table 3; 5.3.3.2 242HA102 Table 22; 5.3.5.1 EFC16293 Table 36.

Figure 3: 18 BIVV001 AUC0-tau by dose in patients with haemophilia A after a single (or first) dose



AUC0-tau = area under the activity-time curve over the dosing interval; SD = standard deviation.
For PKM17085 and 242HA101, numbers correspond to AUC
Source: Table 2.7.2 - 9 and Table 2.7.2 - 13; 5.3.3.2 242HA101, 15.4 Pharmacokinetic data Table 3; 5.3.3.2 242HA102 Table 22.

Additionally, the population PK model could adequately characterise the dose-proportional pharmacokinetics of BIVV001 (POH0731).

Once-weekly dosing of BIVV001 at 50 or 65 IU/kg for 4 weeks (242HA102) as well as at 50 IU/kg dosing for 26 weeks (EFC16293), resulted in minimal accumulation (Table 3), indicating that steady state was achieved after the first dose.

Table 3: Summary of BIVV001 PK parameters across doses for baseline-corrected FVIII activity based on OSC assay in adult and adolescent patients with haemophilia A at steady state

Mean (SD)	50 IU/kg - 242HA102 N=9	50 IU/kg - EFC16293 N=17
C_{maxss} (IU/dL)	135 (31.0)	154 (29.7)
$AUC_{0\text{-}tau}$ (h*IU/dL)	8390 (1340)	11800 (2720)
$t_{1/2z}$ (h)	41.6 (5.94)	47.9 (9.27)

AUC0-tau = area under the activity-time curve over the dosing interval; Cmaxss = maximum FVIII activity at steady state; t1/2z = terminal half-life; SD = standard deviation.
EFC16293: Week 26 sequential PK subgroup (Arm A), 242HA102: Day 22

Target population

Study PKM17085

This was a Phase 1, open-label, single centre, 3 period fixed sequence crossover study to characterise the PK of FVIII products: BIVV001, a SHL rFVIII (Advate), and an EHL rFVIII (Adynovi). The participants (n=13) were adult male PTPs (>150 EDs) 18 to 65 years of age with severe haemophilia A.

Each participant was sequentially dosed with a single dose of 50 IU/kg of Advate (first), Adynovi (second), and BIVV001(third), as a slow push IV injection over 8 ± 2 minutes. Each administration was followed by PK sampling and a washout period, as applicable.

The measured C_{max}, V_{ss}, and IR values indicated recovery is consistent for all 3 FVIII products (Table 4). Compared with Advate and Adynovi, a single 50 IU/kg dose of BIVV001 exhibited reduced CL (17% and 28% of the respective comparator), which resulted in longer half-life (3.94- and 2.82-fold, respectively) and higher exposure (AUC, 6.03- and 3.57-fold, respectively).

Table 4: PKM17085: Summary of PK parameters for baseline-corrected FVIII activity following a single dose of Advate, Adynovi, and BIVV001 based on OSC assay - PK analysis set

PK Parameters	Advate (Mean ± SD)	Adynovi (Mean ± SD)	BIVV001 (Mean ± SD)
n	13	13	13
C_{max} (IU/dL)	119 ± 14.7	151 ± 30.3	140 ± 16.9
IR (IU/dL per IU/kg)	2.37 ± 0.295	3.02 ± 0.605	2.80 ± 0.338
AUC (IU*h/dL)	1820 ± 748	2950 ± 905	10200 ± 1560
CL (mL/h/kg)	3.26 ± 1.48	1.86 ± 0.618	0.503 ± 0.0974
V_{ss} (mL/kg)	40.1 ± 6.82	34.5 ± 6.60	31.3 ± 3.44
$t_{1/2z}$ (h)	11.7 ± 4.55	16.3 ± 5.63	44.4 ± 10.4

AUC = area under the activity-time curve extrapolated to infinity; CL = clearance; Cmax = maximum FVIII activity; IR = incremental recovery; PK = pharmacokinetic; SD = standard deviation; t1/2z = terminal half-life; Vss = volume of distribution at steady state.

Study EFC16293 (XTEND-1)

This Phase 3, open-label, multinational, multi-centre study investigated efficacy, safety and PK of BIVV001 in PTPs (>150 EDs) being ≥12 years of age with severe haemophilia A. The study included a prophylactic treatment arm (Arm A) and an on-demand treatment arm (Arm B). On a subgroup of Arm A (n=17) sequential PK sampling was performed on week 26.

A 50 IU/kg dose of BIVV001 resulted in high sustained FVIII activity levels in the normal to near-normal range (>40 IU/dL) for 3 to 4 days in the overall population (i.e. abbreviated and sequential PK subgroups); FVIII activity levels remained in the mild haemophilia range at the end of the weekly dosing interval. Mean (SD) FVIII activity levels after the first dose were 56.59 (13.69) IU/dL at 72 hours and 11.92 (4.55) IU/dL at 168 hours. Mean half-life of BIVV001 was 47.6 hours (Table 5), which is 2- to 3-fold longer than the half-life of other FVIII products.

On Day 1 the majority of participants had FVIII levels below the upper physiological limit of 150 IU/dL. Twenty-six participants had a Cmax above 150 IU/dL (including 4 above 200 IU/dL) with a mean (SD) duration of predicted FVIII activity levels above 150 IU/dL of 4.35 (3.96) hours (<3% of the weekly dosing interval). Mean peak (15-min post-dose) values were lower than 150 IU/dL across all visits.

However, at least one result of peak FVIII activity >150 IU/dL was measured in 69% of the participants at any time during study EFC16293 (baseline, week 4, week 13, week 26, week 39 and/or week 52).

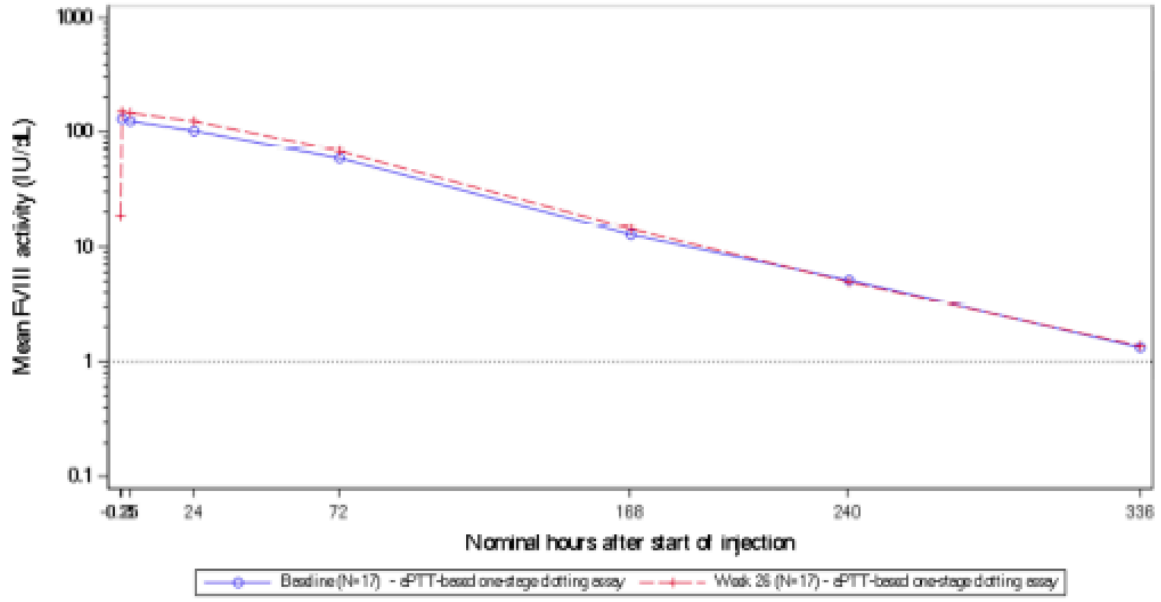
Table 5: EFC16293: Summary of PK parameters for baseline-corrected FVIII activity based on OSC assay on Day 1 (overall population) – PK analysis set

	C_{max} (IU/dL)	IR (IU/dL per IU/kg)	$AUC_{0\text{-}tau}$ (h*IU/dL)	$DN\_AUC_{0\text{-}tau}$ (h*kg*IU/dL/IU)	CL (mL/h/kg)	V_{ss} (mL/kg)	$t_{1/2z}$ (h)	MRT (h)
n	159	159	153[a]	153[a]	153[a]	153[a]	159	153[a]
Mean	131	2.60	9600	191	0.508	31.7	47.6	63.2
SD	33.0	0.648	2010	39.9	0.124	7.44	8.86	9.70

AUC0-tau = area under the activity-time curve over the dosing interval; CL = clearance; Cmax = maximum FVIII activity; DN_AUC0-tau = dose normalised area under the activity-time curve over the dosing interval; IR = incremental recovery; MRT = mean residence time; SD = standard deviation; t1/2z = terminal half-life; Vss = volume of distribution at steady state.
'Overall' corresponds to abbreviated and sequential PK subgroups combined
a Six participants were excluded from descriptive statistics as their AUC extrapolation exceeded 30%.

Mean baseline-corrected FVIII activity over time profiles for Day 1 and Day 183 (Week 26) based on the OSC assay indicated minimal accumulation with once-weekly 50 IU/kg regimen of BIVV001 for 26 weeks (Figure 4).

Figure 4: EFC16293: Semi-log plot of mean baseline-corrected FVIII activity over time based on OSC assay - Sequential PK subgroup – PK analysis set



Note: 1: For aPTT-based one-stage clotting assay, values below 1 IU/dL (i.e., LLOQ) are imputed as zero.
2: The horizontal dash line at y= 1 IU/dL represents LLOQ.
PGM=PRODOPS/BIVV001/EFC16293/CSR_01/REPORT/PGM/fviii_ovr_time_mean_log_f.sas
OUT=REPORT/OUTPUT/fviii_ovr_time_mean_log_f_x.rtf (30MAR2022 22:39)

Mean C_{trough} observed at steady state was 18.5 IU/dL (Table 6), further demonstrating that BIVV001 maintained high sustained FVIII activity levels with 50 IU/kg once-weekly regimen. After 26 weeks of once-weekly 50 IU/kg BIVV001 treatment, the mean time in the normal to near-normal range (>40 IU/dL) was 98.2 hours (4.1 days) and time above 10 IU/dL was 200 hours (8.3 days).

Table 6: EFC16293: Summary of PK parameters for baseline-corrected FVIII activity based on OSC assay on Day 183a - Sequential PK subgroup - PK analysis set

	C_{maxss} (IU/dL)	IR (IU/dL per IU/kg)	$AUC_{0\text{-}tau}$ (h*IU/dL)	$DN\_AUC_{0\text{-}tau}$ (h*kg*IU/dL/IU)	CL_{ss} (mL/h/kg)	V_{ss} (mL/kg)	$t_{1/2z}$ (h)	MRT (h)	C_{trough} (IU/dL)	AI
n	17	17	17	17	17	17	17	17	17	15*
Mean	154	3.05	11800	234	0.449	29.6	47.9	65.9	18.5	1.17
SD	29.7	0.592	2720	53.5	0.101	8.26	9.27	11.3	8.71	0.160

AI = accumulation index (AI is computed as AUCDay183/AUCDay1 ratio); AUC0-tau = area under the activity-time curve over the dosing interval; CLss = total clearance at steady state; Cmaxss = maximum FVIII activity at steady state; Ctrough = trough activity; DN_AUC0-tau = dose normalised area under the activity-time curve over the dosing interval; IR = incremental recovery; MRT = mean residence time; SD = standard deviation; t1/2z = terminal half-life; Vss = volume of distribution at steady state.
a Participant 348-0312-00002 was re-sampled on Day218 to substitute Day183 samples, while Participant 348-0312-00003 was re-sampled
on Day246 to substitute Day183 samples, as both patients took unscheduled dose prior Day183. AI was not calculated for both these participants.

PK parameters for the CS assay on Day 1 for the overall population show that the mean (SD) half-life of BIVV001 was 43.6 (6.50) hours similar to what was observed with the OSC assay (i.e., 47.9 [9.27] hours). Higher values for C_{max} (419±80.4), $AUC_{0\text{-}tau}$ (23 300±5190), and IR (8.31±1.59) were observed for CS assay and lower values for CL (0.212±0.0514) and V_{ss} (11.6±3.02) were observed for CS assay.

Special populations

Gender

The impact of sex on BIVV001 could not be studied as there was only 1 female participant in the clinical studies, considering that haemophilia A is an X-chromosome linked disorder that occurs predominantly in males.

Race

The population PK analysis included 177 Caucasian, 5 African American and 40 Asian patients, as well as 8 patients with other race and 30 patients with race not reported.

Based on the population PK analysis, Asian race was identified as a statistically significant covariate on CL, with the CL being 10.4% lower in an Asian patient versus a non-Asian patient of identical body weight (POH0731).

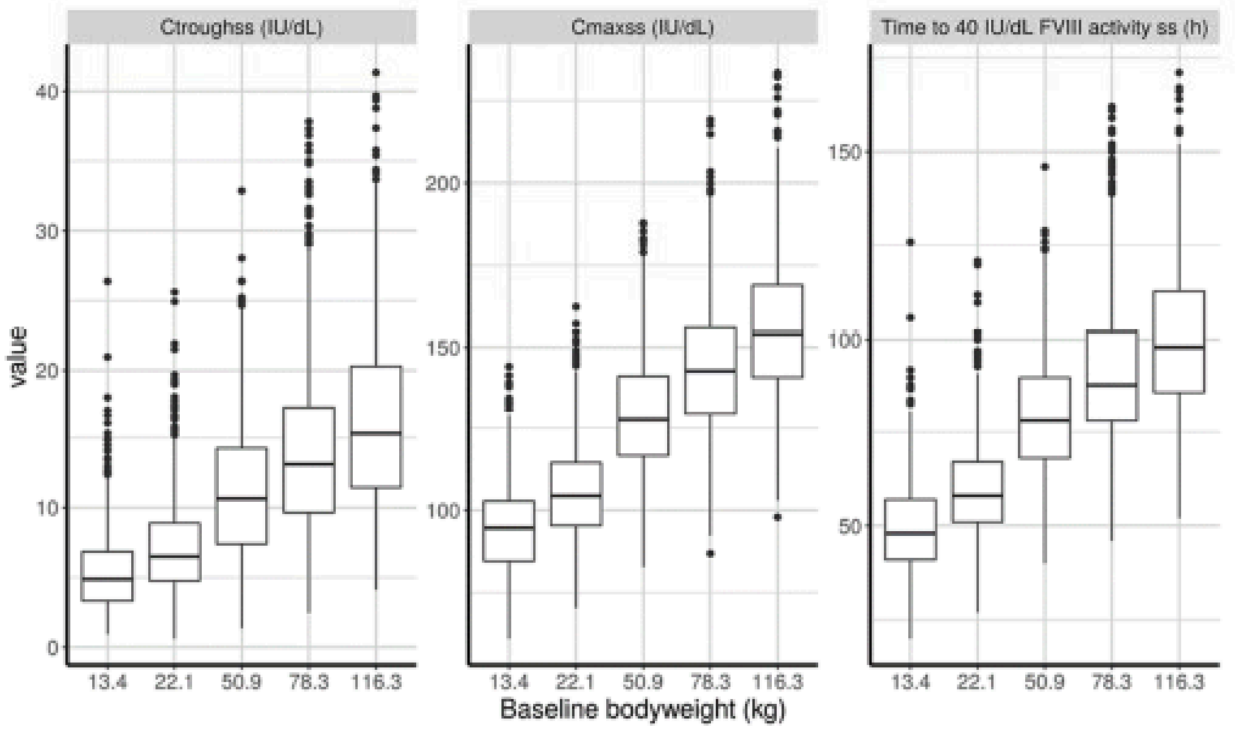
These simulations demonstrated that Asian race was a statistically significant PK covariate, with higher FVIII activity in Asians compared to non-Asians. However, there were no unique patterns or trends identified in reported TEAEs for Asian participants in the pivotal Phase 3 study EFC16293, confirming the difference was not clinically meaningful.

Weight

The impact of body weight on exposure was assessed by using the final covariate population PK model to simulate FVIII activity for the 50 IU/kg once-weekly dosing regimen in adult, adolescent, and paediatric patients (Figure 5).

For adults and adolescents, simulations were conducted for the 5th percentile, median, and 95th percentile baseline body weights from 242HA101, 242HA102 and EFC16293 (50.9 kg, 78.3 kg, and 116.3 kg, respectively). For paediatric patients, simulations were conducted for the 5th percentile and median baseline body weights of patients from EFC16295 (13.4 kg and 22.1 kg, respectively). The 95th percentile baseline body weight of patients from EFC16295 (56.1 kg) was not included in the simulations as it was assumed that the FVIII activity profile would be similar to the representative adult/adolescent patient with baseline body weight of 50.9 kg.

Figure 5: Distribution of steady state Ctrough, Cmaxss and time to 40 IU/dL FVIII activity across the baseline body weight range for adult, adolescent and paediatric population (POH0731)



Source: 5.3.3.5 POH0731 Figure 20.

The effect of body weight was integrated into the weight-based dosing regimen of 50 IU/kg once weekly for all age groups. While this did not result in complete exposure matching between adult and paediatric patients, the majority of children <12 years maintained normal to near-normal levels (>40 IU/dL) for 2 to 3 days and remained in the mild haemophilia range (>5 IU/dL) at the end of the weekly dosing interval with 50 IU/kg once-weekly regimen; this is well above the standard of care where FVIII activity is maintained at >1 IU/dL over the dosing interval.

In study EFC16293, the numbers and proportions of participants with peak FVIII activity levels >150 IU/dL were observed more frequently in patients with BMI values in the overweight to obese range.

Repeatedly high peaks were rarely observed in this paediatric population.

Elderly

No specific analysis regarding elderly patients was conducted. However, in study EFC16293, five patients between 65 and 72 years of age have been included. Four subjects were in the prophylactic Arm A and one subject was in the on-demand Arm B. The PK parameters for participants ≥65 years of age were comparable with those of participants <65 years of age.

	Age 65-74 (Older subjects number /total number)	**Age 75-84 (Older subjects number /total number)**	**Age 85+ (Older subjects number /total number)**
PK Trials	5	0	0

Children

Results from the NCA across various age groups indicated that there was an increase in clearance with decreasing age (Table 7), which is consistent with the observations for other FVIII products. This observation was attributed to body weight increasing with age in paediatric population. Therefore, age (range: 1.4 to 72 years; 5 patients >65 years) was not tested as a covariate in the population PK analysis and instead, the effect of body weight (range: 12.5 to 133.0 kg) on CL and V was included in the model.

Table 7: Pharmacokinetic parameters for baseline-corrected FVIII activity following a single dose of BIVV001 by age based on OSC assay

PK parameters Mean (SD)	Children <12 years of age EFC16295		Adolescent and adult population EFC16293	
	<6 years N=19	6 to <12 years N=18	12 to <18 years N=25	≥18 years N=134
C_{max} (IU/dL)	143 (57.8)	113 (22.7)	118 (24.9)	133 (33.8)
IR (IU/dL per IU/kg)	2.81 (1.10)	2.24 (0.437)	2.34 (0.490)	2.64 (0.665)
AUC_{0-tau} (h*IU/dL)	6800 (1120)[a]	7190 (1450)	8350 (1550)	9850 (2010)[b]
CL (mL/h/kg)	0.742 (0.121)[c]	0.681 (0.139)	0.582 (0.115)	0.493 (0.121)[b]
V_{ss}	36.6 (5.59)[c]	38.1 (6.80)	34.9 (7.38)	31.0 (7.32)[b]
$t_{1/2z}$ (h)	38.0 (3.72)[c]	42.4 (3.70)	44.6 (4.99)	48.2 (9.31)

AUC0-tau = area under the activity-time curve over the dosing interval; Cl = clearance; Cmax = maximum FVIII activity; IR = incremental recovery; SD = standard deviation; t1/2z = terminal half-life Vss: volume of distribution.
a. N=17
b. N=128
c. N=18

The half-life and $AUC_{0\text{-}tau}$ were slightly lower in participants <6 years as compared to participants 6 to <12 years. This is attributed to a higher CL (approximately 10%) on average in patients <6 years of age as compared to participants between the age of 6 and 12 years (Table 7). After the first 50 IU/kg dose of BIVV001, the mean time in the normal to near-normal range (>40 IU/dL) was 68.0 hours and 80.6 hours in the <6 years age cohort and 6 to <12 years age cohort, respectively. The time above 10 IU/dL was 150 hours and 173 hours in the <6 years age cohort and 6 to <12 years age cohort, respectively Overall, BIVV001 maintained high sustained FVIII activity in the paediatric population.

Mean C_{max} was below 150 IU/dL in both age cohorts. Eight participants had a C_{max} above 150 IU/dL detected at the baseline visit, all of which occurred at 15 minutes post-infusion. In all but 1 participant, values returned to below 150 IU/dL by 3 hours post-infusion and in all participants by 24 hours post-infusion. Simulation of PK profiles for paediatric populations aged 6 to 12 years, 2 to 6 years, and 0 to 2 years were only conducted with final PBPK model (PBM0083). In general, the simulated PK results of BIVV001 agree with the observed data (Studies 242HA101 and 242HA102).

Pharmacokinetic interaction studies

Von Willebrand factor antigen level was not identified as a statistically significant covariate in population PK analysis (POH0731). However, impact of VWF on BIVV001 is being evaluated in the ongoing PKM16978 study.

Pharmacokinetics using human biomaterials

Not applicable.

2.6.2.2. Pharmacodynamics

Mechanism of action

In haemophilia A, the severity of bleeding phenotype is related to the severity of the FVIII deficiency with severe haemophilia defined by FVIII activity <1 IU/dL, moderate haemophilia with FVIII activity between 1 and 5 IU/dL, and mild haemophilia with FVIII activity between 5 and 40 IU/dL). Patients with mild haemophilia have lower bleeding risk compared to patients with severe haemophilia, indicating the benefit of maintaining FVIII activity >5 IU/dL.

Simulations with various BIVV001 prophylactic dosing regimens showed that the risk of having a first bleed within 1 year decreases with increasing FVIII activity (POH0989). The trend was similar for Eloctate (POH0886), but remained higher than the risk with BIVV001, further confirming the benefit of higher sustained FVIII levels.

Based on the RTTE model simulations for a typical patient, the probability of zero bleeds in 1 year with BIVV001 50 IU/kg once-weekly regimen was predicted to be 71% (95% CI: 50%-83%), indicating a low risk of bleed for BIVV001. The probability of first bleed in 1 year with BIVV001 50 IU/kg once-weekly regimen was 35% lower compared to the hypothetical 10 IU/kg continuous infusion regimen that maintained FVIII activity stable at 10.8 IU/dL, thus highlighting the benefit of normal to near-normal FVIII levels (>40 IU/dL).

Primary and secondary pharmacology

Not applicable.

2.6.3. Discussion on clinical pharmacology

The Pharmacokinetic (PK) profile of Altuvoct was characterised in adult and paediatric previously treated patients (PTPs >150 EDs) with severe haemophilia A across five clinical studies i.e. three Phase 1(/2a) studies and two Phase 3 studies.

Study 242HA101 investigated a single dose of Advate followed by a single dose of BIVV001 (after a washout period) in two different dose cohorts (low dose, 25 IU/kg, N=7; high dose, 65 IU/kg, N=9).

Study 242HA102 investigated four once-weekly doses of BIVV001 at two different dose levels (Cohort 1: 50 IU/kg, N=10; Cohort 2: 65 IU/kg, N=14).

Study PKM17085 investigated a single dose of three different products (50 IU/kg each), namely Advate, followed by Adynovi and BIVV001 (separated by washout periods), in 13 patients.

In addition, phase 3 PK data are available from Study EFC16293 in adults and adolescents 12 years of age and above (N=159), and Study EFC16295 in children below 12 years of age (N=74). For all adult and adolescent patients, peak and trough values were determined at certain visits (Week 4, Week 13, Week 39, Week 52) and additional sampling was performed throughout the Week 1. For a dedicated PK subgroup (N=17), the dose at the beginning of Week 2 was skipped in order to determine two-week PK data. This two-week PK exercise was repeated at Week 26 (skipped Week 27 dose). During the paediatric study, peak and trough samples were taken for all participants at certain study visits (Week 4, Week 13, Week 39, Week 52), while again additional samples were taken throughout Week 1 for dedicated PK subgroups (<6 years: N=19, 6 to <12 years: N=18).

Population PK modelling was performed based on the two initial studies (242HA101 and 242HA102) to inform the dose of the Phase 3 trials. The population PK model was updated by including data from the phase 3 trials. A repeated time to event (RTTE) approach was used for the PK/PD analyses since bleeding events are both exposure- and time-dependent observations. The objectives of these analyses were to build RTTE models, to identify covariates that may be significant determinants of variability in the model parameters, and to conduct simulations to investigate the relationship between FVIII activity and bleed hazard.

Overall, the provided PK data fulfil the requirements described in the Guideline on the clinical investigation of recombinant and human plasma-derived factor VIII products (EMA/CHMP/BPWP/144533/2009 rev. 2). The number of recruited patients is sufficient and all requested PK parameters were investigated. Re-testing was performed in the adult and adolescent population (EFC16293) after ~6 months, which is endorsed and in accordance with the GL. The PK sampling times are overall acceptable.

Change of manufacturing process:

The BIVV001 DS manufacturing process evolved during clinical development The observed difference in specific activity (i.e. reduced FVIII one-stage activity) is not considered of significant concern for FVIII molecules such as BIVV001 and would be acceptable. Since FVIII dosing is based on IU/kg no important impact on the clinical outcomes is expected. The omission of clinical comparability studies is further justified by the results of extensive analytical characterisation studies. In addition, the PK of GMP material manufactured used for Ph1/2a studies () and GMP material manufactured for the Phase 3 trials () were compared *in vivo* in Haemophilia A mice. PK profiles of BIVV001 generated from the 2 processes and based on FVIII activity levels were well comparable. Therefore, it is agreed that a clinical comparability study was not conducted.

Bioanalytical assays

All bioanalytical methods used to support the BIVV001 clinical studies are described and validated. These assays were used to analyse samples from clinical Phase 1 through Phase 3 studies for PK/PD (determination of FVIII activity).

The one-stage clotting assay using an OSC assay with Dade Actin FSL aPTT reagent on a Siemens BCS XP analyser (Siemens Healthcare Diagnostics) was applied as the primary assay system to measure plasma FVIII activity for screening and PK assessment of recombinant FVIII products (Advate, Adynovi and BIVV001) in human plasma. In addition, two-stage chromogenic substrate FVIII activity assays have been used for PK/PD assessment in BIVV001 clinical studies.

To address the laboratory assay variability on the assessment of BIVV001 FVIII activity, the applicant performed a blinded, international, multicentre (13 countries, 35 laboratories) field study to evaluate the FVIII activity assay performance of BIVV001 in global clinical haemostasis laboratories, where a variety of aPTT and chromogenic reagents and different instruments were used for measuring BIVV001 and Advate activity in spiked plasma samples in a blinded manner. Overall, this study found that while the OSC assay could reliably measure BIVV001 activity using Actin FSL and multiple other aPTT reagents, under- and overestimation of BIVV001 FVIII activity occurred, as expected, with a similar variability compared to other marketed modified FVIII products. However, a clinically relevant overestimation of approximately 2.5-fold was noted, with respect to assigned nominal activity, when using CS assays or using the OSC assay with an Actin FS reagent. The provided scientific justification for the observed significant discrepancies between the CS assay and aPTT-based OSC assay is noted.

A post-hoc analysis was performed using all available subject PK data where parallel testing by the OSC (Actin FSL) and CS assays was done in the completed Phase 3 studies (EFC16293 and EFC16295). Based on all time points with available data from both assays, the overall mean CS/OSC ratio was 2.53 (n=3353) across all FVIII activity levels. In addition, the requested Bland-Altman plot of the difference in the log transformed Factor VIII activity data was provided. In principle, the shape of this plot is reassuring. However, a large intra- and inter-subject variability (mean: 2.53, SD: 1.54, Q1: 1.98, Q3: 2.96) was noted. The wide range of ratios observed for individual patients (half of the measurements were outside the interval (1.96, 2.96)) illustrates that a factor of 2.5 will not be very accurate in a lot of cases. Therefore, a factor of 2.5 can only be considered as a rough estimate. Discrepancies of the assays are addressed in section 4.2 and 4.4 of the SmPC.

While a mean factor of 2.5 in FVIII activity was determined for the difference between the chromogenic and the one-stage clotting results based on the phase 3 data, such difference was not noted during the Phase 1 studies (242HA101, 242HA102). The applicant clarified that a BIVV001 product-specific self-standard was used for validation of the OSC and CS assays used during the Phase 1/2 studies, whereas a plasma standard calibrated against the WHO 6th International Standard was used in all Phase 3 studies. While the FVIII activity was roughly 2.5-fold higher with the CS assay compared to the OSC assay when the WHO standard was used, such differences were not noted with the product specific standard.

Baseline corrected FVIII activity levels were used to analyse relevant PK parameters by NCA. In general, the uncorrected baseline values were very low (< 1 IU/dL).

Results

The PK data currently shown in the SmPC and Summary of Clinical Pharmacology represent results mainly derived from the OSC assay with Actin FSL. From the current point of view, this procedure seems acceptable.

The data from the first Phase 1/2a Study 242HA101 revealed a clearly prolonged mean half-life of BIVV001 (25 IU/kg: 37.61 hours, 65 IU/kg: 42.54 hours), compared with Advate (25 IU/kg: 9.12 hours, 65 IU/kg: 13.15 hours), which represents a 4.13-fold and 3.24-fold half-life increase for the 25 IU/kg and the 65 IU/kg, respectively. The AUC (h*IU/ dL) increased 7-fold for the 25 IU/kg dose and 6.54-fold for the 65 IU/kg dose.

Results from the repeated-dose Study 242HA102 supported the choice of the lower dose (50 IU/kg, Cohort 1, N=9) with a mean C_{maxss} of 135 IU/dL (SD 31.0), because the mean C_{max} at steady state was 173 IU/dL (SD 24.4) for the 14 participants in Cohort 2 (65 IU/kg) and thus well above the upper limit (150 IU/dL) of the target range. The C_{trough} values were slightly lower with the 50 IU/kg dose but comparable (Cohort 1: 9.83 [SD 3.85] IU/dL; Cohort 2: 11.8 [SD 4.94] IU/dL).

Study PKM17085 confirmed the advantage of BIVV001 regarding half-life (44.4 hours, clearance: 0.503), compared to the standard half-life product Advate (11.7 hours, clearance: 3.26) and the extended half-life product Adynovi (16.3 hours, clearance: 1.86).

The phase 3 Study EFC16293 revealed a slightly higher mean half-life (47.6 hours in the overall population, N=159) compared to Study PKM17085 (described above). The mean incremental recovery (IR) was approximately 2.6 IU/dL per IU/kg, which is comparable to approved FVIII products. The IR remained consistent during the study for 52 weeks. The mean (SD) C_{trough} was 18.5 IU/dL (8.71) in the sequential PK subgroup (N=17) on Day 183. In the overall population, the pre-dose (=C_{trough}) mean FVIII activity levels were 14.57 (10.18) at Week 26, 16.26 (10.73) at Week 39, and 16.64 (15.66) at Week 52. In principle, these data support the once weekly regimen, as a maintained prophylactic potential could be expected even at the end of the dosing interval.

After the first administration (15 minutes post-dose), the mean (SD) C_{max} was 128.85 IU/dL (32.33) and remained below the upper limit of the target range of 150 IU/dL. However, the mean values at Week 26 (147.90 [37.03]), Week 39 (148.18 [47.56], and Week 52 (145.45 [35.60]) were very close to the upper limit of 150 IU/dL. In fact, a total of 109 (69%) out of 159 adult and adolescent participants had a peak FVIII activity level >150 IU/dL at any time in study 16293 and a total of 38 out of 73 paediatric participants with post-baseline FVIII activity measurements had a peak FVIII activity level >150 IU/dL at ≥1 visit during the 52-week study 16295. Of the 60 adult/adolescent participants with 3 or more peak FVIII activity levels >150 IU/dL, 53 (88%) were overweight or obese. There were 26 participants with a peak FVIII activity level >200 IU/dL at ≥1 study visit. Of these participants, 20 (77%) were overweight or obese. Although no safety issue was detected in this small population, a clear trend towards higher incidences of elevated FVIII activity levels in patients with BMI values in the overweight to obese range is noted. Furthermore, in these subjects ~~these~~ high FVIII activity levels (>150 IU/dL) will remain for a longer time period than in subjects with lower body weight.

The final report of the paediatric Study EFC16295 showed, that the first dose of Altuvoct 50 IU/kg maintained mean FVIII activity in the normal to near-normal range (>40 IU/dL) for 2 to 3 days, and a mean FVIII activity >5 IU/dL for 7 days, with similar PK profiles in both age cohorts. For the majority of participants, peak FVIII activity levels (mean Cmax 128 IU/dL) remained below the upper physiological limit of 150 IU/dL. The mean (SD) terminal half-life of Altuvoct was 40.2 (4.29) hours.

At steady state, mean FVIII activity levels remained above near-normal levels (>40 IU/dL) for 3 days and above 10 IU/dL for approximately 7 days, indicating high sustained FVIII activity over the weekly dosing interval. Mean trough (pre-dose) FVIII activity levels ranged from 8.54 IU/dL at Week 4 to 13.68 IU/dL at Week 52/EOS and mean values at 15-min post dose were consistently below 150 IU/dL across all visits.

Pharmacokinetic characteristics of Altuvoct have not been studied in the following special populations: 1) Previously untreated patients; 2) Subjects over 65 years of age; 3) Subjects with impaired renal function; 4) Subjects with impaired hepatic function. The lack of experience in elderly is reflected as missing information in the RMP. A study in PUP is planned.

Population PK modelling was applied to further characterise the PK of Altuvoct. The developed model seems adequate, and the presented results are substantiated with clinical data. The population PK model revealed that only body weight and Asian race were significant covariates. The FVIII activity (C_{trough}, C_{maxss}, and time to 40 IU/dL) increased with increasing body weight and was higher in Asians compared to non-Asians. The impact of body weight is well-known for FVIII products. Regarding Asian race, the applicant did not detect a clinically meaningful impact on TEAEs. However, the small sample size needs to be considered (n=29 in Study EFC16293, n= 8 in Study EFC16295). Other covariates (VWF antigen levels, haematocrit, blood type, and HCV/HIV status) had no impact on Altuvoct PK profiles. In fact, VWF was not identified as a statistically significant covariate. In addition, the applicant showed, that no obvious effect of VWF antigen on the PK of efanesoctocog alfa has been observed due to PopPK modelling and correlation of efanesoctocog alfa half-life with VWF activity levels.

A physiologically based PK (PBPK) modelling based on Eloctate was used to understand the effect of age ontogeny on Altuvoct PK profile in the youngest children (<2 years of age) and to further support paediatric dose selection of Altuvoct.

In addition, the applicant presented a repeated time to event (RTTE) model, which seems to describe the collected data well. Respective simulations suggest a 29% (95% CI: 17% to 50%) probability of first bleed in 1 year for a 50 IU/kg once-weekly routine prophylaxis with Altuvoct, compared to 64.0% (95% CI: 44.0-84.0) with a hypothetical continuous infusion regimen that maintained a stable and flat FVIII activity at 10.8 IU/dL, or 64.0% (52.0-74.0) with a label-recommended regimen (standard-of-care) of Eloctate (50 IU/kg every 4 days). The repeated time to event analyses is of limited importance for this application, as no extrapolation is intended.

Furthermore, Altuvoct showed a low immunogenic potential in previously treated patients (PTPs) with haemophilia A since no FVIII Inhibitor antibody development was detected in any of the clinical studies. Only 4 Altuvoct-treated patients developed treatment-emergent anti-drug antibodies (ADAs) which were transient ADAs. Available data indicate that there is no evident impact of ADAs on FVIII PK and clinical outcomes.

2.6.4. Conclusions on clinical pharmacology

The FVIII activity (PK) following Altuvoct dosing in patients with severe haemophilia A has comprehensively been characterised. Altuvoct consistently showed high sustained FVIII activity levels and a long half-life across all age groups of PTPs with haemophilia A. The clinical pharmacology data along with the efficacy data support the dosing recommendations of 50 IU/kg once weekly for routine prophylaxis, as well as the doses for on-demand treatment and control of bleeding episodes, and perioperative management of bleeding. Overall, the provided PK data fulfil the requirements described in the respective guideline (EMA/CHMP/BPWP/144533/2009 rev. 2).

2.6.5. Clinical efficacy

2.6.5.1. Main study

A Phase 3 Open-Label, Multicenter Study of the Safety, Efficacy, and Pharmacokinetics of Intravenous Recombinant Coagulation Factor VIII Fc-von Willebrand Factor-XTEN Fusion Protein (rFVIIIFc-VWF-XTEN; BIVV001) in Previously Treated Patients ≥ 12 Years of Age With Severe Haemophilia A (EFC16293)

Methods

- **Study Participants**

The studies were performed in PTPs with severe haemophilia A. Previous treatment for haemophilia A (prophylaxis or on-demand) consisted of treatment with any recombinant and/or plasma-derived FVIII, or cryoprecipitate for at least 150 exposure days (EDs) for patients ⩾6 years of age and at least 50 EDs for patients <6 years of age.

Severe haemophilia diagnosis had to be documented by FVIII activity (defined as <1 IU/dL [<1%] endogenous FVIII activity) or genotype. In addition, participants on pre-study on-demand treatment had to have at least 12 bleeding episodes in the previous 12 months or at least 6 bleeding episodes in the previous 6 months prior to study enrolment, which provided additional confirmation of a severe bleeding phenotype prior to enrolment in EFC16293.

Patients known to be HIV positive had to be immunocompetent with CD4 lymphocytes >200/μL and a viral load <400 copies/mL. Patients with a history of a positive inhibitor test or with a positive inhibitor test result at Screening were excluded from participation.

- **Treatments**

Table 8: BIVV001 dosing regimens in the Phase 3 programme

Indication	Dosage	Frequency
Prophylaxis	50 IU/kg	Once weekly
Bleeding episode[a]	50 IU/kg	Single dose for all bleeding episodes. Additional and adjusted doses only after consultation with the Investigator based on the participant's clinical condition: If a bleeding episode did not improve, additional doses of 30 or 50 IU/kg every 2 to 3 days were to be considered. For minor/moderate bleeding episodes occurring within 2 to 3 days after a recent prophylactic dose, an initial 30 IU/kg dose could have also been used.
Minor surgery	50 IU/kg	Single dose prior to surgery
Major surgery, allowed after 6 EDs	50 IU/kg	Additional doses of 30 or 50 IU/kg every 2 to 3 days could have been administered.

- **Objectives**

Efficacy objectives:

- To evaluate the efficacy of BIVV001 as a prophylaxis treatment
- To evaluate the efficacy of BIVV001 in the treatment of bleeding episodes
- To evaluate BIVV001 consumption for the prevention and treatment of bleeding episodes
- To evaluate the effect of BIVV001 prophylaxis on joint health outcomes
- To evaluate the effect of BIVV001 prophylaxis on Quality of Life (QoL) outcomes
- To evaluate the efficacy of BIVV001 for perioperative management

Exploratory objectives

- To evaluate joint-health structural outcomes via ultrasound using the Joint Activity and Damage Exam (JADE) protocol and/or Haemophilia Early Arthropathy Detection with Ultrasound (HEAD-US)
- To assess the impact of BIVV001 treatment on patient reported outcome (PRO) measurements and physical activity (measures per study arm and treatment regimen)

- **Outcomes/endpoints**

Table 9: Efficacy endpoints in Study EFC16293

Efficacy endpoints	Routine prophylaxis	Treatment of bleeds	Perioperative management
Primary	• Annualized bleeding rate (ABR) in Arm A		
Key secondary	• Intra-participant comparison of ABR during the BIVV001 weekly prophylaxis treatment period versus the historical prophylaxis ABR for participants in Arm A who participated in Study 242HA201/ OBS16221, an observational study		
Secondary	• Annualized bleeding rate (ABR) by type and location for prophylaxis treatment per study arm • Annualized bleeding rate (ABR) for all bleeding episodes (including untreated bleeding episodes) for prophylaxis treatment per study arm • Intra-participant comparison of ABR during the QW prophylaxis treatment period versus the ABR during the on-demand treatment period in Arm B • Percentage of participants who maintain FVIII activity levels over 1%, 5%, 10%, 15%, and 20% in Arm A **Joint health outcomes** • Change from Baseline to Week 52 in total score and domain scores (eg, swelling and strength) assessed by the Hemophilia Joint Health Score (HJHS) in Arm A • Annualized joint bleeding rate (AJBR) per study arm and treatment regimen • Target joint resolution at Week 52, based on International Society on Thrombosis and Haemostasis (ISTH) criteria in Arm A **BIVV001 Consumption for prevention of bleeding episodes** • Total annualized BIVV001 consumption per participant per study arm and treatment regimen **Quality of life** • Changes in Haem-A-QoL (≥17 years old) total score and physical health score measures from baseline to Week 52 in Arm A • Changes in PROMIS Pain Intensity 3a first item from Baseline to Week 52 in Arm A	• Number of injections and dose of BIVV001 to treat a bleeding episode per study arm and treatment regimen • Percentage of bleeding episodes treated with a single injection of BIVV001 per study arm and treatment regimen • Assessment of response to BIVV001 treatment of individual bleeding episodes based on the ISTH 4-point response scale per study arm and treatment regimen • Physician's global assessment (PGA) of participant's response to BIVV001 treatment based on a 4-point response scale per study arm and treatment regimen	• Investigators' or Surgeons' assessment of participant's hemostatic response to BIVV001 treatment on the ISTH 4-point response for surgical procedures scale • Number of injections and dose to maintain hemostasis during perioperative period for major surgery • Total BIVV001 consumption during perioperative period for major surgery • Number and type of blood component transfusions used during perioperative period for major surgery • Estimated blood loss during perioperative period for major surgery

- **Sample size**

Sample size for pivotal study EFC16293 was determined based on clinical and statistical considerations. Sample size was calculated to exclude a greater-than-acceptable risk for immunogenicity. Assuming a drop-out rate of approximately 15%, a sample size of 124 participants in the prophylaxis arm was expected to provide 104 evaluable participants with at least 50 EDs. If ≤2 participants out of 104 evaluable participants developed an inhibitor, then the upper bound of an exact 95% confidence interval (CI) would exclude 6.8%, a threshold determined at the FDA Factor VIII Inhibitor Workshop in 2003.

The primary efficacy objective of this study was to evaluate the efficacy of BIVV001 weekly prophylaxis as estimated by the mean ABR and one-sided 97.5% CI in Arm A. Based on 2000 simulations of a negative binomial regression model with mean ABR of 2.9 and dispersion factor of 2.3, a sample size of 124 participants will provide at least 90% power for the upper bound of the one-sided 97.5% confidence interval to exclude an ABR greater than 6, assuming a 15% drop out rate.

For the key secondary efficacy endpoint, an intra-patient comparison of ABR during the BIVV001 weekly prophylaxis treatment period versus the historical prophylaxis ABR will be performed using non-inferiority testing for participants in Arm A who have at least 6 months of participation in this study and at least 6 months of historical data on prophylaxis treatment from observational study 242HA201/OBS16221. For a non-inferiority test of the null hypothesis (median difference in ABR exceeds or is equal to non-inferiority margin) versus the alternative hypothesis (median difference in ABR is less than non-inferiority margin), a sample size of 63 achieves 90% power to detect noninferiority using a one-sided paired Wilcoxon Signed Rank test at a 0.025 significance level when the actual mean of paired differences is 0 and the non-inferiority margin is 4. Without prior knowledge of the standard deviation of the paired differences, a conservative estimate of 10 was assumed. In order to account for drop-out and the use of the Per Protocol Set, at least 75 participants who have completed at least 6 months of participation in observational Study 242HA201/OBS16221 will be enrolled in Arm A.

- **Randomisation and Blinding (masking)**

All BIVV001 studies were open-label and non-randomised, due to ethical considerations based on the severity of the disease, the existence of effective therapies, and the potential life- threatening consequences of placebo treatment in the setting of an acute bleeding episode.

In Study EFC16293, participants were assigned to one of the two study arms based on their pre-study treatment regimen.

Sites who participated in observational Study 242HA201/OBS16221 were expected to enrol qualified participants into the EFC16293 study with prior participation in the observational study. In addition, at least 75 participants with at least 6 months of participation from the observational study were to be targeted to enrol in Arm A before additional participants from the observational study were enrolled in Arm A. Additional sites that were not participating in the observational study were able to enrol participants directly into this Phase 3 study.

- **Statistical methods**

Analysis populations

The following populations for analyses were defined:

Population	Description
All-Enrolled Analysis Set	All participants who were enrolled in the study, regardless of whether they were dosed with study drug or not. Participants will be considered enrolled when the Investigator has verified that they are eligible according to the criteria in Section 5 of the protocol. Participant disposition and enrollment summaries will be based on the All-Enrolled Analysis Set.
Full Analysis Set (FAS)	All participants who receive at least one dose of study drug. All analyses of demographics, baseline characteristics, and efficacy will be based on the FAS, unless otherwise specified.
Per Protocol Set	A subset of the Full Analysis Set including participants who do not have important protocol deviations potentially impacting efficacy. The Per Protocol Set will be utilized for analysis of the key secondary efficacy endpoint, as well as sensitivity analysis of the primary endpoint.
Safety Analysis Set	The safety analysis set is the same as the full analysis set and will include all participants who receive at least one dose of study drug. All analyses of safety will be based on the Safety Analysis Set, unless otherwise specified.
PK Analysis Set (PKAS)	All participants who have completed adequate blood sample collection to assess key PK parameters, as determined by the PK scientist. All analyses of PK will be based on the PKAS, unless otherwise specified.
Sequential Pharmacokinetic Subgroup	All participants who have evaluable PK profiles for both the Baseline and Repeat PK profiles, as determined by the PK scientist.
Surgery Subgroup	All participants who have undergone major surgery after the first dose of study drug.

Analysis strategy

The primary endpoint of ABR was analysed using an estimation approach. The mean ABR and one-sided 97.5% confidence interval were estimated using a Negative-Binomial regression model for the weekly prophylaxis treatment arm (Arm A) based on FAS. If the upper limit of the confidence interval is less than or equal to 6, the weekly prophylaxis treatment regimen was considered to provide adequate bleeding control.

As a key secondary endpoint, an intra-patient comparison of ABR between BIVV001 weekly prophylaxis treatment and historical prophylaxis treatment for participants in Arm A who have at least 6 months of participation in this study and at least 6 months of historical data on prophylaxis treatment from observational Study 242HA201/OBS16221 was performed using a Negative-Binomial regression model using the PPS (as primary analysis) and FAS (as supportive analysis) under the following statistical hypotheses:

H0 (null): Paired ABR difference (BIVV001 prophylaxis – historical prophylaxis) ≥ M versus H1

(alternative): Paired ABR difference (BIVV001 prophylaxis – historical prophylaxis) < M

where M is the non-inferiority margin. The null hypothesis was declared if the upper bound of the one-sided 97.5% CI is less than 4. If non-inferiority is achieved, then superiority was evaluated sequentially using a Negative-Binomial regression model using the FAS. The paired ABR ratio and 95% CI were estimated using the FAS. The null hypothesis that the paired ABR ratio (BIVV001 prophylaxis: historical prophylaxis) is ≥1 was tested against the alternative hypothesis that the ABR ratio is <1. Superiority was declared if the upper bound of the one-sided 97.5% confidence interval is less than 1.

In addition, the 3 secondary endpoints – change from baseline to Week 52 in Haem-A-QoL physical health score, PROMIS Pain Intensity 3a, and HJHS total score – were analysed via mixed-effects model repeated measures (MMRM).

Primary endpoint analysis

The ABR for each individual participant was calculated using the following formula:

ABR = (Number of treated bleeding episodes during the efficacy period/ Total number of days during the efficacy period) × 365.25

A bleeding episode was counted in the primary analysis if it was treated with BIVV001.

The efficacy period was defined as follows:

Arm A: The efficacy period for the prophylactic regimen starts with the date and time of the first prophylactic dose following the completed PK sampling period (i.e., 168 or 336 hours), and ends with the end of the treatment regimen as defined in Section 4.1.1.1 of the SAP. That is, if the initial PK sampling period is incomplete due to an aborted collection of blood samples following the PK injection (e.g., because of a bleeding episode that required treatment), then the efficacy period will begin following a subsequent fully executed PK sampling period.

Arm B (on-demand regimen): The efficacy period for the on-demand regimen starts 1 minute after the date and time of the last sampling time point (i.e., 168 hours) for the PK dose and ends with the end of the treatment regimen as defined in Section 4.1.1.1 of the SAP.

Arm B (prophylaxis regimen): The efficacy period for the prophylactic regimen starts with the date and time of the first prophylactic dose (or, if the time of the first prophylactic dose is not available, at 00:01 on the day of the first prophylactic dose) and ends with the end of the treatment regimen as defined in Section 4.1.1.1 of the SAP.

In addition, efficacy periods were interrupted for surgical/rehabilitation periods (major and minor) and large injection intervals as described in the SAP.

Multiplicity

Type I error for secondary endpoints was controlled through a hierarchical testing framework. The alpha level was 0.05. Following the estimation approach described in Section 4.3.2 of the SAP for the primary endpoint (ABR in Arm A), the key and selected secondary endpoints are included in the hierarchy in the following order:

1. Arm A intra-patient comparison non-inferiority (NI): ABR of BIVV001 weekly prophylaxis treatment vs. historical prophylaxis treatment.

2. Arm A intra-patient comparison superiority: ABR of BIVV001 weekly prophylaxis treatment vs. historical prophylaxis treatment.

3. Arm A change from Baseline to Week 52: Haem-A-QoL physical health score.

4. Arm A change from Baseline to Week 52: PROMIS Pain intensity 3a past 7 days intensity of pain at its worst score (PAINQU6).

5. Arm A change from Baseline to Week 52: HJHS total score.

No multiplicity adjustment was made on other secondary efficacy variables than mentioned above.

Changes in the SAP, protocol and statistical analyses

The original protocol was dated 17 June 2019 which was followed by 5 amendments. The original statistical analysis plan was dated 10 June 2021 and was amended once.

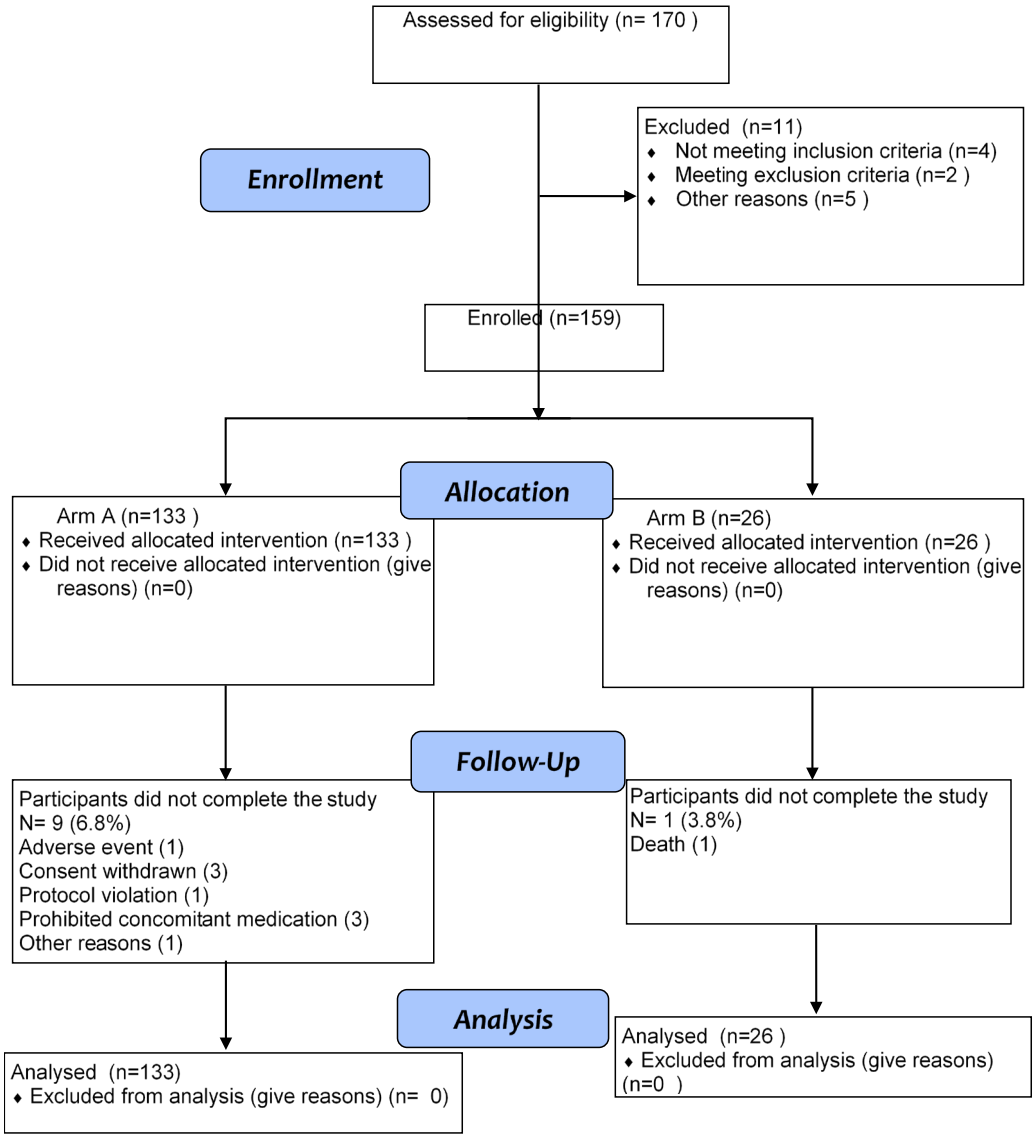
The protocol amendment 5 (dated 20 August 2021) was amended with the following main changes:

- Addition of statistical testing for some secondary endpoints
- Multiplicity added

As per summary of changes in the protocol, these changes were made to be consistent with the Statistical Analysis Plan (SAP). The SAP version 2 (dated 11 August 2021) was based on the protocol dated 13 May 2020.

Results

- **Participant flow**



- **Recruitment**

Study EFC16293 was initiated on 19 November 2019 (signed informed consent) and completed on 3 February 2022 (last participant last visit). The analyses presented in this report are based on a database lock date of 24 February 2022.

A total of N=159 participants were enrolled:

- Arm A: N=133 participants (including N=82 participants rolled over from observational study OBS16211)
- Arm B: N=26 participants (including N=10 participants rolled over from observational study OBS16221)

- **Conduct of the study**

Major protocol deviations were reported in 46 (28.9%) participants. The most frequently reported deviation was related to dispensation and/or administration of expired IP or IP that was subject to a temperature excursion (9 [5.7%] participants). Among the 9 participants in whom these protocol deviations were identified, 6 had no reported TEAEs during the study. In the remaining 3 participants, reported TEAEs included limb injury, oedema peripheral (verbatim: "mild edema, right thigh"), pulpitis dental, influenza like illness (verbatim "flu like symptoms due to COVID-19 vaccination"), vaccination site pain, fatigue (verbatim: "general feeling of fatigue due to 2nd dose of COVID-19 vaccine"), and vaccination site swelling in 1 participant; back pain, eye infection, and fatigue in 1 participant; and gingival ulceration, headache, constipation, and fatigue in 1 participant. All were assessed by the Investigator as non-serious and not related to BIVV001. Overall, there was no pattern in the type or temporality of reported TEAEs to suggest an association with the use of expired IP or IP subject to temperature excursion.

Important protocol deviations potentially impacting efficacy evaluation as defined in the SAP and resulting in exclusion from the PPS were reported in 5 (3.1%) participants, 4 in Arm A and 1 in Arm B. The 4 participants in Arm A took a prohibited concomitant medication (FVIII products other than BIVV001 in 3 participants and aspirin in 1 participant).

The participant in Arm B was on a pre-study prophylaxis treatment but was enrolled in the on-demand arm which was reported as a protocol deviation to inclusion/exclusion criteria.

One major protocol deviation related to an impact of the COVID-19 pandemic on study conduct was reported in 1 participant in Arm A and was due to a study visit that was not completed at Week 39.

Two major protocol deviations in 1 participant (No. 016293-840-0911-00501) in Arm A were identified after database lock. This participant was on systemic corticosteroid treatment (prednisone 5 mg/day) for polymyalgia at the screening visit and was enrolled despite meeting exclusion criteria E13. In addition, treatment with systemic corticosteroid was continued throughout the study until the EOS visit which constituted a major deviation to the protocol due to the use of a prohibited concomitant medication. This participant who had an efficacy period of 0.93 years, reported 2 bleeds during the study (1 bleed treated with a single BIVV001 injection and 1 untreated bleed) and underwent 2 minor surgeries for cataract with a haemostatic response rated as excellent by the Investigator/Surgeon. Reported TEAEs in this participant included arthralgia, pain in extremity, back pain, fall, contusion and cataract. These 2 major protocol deviations are considered of limited or no impact on overall study efficacy and safety results.

- **Baseline data**

The study was conducted worldwide in 19 countries/regions (Argentina, Australia, Belgium, Brazil, Bulgaria, Canada, France, Germany, Greece, Hungary, Italy, Japan, Mexico, Netherlands, Spain, South Korea, Taiwan, UK, and USA) at 51 active centres (defined as centres that screened at least one participant). Participants were enrolled in 48 of the 51 active centres.

Table 10: Summary of demographic and baseline characteristics - full analysis set

	Arm A	Arm B			
	Prophylaxis (N=133)	On-demand (N=26)	Prophylaxis (N=26)	Surgery Subgroup (N=13)	Overall (N=159)
Age (years)[a]					
Number	133	26	26	13	159
Mean (SD)	33.9 (15.3)	42.8 (11.7)	42.8 (11.7)	44.3 (12.8)	35.4 (15.1)
Median	34.0	39.0	39.0	46.0	35.0
Min ; Max	12 ; 72	23 ; 68	23 ; 68	12 ; 64	12 ; 72
12 - 17	25 (18.8)	0	0	1 (7.7)	25 (15.7)
18 - 64	104 (78.2)	25 (96.2)	25 (96.2)	12 (92.3)	129 (81.1)
>=65	4 (3.0)	1 (3.8)	1 (3.8)	0	5 (3.1)
Sex, n (%)					
Number	133	26	26	13	159
Male	132 (99.2)	26 (100)	26 (100)	13 (100)	158 (99.4)
Female	1 (0.8)	0	0	0	1 (0.6)
Race, n (%)					
Number	133	26	26	13	159
Asian	29 (21.8)	0	0	3 (23.1)	29 (18.2)
Black or African American	3 (2.3)	0	0	0	3 (1.9)
White	71 (53.4)	26 (100)	26 (100)	7 (53.8)	97 (61.0)
Not reported due to confidentiality regulations	26 (19.5)	0	0	3 (23.1)	26 (16.4)
Other	4 (3.0)	0	0	0	4 (2.5)
Region[b], n (%)					
Number	133	26	26	13	159
Asia/Pacific	33 (24.8)	0	0	4 (30.8)	33 (20.8)
Europe	67 (50.4)	14 (53.8)	14 (53.8)	5 (38.5)	81 (50.9)

North America	26 (19.5)	0	0	3 (23.1)	26 (16.4)
South America	7 (5.3)	12 (46.2)	12 (46.2)	1 (7.7)	19 (11.9)
Weight (kg)					
Number	133	26	26	13	159
Mean (SD)	78.00 (19.29)	80.80 (18.04)	80.80 (18.04)	77.31 (9.66)	78.46 (19.06)
Median	78.00	77.90	77.90	78.00	78.00
Min ; Max	33.9 ; 132.8	50.0 ; 119.5	50.0 ; 119.5	63.0 ; 100.0	33.9 ; 132.8
Body Mass Index(BMI) (kg/m2)					
Number	133	25	25	13	158
Mean (SD)	25.59 (5.00)	26.91 (5.56)	26.91 (5.56)	25.68 (1.50)	25.80 (5.10)
Median	25.51	26.35	26.35	25.47	25.74
Min ; Max	15.0 ; 39.8	16.7 ; 40.8	16.7 ; 40.8	22.6 ; 28.4	15.0 ; 40.8
< 25	57 (42.9)	9 (36.0)	9 (36.0)	3 (23.1)	66 (41.8)
>= 25 - < 30	52 (39.1)	9 (36.0)	9 (36.0)	10 (76.9)	61 (38.6)
>= 30	24 (18.0)	7 (28.0)	7 (28.0)	0	31 (19.6)

Note 1: Percentages are based on the number of participants with non-missing data in the Full Analysis Set.
Note 2: Participants are included in each study arm and treatment regimen (including surgery subgroup) they participated in for the duration of time on that regimen and, as such, may appear in more than one treatment regimen. Each participant is counted only once in the overall column.
a. Age = year of informed consent - year of birth.
b. Asia/Pacific includes Australia, Japan, Korea and Taiwan. Europe includes Belgium, Bulgaria, France, Germany, Greece, Hungary, Italy, Netherlands, Spain and the United Kingdom. North America includes Canada, Mexico, and the United States. South America includes Argentina and Brazil.

Disease characteristics at baseline

At study entry, all participants had a documented FVIII activity level below 1% or a documented genotype known to produce severe haemophilia A. All participants had at least 150 EDs to FVIII prior to study entry.

At study entry, the majority of the participants (125 [78.6%]) had no family history of a FVIII inhibitor. The distribution of FVIII genotypes was representative of a population with severe haemophilia A, and almost half of the participants had genotypes associated with an increased risk of inhibitor development such as intron 22 inversions (57 [36.1%] participants) and nonsense mutations (15 [9.5%] participants).

The only female participant suffered from severe haemophilia A confirmed by laboratory testing and documented genotype receiving standard treatment. The medical history includes joint bleeds and haemophilic arthropathy.

Those using on-demand dosing had a severe bleeding phenotype, as demonstrated by higher mean (SD) number of bleeding episodes reported in the 12 months prior to the study in Arm B (35.7 [22.2]) compared with Arm A (3.2 [5.4]). The mean (SD) number of joint bleeds (including both spontaneous and traumatic joint bleeds) was 27.4 (18.6) in Arm B and 2.3 (4.5) in Arm A.

At baseline, 26 (19.5%) participants in Arm A and 23 (88.5%) participants in Arm B reported at least 1 target joint. The mean (SD) HJHS total scores were 18.1 (18.4) in Arm A and 26.3 (13.2) in Arm B.

- **Numbers analysed**

Table 11: Participant disposition - all-enrolled analysis set

	Arm A	Arm B		
n (%)	Prophylaxis (N=133)	On-Demand (N=26)	Prophylaxis (N=26)	Overall (N=159)
Number of participants in				
Full Analysis Set [a]	133 (100)	26 (100)	26 (100)	159 (100)
Participants with an efficacy period [b]	133 (100)	26 (100)	26 (100)	159 (100)
Safety Analysis Set [c]	133 (100)	26 (100)	26 (100)	159 (100)
Per-protocol Set [d]	129 (97.0)	25 (96.2)	25 (96.2)	154 (96.9)
PK Analysis Set [e]	133 (100)	26 (100)	26 (100)	159 (100)
Sequential PK subgroup [f]	17 (12.8)	0	0	17 (10.7)
Surgery subgroup [g,h]	10 (7.5)	0	1 (3.8)	13 (8.2)
Number of major surgeries	11	0	1	14
Participants with at least one minor surgery [h]	12 (9.0)	2 (7.7)	1 (3.8)	15 (9.4)
Number of minor surgeries	15	2	1	19
COVID19 non-impacted population [i]	132 (99.2)	26 (100)	26 (100)	158 (99.4)
Completion status				
Completed	124 (93.2)	26 (100)	25 (96.2)	149 (93.7)
Discontinued	9 (6.8)	0	1 (3.8)	10 (6.3)
Adverse event	1 (0.8)	0	0	1 (0.6)
Lost to Follow-Up	0	0	0	0
Protocol violation	1 (0.8)	0	0	1 (0.6)
Death	0	0	1 (3.8)	1 (0.6)
Consent withdrawn	3 (2.3)	0	0	3 (1.9)
Inability/Unwillingness to comply with protocol	0	0	0	0
Prohibited concomitant medications due to medical need as determined by investigator	3 (2.3)	0	0	3 (1.9)
Investigator decision	0	0	0	0
Withdrawal Criteria	0	0	0	0
Other	1 (0.8)	0	0	1 (0.6)

1: Percentages are based on the number of participants in the All-Enrolled Analysis Set.
2: Participants are included in each study arm and treatment regimen they participated in for the duration of time on that regimen and, as such, may appear in more than one treatment regimen. Each participant is counted only once in the overall column.
a All participants who received at least one dose of study drug.
b FAS population with at least 1 day of treatment for episodic regimen or at least 2 prophylactic injections for prophylactic regimen
c All participants who received at least one dose of study drug.
d A subset of FAS including participants who do not have important protocol deviations potentially impacting efficacy.
e Participants who have completed adequate blood sample collection to assess key PK parameters, as determined by the PK scientist.
f Participants who have evaluable PK profiles for both the baseline and repeat PK profiles, as determined by the PK scientist.
g Participants who have undergone major surgery after the first dose of study drug.
h Surgery reported after the last BIVV001 injection is not counted in the specific treatment arm and regimen, but counted in the overall column.
i Participants are without any major deviation related to COVID19.

- **Outcomes and estimation**

All 159 participants included in study EFC16293 received at least one dose of BIVV001. The mean (SD) duration of BIVV001 dosing was 49.64 (8.34) weeks overall, 49.76 (8.74) in Arm A, 26.13 (1.21) in Arm B with on-demand treatment and 22.89 (6.00) in Arm B with prophylaxis treatment.

One hundred and fifteen (115) participants (72.3%) had 50 or more EDs. The mean (SD) total number of EDs was 48.4 (10.5) in the overall population, 50.9 (9.1) in Arm A, 11.9 (4.3) in Arm B with on-demand treatment and 23.8 (6.1) in Arm B with prophylaxis treatment.

The mean total numbers of injections per participant were similar to the respective mean number of EDs in each arm and overall.

Overall, the mean (SD) average dosing interval was 7.01 (0.26) days and the mean (SD) average weekly dose of BIVV001 was 51.28 (2.13) IU/kg for the participants who received BIVV001 prophylaxis (in Arm A or in Arm B prophylaxis).

Primary efficacy endpoint

The primary objective of the study was to evaluate the efficacy of BIVV001 weekly prophylaxis as estimated by the mean ABR and 1-sided 97.5% CI in Arm A.

Weekly prophylaxis with BIVV001 50 IU/kg resulted in an estimated mean ABR of 0.71 (95% CI: 0.52 to 0.97) in Arm A; the median (Q1; Q3) ABR was 0.00 (0.00; 1.04). The upper limit of the 1 sided 97.5% CI was substantially less than the prespecified value of 6.

Table 12: Summary of annualised bleeding rates - full analysis set - EFC16293

	Arm A	Arm B	
	Prophylaxis (N=133)	On-demand (N=26)	Prophylaxis (N=26)
Number of participants with an efficacy period	133	26	26
Total number of treated bleeding episodes	86	268	8
Total participant-years followed	121.2	12.5	11.4
Duration of efficacy period (weeks)			
Number	133	26	26
Mean (SD)	47.55 (8.77)	25.12 (1.07)	22.89 (6.00)
Median	50.09	25.00	25.08
Q1 ; Q3	48.06 ; 51.09	24.72 ; 25.02	22.07 ; 27.06
Min ; Max	0.1 ; 54.1	23.9 ; 29.3	1.1 ; 27.1
Annualized bleeding rate (ABR)			
Number	133	26	26
Mean (SD)	0.71 (1.43)	21.42 (7.41)	0.69 (1.35)
Median	0.00	21.13	0.00
Q1 ; Q3	0.00 ; 1.04	15.12 ; 27.13	0.00 ; 0.00
Min ; Max	0.0 ; 11.0	8.3 ; 33.4	0.0 ; 4.1
0	86 (64.7)	0	20 (76.9)
>0-5	45 (33.8)	0	6 (23.1)
>5-10	1 (0.8)	1 (3.8)	0
>10-20	1 (0.8)	10 (38.5)	0
>20	0	15 (57.7)	0
ABR, model based[a]			
Mean (95% CI)	0.71 (0.52; 0.97)		

Note: 1: Summaries are based on treated bleeds.
2: Percentages are based on the number of participants in each study arm and treatment regimen with an evaluable efficacy period.
3: The efficacy period reflects the sum of all intervals of time during which participants are treated with BIVV001 according to the study arms and treatment regimens excluding periods of PK evaluations, surgery/rehabilitation (minor and major), and large injection intervals (>28 days).
4: Participants are included in each study arm and treatment regimen they participated in for the duration of time on that regimen and, as such, may appear in more than one treatment regimen.
a Estimated using a negative binomial model with the total number of treated bleeding episodes during the efficacy period as the response variable and log-transformed efficacy period duration (in years) as an offset variable.

Sensitivity analyses performed on the primary endpoint (PPS, FAS including participants with an efficacy period of at least 26 weeks) showed results consistent with those of the primary analysis.

The low ABR observed in Arm A was consistent across all prespecified subgroups, including age categories, bleeding phenotype at baseline, number of target joints at screening or dosing and dosing interval compliance, confirming the primary endpoint.

Secondary efficacy endpoints – Routine prophylaxis

Intra-participant comparison of BIVV001 weekly prophylaxis versus prestudy prophylaxis

The key secondary endpoint for this study consisted of an intra-participant comparison of ABR between BIVV001 weekly prophylaxis treatment and pre-study prophylaxis treatment with a marketed FVIII product. This comparison was performed in 77 participants in Arm A who previously participated in the observational Study OBS16221 and had an efficacy period of ≥26 weeks in each of studies EFC16293 and OBS16221.

Table 13: Intra-participant comparison of annualised bleeding rates: BIVV001 versus historical prophylaxis - per protocol set

	Arm A	
	Historical Prophylaxis (OBS16221) (N=77)	**BIVV001 Prophylaxis (EFC16293) (N=77)**
Number of participants with an observation or efficacy period	77	77
Total number of treated bleeding episodes	212	51
Total participant-years followed	69.7	73.5
Duration of observation or efficacy period (weeks)		
Number	77	77
Mean (SD)	47.26 (6.72)	49.80 (2.47)
Median	50.15	50.09
Q1 ; Q3	43.86 ; 52.10	49.07 ; 51.18
Min ; Max	27.4 ; 54.0	39.1 ; 54.1
Annualized bleeding rate (ABR)		
Number	77	77
Mean (SD)	2.98 (5.21)	0.69 (1.51)
Median	1.07	0.00
Q1 ; Q3	0.00 ; 3.74	0.00 ; 1.04
Min ; Max	0.0 ; 35.6	0.0 ; 11.0
0	32 (41.6)	49 (63.6)
>0-5	28 (36.4)	27 (35.1)
>5-10	11 (14.3)	0
>10-20	5 (6.5)	1 (1.3)
>20	1 (1.3)	0
Negative Binomial regression model[a]		
Mean ABR (95% CI)	2.99 (2.03; 4.42)	0.69 (0.43; 1.12)
Mean difference (95% CI)		-2.30 (-3.49; -1.11)
Rate ratio (95% CI)		0.23 (0.13; 0.42)
p-value (superiority)[b]		<.0001
Wilcoxon Signed Rank test		
Median ABR (Q1, Q3)	1.07 (0.00; 3.74)	0.00 (0.00; 1.04)
Median of paired difference (95% CI)[c]		-1.36 (-2.41; -0.57)
p-value (non-inferiority)[d]		<.0001

Notes: 1: Summaries are based on treated bleeds.
2: Percentages are based on the number of participants in the prophylaxis treatment regimen of each study with an evaluable observation or efficacy period.
3: The analysis is based on the Per Protocol Set and including participants in Arm A who have at least 6 months of efficacy period in the EFC16293 study and at least 6 months of observation period on prophylaxis collected in Study OBS16221.
4: The efficacy period reflects the sum of all intervals of time during which participants are treated with BIVV001 according to the study arms and treatment regimens excluding periods of PK evaluations, surgery/rehabilitation (minor and major), and large injection intervals (>28 days).
a. Estimated using a negative binomial regression model with treatment (BIVV001 prophylaxis vs historical prophylaxis) as covariate.
b. P-value relates to the null hypothesis: rate ratio (BIVV001 prophylaxis/historical prophylaxis) =1.
c. Estimated using the Hodges-Lehmann method.
d. P-value relates to the null hypothesis: median of paired difference (BIVV001 prophylaxis – historical prophylaxis) =4 based on Wilcoxon Signed Rank test.
PGM=PRODOPS/BIVV001/EFC16293/CSR_01/REPORT/PGM/intra_abr_eff_t.sas OUT=REPORT/OUTPUT/intra_abr_eff_t_i.rtf (05MAY2022 15:33)

The non-inferiority of prophylaxis treatment with BIVV001 over historical prophylaxis on the key efficacy endpoint was tested as part of the prespecified hierarchical step-down testing procedure. Non-inferiority of prophylaxis treatment with BIVV001 over historical prophylaxis on mean ABR was demonstrated in the PPS as the upper bound of the 1-sided 97.5% CI of the difference between BIVV001 prophylaxis and historical prophylaxis (estimated mean difference: 2.30 [95% CI: 3.49 to -1.11]) was below the prespecified non-inferiority margin of 4 bleeds per year. The superiority of BIVV001 prophylaxis compared with pre-study prophylaxis in the FAS was also achieved by the prespecified hierarchical step-down testing procedure, as the upper limit of the 1-sided 97.5% CI was less than the prespecified value of 1 (rate ratio: 0.23 [95% CI: 0.13 to 0.42]; p<0.0001).

Supplementary analyses (by using the Wilcoxon signed rank test for noninferiority, then same Negative-Binomial regression model for superiority) also confirmed noninferiority and superiority of BIVV001 prophylaxis over historical prophylaxis.

ABR by type and location

The ABRs were consistently low with prophylaxis treatment in Arm A across bleeding type, with the estimated mean spontaneous ABR (AsBR) of 0.27 (95% CI: 0.18 to 0.41) and traumatic ABR (AtBR) of 0.37 (95% CI: 0.25 to 0.54). In Arm B, the estimated mean AsBR and AtBR decreased after participants had switched to prophylaxis treatment (AsBR: 0.44 [95% CI: 0.16 to 1.20]; AtBR: 0.17 [95% CI: 0.01 to 1.89]) as compared to on-demand treatment (AsBR: 15.83 [95% CI: 12.27 to 20.43]; AtBR: 4.85 [95% CI: 3.04 to 7.74]).

In both Arm A and Arm B, joints were the most common location for bleeds. In Arm A, the mean AJBR was 0.51 (95% CI: 0.36 to 0.72) (5.3.5.1 EFC16293 Table 17). In Arm B, the estimated mean AJBR was lower with prophylaxis treatment (0.62 [95% CI: 0.25 to 1.52]) as compared to on-demand treatment (17.48 [95% CI: 14.88 to 20.54]).

ABR for all bleeding episodes

The estimated ABR based on all bleeding episodes (i.e., treated and untreated) was low with BIVV001 prophylaxis treatment, consistent with results for the primary endpoint using only treated bleeds. The estimated mean ABR based on all bleeding episodes was 1.11 [95% CI: 0.83 to 1.48]) in Arm A, whereas, in Arm B, the estimated mean ABR was 22.21 (95% CI: 19.41 to 25.42) with on-demand treatment and 0.88 (95% CI: 0.42 to 1.84) when participants switched to prophylaxis treatment (5.3.5.1 EFC16293 Section 5.1.4.2).

Intra-participant comparison of ABR during weekly prophylaxis and on-demand treatment

For 26 participants in Arm B, the efficacy of BIVV001 prophylaxis treatment in terms of ABR was compared to on-demand treatment with BIVV001. Intra-participant comparison of ABR indicated a clinically important reduction in ABR with prophylaxis treatment as compared with on demand treatment with BIVV001 (rate ratio for prophylaxis versus on demand treatment of 0.03 [95% CI: 0.02 to 0.07]), corresponding to a clinically important reduction of 97% (95% CI: 93% to 98%).

The majority of participants (96.2%) had an ABR greater than 10 with on-demand treatment, whereas after switching to prophylaxis treatment, the majority of participants (76.9%) had no bleeds (Table 18).

Percentage of participants who maintained FVIII activity levels above prespecified levels during the study

Of 103 participants with postbaseline trough samples within 168±5 hours from the previous dose, 102 (99.0%) participants maintained FVIII activity levels above 5% and 86 (83.5%) participants maintained FVIII activity levels above 10% for 7 days after dosing with once weekly 50 IU/kg of BIVV001 prophylaxis in Arm A. Maintenance of FVIII activity levels above 15% and 20% were observed in 42 (40.8%) and 18 (17.5%) participants, respectively (5.3.5.1 EFC16293 Section 5.1.4.4).

Annualised joint bleeding rate

Regardless of treatment arm, results for AJBR were consistent with the results for ABR. The mean estimated AJBR was 0.51 (95% CI: 0.36 to 0.72) (based on 61 treated joint bleeds) in Arm A, 17.48 (95% CI: 14.88 to 20.54) (based on a total of 219 treated joint bleeds) in Arm B with on demand treatment and decreased to 0.62 (95% CI: 0.25 to 1.52) (based on a total of 7 treated joint bleeds) after the participants switched to prophylaxis treatment. In addition, in Arm B, there was a clinically important reduction in AJBR in participants switching from on-demand to prophylaxis with BIVV001 (rate ratio: 0.04 [95% CI: 0.01 to 0.08]) corresponding to a clinically important reduction of 96% (95% CI: 92% to 99%) in AJBR.

In addition, summary of ABR by location and age showed that the estimated mean AJBR was generally lower in adolescents 12 to 17 years of age compared to participants 18 years or older.

Haemophilia joint health score

Routine prophylaxis with BIVV001 in participants on prior standard-of-care prophylactic FVIII therapy (Arm A) resulted in a statistically significant improvement in functional measure of joint health as demonstrated by the change in HJHS total score from baseline to Week 52 (LS mean change: -1.54 [95% CI: -2.70 to -0.37]; p =0.0101). Sensitivity analysis performed for participants who had rolled over from the OBS16221 study also showed an improvement in HJHS total score. This improvement is supported by a post-hoc analysis evaluating the cumulative distribution function (CDF) curve of the change from baseline to Week 52 in HJHS total score, showing that 80.4% of participants maintained or improved (i.e., decrease) their clinical joint score from baseline (Appendix Figure 2.7.3 - 7).

In Arm B, the mean (SD) change from baseline to Week 52 in HJHS total score was -4.1 (8.7), also indicating an improvement in joint health.

The improvement in the joint health status from baseline to Week 52 was supported by the improvement in strength (mean [SD] change: -1.2 [2.4]) and flexion loss (mean [SD] change: 0.7 [3.1]). Other domains of the HJHS were also improved including swelling and crepitus on motion.

Target joint resolution

At baseline, 26 participants in Arm A reported a total of 80 target joints. Of these, 14 participants had at least 12 months of exposure to BIVV001 prophylaxis and reported a total of 45 target joints at baseline. Analysis based on spontaneous bleeds showed that all 45 target joints for all 14 participants with at least 12 months of exposure to BIVV001 prophylaxis had resolved at Week 52.

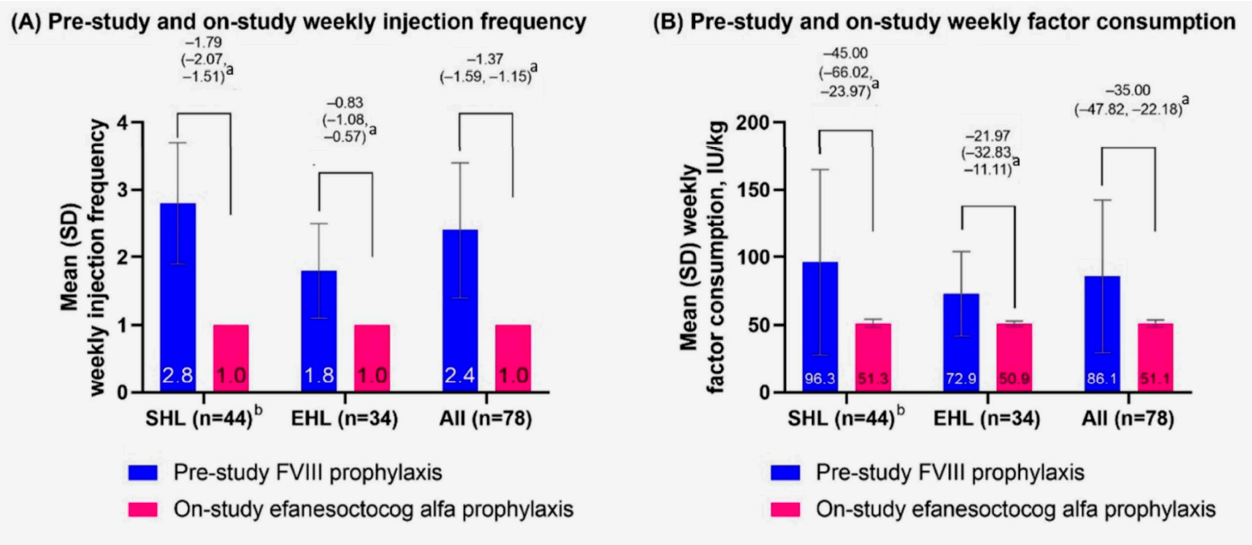
BIVV001 consumption and injection frequency

The total consumption of BIVV001 corresponds to the sum of doses of BIVV001 received as part of the prophylaxis treatment, and if any, of the doses of BIVV001 for the treatment of bleeding episodes. The mean (SD) annualised BIVV001 consumption per participant during the efficacy period was 3131.75 (4113.19) IU/kg for participants in Arm A, 1135.32 (404.94) IU/kg for participants in Arm B with on-demand treatment and 2751.54 (88.26) IU/kg after participants in Arm B switched to prophylaxis treatment. Median annualised BIVV001 consumption was 2756.99 IU/kg for participants in Arm A, 1212.27 IU/kg for participants in Arm B with on-demand treatment, and 2737.53 IU/kg after participants in Arm B switched to prophylaxis treatment.

A post-hoc analysis was performed to compare weekly FVIII consumption and injection frequency during pre-study prophylaxis and during BIVV001 prophylaxis in 78 participants who had received ≥6 months standard-of-care FVIII prophylaxis (SHL FVIII [recombinant or plasma-derived FVIII; n=44] or EHL rFVIII [n=34]) in the observational Study OBS16221 and were then enrolled in Arm A to receive weekly BIVV001 prophylaxis (Figure 6).

With BIVV001 prophylaxis, mean overall weekly injection frequency decreased from 2.4 to 1.0 injections per week and weekly FVIII consumption decreased from 86.1 to 51.1 IU/kg per week, compared to pre-study prophylaxis. Mean (95% CI) changes in weekly injection frequency and in weekly consumption were −1.37 (−1.59, −1.15) injections per week and −35.00 (−47.82, −22.18) IU/kg per week, respectively.

Figure 6: Pre-study and on-study weekly injection frequency and FVIII consumption



Abbreviations: CI, confidence interval; EHL, extended half-life; FVIII, factor VIII; SD, standard deviation; SHL, standard half-life.
a. Mean difference, 95% CI.
b. Pre-study SHL includes SHL rFVIII and plasma-derived FVIII.
Source: Figure 2.7.3 - 3

Secondary efficacy endpoints – Treatment of bleeding episodes

Number of injections and dose of BIVV001 to treat a bleeding episode

A total of 362 bleeds were treated with BIVV001 across 2 treatment arms. Analysis per bleeding episode showed that overall, all but 1 bleeding episode (99.7%) were controlled with ≤2 injections of BIVV001, with 96.7% controlled by only 1 injection (Table 14). No bleeding episode required more than 3 injections. The mean (SD) number of injections (i.e., including initial and follow-up injections) required for resolution of a bleeding episode was 1.0 (0.2). Per bleeding episode, the mean (SD) total dose was 51.18 (10.00) IU/kg. Results were generally similar between Arm A and Arm B on demand with regards to the number of injections and the mean dose to treat a bleeding episode.

The analysis of the number of injections and dose per injection for resolution of a bleeding episode showed consistent results when examined on a per episode or a per participant basis.

Table 14: Summary of number of BIVV001 injections required for resolution of a bleeding episode - full analysis set

	Arm A	Arm B		
	Prophylaxis (N=133)	On-Demand (N=26)	Prophylaxis (N=26)	Overall
Number of participants with an efficacy period	133	26	26	159
Injections per bleeding episode				
Number[a]	86	268	8	362
Mean (SD)	1.1 (0.3)	1.0 (0.2)	1.0 (0.0)	1.0 (0.2)
Median	1.0	1.0	1.0	1.0
Q1 ; Q3	1.0 ; 1.0	1.0 ; 1.0	1.0 ; 1.0	1.0 ; 1.0
Min ; Max	1 ; 3	1 ; 2	1 ; 1	1 ; 3
1	81 (94.2)	261 (97.4)	8 (100)	350 (96.7)
2	4 (4.7)	7 (2.6)	0	11 (3.0)
3	1 (1.2)	0	0	1 (0.3)
4	0	0	0	0
>4	0	0	0	0

Notes: 1: The efficacy period reflects the sum of all intervals of time during which participants are treated with BIVV001 according to the study arms and treatment regimens excluding periods of PK evaluations, surgery/rehabilitation (minor and major), and injection intervals (>28 days).
2: Participants are included in each study arm and treatment regimen they participated in for the duration of time on that regimen and, as such, may appear in more than one treatment regimen.
a. Number = total number of treated bleeding episodes. Percentages are based on this number.
PGM=PRODOPS/BIVV001/EFC16293/CSR_01/REPORT/PGM/bleed_inj_t.sas
OUT=REPORT/OUTPUT/bleed_inj_t_i.rtf (05MAY2022 15:43)

Assessment of participants' response to BIVV001 treatment of bleeding episodes

Overall, across the 2 treatment arms, 375 injections of BIVV001 were given to treat 362 bleeding episodes during the efficacy period, of which 334 were evaluated for response. The majority of BIVV001 injections (94.9%) were rated as producing an excellent or good response.

For the 3 participants who reported no response to therapy, 2 required no follow-up injections and 1 required 1 follow up injection.

Among the 14 participants who reported moderate response to therapy, 2 participants, in Arm A, had a follow-up injection within 72 hours after the first injection. Analysis based on first injections for treating a bleeding episode showed similar results (Table 15).

Table 15: Summary of participant's assessment of response to BIVV001 treatment of bleeding episodes - full analysis set

	Arm A	Arm B		
n(%)	**Prophylaxis (N=133)**	**On-demand (N=26)**	**Prophylaxis (N=26)**	**Overall (N=159)**
Number of participants with an efficacy period	133	26	26	159
Each injection				
Based on injections with an evaluation				
Number[a]	73	255	6	334
n(%)	**Prophylaxis (N=133)**	**On-demand (N=26)**	**Prophylaxis (N=26)**	**Overall (N=159)**
Excellent or Good	60 (82.2)	251 (98.4)	6 (100)	317 (94.9)
Excellent	39 (53.4)	195 (76.5)	5 (83.3)	239 (71.6)
Good	21 (28.8)	56 (22.0)	1 (16.7)	78 (23.4)
Moderate	10 (13.7)	4 (1.6)	0	14 (4.2)
None	3 (4.1)	0	0	3 (0.9)
Based on all injections				
Number[b]	92	275	8	375
Excellent or Good	60 (65.2)	251 (91.3)	6 (75.0)	317 (84.5)
Excellent	39 (42.4)	195 (70.9)	5 (62.5)	239 (63.7)
Good	21 (22.8)	56 (20.4)	1 (12.5)	78 (20.8)
Moderate	10 (10.9)	4 (1.5)	0	14 (3.7)
None	3 (3.3)	0	0	3 (0.8)
Response not provided	19 (20.7)	20 (7.3)	2 (25.0)	41 (10.9)

Note:
1: 'None' means that there was no improvement, not that the participant did not provide a response.
2: The efficacy period reflects the sum of all intervals of time during which participants are treated with BIVV001 according to the study arms and treatment regimens excluding periods of PK evaluations, surgery/rehabilitation (minor and major), and large injection intervals (>28 days).
3: Participants are included in each study arm and treatment regimen they participated in for the duration of time on that regimen and, as such, may appear in more than one treatment regimen.
a Number = number of injections (or bleeding episodes as appropriate) with a response. Percentages are based on the number during the efficacy period.
b Number = number of injections (or bleeding episodes as appropriate) reported. Percentages are based on this number during the efficacy period
PGM=PRODOPS/BIVV001/EFC16293/CSR_01/REPORT/PGM/bleed_pat_asses_t.sas
OUT=REPORT/OUTPUT/bleed_pat_asses_t_i.rtf (05MAY2022 15:44)

Physician's global assessment of participant's response to BIVV001 treatment of bleeding episodes

Consistent with the high number of bleeding episodes controlled with a single injection and the participants' assessment of response to treatment with BIVV001, the participants' response to their BIVV001 regimen was rated as excellent by the physician for 95.7% and effective for 4.3% of all visits in Arm A. No participants had a response to the BIVV001 treatment assessed as partially effective or ineffective by the physician at any visit.

The assessments were generally consistent over the course of the study: 92.9% to 97.6% of participants had a global response to the BIVV001 treatment assessed by the Physician as excellent during the study.

In Arm B, the physician's global assessment of the participant's response to their BIVV001 on demand treatment was excellent for 96.1% and effective for 3.9% for all visits and the response to BIVV001 prophylaxis treatment was excellent for 93.2% and effective for 6.8% for all visits.

- **Ancillary analyses**

Not Applicable.

- **Summary of main efficacy results**

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

Table 16: Summary of efficacy for trial EFC16293

Title: A Phase 3 Open-Label, Multicenter Study of the Safety, Efficacy, and Pharmacokinetics of Intravenous Recombinant Coagulation Factor VIII Fc-von Willebrand Factor-XTEN Fusion Protein (rFVIIIFc-VWF-XTEN; BIVV001) in Previously Treated Patients ≥12 Years of Age With Severe Haemophilia A (XTEND-1)			
Study identifier	EFC16293 IND: 17464 EudraCT: 2019-002023-15 NCT: NCT04161495		
Design	Phase 3, open-label, non-randomised, multinational, multicentre		
	Duration of main phase: Duration of screening phase Duration of Run-in phase: Duration of Extension phase:		52 weeks 8 weeks ≥ 26 weeks (observational Study OBS16221) N/A
Hypothesis	Efficacy		
Treatments groups	Arm A		Prophylaxis: 50 IU/kg once weekly, 52 weeks, n=133
	Arm B		On-demand, 50 IU/kg single dose, 26 weeks, n=26 followed by Prophylaxis: 50 IU/kg once weekly, 26 weeks, n=26
Endpoints and	Primary endpoint	ABR	Efficacy of BIVV001 weekly prophylaxis as estimated by the mean ABR and CI in Arm A

Title: A Phase 3 Open-Label, Multicenter Study of the Safety, Efficacy, and Pharmacokinetics of Intravenous Recombinant Coagulation Factor VIII Fc-von Willebrand Factor-XTEN Fusion Protein (rFVIIIFc-VWF-XTEN; BIVV001) in Previously Treated Patients ≥12 Years of Age With Severe Haemophilia A (XTEND-1)			
Study identifier	EFC16293 IND: 17464 EudraCT: 2019-002023-15 NCT: NCT04161495		
definitions	Key secondary Endpoint	Intra-ABR Arm A	Intra-participant comparison of ABR between BIVV001 weekly prophylaxis and historical prophylaxis in Arm A
	Secondary Endpoint	Intra-ABR Arm B	Intra-participant comparison of ABR between on-demand and prophylaxis in Arm B
	Secondary Endpoint	Injections	Number of injections to treat a bleeding episode based on all injections
	Secondary Endpoint	Response	Individual assessment of response to treat a bleeding episode based on the ISTH-4-point scale
Database lock	24 February 2022		

Results and Analysis

Analysis description	**Primary Analysis**			
Analysis population and time point description	Full-Analysis-Set			
	Treatment group	Arm A	Arm B On-demand	Arm B Prophylaxis
	Number of subjects	133	26	26
	ABR, Mean (SD)	0.71 (1.43)	21.42 (7.41)	0.69 (1.35)
	Injections, Mean (SD)	1.1 (0.3)	1.0 (0.2)	1.0 (0.0)
	Response/ Number of injections n (%) Excellent/ good Moderate None	73 60 (82.2) 10 (13.7) 3 (4.1)	255 251 (98.4) 4 (1.6) 0	6 6 (100) 0 0
Effect estimate per comparison	Primary endpoint	Comparison group	BIVV001 Prophylaxis Arm A (N=133)	
		Mean ABR (95% CI), based on Negative Binomial regression model	0.71 (0.52; 0.97)	

Title: A Phase 3 Open-Label, Multicenter Study of the Safety, Efficacy, and Pharmacokinetics of Intravenous Recombinant Coagulation Factor VIII Fc-von Willebrand Factor-XTEN Fusion Protein (rFVIIIFc-VWF-XTEN; BIVV001) in Previously Treated Patients ≥12 Years of Age With Severe Haemophilia A (XTEND-1)			
Study identifier	EFC16293 IND: 17464 EudraCT: 2019-002023-15 NCT: NCT04161495		
	Key-secondary endpoint	Comparison groups	BIVV001 Prophylaxis Partially Arm A (n=77) Historical Prophylaxis (OBS16221) (n=77)
		Mean difference (95% CI)	-2.30 (-3.49; -1.11)
		Negative Binomial regression model p-value (superiority)	< 0.0001
	Secondary endpoint	Comparison groups	On-demand Arm B (n=26) Prophylaxis Arm B (n=26)
		Rate ratio (95% CI)	0.03 (0.02; 0.07)

2.6.5.2. Clinical studies in special populations

The paediatric Phase 3 study in male PTPs <12 years of age has been completed and final data are available in the clinical study report (CSR EFC16295) completed on 11 May 2023. This is a single treatment arm study in 2 age cohorts of children (<6 years and 6 to <12 years), with all participants to receive BIVV001 at a dose of 50 IU/kg IV once weekly for 52 weeks. The study was initiated when data from at least 20 PTPs ⩾12 years of age from the Phase 3 adult adolescent study were available. Approximately 65 participants were planned to be enrolled to achieve at least 50 participants (25 participants <6 years of age and 25 participants 6 to <12 years of age) completing approximately 52 weeks of treatment to obtain at least 50 EDs.

Disposition of study participants

Overall, 74 male participants were enrolled in the study in 2 age cohorts (<6 years and 6 to <12 years) and received at least one dose of Altuvoct. There were 38 participants in the <6 years of age cohort and 36 in the 6 to <12 years of age cohort. A total of 72 (97.3%) participants completed the study, with 2 (2.7%) premature discontinuations related to extreme fear of blood drawing in 1 participant and a positive low-titre FVIII inhibitor test at Baseline (prior to first dose) in the other participant.

Demographic characteristics

The mean (SD) ages of the participants were 5.99 (2.91) years overall, 3.69 (1.21) years in the <6 years of age cohort, and 8.42 (2.08) years in the 6 to <12 years of age cohort. Participants represented 3 geographic regions: North America (37.8%), Europe (36.5%), and Asia/Pacific (25.7%). Baseline disease characteristics were representative of a paediatric population with severe haemophilia A. All participants, except 1, were on prophylaxis treatment prior to study enrolment. The mean (SD) total number of bleeding episodes reported in the 12 months prior to the study was 2.1 (4.2) overall, with 27 (38.6%) participants reporting no bleeding

episodes and 39 (55.7%) participants reporting 1 to 5 bleeding episodes. The mean (SD) number of joint bleeding episodes reported in the 12 months prior to the study was 1.1 (3.9) across the study population.

Secondary efficacy endpoints

Prevention of bleeds

Altuvoct was effective for routine prophylaxis in children under 12 years of age with severe haemophilia A. Once-weekly routine prophylaxis with Altuvoct resulted in an overall estimated mean ABR of 0.89 (95% CI: 0.56 to 1.42) in study participants with an efficacy period (n = 74), with similarly low ABRs in both age cohorts (0.48 [95% CI: 0.30; 0.77) and 1.33 [95% CI: 0.64; 2.76], respectively). The overall estimated mean ABR in an ad hoc sensitivity analysis that excluded 1 participant in the 6 to <12 years of age cohort who did not receive the weekly prophylaxis treatment as specified in the protocol for an extended period of time was 0.61 [95% CI: 0.42 to 0.90]. The observed median (Q1; Q3) ABR was 0.00 (0.00; 1.02). The majority of the participants overall (63.5%) reported no bleeding episodes across both age cohorts (63.2% and 63.9%, respectively, with 64.4% in the ad hoc sensitivity analysis).

ABRs were consistently low with Altuvoct weekly prophylaxis, across type and location of bleeding, when including untreated and treated bleeding episodes, as well as in the 3 subgroups studied (bleeding phenotype, number of targets joints, regimen compliance).

All participants maintained FVIII activity levels >3 IU/dL at any study visit at 7 days after administration of Altuvoct, with the majority (86.9%) >5 IU/dL. Trough FVIII activity levels >10 IU/dL were maintained in 18.8% of children <6 years and in 51.7% of children aged 6 to <12 years.

The physician's global assessment of the participant's response to Altuvoct treatment was excellent for 96.6% of study visits.

Treatment of bleeding episodes

Altuvoct was effective for the treatment of bleeding episodes in children <12 years of age with severe haemophilia A. Across the 2 age cohorts, 95.3% of 43 bleeding episodes treated with Altuvoct were controlled with a single injection (ad hoc sensitivity analysis).

The mean (SD) total dose per bleeding episode was 51.14 (11.10) IU/kg (ad hoc sensitivity analysis).

As only the first injections to treat a bleed were evaluated for response to treatment, 37 out of 43 bleeding episodes were evaluated, with the majority (97.3%) having an excellent or good response (ad hoc sensitivity analysis).

Altuvoct consumption

The mean (SD) annualised Altuvoct consumption per participant during the efficacy period was 3003.24 (394.01) IU/kg overall, 3115.57 (488.64) IU/kg for participants in the <6 years of age cohort, and 2884.67 (207.88) IU/kg in the 6 to <12 years of age cohort.

Perioperative management

A total of 2 major surgeries (dental restoration including a tooth extraction and circumcision) were performed in 2 participants, both in the <6 years of age cohort. In addition, 9 minor surgeries were reported during the study involving port removal or replacement, dental extraction, or gastroendoscopy. A single loading dose of Altuvoct was sufficient to maintain haemostasis during all these surgeries and the haemostatic responses to Altuvoct were rated as excellent for both major surgeries by the investigators/surgeons.

2.6.5.3. In vitro biomarker test for patient selection for efficacy

Not applicable.

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

Efficacy in perioperative management

As of the data cut-off date of 17 January 2023, a total of 49 major surgeries were performed in 41 participants during the Phase 3 programme, with the majority of procedures being orthopaedic or complicated dental procedures. The majority of the major surgeries were conducted at sites in Europe, Australia, China, and Canada. Most of the participants' haemostatic response during surgery was rated by the Investigator or Surgeon as excellent (43 major surgeries) or good (5 major surgeries), indicating that intraoperative and postoperative blood loss was deemed comparable to what would be expected for a patient without haemophilia. In 1 participant who underwent left hip and knee joint replacement surgery on the same day, the response was rated as fair by the Investigator or Surgeon. No participant had a response to BIVV001 treatment assessed as ineffective.

Most of the major surgeries (89.8%) required a single preoperative loading dose of BIVV001 to maintain haemostasis during the surgery.

During the perioperative period for major surgery (from the day before the surgery [Day -1] until Day 14), the mean (SD) total BIVV001 consumption was 171.85 (51.97) IU/kg. The mean (SD) number of BIVV001 injections was 3.9 (1.4). Postoperative dosing on Days 1 to 3 was variable with a mean (SD) of 1.1 (0.3) injections and mean (SD) dose of 39.57 (15.85) IU/kg given for 30 major surgeries.

32 minor surgeries in 28 participants were performed across the Phase 3 studies. Haemostasis was assessed in 25 minor surgeries, all of which were rated as excellent by the Investigator or Surgeon. Twenty-seven (84.4%) minor surgeries required a single injection of BIVV001 to maintain haemostasis during the surgery. No preoperative loading dose was given for the remaining 5 minor surgeries conducted solely under the coverage of weekly BIVV001 prophylaxis.

2.6.6. Discussion on clinical efficacy

Design and conduct of clinical studies

Efficacy data are derived from three phase 3 clinical studies, namely study EFC16293 in PTPs ≥12 years of age, study EFC16295 in PTPs <12 years of age, and the long-term study LTS16294 in PTPs of all age groups. Surgery data are available from the phase 3 study programme. The extension study LTS16294 is thought to fulfil the required post-marketing investigations on immunogenicity (inhibitor formation), efficacy & safety, as laid out in the relevant guidance document (EMA/CHMP/BPWP/144533/2009 rev. 2).

All trials were open-label, multicentre trials which is considered acceptable for FVIII products. The designs of the pivotal trials follow the relevant guidance (EMA/CHMP/BPWP/144533/2009 rev. 2) with respect to sample size (for pre-authorisation trials), recruited population, exposure days (participants with 50 EDs fulfilled for study EFC16293 and study EFC16295), duration of long-term prophylaxis, and efficacy data from surgical procedures.

Design and conduct of Study EFC16293 in adults and adolescents ≥12 years of age

The study included two treatment arms. Participants in Arm A were on pre-study PPX with marketed FVIII products prior to study start and were assigned to receive weekly PPX with BIVV001 for 52 weeks. Participants in Arm B were on on-demand treatment and were assigned to receive 26 weeks of on-demand treatment with the IP, followed by PPX for additional 26 weeks.

The pre-specified definitions of bleeding episodes and rebleeds as well as the assessment of treatment of acute BEs and haemostatic response to surgical bleeds follow standardised ISTH (International Society on Thrombosis and Haemostasis) criteria.

The primary endpoint (ABR, upper limit of the CI below a certain threshold) of the pivotal trial in adults and adolescents defines an upper bound of 6 for the ABR which is not supported from a clinical point of view and not sufficiently justified from a statistical point of view. However, due to the rather clear efficacy results from Study EFC16293, the lack of proper justification can be considered of limited relevance in this particular case.

The inclusion of Arm B investigating an intra-patient comparison of the ABR between on-demand treatment with BIVV001 during a 26-week period, followed by a 26-week prophylaxis period is regarded critical due to several reasons e.g. treatment standard in Western Europe, potential seasonal bias caused by the 26-week periods, ABR in on-demand therapy representing the phenotypical disease-severity and not the efficacy of the treatment.

A total of 159 patients (Arm A: N=133, including 82 participants who rolled over from observational study OBS16221; Arm B: N=26) were enrolled and received at least one dose of BIVV001. The mean (SD) age of the participants at informed consent was 35.4 (15.1) years (range: 12 to 72 years); 25 (15.7%) participants were between 12 and 17 years, 129 (81.1%) were between 18 and 64 years and 5 (3.1%) were 65 years or older. All adolescents were in Arm A. One participant was female.

The participants were to receive a prophylactic dose (50 IU/kg) of BIVV001 once every week throughout the efficacy period. The treatment compliance was high with 96.9% of the participants being compliant to both the dosing and the dosing interval (98.5% in Arm A and 88.5% in Arm B). The somewhat lower compliance rate in Arm B may be explained by the fact that these patients were likely more experienced and used to on-demand treatment. The mean (SD) weekly dose was 51.28 (2.13) IU/kg and the mean (SD) dosing interval was 7.01 (0.26) days.

In Arm A, 9 participants did not complete the study due to different reasons (1x adverse event [CD4 lymphocytes decreased in an HIV positive patient], 3x consent withdrawn, 3x prohibited medication, 1x protocol violation [related to a prohibited medication], 1x other reasons [participant moved abroad]). In Arm B, one participant died ("pancreas cancer with multiple nodules on liver").

The number of participants with major protocol deviations was high (N=46, 28.9%). This was mainly caused by participants with missed inhibitor test (N=13, 8.2%), administration of expired IP or IP that has undergone a temperature excursion (N=9, 5.7%), deviations regarding the informed consent (N=15, 9.4%), failure to report SAEs/AESI/pretreatment event/symptomatic overdose within 24 hours of site staff becoming aware to CRO or Sponsor (N=4, 2.5%), or failure to conduct a study visit resulting in lack of assessment for a given time point (N=3, 1.9%). Of note, 4 participants (2.5%) used prohibited concomitant medications. Three participants took FVIII products other than BIVV001, and one participant took aspirin. All four participants were discontinued due to these protocol violations. Overall, while the percentage of participants with major protocol deviations is high, the type and/or extent of deviations are not expected to have a strong impact on the efficacy outcome.

For a subpopulation of Arm A (N=82), the pre-study data regarding bleeding episodes during prophylaxis with marketed FVIII products (for the intra-patient comparison) were prospectively collected during the observational study 242HA201 (OBS16221). A total of 157 subjects who consented to participate in the study and had at least 1 injection on-study, were included in the FAS. These subjects received at least 1 day of treatment for an on-demand regimen (19 subjects) or at least 2 prophylactic injections for a prophylaxis regimen (139 subjects), and were included in the observational period. More than 80% of subjects (127/157 subjects [80.9%]) completed the study (i.e., subjects who completed 12 months of observation or enrolled in the Phase 3 study). No inconsistencies are noted.

Design and Conduct of Study EFC16295 in children <12 years of age

The paediatric study EFC16295 included only one treatment arm for a weekly prophylactic dose (50 IU/kg) of Altuvoct. The study did not include a formal hypothesis testing and all statistical analyses were descriptive in nature. The primary endpoint was a safety endpoint (occurrence of inhibitors). The secondary endpoints included efficacy endpoints typical for FVIII products, such as ABR, amount of IP consumption, percentage of trough FVIII levels above certain activity thresholds, assessment of response to treatment of breakthrough bleeds (4-point scale), and different PRO questionnaires. The design was agreed by PDCO, is in line with the FVIII guidance.

A total of 74 children (38 children <6 years of age; 36 children 6 to <12 years of age) were enrolled and received at least one dose of Altuvoct. In the <6 years of age cohort, the mean (SD) age was 3.69 (1.21) years, and in the 6 to <12 years of age cohort, the mean (SD) age was 8.42 (2.08) years (range: 6.0 to 11.0 years).

Efficacy data and additional analyses

Efficacy in adults and adolescents ≥12 years of age (Study EFC16293)

The primary objective was met since the upper limit of the 1-sided 97.5% CI of the estimated ABR (based on a negative-binomial model) was ≤6. The 133 patients (FAS) in Arm A were followed for in total 121.2 patient-years (mean [SD] duration of efficacy period: 47.55 [8.77] weeks) and experienced 86 treated bleeding episodes, which resulted in a model-based mean (95% CI) ABR of 0.71 (0.52; 0.97). Of note, an estimated mean (95% CI) ABR of 1.11 (0.83; 1.48) was observed if all BEs are considered (treated and untreated BEs).

Sensitivity analyses of the estimated mean ABRs on the PPS (N=129) or on a population including only participants with an efficacy period of at least 26 weeks (N=128) resulted in nearly identical results. *Subgroup analyses* on the FAS based on age categories, bleeding phenotype at baseline (estimated number of BEs in prior 12 months), or number of target joints at screening revealed comparable results.

For the 26 patients in Arm B, the model-based estimated mean ABR (95% CI) was 21.41 (18.81; 24.36) during the on-demand period, compared to 0.70 (0.33; 1.48) during the prophylaxis period. While including Arm B was not supported by SAWP/CHMP in a previous EMA-SA procedure, it is reassuring that Arm B patients reported comparable ABRs during prophylaxis compared to Arm A patients who were on prophylaxis already before study start.

The key secondary objectives (intra-patient comparison of ABR between Altuvoct prophylaxis and pre-study FVIII prophylaxis; non-inferiority and superiority testing) were also met. The estimated mean ABR (95%) was lower during Altuvoct prophylaxis (0.68 [0.43; 1.12]) compared to pre-study FVIII PPX (2.99 [2.03; 4.42]) and non-inferiority was confirmed since the estimated mean difference in ABRs (95% CI) was -2.30 (-3.49; -1.11) and thus well below the prespecified non-inferiority margin of 4 bleeds per year. Considering

this result, it is of limited relevance that the non-inferiority margin does not seem well-justified. Superiority (prespecified in the hierarchical step-down testing procedure) was also achieved as the upper limit of the 1-sided 97.5% CI was less than the prespecified value of 1 (rate ratio: 0.23 [95% CI: 0.13 to 0.42]).

Other secondary endpoints:

The following mean (SD) ABRs were reported by type of bleeding: Participants in Arm A had an ABR of 0.29 (0.73) for spontaneous BEs and an ABR of 0.36 (0.83) for traumatic BEs. Of note, some BEs were not assigned (mean ABR 0.06). Regarding location of bleed, the study revealed the following mean (SD) ABRs: Participants in Arm A had an ABR of 0.52 (1.09) for joint BEs, an ABR of 0.20 (0.93) for muscle BEs, an ABR of 0.05 (0.26) for internal bleeds, and an ABR of 0.12 (0.62) for skin/mucosa BEs.

The analysis of participants who maintained trough FVIII activity levels above certain levels revealed that nearly all (except one) participants in Arm A (of Study EFC16293) remained above 5% mean FVIII activity at the end of the week. A high proportion (83.5%) remained above 10% mean FVIII activity at trough. Overall, the C_{trough} levels of FVIII activity are considered reassuring regarding the potential long-term effect of BIVV001 in the overall population, even towards the end of the dosing interval. Although an increasing trend of treated bleeds is noted over time, the extent of this increase is not considered critical. The efficacy data of both phase 3 trials show that a once-weekly administration of BIVV001 was sufficiently efficacious in preventing bleeding episodes in the recruited population.

A total of 375 injections were administered to treat 362 bleeding episodes across both arms (including the on-demand phase of Arm B) and the responses to 94.9% of these injections were assessed as either excellent or good on the standardised ISTH 4-point scale. It is however noted that this rate was lower in Arm A, with 82.2% of the injections (that were evaluated) having an assessment of excellent or good, or even lower (65.2%) when injections without assessment (N=19, 20.7% of all injections) are considered. Further provided information on the 13 treatment responses rated as moderate or none of 12 patients showed that only 2 out of these 13 bleeds required a follow-up injection for treatment of the bleed. No FVIII activity levels are available during these episodes. But the PK profiles of these subjects do not reveal differences to the whole study population. Therefore, it can be concluded that haemostatic assessments of the study participants were highly individual and subjective.

Of the 86 treated BEs in Arm A, 81 (94.2%) bleedings were treated with a single injection of the IP, four (4.7%) BEs were treated with two injections, and one (1.2%) episode was treated with three injections.

The mean (SD) annualised BIVV001 consumption per participant was 3131.75 (4113.19) IU/kg in Arm A, 1135.32 (404.94) during the on-demand period in Arm B, and 2751.54 (88.26) during the prophylaxis period in Arm B. Further, analysis of consumption data for Altuvoct prophylaxis showed a decrease of mean injection frequency (2.4 to 1.0 injections per week) and mean FVIII consumption (86.1 to 51.1 IU/kg per week) compared to pre-study prophylaxis using SHL or EHL products.

In Arm A, there were 26 participants who reported a total of 80 target joints at baseline. This appears high for PPX treatment and may indicate that the participants were not compliant to PPX prior to study start and not well-controlled. However, among those patients who were included in the intra-patient comparison, 10 (12.8%) participants reported at least 1 target joint, with a total of 30 reported target joints. This is lower than the target joint incidence in Arm A overall (26/133 participants, 19.5%) and reassuring.

Among participants with at least 12 months of continuous exposure, 45 target joints were reported and all target joints resolved until the end of the study.

The results of 3 PRO questionnaires (Haem-A-QoL physical health score, PROMIS Pain Intensity 3a, Haemophilia Joint Health Score) have been provided. While a positive trend throughout these results is recognised, the outcomes are not considered relevant and robust enough for presentation in the SmPC.

Final efficacy data in children <12 years of age (Study EFC16295)

Of the 74 participants who received at least 1 dose of Altuvoct, 66 (89.2%) achieved 50 or more EDs: 31 (81.6%) participants in the <6 years of age cohort and 35 (97.2%) participants in the 6 to <12 years of age cohort. The mean (SD) number of EDs was 52.5 (7.2) overall, 51.2 (8.6) in the <6 years of age cohort, and 53.9 (4.9) in the 6 to <12 years of age cohort.

The estimated mean ABR from the negative binomial model was 0.89 (95% CI: 0.56 to 1.42) across both age subgroups, 0.48 (95% CI: 0.30 to 0.77) in patients <6 years of age, and 1.33 (95% CI: 0.64 to 2.76) in patients from 6 to <12 years of age. The observed median (Q1; Q3) ABR in 74 participants with an efficacy period was 0.00 (0.00; 1.02). Of the 74 participants, 47 (63.5%) had an ABR of 0 and 25 (33.8%) had an ABR of >0 to 5. Two participants in the 6 to <12 years of age cohort had higher ABR with 7.2 in one participant and 21.4 in the other participant. No meaningful differences were noted when the ABRs were calculated for different subgroups.

Overall, the described efficacy results in children below 12 years of age are very well in line with the data in adults and adolescents. Most of the participants (86.9%) had mean trough FVIII activity levels above the threshold for moderate haemophilia (>5%) at the end of the weekly dosing interval.

Efficacy in perioperative management (combined data from studies EFC16293, EFC16295, LTS16294)

A total of 49 major surgeries were performed in 41 participants (in 39 adults/adolescents and 2 children). These procedures included orthopaedic surgeries such as hip, knee, or elbow arthroplasty and rhinoplasty/mentoplasty. Most of the participants' haemostatic response during surgery was rated as excellent (43 major surgeries) or good (5 major surgeries) by the Investigators/Surgeons for all procedures based on the criteria pre-specified in the protocol (ISTH definition, Blanchette *et al.* 2008). In 1 participant who underwent left hip and knee joint replacement surgery was rated as fair by the Investigator or Surgeon. No blood component transfusions were required and no extraordinarily high doses of the IP were administered.

With regards to the guideline requirement of least 10 surgical procedures in 5 patients (in the adult population), the presented data clearly show that BIVV001 is sufficiently effective in perioperative management, including orthopaedic major surgeries.

Efficacy in elderly

The oldest patient was 72 years of age (at the time of informed consent of Study EFC16293). A total of 5 patients were ≥65 years of age were recruited. Due to the rarity of the disease, the guideline does not include any recruitment targets or other requirements for elderly patients. Of four patients included in Arm A, the model based ABR was 0.34 (95% CI: 0.05; 2.38) and no concern is raised.

2.6.7. Conclusions on the clinical efficacy

The presented clinical data provide sufficient evidence that a once weekly administration of BIVV001 is effective for prophylaxis, treatment of bleeding episodes and perioperative management in subjects with severe haemophilia A. No dose adjustment has been performed across all age groups of the entire Phase 3 study programme. Even in the paediatric study no dose adjustment has been done despite shortening of the weekly dosing interval would have been an option. Number of breakthrough bleedings was low in all age groups. Overall, in the pivotal study EFC16293 and in the paediatric study EFC16295, clinical efficacy of Altuvoct has been demonstrated for prophylactic treatment using 50 IU/kg weekly and on-demand treatment of 50 IU/kg as single dose in an adequate number of adults, adolescents and children with severe haemophilia A.

2.6.8. Clinical safety

2.6.8.1. Patient exposure

Safety data from the following completed and ongoing studies in the BIVV001 clinical development programme are included in the Summary of Clinical Safety: Phase 3 studies EFC16293, EFC16295, and LTS16294, Phase 1/2a studies 242HA101 (TDU16220) and 242HA102 (TDR16219), and Phase 1 studies PKM17085 and PKM16978.

Six studies enrolled previously treated patients (PTPs) with severe haemophilia A (HA) and 1 study enrolled patients with von Willebrand disease.

Across the three Phase 3 clinical studies (EFC16293, EFC16295, and LTS16294) a total of 277 unique participants received at least one dose of BIVV001

Table 17: Patient exposure (cut off 17 Jan 2023)

	Patients exposed (n)	Patients exposed to the proposed dose range (n)	≥ 50 EDs (n)
EFC16293	159	159	148
EFC16295	74	74	66
LTS16294 Arm A Arm B Arm C		 198*37 7	249* 31 4
242HA101	15[a]		
242HA102	24[b]	10	
PKM17085		13	
PKM16978	5[c]		

a. 25 IU/kg n=6, 65 IU/kg n=9
b. 65 IU/kg n=14
c. 25 IU/kg

*.Patients rolled over from EFC16293 and EFC 16295

2.6.8.2. Adverse events

Phase 3 studies pooled data (17 Jan 2023 cut off)

Of the 277 participants in the Overall Safety Analysis Set (overall group), 230 (83.0%) participants experienced at least 1 TEAE. (Table 18).

Table 18: Overview of treatment-emergent adverse events in Phase 3 studies - safety analysis set

n (%)	EFC16293 (N=159)	EFC16295 (N=74)	LTS16294 Arm B (N=37)	LTS16294 Arm C (N=7)	Overall (excluding surgery subgroup) (N=234)	Surgery subgroup[a] (N=43)	Overall total (N=277)
Participants with at least one TEAE	135 (84.9)	63 (85.1)	26 (70.3)	5 (71.4)	190 (81.2)	10 (23.3)	230 (83.0)
Participants with at least one related TEAE	9 (5.7)	4 (5.4)	3 (8.1)	0	12 (5.1)	1 (2.3)	16 (5.8)
Participants with at least one TESAE	27 (17.0)	9 (12.2)	6 (16.2)	1 (14.3)	22 (9.4)	1 (2.3)	44 (15.9)
Participants with at least one related TESAE	1 (0.6)	0	1 (2.7)	0	1 (0.4)	0	2 (0.7)
Participants with at least one TEAESI	6 (3.8)	1 (1.4)	1 (2.7)	0	6 (2.6)	0	8 (2.9)
Participants with at least one related TEAESI	0	0	1 (2.7)	0	0	0	1 (0.4)
Participants with TEAEs leading to death	1 (0.6)	0	0	0	1 (0.4)	0	1 (0.4)
Participants with TEAEs leading to treatment discontinuation	4 (2.5)	0	0	0	3 (1.3)	0	4 (1.4)

Note: Data cutoff for study LTS16294 was 17 January 2023.

Phase 3 studies include EFC16293, EFC16295, LTS16294.

MedDRA [dictionary version 25.1]

Percentages are based on the number of participants in the Safety Analysis Set.

a. Only includes AEs occurring during a major surgical/rehabilitation period. But AEs which occur on the day of the major surgical/rehabilitation period starts are included in the columns by parent study/arm, they are not included in the column of surgery subgroup. Each participant is counted only once in each column.

TESAE=treatment-emergent serious adverse event; TEAESI=treatment emergent adverse events of special interest; TEAE=treatment-emergent adverse event. Source: Pooled Safety Report, Table 8.

The most frequently reported TEAEs by PT (>5% of participants) were arthralgia (46 [16.6%] participants), headache (44 [15.9%] participants), COVID-19 (35 [12.6%] participants), nasopharyngitis (32 [11.6%] participants), upper respiratory tract infection (29 [10.5%] participants), SARs-CoV-2 test positive (22 [7.9%] participants), asymptomatic COVID-19 (18 [6.5%] participants), pyrexia (17 [6.1%] participants), fall and pain in extremity (16 [5.8%] participants each).Of the 229 (82.7%) participants who had at least 1 TEAE, 123 (44.4%) participants had at least 1 TEAE classified as mild in severity and 82 (29.6%) participants had at least 1 TEAE classified as moderate in severity. A total of 24 (8.7%) participants had 31 TEAEs classified as severe in severity (reference: Pooled Safety Report Section 4.1.1.2).

The following TEAEs by PT were classified as severe: migraine (2 events), status epilepticus (2 events) and all other severe TEAEs were single events; bacteraemia, meningitis viral, skin infection, pancreatic carcinoma metastatic, gout, fear of injection, cerebral infarction, angina pectoris, atrial fibrillation, eosinophilic oesophagitis, haemophilic arthropathy, arthropathy, mobility decreased, osteoarthritis, synovitis, CD4 lymphocytes decreased, chest injury, vascular device occlusion, fall, femur fracture, head injury, joint injury, multiple injuries, thermal burn, wrist fracture, circumcision, and device breakage.

A total of 22 TEAE PTs in the overall group were assessed by the Investigator as related to BIVV001 in 16 (5.8%) participants. The most frequently reported treatment-related TEAEs included coagulation factor VIII level increased (4 [1.4%] participants), reported after injection and possibly related to overestimation of FVIII activity by chromogenic assay, headache and alanine aminotransferase increased (2 [0.7%] participants each). Other treatment-related TEAEs were varicella, hyperuricaemia, dysphoria, facial paralysis, thrombosis, haematochesia, liver injury, injection site dermatitis, malaise, aspartate aminotransferase increased, CD4 lymphocytes decreased, coagulation factor VIII level decreased, protein urine present, and Von Willebrand's factor antigen increased reported in 1 [0.4%] participant each. The TEAE of CD4 lymphocytes decreased was assessed by the Investigator as serious and resulted in discontinuation of BIVV001.

Adverse events of special interest

In the overall group of the pooled Phase 3 data, a total of 8 (2.9%) participants experienced TEAESIs (Table 20).

Table 19: Number (%) of participants with treatment-emergent adverse events of special interest by SOC and PT in Phase 3 studies by parent study/arm - safety analysis set

System organ class Preferred term, n (%)	EFC16293 (N=159)	EFC16295 (N=74)	LTS16294 Arm B (N=37)	LTS16294 Arm C (N=7)	Overall (N=277)
Participants with at least one TEAESIs	6 (3.8)	1 (1.4)	1 (2.7)	0	8 (2.9)
NERVOUS SYSTEM DISORDERS	1 (0.6)	0	0	0	1 (0.4)
Cerebral infarction	1 (0.6)	0	0	0	1 (0.4)
VASCULAR DISORDERS	1 (0.6)	0	1 (2.7)	0	2 (0.7)
Deep vein thrombosis	1 (0.6)	0	0	0	1 (0.4)
Thrombosis	0	0	1 (2.7)	0	1 (0.4)
SKIN AND SUBCUTANEOUS TISSUE DISORDERS	0	1 (1.4)	0	0	1 (0.4)
Urticaria	0	1 (1.4)	0	0	1 (0.4)
SOCIAL CIRCUMSTANCES	4 (2.5)	0	0	0	4 (1.4)
Pregnancy of partner	4 (2.5)	0	0	0	4 (1.4)

Note: Data cutoff for study LTS16294 was 17 January 2023.
Phase 3 studies include EFC16293, EFC16295, LTS16294.
MedDRA [dictionary version 25.1]
Percentages are based on the number of participants in the Safety Analysis Set.
Participants are counted once if they reported multiple events in the same system organ class or preferred term.
Table sorted by SOC internationally agreed order and decreasing frequency of PT in the overall group.
AEs occurring during a major surgical/rehabilitation period are excluded with the exception of those occurring on the start date of the major surgical/rehabilitation period which are included.
TEAESI=treatment-emergent adverse event of special interest; SOC=System organ class; PT=Preferred term.

As of the 17 January 2023 data cut-off date, there were no reports of inhibitor development to FVIII in the BIVV001 clinical development programme.

In the overall group of the pooled analysis, 1 TEAESI of urticaria described as "hives around eyes, mouth, face, and chest" after eating chocolate was reported in a child Study EFC16295. The event occurred approximately 3 months after the first dose of BIVV001 (weekly prophylaxis) and 3 days after the last injection. The participant was treated with 2 doses of intramuscular epinephrine (by Emergency Medical Services), oral dexamethasone (in Emergency Department), and oral cetirizine (in Emergency Department) with resolution. The Investigator assessed the event as non-serious and not related to BIVV001. There was no action taken with BIVV001 and no report of recurrent events in this participant.

In addition to reported TEAESIs, a broad Standardised MedDRA Query (SMQ) (v25.1) was used to identify potential events of allergic/hypersensitivity reactions. Of the events captured by this hypersensitivity SMQ, all but 2 events of Injection site dermatitis reported in 1 participant were assessed by the Investigator as not related to BIVV001/study procedures. No action was taken with BIVV001 for any of the events identified in the SMQ search.

Following medical review of the events identified in the SMQ search, infections and disease-related events were judged to be not related to BIVV001 and were considered not relevant for further investigation. The remaining 38 events were considered potentially consistent with allergic /hypersensitivity reactions were selected for detailed review. The majority of PTs were reported by a single participant. Two PTs (seasonal allergy and eczema) were reported by more than 2% of participants. Based on the detailed assessment, events of eczema, rash/rash papular, and urticaria/urticaria papular were identified as ADRs.

In the overall group, thrombotic events were reported in 3 (1.1%) participants (deep vein thrombosis [Arm A of Study LTS16294], thrombosis [Arm B of Study LTS16294], and cerebral infarction [Arm A of Study LTS16294]).

The events of thrombosis described below in the 3 patients were primarily related to the underlying risk factors for thrombosis in each of them, and the events were not regarded related to BIVV001:

- The study participant who experienced the event of deep vein thrombosis (DVT) had orthopaedic surgery for a distal femur fracture after a skiing accident. Of note, perioperative management of this surgery was conducted using another FVIII product (NovoEight) after last dose of BIVV001(7 days prior to the event). The sponsor agrees with the Investigator's assessment that this event of DVT was not related to BIVV001, as it was associated with a risk factor for thrombosis (femur fracture and resulting surgery) in the context of receiving another FVIII product.
- The study participant with the event of thrombosis had a history of ongoing haemangioma which can lead to slow blood flow. The thrombosis event was considered not related to BIVV001 by the sponsor as it was associated with a pre-existing risk factor for thrombosis (haemangioma/venous malformation) and the events were developing prior to first BIVV001 administration.
- The study participant with the event of cerebral infarction had multiple pre-existing contributing factors including a history of chronic atrial fibrillation with no anticoagulant or antiplatelet drug treatment, dyslipidaemia, and HIV infection.

Adverse events during major surgery/rehabilitation period

In the surgery subgroup (N=43) of the pooled Phase 3 data, a total of 14 TEAEs were reported by 10 (23.3%) participants during a major surgical/rehabilitation (Pooled Safety Report Section 4.1.1.4). Of the 14

TEAEs, 13 TEAEs were considered as non-serious and assessed by the Investigator as mild in severity and not related to BIVV001. One of the 14 TEAEs (catheter site pain) was considered by the Investigator to be a serious event, moderate in severity, and not related to BIVV001 treatment.

Adverse drug reactions

Proposed ADRs were identified after review of all TEAEs that were included in the pooled safety data across the Phase 3 studies (EFC1693, EFC16295, and LTS16294). TEAEs were selected for further review based on the applicant's knowledge of the product, clinical significance, time to onset, biological plausibility, and experience with other haemophilia products. Causality assessment was performed for each identified potential ADR using the modified Bradford Hill Criteria.

Following causality assessment, a total of 111 (40.1%) of 277 participants experienced at least 1 or more ADRs in the pooled studies (Table 20). In the overall group, 13 PTs were determined to represent ADRs (arthralgia [16.6%], headache [15.6%], pyrexia [6.1%], pain in extremity [5.8%], back pain [4.3%], vomiting [3.6%]), eczema [2.2%], rash [ADR includes rash (1.4%) and rash maculo-papular (0.4%)], urticaria [ADR includes urticaria (0.7%) and urticaria popular (0.4%)] and injection site reactions [ADR includes infusion site hematoma (0.4%) and injection site dermatitis (0.4%)]. All identified ADRs were assessed by the Investigator as non-serious, and none resulted in discontinuation of BIVV001.

Table 20: Number (%) of participants with adverse drug reactions (ADRs) by SOC and PT in Phase 3 studies by parent study/arm - safety analysis set

System organ class Preferred term, n (%)	EFC16293 (N=159)	EFC16295 (N=74)	LTS16294 Arm B (N=37)	LTS16294 Arm C (N=7)	Overall (N=277)
Participants with at least one ADR	79 (49.7)	26 (35.1)	3 (8.1)	3 (42.9)	111 (40.1)
NERVOUS SYSTEM DISORDERS	38 (23.9)	4 (5.4)	0	2 (28.6)	44 (15.9)
Headache	38 (23.9)	4 (5.4)	0	2 (28.6)	44 (15.9)
GASTROINTESTINAL DISORDERS	2 (1.3)	8 (10.8)	0	0	10 (3.6)
Vomiting	2 (1.3)	8 (10.8)	0	0	10 (3.6)
SKIN AND SUBCUTANEOUS TISSUE DISORDERS	8 (5.0)	6 (8.1)	0	0	14 (5.1)
Eczema	3 (1.9)	3 (4.1)	0	0	6 (2.2)
Rash	4 (2.5)	0	0	0	4 (1.4)
Rash maculo-papular	0	1 (1.4)	0	0	1 (0.4)
Urticaria	0	2 (2.7)	0	0	2 (0.7)
Urticaria papular	1 (0.6)	0	0	0	1 (0.4)
MUSCULOSKELETAL AND CONNECTIVE TISSUE DISORDERS	48 (30.2)	9 (12.2)	1 (2.7)	2 (28.6)	60 (21.7)
Arthralgia	38 (23.9)	7 (9.5)	0	1 (14.3)	46 (16.6)
Back pain	11 (6.9)	0	0	1 (14.3)	12 (4.3)
Pain in extremity	10 (6.3)	5 (6.8)	1 (2.7)	0	16 (5.8)
GENERAL DISORDERS AND ADMINISTRATION SITE CONDITIONS	7 (4.4)	10 (13.5)	2 (5.4)	0	19 (6.9)
Infusion site hematoma	1 (0.6)	0	0	0	1 (0.4)
Injection site dermatitis	1 (0.6)	0	0	0	1 (0.4)
Pyrexia	5 (3.1)	10 (13.5)	2 (5.4)	0	17 (6.1)

TEAE=treatment-emergent adverse event; SOC=System organ class; PT=Preferred term. Percentages are based on the number of participants in the Safety Analysis Set. Events are coded using MedDRA version 25.1. Participants are counted once if they reported multiple events in the same system organ class or preferred term. AEs which occur during a major surgical/rehabilitation period are excluded from this table, but AEs which occur on the day of the major surgical/rehabilitation period starts will be included

Studies 242HA101, 242HA102, PKM17085, PKM16978

BIVV001 was well tolerated and no safety concerns were identified. Inhibitor development to FVIII was not detected and there were no reports of serious allergic reaction, or anaphylaxis.

2.6.8.3. Serious adverse event/deaths/other significant events

In the overall group of the pooled Phase 3 data, 43 (15.5%) participants experienced at least 1 TESAE (Pooled Safety Report, Table 13). The most frequently reported TESAE was haemophilic arthropathy, which was reported in 4 (1.4%) participants. Arthropathy, osteoarthritis, vascular device infection, and femur fracture were reported in 2 (0.7%) participants each; all other TESAEs were reported in 1 (0.4%) participant each. The majority of TESAEs were assessed by the Investigator as not related to BIVV001. There were only 2 TESAEs that were considered by the Investigator to be related to BIVV001: CD4 lymphocytes decreased and thrombosis (back of right hand, palm of right hand).

One unrelated TESAE of pancreatic carcinoma metastatic had a fatal outcome.

2.6.8.4. Laboratory findings

In the 3 Phase 3 studies, there were no clinically meaningful patterns or trends observed in the mean actual value or mean change from baseline over time in any haematology parameter, any clinical chemistry parameter and in either VWF ristocetin cofactor activity or VWF antigen.

In study LTS16294 Arm B 2 TEAEs were reported due abnormalities of haematological parameters: one with increased haematocrit and increased haemoglobin and the other one with microcytic anaemia. Both were assessed by the Investigator as mild in severity and not related to study drug.

In study 242HA101, elevations in D-Dimer, TAT complex, and prothrombin fragment 1+2 following administration of BIVV001 (BIVV001 1-hour time point and beyond) were identified in 14 of 15 subjects treated with BIVV001 showing abnormalities in at least 1 of these parameters. The subjects had no relevant medical history and no potentially relevant TEAEs were reported. Elevations of these markers were also identified in screening phase and the Advate treatment phase.

In study 242HA102, potentially clinically significant criteria were met for the following coagulation parameter abnormalities: D-dimer (>ULN): 13 subjects (54.2%), prothrombin fragment 1+2 (>ULN): 23 subjects (95.8%) and thrombin anti-thrombin complex (>ULN): 20 subjects (83.3%). There were no corresponding clinical sequelae reported in any subject with an elevation.

2.6.8.5. In vitro biomarker test for patient selection for safety

Not Applicable.

2.6.8.6. Safety in special populations

Study EFC16293

There were no unique patterns or trends identified in any of the subgroups examined (i.e., age, BMI, race, HIV status, and HCV status).

2.6.8.7. Immunological events

Inhibitor development

Inhibitor development to FVIII was not detected in any of the seven studies.

Anti-drug antibodies

An ADA positive participant was defined as a participant either having a treatment-induced ADA response (no positive ADA response at screening/baseline and any positive response in the post screening/baseline period), or a treatment-boosted ADA response (a positive ADA response at screening/baseline and an increase in titre in the post screening/baseline period).

Table 21: Summary of anti-drug antibody status - safety analysis set

Study code	Participants (n)	Positive at baseline	Treatment-induced ADA	Treatment-boosted ADA	Transient response
EFC16293	159	11	3	1	4
EFC16295	73	3	0	0	0
LTS16294*					
Arm B	37	3	0	0	0
Arm C	7	0	0	0	0
242HA101	15	0	0	0	0
242HA102	23	0	1	0	0**
PKM17085	13	2	1	0	1

*One participant in the 65 IU/kg cohort was tested positive for ADAs at the Day 50 (EOS) visit, follow-up unclear.
Source: 5.3.5.3 Integrated summary of immunogenicity

Further ADA characterisation in these 5 participants with treatment-emergent ADA showed that samples were positive against XTEN polypeptide in 1 participant, positive against Fc in 1 participant, positive against FVIII and D'D3 in 1 participant. Two participants were negative against all the tested components of BIVV001 (VWF D'D3, FVIII, IgG1 Fc, and XTEN polypeptides).

PK exposure parameters at steady state obtained from popPK post-hoc analysis were compared between the 4 ADA positive participants and ADA negative participants). Results indicate that the profiles of the 4 participants with treatment-emergent ADAs in Study EFC16293 are well within the range of the ADA negative profiles and their PK parameters are comparable to the mean of ADA negative participants.

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

Not Applicable.

2.6.8.9. Discontinuation due to adverse events

In the overall group of the pooled Phase 3 data, 4 (1.4%) participants had TEAEs (all were TESAEs) that resulted in permanent discontinuation of treatment. The TEAEs were deep vein thrombosis (this subject withdrawn from study due to the use of prohibited medication), CD4 lymphocytes decreased, combined tibia-fibula fracture, and femur fracture. All were originally participants in Study EFC16293 in which DVT and femur fracture occurred in study LTS16294.

2.6.8.10. Post marketing experience

Efanesoctocog alfa was approved in the United States on 22 February 2023 for routine prophylaxis, on-demand treatment and control of bleeding episodes, and perioperative management of bleeding in adults and children with haemophilia A. At the time of the data cut-off (17 January 2023), there was no marketing experience.

2.6.9. Discussion on clinical safety

The safety of Altuvoct was evaluated in 7 clinical studies (6 clinical trials in PTPs with haemophilia A and 1 PK Phase 1 trial in subjects with type 2N or 3 von Willebrand disease). Five studies including the pivotal Phase 3 study in adult and adolescent PTPs (EFC16293) and the Phase 3 study in paediatric PTPs (EFC16295 were completed, while 2 studies are still ongoing: a Phase 3 long-term safety study (LTS16294) in all age groups, as well as a Phase 1 study PKM16978 in patients with VWD. A pooled analysis of safety data was provided for the three phase 3 studies EFC16293, EFC16295, LTS16294 after finalisation of the paediatric study. Methods of safety evaluation are considered acceptable.

Exposure

The extent of the clinical development programme of BIVV001 (including ongoing studies) is in principle in accordance with the guideline on clinical investigation of recombinant and human plasma-derived FVIII products (EMA/CHMP/BPWP/144533/2009). However, are based on presented interim data (cut-off date 24 January 2022) complemented with additional safety data (exposure, adverse events, and inhibitor data) with a cut-off date of 30 June 2022, which were provided as part of the 120-Day Safety Update report submitted to the FDA. Pooled Safety Report with a cut-off date of 17 Jan 2023, and completed CSRs for pivotal EFC16293 and EFC16295 were also provided as part of the responses to EMA Day120 LoQ (see also data presented in section 2.6.8).

In the pivotal EFC16293 study, 115 PTPs receiving weekly prophylaxis treatment (50 IU/kg) reached ≥ 50 EDs, with a maximum of 62 EDs, and a mean (SD) number of 51.1 (9.2) injections per participants. Thus, the exposure within the adult and adolescent population fulfils guideline requirements (EMA/CHMP/BPWP/144533/2009 rev. 2).

For study EFC16295, the final report dated 11 May 2023 has been submitted. Of the 74 participants who received at least 1 dose of BIVV001, 66 (89.2%) achieved 50 or more EDs: 31 (81.6%) participants in the <6 years of age cohort and 35 (97.2%) participants in the 6 to <12 years of age cohort. This is in line with the applicable FVIII guideline on recombinant and plasma-derived FVIII products (EMA/CHMP/BPWP/144533/2009).

Only limited information from the long-term safety study LTS16294 was submitted and no (interim) CSR was available for review. Data provided for this study is based on the 30 June 2022 cut off.

AEs

In the adults and adolescents study EFC16923, 123/159 (77.4%) participants experienced a total of 394 TEAEs (358 TEAEs in 108 participants of arm A (prophylaxis) and 33 TEAEs in 20 participants of arm B (on-demand/prophylaxis). TEAEs were most commonly reported in the SOCs of musculoskeletal and connective tissue disorders (56 participants, 35.2%, most common TEAE arthralgia), nervous system disorders (43 participants, 27.0%, most common TEAE headache), injury, poisoning and procedural complications (30 participants, 18.9%, most common TEAE fall), infection and infestations (34 participants, 21.4%, most common TEAE COVID-19), general disorders and administration site conditions (20 participants, 12.6%, most common TEAE fatigue), gastrointestinal disorders (22, 13.8%, most common TEAE toothache), and investigations (18, 11.3%, most common TEAE coagulation factor VIII level increased).

The frequency and nature of TEAEs are consistent with safety data known from other FVIII products and raise no concerns.

No major imbalances were observed when TEAEs were presented by age, BMI, geographic region, race and HIV/HCV status. The incidence of serious TEAEs was low. 15 patients experienced a total of 18 TESAEs (further described below). 18 TEAEs in 8 participants were classified as related to BIVV001 (all arm A). 2 TEAEs in 2 participants resulted in discontinuation of treatment (1 due to the TEAE of CD4 lymphocytes decreased, 1 due to use of another FVIII product in a patient with combined tibia-fibula fracture).

In the paediatric study EFC16295, 62/74 (83.3%) of participants experienced a total of 255 TEAEs (146 TEAEs in 33 children <6, 108 TEAEs in 29 children 6-12 years of age). SARS-CoV-2 test positive and upper respiratory tract infection were most frequently reported. No TEAEs resulting in death or leading to treatment discontinuation were reported.

Across the three study arms of the long-term safety study LTS16294, the following data on AE frequencies were reported: in arm A, 79/176 (44.9%) participants experienced 224 TEAEs and 12 (6.8%) participants experienced 17 TESAEs. In arm B, 18/37 (48.6%) participants experienced 37 TEAEs, 3 (8.1%) participants experienced 6 TESAEs. In arm C, 4/5 participants experienced 165 TEAEs, 1 participant experienced 1 TESAE. 2 participants experienced TEAEs that led to treatment discontinuation in the long-term safety study, both in arm A. They included femur and wrist fractures caused by a fall in one participant and a DVT in another participant.

Related TEAEs

In study EFC16293, there were 18 related TEAEs reported in 8 patients, including events of coagulation factor VIII level increased, CD4 lymphocytes decreased, headache, protein urine present, malaise and injection site dermatitis.

In the paediatric study EFC16295, a total of 5 related TEAEs were reported in 3 participants, all in the <6 years age cohort. Related TEAEs included haematochezia, alanine aminotransferase increased, aspartate aminotransferase increased, coagulation factor VIII level increased (chromogenic assay), and Von Willebrand's factor antigen increased (1 [1.4%] participant, each).

In the long-term safety study LTS16294, a total of 2 participants (1 in arm A, 1 in arm B) experienced TEAEs classified as related to study drug, namely facial paralysis and thromboses.

To identify ADR’s the applicant performed a review of all TEAEs that were included in the pooled safety data across the Phase 3 studies (EFC1693, EFC16295, and LTS16294). TEAEs were selected for further review based on the applicant's knowledge of the product, clinical significance, time to onset, biological plausibility,

and experience with other haemophilia products. Causality assessment was performed for each identified potential ADR using the modified Bradford Hill Criteria. Further, causality assessment provided by the Investigator was considered to review potential ADRs, along with additional factors. In addition, the TEAEs alanine aminotransferase increased, aspartate aminotransferase increased, liver injury, varicella, hyperuricaemia, thrombosis, haematochezia, Von Willebrand's factor antigen increased, coagulation factor VIII level decreased, protein urine present, malaise, and dysphoria, which were judged as related to study treatment by the Investigator, were not considered as ADRs. Difficulties in causality assessment based on, in some instances, limited information and in the absence of a placebo control arm were the reason. Nature of the TEAE, duration, BIVV001 treatment continuation (negative re-challenge), bleeding episodes, concomitant medication and other TEAEs in temporal proximity were considered for additional causality evaluation and/or alternative aetiology identification. This is endorsed. Thus, the current ADRs reflected in section 4.8 of the SmPC are acceptable.

In studies EFC16293 and EFC16295, instances related to study treatment of "coagulation factor VIII level increased" (SOC "Investigations") were reported. No additional safety events of concern were identified in these patients and these cases potentially seem to be a consequence of the FVIII activity overestimation when employing the chromogenic assay, which was demonstrated in the field study addressing laboratory assay variability on the assessment of BIVV001 FVIII activity and in the pharmacokinetic assessment of clinical samples in study EFC16293, where overestimations of 2-3-fold (field study) and 2.5-fold (EFC16293) were observed. This issue has been reflected in the SmPC in section 4.2 and 4.4.

Deaths

Across the clinical programme of Altuvoct, 1 death was reported (cut-off date 17 Jan 2023). A participant in study EFC16293 died of a metastatic pancreas carcinoma. The patient had no relevant medical history for this event and was enrolled in the on-demand treatment arm for 26 weeks. The event was classified as not related to study drug, which is agreed.

Serious TEAEs (TESAE)

In study EFC16293, 15/159 (9.4%) patients experienced a total of 18 TESAEs (16 TESAEs in 13 participants from arm A (prophylaxis) and 2 TESAEs in 2 participants from arm B (on-demand/prophylaxis). Only one of the TESAEs was classified as related to study drug, which was an event of decreased CD4 lymphocytes reported in an elderly patient with a history of HIV infection. BIVV001 treatment was subsequently discontinued on study day 85 and after 13 injections. The event was reported as not recovered.

In the paediatric study EFC16295, 9 (12.2%) participants experienced a total of 10 TESAEs: 5 (13.2%) participants aged <6 years and 4 (11.1%) participants aged 6 to <12 years. The majority of TESAEs were assessed by the Investigator as mild to moderate in severity. All TESAEs were evaluated as not related to IMP.

From the long-term safety study LTS16294, the following information on TESAEs were reported at the cut-off date: in arm A, 12/176 (6.8%) participants experienced a total of 17 TESAEs. In arm B, 3/37 (8.1%) participants experienced a total of 6 TESAEs. In arm C. one participant experienced 1 TESAE.. One of the TESAEs was an event of cerebral infarction classified as not related to study drug. Dose was not changed and the outcome was reported as recovered. The participant was later discontinued due to use of anticoagulation.

TEAESIs

Among the most concerning safety events upon factor VIII replacement therapy are inhibitors, anaphylactic reactions, and thrombotic/embolic events. These were defined as AESIs.

Allergic reactions (grade 3 or higher) and anaphylactic reactions

No allergic reactions grade 3 or greater or anaphylaxis in association with study treatment were reported for study EFC16293 and at the cut-off date of study LTS16294.

In study EFC16295, one case of urticaria ("hives around eyes, mouth, face, and chest") classified as TEAESI was evaluated as a non-related event in a young child. The event occurred 3 months after the first Altuvoct dose (weekly prophylaxis) and 3 days after the last injection. The event was marked as resolved on the same day, dose was not changed, and there was no report of recurrence.

In addition, the applicant performed a review of TEAE in study EFC16293, which were potentially consistent with allergic reactions. This strategy is in principle endorsed as allergic and hypersensitivity reactions pose significant safety information for FVIII replacement therapy. Following medical review of identified events, infections and disease-related events were excluded. The remaining 38 events were considered potentially consistent with allergic /hypersensitivity reactions and were selected for detailed review. Two PTs (seasonal allergy and eczema) were reported by more than 2% of participants. Based on the detailed assessment, events of eczema, rash/rash papular, and urticaria/urticaria papular were identified as ADRs and considered in section 4.8 of the SmPC.

Embolic or thrombotic events

As of the cut-off date of 17 Jan 2023, a total of 5 embolic or thrombotic events in 3 participants were reported across the clinical programme of Altuvoct, all from the long-term safety study LTS16294.

In arm A (roll-over arm), one event of deep vein thrombosis and one event of cerebral infarction were reported. An adult patient experienced a lower extremity deep vein thrombosis correlated to a fall, classified by investigator and sponsor as not related to study drug due to the existence of a risk factor (femur fracture and surgery). No FVIII activity levels above ULN were detected. The participant was treated with prohibited medications (NovoEight and Lovenox) and was therefore subsequently withdrawn from the study. The deep vein thrombosis has probably been caused by the bone fracture followed by surgery and immobilisation as well as the administration of another rFVIII product rather than by efanesoctocog alfa which has been administered a week before.

The second case involved an elderly patient with a medical history of chronic atrial fibrillation, dyslipidaemia and HIV infection, who experienced a cerebral infarction which was treated with a thrombectomy and low molecular weight heparin, which was changed to dabigatran two days later. Treatment with BIVV001 was subsequently discontinued due to use of anticoagulation medication. Since cerebral infarction developed after efanesoctocog alfa administration the day before. A contribution of efanesoctocog alfa to the possibly multifactorial genesis cannot completely ruled out. Factor VIII activity level of approximate 90% was measured in a local laboratory.

In arm B, three thrombosis events were reported in a teenager with a medical history of haemangioma. It is acknowledged that the thromboses of the adolescent were finally assessed as not related to efanesoctocog alfa as they were associated to a pre-existing risk factor for thrombosis, i.e., haemangioma/venous malformation, (thrombosis is a frequent complication in venous malformations as these are low-flow vascular anomalies with blood stasis and localised intravascular coagulopathy malformation), and the events were already developing prior to first efanesoctocog alfa administration. The newly received information further supports the company's original causality assessment. Ultimately, the participant was withdrawn from the study when historic inhibitor data (prior to enrolment in the long-term safety study LTS16294) were discovered. No FVIII activity levels (one-stage assay) were detected above the ULN.

Thus, there were three subjects, who developed thromboembolic events during the extension study. All of them demonstrated pre-existing risk factors. Serious vascular thromboembolic event is identified as an important potential risk for efanesoctocog alfa treatment and is included in the Summary of safety concerns in the EU RM.

Clinical laboratory and vital signs

Overall, no concerns arise from laboratory findings (haematology, clinical chemistry and van Willebrand panel) and vital signs in study EFC16293 and EFC16295. But, in the Phase 1/2a studies 242HA101 and 242HA102 abnormalities of coagulation markers i.e. Dimer, TAT complex, and prothrombin fragment 1+2 have been detected. This issue has not been pursued in the following studies.

No data on vital signs were available for study LTS16294.

Immunogenicity

Inhibitor testing was carried out according to GL requirements (EMA/CHMP/BPWP/144533/2009 rev. 2).

None of the PTPs exposed to BIVV001 developed an inhibitory antibody to FVIII of ≥ 0.6 BU/mL across all studies in the clinical programme.

Overall, 6 patients developed treatment-emergent ADAs. This concerned 4 patients, all enrolled in arm B (on-demand treatment) of the pivotal Phase 3 EFC16923 study, and 1 patient each in studies PKM17085 and 242HA102. The occurrence of ADAs was transient, except for one patient enrolled in study 242HA102, which displayed a positive ADA result only at EOS and for which follow-up data is not known. Based on available data, there was no obvious impact of ADAs on the FVIII activity, bleeding episodes, or safety.

The overall immunogenicity in previously-treated adults and adolescents appears low. However, given that the clinical relevance of ADA development is not known and that BIVV001 contains domains with limited clinical experience (e.g. XTEN polypeptide), brief information on ADA emergence across the clinical programme is provided in section 5.1 of the SmPC.

Special populations

No data on previously untreated patients (PUPs) are available. Currently, use in PUPs is reported as missing information in the presented RMP and the safety profile in PUPs will be monitored post-approval through an observational study and a disease registry. This is acceptable and in line with the FVIII GL (EMA/CHMP/BPWP/144533/2009 rev. 2).

There are no specific guideline recommendations concerning the elderly population, but the inclusion of elderly patients is endorsed as the elderly haemophilic population is of increasing importance, which may display additional age-related co-morbidities such as an increased risk for thrombotic and embolic events. Study EFC16293 enrolled 5 subjects with ≥65 years of age. While the subgroup is too small to deduce in a meaningful way whether their safety profile is different from other patients, existing data do not raise specific concerns.

Additional long-term data will be collected in three category 3 trials. The study on long-term safety and efficacy of Altuvoct 1 in PTP with Haemophilia A (LTS16294) is ongoing. A study in PUPs and participation in the European Haemophilia Safety Surveillance System (EUHASS) registry are planned. All these studies will address open issues regarding immunogenicity and thrombogenicity of Altuvoct.

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

2.6.10. Conclusions on the clinical safety

Clinical safety has been analysed from the data of seven clinical studies. The presented results are considered acceptable. No unexpected patterns in the reported adverse events and serious adverse events were observed. TESAE of thromboembolic events were reported in three patients with pre-existing risk factors. None of the TESAEs and no death were judged as being Altuvoct-related. There were no serious anaphylactic or allergic reactions and no inhibitor development.

The safety profile of BIVV001 is generally considered to be in line with other FVIII products. Quality and quantity of detected AEs in the study population do not give rise to concerns.

2.7. Risk Management Plan

2.7.1. Safety concerns

Table 22: Summary of safety concerns

Summary of safety concerns	
Important identified risks	Inhibitor development to FVIII
Important potential risks	Serious vascular thromboembolic events
Missing information	Use in previously untreated patients Long term use Safety in elderly patients ≥ 65 years of age

2.7.2. Pharmacovigilance plan

Table 23: On-going and planned additional pharmacovigilance activities

Status	Summary of objectives	Safety concerns addressed	Milestones	Due dates
Category 3 – Required additional pharmacovigilance activities				
Long-term safety and efficacy of BIVV001 in previously treated patients with Hemophilia A (LTS16294) Ongoing	To determine the long-term safety and efficacy of BIVV001 administered as once-weekly prophylaxis treatment in previously treated patients with severe hemophilia A. The primary objective is to evaluate the long-term safety of BIVV001 as indicated by the occurrence of inhibitor development. Secondary objectives include further evaluation of long-term safety as well as long term efficacy of BIVV001.	Inhibitor development to FVIII Serious vascular thromboembolic events Long term use Safety in Elderly ≥65 years old	Final study report	Data will be reviewed on an ongoing basis as part of signal detection and reported within PSURs. Final study report is expected Q2 2027
Observational Registry Study in Previously Untreated Patients (PUPs) with Hemophilia A (ATHN) Planned	A collaborative study with American Thrombosis and Hemostasis Network (ATHN). To evaluate the safety profile of efanesoctocog alfa in previously untreated patients (PUPs). The primary objective is to describe safety and tolerability in PUPs treated with efanesoctocog alfa. The primary endpoints are inhibitor development to FVIII as measured by the Nijmegen modified Bethesda assay and the occurrence of adverse events of special interest.	Inhibitor development to FVIII Serious vascular thromboembolic events Use in previously untreated patients	Final study report	Data will be reviewed on an ongoing basis as part of signal detection and reported within PSURs when available. Study started in Feb 2024. An interim analysis is expected in Q1 2027. Final study report is expected in Q1 2029.

Status	Summary of objectives	Safety concerns addressed	Milestones	Due dates
Additional PV activity				
PedNet Hemophilia Registry Planned	The general objective is to evaluate safety of efanesoctocog alfa by reviewing data collected prospectively following birth cohorts of unselected previously untreated children with Hemophilia A.	Inhibitor development to FVIII Serious vascular thromboembolic events Use in previously untreated patients	Annual report	Data will be reviewed on an ongoing basis as part of signal detection. Annual reports will be reviewed and reported within PSURs.
EUHASS Registry Planned	To evaluate safety (Adverse events reported during surveillance) of efanesoctocog alfa in patients with hemophilia A under observational ('real world') conditions of routine clinical care.	Inhibitor development to FVIII Serious vascular thromboembolic events	Quarterly and annually	Data will be reviewed on an ongoing basis as part of signal detection. Quarterly and annual reports will be reviewed and reported within PSURs.

2.7.3. Risk minimisation measures

Safety concern	Risk minimization measures	Pharmacovigilance activities
Inhibitor development to FVIII	**Routine risk minimization measures:** SmPC 4.8: Information about the risk of inhibitor development in patients with hemophilia A treated with factor VIII, including with efanesoctocog alfa. SmPC section 4.4: Recommendation for monitoring all patients for the development of FVIII inhibitors by appropriate clinical observations and laboratory tests and performing appropriate testing if the patient's plasma FVIII level fails to increase as expected or if bleeding is not controlled after efanesoctocog alfa administration. PL section 2.0: Information on how to detect early signs of inhibitor development. **Other routine risk minimization measures beyond the Product Information:** None **Pack size:** None **Legal status:** Prescription only medicine.	**Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection:** Specific adverse drug reaction follow-up questionnaire. **Additional pharmacovigilance activities:** Long-term safety and efficacy of efanesoctocog alfa in previously treated patients with Hemophilia A (LTS16294) Observational Registry Study in Previously Untreated Patients (PUPs) with Hemophilia A (ATHN). European Hemophilia Safety Surveillance System (EUHASS) participation and data collection. The PedNet Hemophilia Registry Data collection in Previously Untreated Patients (PUPs)

Safety concern	Risk minimization measures	Pharmacovigilance activities
Serious vascular thromboembolic events	**Routine risk minimization measures:** SmPC section 4.4: Information about risk of cardiovascular events in patient with existing cardiovascular risk factors and risk of catheter-related complications, including catheter site thrombosis. PL section 2.0: Information about risk of catheter-related complications, including catheter site thrombosis. **Other routine risk minimization measures beyond the Product Information:** None. **Pack size:** None. **Legal status:** Prescription only medicine.	**Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection:** Specific adverse drug reaction follow-up questionnaire. **Additional pharmacovigilance activities:** Long-term safety and efficacy of efanesoctocog alfa in previously treated patients with Hemophilia A (LTS16294) Observational Registry Study in Previously Untreated Patients (PUPs) with Hemophilia A (ATHN). The PedNet Hemophilia Registry Data collection in PUPs. European Hemophilia Safety Surveillance System (EUHASS) participation and data collection.
Safety in previously untreated patients	**Routine risk minimization measures:** SmPC section 4.4: Recommendation for monitoring all patients for the development of FVIII inhibitors by appropriate clinical observations and laboratory tests and performing appropriate testing if the patient's plasma FVIII level fails to increase as expected or if bleeding is not controlled after efanesoctocog alfa administration. PL section 2.0: Information how to detect early signs and symptoms of inhibitor development. **Other routine risk minimization measures beyond the Product Information:** None. **Pack size:** None. **Legal status:** Prescription only medicine.	**Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection:** None **Additional pharmacovigilance activities:** Observational Registry Study in Previously Untreated Patients (PUPs) with Hemophilia A (ATHN). The PedNet Registry Data collection in PUPs.

Safety concern	Risk minimization measures	Pharmacovigilance activities
Long term use	**Routine risk minimization measures:** SmPC section 5.1: The long-term safety and efficacy of ALTUVOCT is also being evaluated in a long-term extension study. **Other routine risk minimization measures beyond the Product Information:** None. **Pack size:** None. **Legal status:** Prescription only medicine.	**Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection:** None **Additional pharmacovigilance activities:** Long-term safety and efficacy efanesoctocog alfa in previously treated patients with Hemophilia A (LTS16294)
Safety in elderly patients ≥ 65 years of age	**Routine risk minimization measures:** SmPC section 4.2: There is limited experience in patients ≥ 65 years. The dosing recommendations are the same as for patients < 65 years. **Other routine risk minimization measures beyond the Product Information:** None. **Pack size:** None. **Legal status:** Prescription only medicine.	**Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection:** None **Additional pharmacovigilance activities:** Long-term safety and efficacy of efanesoctocog alfa in previously treated patients with Hemophilia A (LTS16294)

2.7.4. Conclusion

The CHMP considers that the risk management plan version 1.0 is acceptable.

2.8. Pharmacovigilance

2.8.1. Pharmacovigilance system

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

2.8.2. Periodic Safety Update Reports submission requirements

The requirements for submission of periodic safety update reports for this medicinal product are set out in the Annex II, Section C of the CHMP Opinion. The applicant did request alignment of the PSUR cycle with the international birth date (IBD). The IBD is 22 February 2023. The new EURD list entry will therefore use the IBD to determine the forthcoming Data Lock Points.

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.*

2.9.2. Additional monitoring

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

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

3. Benefit-Risk Balance

3.1. Therapeutic Context

3.1.1. Disease or condition

Haemophilia A is a rare, congenital, X-linked coagulation disorder defined by a deficiency of coagulation FVIII activity, resulting in recurrent spontaneous and traumatic bleeding into the soft tissue and joints, leading to haemophilic arthropathy, muscle contractures, and significant disability. Central nervous system (CNS) bleeding is a severe complication and intracranial haemorrhage (ICH) is one of the leading causes of death from bleeding in haemophilia A, with a 20% mortality rate (Witmer *et al.* 2011). In severe haemophilia, however, joint bleeding is the most frequent bleeding manifestation in children and adults (Bolton-Maggs *et al.* 2003, Berntorp *et al.* 2021).

The agreed indication for Altuvoct is the following: treatment and prophylaxis of bleeding in patients with haemophilia A (congenital factor VIII deficiency). Altuvoct can be used for all age groups.

3.1.2. Available therapies and unmet medical need

The World Federation of Haemophilia (WFH) and the Medical and Scientific Advisory Committee (MASAC) of the National Haemophilia Foundation both recommend prevention of bleeding using prophylaxis, which is preferred over on-demand treatment because it prevents bleeding and mitigates joint disease (Srivastava *et al.* 2020, MASAC 2022a).

Conventional SHL FVIII replacement therapies for haemophilia A have a half-life of approximately 11 to 14 hours, making prophylactic treatment a demanding procedure requiring I.V. injections every other day to 2 to 3 times per week. Even with currently available EHL FVIII products, injections every 3 to 5 days are needed. Despite the known benefits of prophylactic treatment, the intensive treatment regimen is an important obstacle to the adoption of prophylactic treatment in a significant proportion of the haemophilia population, and it is also associated with decreased compliance with treatment for those undertaking prophylaxis (Thornburg *et al.* 2017, Zanon *et al.* 2020). Although the WFH guidelines have recently been updated to include that trough levels of >3% to 5% or higher are preferred (Srivastava *et al.* 2020), even these trough levels are not adequate to protect patients from all bleeds and the resulting morbidity (e.g., joint damage) associated with such bleeding episodes, especially in the joints (Soucie *et al.* 2018, De la Corte-Rodriguez *et al.* 2022).

Non-factor replacement therapy with emicizumab, a bispecific factor IXa- and X-directed antibody is also available as a subcutaneous prophylaxis treatment option. However, breakthrough bleeds are still possible and will likely result in the need for concomitant use of factor replacement therapy in patients without FVIII inhibitors (MASAC 2022b).

Another treatment option is gene therapy: Valoctocogene roxaparvovec, an adeno-associated viral serotype 5 (AAV5) vector containing a B-domain-deleted variant of human FVIII, has the potential to provide sustained FVIII activity levels and recently received conditional approval in the EU. This therapy is restricted to adult patients with severe Haemophilia A who have a negative history of FVIII inhibitors and no detectable antibodies to AAV5, are without pre-existing liver disease and require contraceptive measures.

3.1.3. Main clinical studies

The pivotal Phase 3 study enrolled 159 adult and adolescent PTPs with severe haemophilia A from 51 sites in 19 countries/regions across Europe, North and South America, and Asia/Pacific. One hundred and fifteen (115) study participants (72.3%) were exposed to Altuvoct for at least 50 EDs. Of the 149 participants who completed Study EFC16293, 123 enrolled in the ongoing extension Study LTS16294. Extensive PK assessment was performed, with sampling conducted on all participants.

The paediatric Study EFC16295, in which 66 (89.2%) of the 74 enrolled participants achieved 50 or more EDs to Altuvoct, provides PK, efficacy, and safety data in children <12 years of age, including 31 (81.6%) participants in the <6 years of age cohort and 35 (97.2%) participants in the 6 to <12 years of age cohort.

Surgical data collected across the 3 Phase 3 studies in 41 subjects who underwent 49 major surgeries evaluated the efficacy of BIVV001 in achieving and maintaining haemostasis during and after surgery.

Data to support the long-term efficacy and safety of BIVV001 will be obtained in ongoing Study LTS16294. In addition, data in PUPs exposed to BIVV001 will be collected post-approval.

3.2. Favourable effects

The efficacy of Altuvoct was evaluated in pivotal Study EFC16293. Weekly prophylaxis with 50 IU/kg Altuvoct reduced the frequency of bleeding episodes demonstrated by a mean ABR of 0.71 (95% CI: 0.52 to 0.97). This prophylactic treatment with Altuvoct also provided superior prevention against bleeds over pre-study FVIII prophylaxis, as was demonstrated in an intra-patient comparison of ABR during Altuvoct prophylaxis versus historical FVIII prophylaxis (ABR rate ratio: 0.23 [95% CI: 0.13 to 0.42], p-value <0.0001), reducing the ABR by 77%.

The efficacy of Altuvoct as on-demand treatment for the control of bleeding episodes was also demonstrated. Most bleeds were controlled by a single injection of BIVV001 50 IU/kg and the haemostatic efficacy was rated as excellent or good in 94.9% of first injections.

Altuvoct was effective in the perioperative management of bleeding with a haemostatic response rated as excellent by the Investigators/Surgeons in all of the major surgeries and the preoperative dose was sufficient to maintain homeostasis in all participants during surgery. The procedures included molar tooth extractions but also several orthopaedic surgeries such as knee, hip, or elbow arthroplasty and rhinoplasty/mentoplasty.

Efficacy data from the paediatric Study EFC16295 showed that Altuvoct 50 IU/kg IV was effective as weekly prophylaxis. Once-weekly routine prophylaxis with Altuvoct resulted in an overall estimated mean ABR of 0.89 (95% CI: 0.56 to 1.42) in study participants with an efficacy period (n = 74), with similarly low ABRs in both age cohorts (0.48 [95% CI: 0.30; 0.77) and 1.33 [95% CI: 0.64; 2.76], respectively). Across the 2 age cohorts, 95.3% of 43 bleeding episodes treated with Altuvoct were controlled with a single injection and the majority (97.3%) of the evaluated bleeding episodes (37/43) had an excellent or good response.

Altuvoct has a prolonged half-life (children <6 years of age: 39.9 hours, children 6 to <12 years of age: 42.4 hours, adolescents 12 to <18 years of age: 44.6 hours, adults: 48.2 hours; based on data following administration of a single dose). Accordingly, Altuvoct showed high sustained FVIII activity: a 50 IU/kg dose of BIVV001 maintained mean FVIII levels in the normal to near-normal range (>40 IU/dL) for 4 days with mean FVIII activity above 10 IU/dL at end of the weekly dosing interval in adults and adolescents.

3.3. Uncertainties and limitations about favourable effects

The efficacy data do not derive from a randomised, controlled clinical trial. However, the design of the clinical studies is seen in the context of the rarity of the targeted disease, that follows EMA scientific advice and complies with the requirements laid down in the EMA guideline on the clinical investigation of recombinant and human plasma-derived factor VIII products (EMA/CHMP/BPWP/144533/2009 rev 2).

The presented analyses of the primary and key secondary EPs exclude periods with large dosing intervals, surgical/rehabilitation periods and time periods from prohibited concomitant therapy. As requested, the applicant demonstrated that including PK sampling periods, surgical/rehabilitation periods and gap periods due to large injection intervals in the analyses of the primary and key secondary endpoints gives very similar results as the original analyses.

Time periods after prohibited concomitant medication have not been included into the analysis based on the treatment policy strategy, possibly using multiple imputation. But only little change in the results is expected considering the ABRs for patients with incomplete efficacy period.

The severity of bleeds was not documented in the phase 3 studies due to the possible inter-individual and intra-individual variability associated with such a subjective judgment. However, the relevant guideline (EMA/CHMP/BPWP/144533/2009 rev. 2) describes the physician's assessment of response in treatment of major bleeds as a parameter which should be studied pre-authorisation. Considering the overall efficacy data and the fact that a single dose was sufficient for treatment of most breakthrough bleeds, there seems to be no reason to assume why BIVV001 would be less efficacious in treatment of severe/major bleeds than comparable FVIII products.

With regards to the performed intra-patient comparison of ABR in Arm A, historical bleeding data (from pre-study PPX) were collected in an observational study as real-world use of prescribed marketed FVIII products. Data show a high variability with regards to used FVIII products (SHL or EHL), dosage, dose interval, concomitant treatment, reporting of bleeding events and other factors. The additional provided information illustrates that participants who rolled over from OBS16221 had lower bleeding rates and fewer target joints at baseline than the overall population in arm A. Nevertheless, the pre-study was prospective.

The investigated number of elderly patients was low.

Throughout the clinical studies, Altuvoct was dosed based on its 1-stage FVIII activity. Importantly, Altuvoct was found to have a >2-fold lower specific FVIII activity when measured by the aPTT-based 1-stage clotting assay compared to the 2-stage chromogenic assay. A roughly 2.5-fold difference in FVIII activity is not only observed between different assays (OSC vs. CS), but also between different reagents used for the OSC assay (Actin FSL vs. Actin FS). This has been addressed in section 4.2 and 4.4 in the SmPC.

Efficacy rating of Altuvoct injection to treat bleeding events according to a 4-point scale has a subjective component.

3.4. Unfavourable effects

Across the 3 Phase 3 clinical studies (EFC16293, EFC16295, and LTS16294) a total of 277unique participants received at least one dose of BIVV001 50 IU/k

The safety database provided for patients ≥12 years of age and < 12 years of age is in line with guidance. In the pivotal EFC16293 study, 115 PTPs receiving weekly prophylaxis treatment (50 IU/kg) reached ≥ 50 EDs, with a maximum of 62 EDs, and a mean (SD) number of 51.1 (9.2) injections per participants.

TEAEs were most commonly reported in the SOCs of musculoskeletal and connective tissue disorders (56 participants, 35.2%), nervous system disorders (43 participants, 27.0%), injury, poisoning and procedural complications (30 participants, 18.9%), infection and infestations (34 participants, 21.4%), general disorders and administration site conditions (20 participants, 12.6%), gastrointestinal disorders (22, 13.8%), and investigations (18, 11.3%). The safety profile of Altuvoct in patients >12 years old is generally considered to be comparable to other FVIII products.

As of the cut-off date (17 January 2023), none of the PTP exposed to Altuvoct developed an inhibitory antibody to FVIII of ≥ 0.6 BU/mL across all studies in the clinical programme.

The overall immunogenicity in previously treated adults and adolescents appears low. Overall, 6 patients developed treatment-emergent ADAs (4 in study EFC16293, 1 in study PKM17085, 1 in study 242HA102). The occurrence of ADAs was transient, except for one patient enrolled in study 242HA102, which displayed a positive ADA result only at EOS and for which follow-up data is not known. No clinical concern regarding safety events were observed.

No death related to study drug was reported throughout the clinical programme of Altuvoct and frequency of related SAEs was low (1 related TESAE of decreased CD4 lymphocytes was reported in study EFC16293, 1 related TESAE of cerebral infarction in study EFC16295 was temporarily classified as related, but ultimately changed to unrelated).

Many participants i.e. 109 adults/adolescents and 38 children had periods with FVIII activity >150 IU/dL at any time in studies 16293 and 16295. Most of these adults and adolescents had more than 1 measurement of elevated FVIII activity. Very high FVIII levels (>200 IU/dL) were also observed in some cases. . There is an uncertainty regarding safety of transient FVIII levels above 150 IU/dL, especially in real life the increased FVIII levels, even if transient, may pose a thromboembolic risk for patients with higher age and cardiovascular disease. Treatment monitoring and dose adjustment may be required (please see RMP).

In study LTS16294, a total of 5 events of vascular thrombosis were reported in 3 participants with pre-existing risk factors for thrombotic events. There was one case of femur fracture with deep vein thrombosis, one subject with cerebral infarction and one subject with haemangioma with three thrombotic events. These events were classified as not related to study drug by the applicant.

3.5. Uncertainties and limitations about unfavourable effects

The safety database, while in line with guidance, is small and rare safety events are therefore likely not detected. Given that only limited clinical experience with the new half-life extending FVIII modifications (e.g. XTEN) is currently available, this poses an uncertainty.

Inhibitor development to FVIII was not detected. Since PTPs rarely develop inhibitors, the available data base might be too small. There are no data in previously untreated patients (PUPs) available.

The reported frequency of related TEAEs seems surprisingly low. TEAEs were selected for further review based on the applicant's knowledge of the product, clinical significance, time to onset, biological plausibility, and experience with other haemophilia products. Causality assessment was performed for each identified potential ADR using the modified Bradford Hill Criteria along with additional factors. Difficulties in causality

assessment based on, in some instances, limited information and in the absence of a placebo control arm were the reason. Nature of the TEAE, duration, BIVV001 treatment continuation (negative re-challenge), bleeding episodes, concomitant medication and other TEAEs in temporal proximity were considered for additional causality evaluation and/or alternative aetiology identification.

There were no reports of serious allergic reactions or anaphylaxis. Allergic reactions are a common pharmacological class effect. The applicant specifically looked for AEs potentially consistent with allergic reactions in study EFC16293. Following medical review of identified events, infections and disease-related events were excluded. The remaining 38 events were considered potentially consistent with allergic /hypersensitivity reactions and were selected for detailed review. Two PTs (seasonal allergy and eczema) were reported by more than 2% of participants. Based on the detailed assessment, events of eczema, rash/rash papular, and urticaria/urticaria papular were identified as ADRs.

In the extension study, 3 patients developed thromboembolic events. All of them demonstrated pre-existing risk factors such as fracture, haemangioma, atrial fibrillation. No direct association to Altuvoct treatment could be made in all three cases regarding Altuvoct injection, the level of FVIII activity and the occurrence of event.

Additional long-term data are needed and will be collected in three category 3 trials. The study on long-term safety and efficacy of Altuvoct in PTP with Haemophilia A (LTS16294) is ongoing. A study in PUPs and participation in the European Haemophilia Safety Surveillance System (EUHASS) registry are planned. All these studies should address open uncertainties regarding immunogenicity and thrombogenicity of Altuvoct (please refer to the RMP).

3.6. Effects Table

Table 24: Effects Table for Altuvoct (data cut-off: 30 June 2022)

Effect	Short Description	Unit	Treatment	Control	Uncertainties/ Strength of evidence	References
Favourable Effects						
ABR	Efficacy of Altuvoct 50 IU/kg weekly prophylaxis as estimated by mean ABR and CI in Arm A	n=133	0.71 (0.52;0.97)	/	Based on negative binominal regression model	CSR EFC16293

Effect	Short Description	Unit	Treatment	Control	Uncertainties/ Strength of evidence	References
Intra-ABR Arm A	Intra-participant comparison of ABR between Altuvoct 50 IU/kg weekly prophylaxis and historical prophylaxis in Arm A by mean difference (95% CI)	n=77	- 2.30 (-3.49; -1.11)	/	Negative Binomial regression model p-value (superiority) < 0.0001 Pre-study OBS16221 = observational study of real world use of prescribed marketed FVIII products	CSR EFC16293 CSR (OBS16221)
Intra-ABR Arm B	Intra-participant comparison of ABR between on-demand and prophylaxis in Arm B by rate ratio	n=26	0.03 (0.02; 0.07)	/	Rate ratio (95% CI)	CSR EFC16293
Unfavourable Effects						
Thrombosis	Safety analysis of Phase 3 studies	N=275	N=3	/	Pre-existing risk factors	LTS16294

Abbreviations: ABR = annual bleeding rate, CSR = clinical study report

3.7. Benefit-risk assessment and discussion

3.7.1. Importance of favourable and unfavourable effects

Patients suffering from severe haemophilia A usually receive prophylactic treatment with FVIII products, which requires regular infusion every 2 to 3 days. Another option for bleeding prophylaxis is the subcutaneous administration of Hemlibra, which needs to be given once a week to once every four weeks.

The prolonged half-life of Altuvoct allows an extended dosing interval of 7 days, which will to some extent decrease the burden of the regular prophylactic infusion for patients with severe haemophilia A, compared to the currently available extended half-life products. The compliance during the pivotal phase 3 study was very high. It is considered likely that the necessity of less frequent administrations could also increase the treatment compliance outside the scenario of a clinical trial.

The FVIII activity levels at the end of the once-weekly dosing interval remained at clinically relevant levels. Even if a considerable variability in individual PK characteristics and bleeding tendency is taken into account,

it seems likely that the vast majority of patients with severe haemophilia A will benefit from a weekly infusion of Altuvoct. Nevertheless, treatment monitoring and dose adjustment may be required in certain cases.

The supportive value of the early phase 1/2 a studies is limited as comparability of material derived from different process versions could not be unequivocally concluded. Considering that PK data are available from the phase 3 studies, this uncertainty is considered negligible. In addition, comparability between clinical trial material and commercial material is supported by analytical and non-clinical data.

The favourable impact of prophylaxis with Altuvoct on the bleeding frequency was evident in the pivotal trial (EFC16293) in adults and adolescents. The most important efficacy results derive from the primary endpoint defined as ABR and the key secondary endpoint defined as intra-patient comparison of ABR. Both endpoints significantly demonstrated efficacy of Altuvoct prophylaxis with 50 IU/kg once weekly. The comparison of ABR between on-demand treatment and sequential prophylaxis in Arm B delivers expected advantage of prophylaxis over on-demand treatment, but also provides valuable efficacy data. These analyses are supported by the efficacy assessment of treatment of bleeding episodes and efficacy data in major surgery. Of patients who experienced breakthrough bleeds, one infusion of Altuvoct was sufficient for successful treatment in most of the cases, which may further improve the treatment management for haemophilia A patients.

Transient FVIII activity >150 IU/dL were observed in many participants at any time in Studies 16293 and 16295. Most of these adults and adolescents had more than 1 measurement of elevated FVIII activity. Very high FVIII levels (>200 IU/dL) were also observed in some cases. Available safety analysis of FVIII activity >150 IU/dL at baseline did not reveal thrombotic events in any of these participants and there were no reported AEs that could be considered attributable to an elevated FVIII level.

The safety profile of BIVV001 is generally considered to be in line with other FVIII products and quality and quantity of detected AEs in the study population do not give rise to major concerns. Due to the mechanism of action of Altuvoct, and of factor VIII products in general, there may be a risk of developing thromboembolic events. The impact of the extended half-life on this potential risk is unknown. Although no inhibitory antibodies were detected so far, inhibitor development is another important potential risk which is reflected in section 4.4 of the SmPC.

The safety profile did not show unexpected patterns in the reported adverse events and serious adverse events. None of the TESAEs leading to death was judged as being Altuvoct related. There were no severe anaphylactic or allergic reactions and no inhibitor development. However, TESAEs of thromboembolic events were reported in three patients (3/275) and are regarded as important safety risks in the risk management plan.

The safety database, while in line with guidance, is small and potential rare safety events were unlikely detected. The limited experience with the new half-life extending modifications (XTEN polypeptides, the FVIII-binding D'D3 domain of human von Willebrand factor) represents another uncertainty. Long-term safety will be investigated as an additional pharmacovigilance activity with study LTS16294 and in registries (please see RMP).

Overall, the described favourable effects are considered of importance for the immediate and long-term health and well-being of patients with severe haemophilia A.

3.7.2. Balance of benefits and risks

In adults and adolescents (≥12 years of age), Altuvoct prophylaxis demonstrated a significantly low ABR, that was reduced in comparison to other rFVIII products, for a prolonged dosing regimen of once weekly. Efficient treatment of bleeding events and excellent haemostatic response during perioperative management have been shown. Similar efficacy was shown in the paediatric population (<12 years of age). The extended half-life of Altuvoct allows a once-weekly administration of prophylactic FVIII replacement in patients with severe haemophilia A patients and represents an important benefit. This may also positively impact treatment compliance in some patients. There were no important safety concerns across studies, but uncertainties posed by the small safety database (rare adverse events were not detectable due to the sample size), a theoretical risk of inhibitor development, and a potentially increased risk for thromboembolic events due to its mechanism of action and the unknown impact of the extended half-life. This will be investigated in the post-marketing study LTS16294 as well as in registries (please see RMP).

Overall, the balance of benefits and risks is considered positive.

3.7.3. Additional considerations on the benefit-risk balance

Not applicable.

3.8. Conclusions

The overall benefit/risk balance of Altuvoct is positive.

4. Recommendations

Similarity with authorised orphan medicinal products

The CHMP by consensus is of the opinion that Altuvoct is not similar to Roctavian within the meaning of Article 3 of Commission Regulation (EC) No. 847/2000. See Appendix on Similarity.

Outcome

Based on the CHMP review of data on quality, safety and efficacy, the CHMP considers by consensus that the benefit-risk balance of Altuvoct is favourable in the following indication:

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

The CHMP therefore recommends the granting of the marketing authorisation subject to the following conditions:

Conditions or restrictions regarding supply and use

Medicinal product subject to medical prescription.

Other conditions and requirements of the marketing authorisation

- **Periodic Safety Update Reports**

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

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

- **Risk Management Plan (RMP)**

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

An updated RMP should be submitted:

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

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

Not applicable.

New Active Substance Status

Based on the CHMP review of the available data, the CHMP considers that Efanesoctocog alfa is to be qualified as a new active substance in itself as it is not a constituent of a medicinal product previously authorised within the European Union.

Paediatric Data

Furthermore, the CHMP reviewed the available paediatric data of studies subject to the agreed Paediatric Investigation Plan P/0382/2022 and the results of these studies are reflected in the Summary of Product Characteristics (SmPC) and, as appropriate, the Package Leaflet.