Medicines & Healthcare products Regulatory Agency

Public Assessment Report

National Procedure

Altuvoct 250 IU powder and solvent for solution for injection
Altuvoct 500 IU powder and solvent for solution for injection
Altuvoct 750 IU powder and solvent for solution for injection
Altuvoct 1000 IU powder and solvent for solution for injection
Altuvoct 2000 IU powder and solvent for solution for injection
Altuvoct 3000 IU powder and solvent for solution for injection
Altuvoct 4000 IU powder and solvent for solution for injection

efanesoctocog alfa (BIVV001)

PLGB 30941/0024-0030

Swedish Orphan Biovitrum AB (publ)

LAY SUMMARY

Altuvoct 250, 500, 750, 1000, 2000, 3000 & 4000 IU powder and solvent for solution for injection
efanesoctocog alfa (BIVV001)

This is a summary of the Public Assessment Report (PAR) for Altuvoct 250, 500, 750, 1000, 2000, 3000 & 4000 IU powder and solvent for solution for injection. It explains how these products were assessed and their authorisation recommended, as well as their conditions of use. It is not intended to provide practical advice on how to use these products.

These products will be referred to as Altuvoct in this lay summary for ease of reading.

These applications were approved under International Recognition procedure (IRP). The Reference Regulator (RR) was the European Medicines Agency (EMA), with the procedure number EMEA/H/C/005968. The procedure followed route B.

These applications were approved under Regulation 50 of the Human Medicines Regulation 2012, as amended (previously Article 8.3 of Directive 2001/83/EC, as amended).

For practical information about using Altuvoct, patients should read the Patient Information Leaflet (PIL) or contact their doctor or pharmacist.

What is Altuvoct and what is it used for?
These applications are full-dossier applications. This means that the results of pharmaceutical, non-clinical and clinical tests have been submitted to show that this medicine is suitable for treating the specified indications.

Altuvoct is used to treat and prevent bleeding in patients 2 years and above with severe or moderate haemophilia A (the factor VIII blood level is 5% or less).

How does Altuvoct work?
Altuvoct contains the active substance efanesoctocog alfa, a replacement factor VIII protein. Factor VIII is a protein naturally found in the body and is necessary for the blood to form clots and stop bleeding. In patients with haemophilia A, factor VIII is missing or not working properly.

Altuvoct replaces the deficient or missing factor VIII. Altuvoct increases factor VIII levels in the blood, helping blood to form clots at the site of bleeding which temporarily corrects the tendency of bleeding.

How is Altuvoct used?
The pharmaceutical form of these medicines is a powder and solvent for solution for injection and the route of administration is intravenous (injection into a vein).

Treatment with Altuvoct will be started by a doctor who is experienced in the care of patients with haemophilia A. Altuvoct is given as an injection into a vein.

After proper training in the correct injection technique, patients or caregivers may be able to administer Altuvoct at home. The patients' doctor will calculate their dose (in International Units

or "IU") for them. This will depend on their weight and whether it is used for prevention or treatment of bleeding.

Keeping a record
Each time the patient uses Altuvoct, they should record the date, the name of the medicine and the batch number.

Prevention of bleeding
The usual dose of Altuvoct is 50 international units (IU) per kg of body weight. The injection is given weekly.

Treatment of bleeding
The dose of Altuvoct is 50 international units (IU) per kg of body weight.
The dose and frequency may be adjusted depending on the severity and location of the bleeding.

Use in children and adolescents
Altuvoct can be used in children 2 years and above, the dose recommendation is the same as in adults.

How Altuvoct is given
Altuvoct is given as an injection into a vein. Patients should see 'Instructions on how to use Altuvoct' in the patient information leaflet (PIL) for more information.

For further information on how Altuvoct are used, refer to the PIL and Summaries of Product Characteristics (SmPCs) available on the Medicines and Healthcare products Regulatory Agency (MHRA) website.

These medicines can only be obtained with a prescription.

The patient or caregiver should always take/give the medicine exactly as their doctor/pharmacist has told them. The patient/caregiver should check with their doctor or pharmacist if they are not sure.

The patient should ask the administering healthcare practitioner if they have any questions concerning their medicine.

What benefits of Altuvoct have been shown in studies?
Altuvoct has been shown to be effective at preventing and treating bleeding in patients with severe haemophilia A.

In a main study involving 159 patients aged 12 years and above with severe haemophilia A, 133 patients received a weekly injection of Altuvoct to prevent bleeding (prophylaxis). After 52 weeks of treatment, patients had an average of around 0.71 70 episodes of bleeds per year. For 77 patients, data on previous treatments were available; in this group, the mean annualised bleeding rate was 0.69 with Altuvoct compared with 2.96 with previous treatments. During the study, most episode of bleeds were successfully treated with a single injection of Altuvoct (on-demand treatment).
In a study involving 74 children under 12 years of age with haemophilia A, treatment with Altuvoct yielded similar results to those in older patients. Altuvoct was therefore considered effective for the treatment of haemophilia A in younger children.

Combined data from 3 studies involving 41 patients with haemophilia A who underwent major surgery showed that Altuvoct is effective at preventing episode of bleeds during and after surgery.

What are the possible side effects of Altuvoct?
For the full list of all side effects reported with these medicines, see Section 4 of the PIL or the SPCs available on the MHRA website.

If a patient gets any side effects, they should talk to their doctor, pharmacist or nurse. This includes any possible side effects not listed in the product information or the PIL that comes with the medicine. Patients can also report suspected side effects themselves, or a report can be made on their behalf by someone else who cares for them, directly via the Yellow Card scheme at https://yellowcard.mhra.gov.uk or search for 'MHRA Yellow Card' online. By reporting side effects, patients can help provide more information on the safety of this medicine.

The most common side effects with Altuvoct (which may affect more than 1 in 10 people) are:
• headache
• arthralgia (joint pain)

Why was Altuvoct approved?
MHRA decided that the benefits are greater than the risks and recommended that these medicines can be approved for use.

What measures are being taken to ensure the safe and effective use of Altuvoct?
As for all newly-authorised medicines, a Risk Management Plan (RMP) has been developed for Altuvoct. The RMP details the important risks of Altuvoct, how these risks can be minimised, any uncertainties about Altuvoct (missing information), and how more information will be obtained about the important risks and uncertainties.

The following safety concerns have been recognised for Altuvoct:

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

The MAH commit to carry out further studies in specific populations or for long-term safety and efficacy data.

Data from the European Haemophilia Safety Surveillance System (EUHASS) registry and the Paediatric Network haemophilia registry (PedNet) registry will also be used to perform additional pharmacovigilance surveillance.
The information included in the SmPC and the PIL is compiled based on the available quality, non-clinical and clinical data, and includes appropriate precautions to be followed by healthcare professionals and patients. Side effects of Altuvoct are continuously monitored and reviewed including all reports of suspected side-effects from patients, their carers, and healthcare professionals.

An RMP and a summary of the pharmacovigilance system have been provided with these applications and are satisfactory.

Other information about Altuvoct
Marketing authorisations were granted in the United Kingdom on 14 February 2025.

The full PAR for Altuvoct follows this summary.

This summary was last updated in May 2025.

TABLE OF CONTENTS

I. INTRODUCTION

Based on the review of the data on quality, safety and efficacy, the Medicines and Healthcare products Regulatory Agency (MHRA) considered that the applications for Altuvoct 250, 500, 750, 1000, 2000, 3000 & 4000 IU powder and solvent for solution for injection (PLGB 30941/0024-0030) could be approved.

The products are approved for the following indications:

Treatment and prophylaxis of bleeding in patients 2 years and above with severe or moderate haemophilia A (≤ 5% endogenous plasma factor VIII activity).

Efanesoctocog alfa is replacement factor VIII therapy. Activated factor VIII acts as a cofactor for activated factor IX, accelerating the conversion of factor X to activated factor X. Activated factor X converts prothrombin into thrombin. Thrombin then converts fibrinogen into fibrin and a clot can be formed. Haemophilia A is an X-linked hereditary disorder of blood coagulation due to decreased levels of functional factor VIII:C and results in bleeding into joints, muscles or internal organs, either spontaneously or as a result of accidental or surgical trauma. By replacement therapy the plasma levels of factor VIII are increased, thereby enabling a temporary correction of the factor deficiency and correction of the tendencies of bleeding.

Of note, annualised rate of bleeding (ABR) is not comparable between different factor concentrates and between different clinical studies.

Altuvoct (efanesoctocog alfa) or recombinant coagulation Factor VIII Fc-Von Willebrand Factor-XTEN is a recombinant fusion protein that temporarily replaces the missing coagulation Factor VIII needed for effective haemostasis.

Efanesoctocog alfa is a protein with FVIII activity that is designed not to bind endogenous VWF in order to overcome the half-life limit imposed by FVIII-VWF interactions. The D'D3 domain of VWF is the region that interacts with FVIII. Appending the D'D3 domain of VWF to a rFVIII-Fc fusion protein provides protection and stability to FVIII and prevents FVIII interaction with endogenous VWF, thus overcoming the limitation on FVIII half-life imposed by VWF clearance.

The Fc region of human immunoglobulin G1 (IgG1) binds to the neonatal Fc receptor (FcRn). FcRn is part of a naturally occurring pathway that delays lysosomal degradation of immunoglobulins by recycling them back into circulation and thus prolonging the plasma half-life of the fusion protein.

Efanesoctocog alfa contains 2 XTEN polypeptides, which further increase its pharmacokinetics (PK). The natural FVIII B domain (except 5 amino acids) is replaced with the first XTEN polypeptide, inserted in between FVIII N745 and E1649 amino acid residues; and the second XTEN is inserted in between the D'D3 domain and Fc.

This application was approved under International Recognition procedure (IRP). The Reference Regulator (RR) was the European Medicines Agency (EMA), with the procedure number EMEA/H/C/005968.

For the scientific discussion of the quality, non-clinical and clinical assessment conducted by the reference regulator, please refer to the public assessment report on the relevant competent

authority's website.

These applications were approved under Regulation 50 of the Human Medicines Regulation 2012, as amended (previously Article 8.3 of Directive 2001/83/EC, as amended).

This application was evaluated for fulfilment of orphan designation criteria and was examined by the Commission on Human Medicines (CHM). The applicant withdrew the application for orphan designation.

In line with the legal requirements for children's medicines, the application included a licensing authority decision on the agreement of a paediatric investigation plan (PIP) MHRA-100465-PIP01-22-M02

The licensing authority issued an opinion on compliance of the PIP MHRA-100465-PIP01-22-M02-C.

The MHRA has been assured that acceptable standards of Good Manufacturing Practice (GMP) are in place for these products at all sites responsible for the manufacture, assembly and batch release of these products.

A Risk Management Plan (RMP) and a summary of the pharmacovigilance system have been provided with these applications and are satisfactory.

Advice was sought from the Commission of Human Medicines (CHM) on 26 September 2024 on grounds relating to clinical safety. Following provision of additional data, the CHM were reassured on the quality of the product.

Marketing authorisations were granted on 14 February 2025.

II. PRODUCT INFORMATION

Summaries of Product Characteristics (SmPCs)

The SmPCs are in line with current guidelines and are satisfactory.

PATIENT INFORMATION LEAFLET (PIL)

The PIL is in line with current guidelines and is satisfactory.

LABEL

The labelling is in line with current guidelines and is satisfactory.

III. QUALITY ASPECTS

MHRA considered that the quality data submitted for these applications is satisfactory.

The grant of marketing authorisations was recommended.

IV. NON-CLINICAL ASPECTS

MHRA considered that the non-clinical data submitted for these applications is satisfactory.

The grant of marketing authorisations was recommended.

V. CLINICAL ASPECTS

Introduction

The safety and efficacy of Altuvoct (BIVV001) has been evaluated in clinical studies described in the table below:

Study code Phase	Study title	Study description - Primary endpoint(s)	Number of participants	BIVV001 dosing regimen and treatment duration	Study population	Study status
EFC16293 Phase 3 Pivotal	A Phase 3, Open-label Interventional Study of an Intravenous Recombinant Coagulation Factor VIII Fc-von Willebrand Factor-XTEN Fusion Protein, BIVV001, in Patients with Severe Hemophilia A (XTEND-1).	Open-label study to assess the safety, efficacy, and PK of BIVV001 in PTPs with severe hemophilia A, ≥12 years of age. - Annualized bleeding rate (ABR) in Arm A.	159 (133 in Arm A; 26 in Arm B)	50 IU/kg once weekly for 52 weeks (Arm A) 50 IU/kg on demand for 26 weeks followed by a switch to 50 IU/kg once weekly for 26 weeks (Arm B) Additional doses for bleed treatment and surgery, if necessary[c]	Adult and adolescent PTPs with severe hemophilia A (≥12 years of age)	Completed
EFC16295 Phase 3 Pediatric	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 pediatric patients <12 years of age with severe hemophilia A (XTEND-Kids).	Open-label study to assess the safety, efficacy, and PK of BIVV001 in pediatric PTPs with severe hemophilia A, <12 years of age. - FVIII inhibitor development.	74 (38 in <6 years of age cohort; 36 in 6 to <12 years of age cohort)	50 IU/kg once weekly for 52 weeks Additional doses for bleed treatment and surgery, if necessary[c]	Pediatric PTPs with severe hemophilia A (<12 years of age)	Completed
LTS16294 Phase 3 Long-term study	A Phase 3 open-label, multicenter study of the long-term safety and efficacy of intravenous recombinant coagulation factor VIII Fc-von Willebrand factor-XTEN fusion protein (rFVIIIFc-VWF-XTEN; BIVV001) in Previously Treated Patients with severe hemophilia A (XTEND-ed).	Open-label study to assess the long-term safety and efficacy of BIVV001 in PTPs with severe hemophilia A. Plus, 2 separate open-label arms with patients newly initiated on BIVV001 in China; and patients who are	Planned: 262 (215 who rolled over from the other Phase 3 studies); 37 Chinese participants in Arm B; up to 10 major surgery participants in Arm C). Enrolled as of the cut-off date of 17 Jan	50 IU/kg once weekly Up to 48 months (Arm A) 52 weeks (Arms B and C) Additional doses for bleed treatment and surgery, if necessary[c]	PTPs with severe hemophilia A (all ages)	Ongoing

Study code Phase	Study title	Study description - Primary endpoint(s)	Number of participants	BIVV001 dosing regimen and treatment duration	Study population	Study status
		planned to undergo major surgery. - FVIII inhibitor development.	2023: N=260: (216 rolled over from EFC16293 [146] and EFC16295 [70] to Arm A; 37 in Arm B; and 7 in Arm C)			
242HA101 (TDU16220) Phase 1/2a	A Safety, Tolerability, and Pharmacokinetics (PK) Study of a Single Intravenous (IV) Injection of Recombinant Coagulation Factor VIII (FVIII) Fc - von Willebrand Factor - XTEN Fusion Protein (rFVIIIFc-VWF-XTEN) (BIVV001) in Previously Treated Adults with Severe Hemophilia A (EXTEN-A).	Open-label, dose escalation, safety, tolerability, and PK of a single IV dose of BIVV001. - Occurrence of AEs - Occurrence of clinically significant abnormalities in laboratory tests. - FVIII inhibitor development.	16 (7 in the low dose cohort; 9 in the high dose cohort)	25 IU/kg (low dose cohort) 65 IU/kg (high dose cohort) Single dose	Adult PTPs with severe hemophilia A (18 to 65 years of age)	Completed
242HA102 (TDR16219) Phase 1/2a	A Phase 1, Open-Label, Single-Site, Safety, Tolerability, and Pharmacokinetics Study of Repeat Doses of BIVV001.	Open-label, safety, tolerability, and PK repeat-dose study of BIVV001. - Occurrence of AEs. - Occurrence of clinically significant abnormalities in laboratory tests. - FVIII inhibitor development.	24 (10 in cohort 1; 14 in cohort 2)	50 IU/kg (cohort 1) 65 IU/kg (cohort 2) 4 once-weekly doses	Adult PTPs with severe hemophilia A (18 to 65 years of age)	Completed

Study code Phase	Study title	Study description - Primary endpoint(s)	Number of participants	BIVV001 dosing regimen and treatment duration	Study population	Study status
PKM17085 Phase 1	A Phase 1, Single-Site, Open-Label Study to Assess Pharmacokinetics of efanesoctocog alfa (BIVV001), Standard Half-Life and Extended Half-Life FVIII after each Single Intravenous Injection in a Fixed Sequence, in Previously Treated Adults with Severe Hemophilia A.	Open-label, Phase 1, 3 period fixed sequence study to assess PK profiles of BIVV001, SHL and EHL rFVIII after a single IV injection in males. - Half-life of BIVV001, SHL rFVIII and EHL rFVIII, as assessed by FVIII activity determined by the one-stage aPTT clotting assay.	13	50 IU/kg Single dose	Adult PTPs with severe hemophilia A (18 to 65 years of age)	Completed
PKM16978[a] Phase 1	A Phase 1, Open-Label Study to Assess the Pharmacokinetics, and Safety and Tolerability of a Single Intravenous Injection of rFVIIIFc-VWF-XTEN (BIVV001) in Adults with type 2N and 3 von Willebrand disease (VWD).	Open-label, Phase 1, multicenter, single-arm study to characterize the PK of BIVV001 after a single IV injection and to assess safety, and tolerability of BIVV001 in adult participants. - PK parameters, assessed as FVIII activity by 2 assay methods.	6	25 IU/kg Single dose	Adult male and/or female patients with type 2N or 3 VWD (18 to 65 years of age)	Completed
242HA201[b] (OBS16221) Prospective study	A Prospective Study in Subjects with Severe Hemophilia A Who are Currently Receiving a Marketed FVIII Therapy.	To prospectively collect data regarding bleeding episodes and treatment information (no BIVV001 administered). - ABR (spontaneous and traumatic).	158	Not applicable (Real world use of prescribed marketed FVIII therapy).	Adults and adolescent PTPs with severe hemophilia A currently receiving and remaining on prescribed marketed FVIII therapy (≥12 years of age)	Completed

Abbreviation: EHL = extended half-life; IV = intravenous; PTP= previously treated patient; SHL = standard half-life.

a. This study does not support BIVV001 registration.

b. Study 242HA201 (OBS16221) was an observational study in participants receiving marketed FVIII therapy. Eligible participants in OBS16221 were invited to roll-over into EFC16293. BIVV001 treatment was not administered in this observational study.

c. Per Phase 3 study protocols, bleeding episodes requiring treatment were to be treated with an initial single dose of 50 IU/kg BIVV001. Additional doses of 30 or 50 IU/kg every 2 to 3 days could be administered if a bleeding episode did not improve and after consultation with the Investigator. Minor surgeries were performed with a single 50 IU/kg (loading) dose prior to surgery. For major surgery, additional doses of 30 or 50 IU/kg every 2 to 3 days could be administered.

The studies have been conducted in accordance with Good Clinical Practice.

Main clinical studies
The applicant has submitted 2 main clinical studies.

Study XTEND-1 is considered a composite of two single arm studies with external controls. Previously treated subjects with severe haemophilia A were ≥12yrs age.

There were 158 male and 1 female subject; mean age 35yrs (range 12 – 72 yrs); 61% White, 18% Asian; median weight 78kg; median body mass index 25.7kg/m2. Baseline characteristics and medical history were typical of a population with severe haemophilia A.

133 subjects in arm A were administered Altuvoct 50 IU/kg once weekly intravenously as prophylaxis for up to 52 weeks (124 subjects completed the study); 26 subjects in arm B were administered Altuvoct 50 IU/kg intravenously on demand for 26 months and then transferred to weekly prophylaxis up to 52 weeks (25 subjects completed the study).

Study XTEND-Kids was a single-arm study without controls of previously treated subjects with severe haemophilia A aged <12yrs.

74 subjects were enrolled; all were male; 74% White, 11% Asian; age range 1.4 to 11yrs; weight range from 11.4kg to 66.5kg. Baseline characteristics and medical history were typical of a population with severe haemophilia A at this age.

Subjects were administered Altuvoct 50 IU/kg once weekly intravenously as prophylaxis for up to 52 week. Overall, 94.6% of the participants were compliant with both the dosing and the dosing interval.

CLINICAL PHARMACOLOGY

Guide to Altuvoct dosing for treatment of episode of bleeds and surgery

Degree of haemorrhage/ Type of surgical procedure	Recommended dose	Additional information
Haemorrhage		
Early haemarthrosis, muscle bleeding or oral bleeding	Single dose of 50 IU/kg	For minor and moderate bleeding episodes occurring within 2 to 3 days after a prophylactic dose, a lower dose of 30 IU/kg dose may be used. An additional dose of 30 or 50 IU/kg after 2 to 3 days may be considered.
More extensive haemarthrosis, muscle bleeding or haematoma	Single dose of 50 IU/kg	Additional doses of 30 or 50 IU/kg every 2 to 3 days may be considered until bleeding is resolved.
Life threatening haemorrhages	Single dose of 50 IU/kg	Additional doses of 30 or 50 IU/kg every 2 to 3 days may be administered until the threat is resolved.
Surgery		
Minor surgery including tooth extraction	Single dose of 50 IU/kg	An additional dose of 30 or 50 IU/kg after 2 to 3 days may be considered.
Major surgery	Single dose of 50 IU/kg	Additional doses of 30 or 50 IU/kg every 2 to 3 days may be administered as clinically needed until adequate wound healing is achieved.

The FVIII activity-based pharmacokinetic (PK) data for Altuvoct were obtained from 6 clinical studies that enrolled previously treated patients (PTPs) with severe haemophilia A (Table below).

The PK of Altuvoct has been characterised in adult and paediatric PTPs (≥150 EDs) with severe haemophilia A across clinical studies. Altuvoct was administered IV as a single dose (25 and 65

IU/kg) or repeated doses for 4 weeks with once weekly regimen (50 and 65 IU/kg) in the Phase 1/2a studies and subsequently with 50 IU/kg once-weekly for up to 52 weeks in the Phase 3 studies. A dense PK sampling schedule was implemented in Phase 1/2a studies, while a combination of dense and sparse PK sampling schemes was used in the Phase 3 studies.

Overview of PK evaluations of Altuvoct in Haemophilia A

Study type	**Study code Phase**	**Number of participants enrolled**	**Treatment duration Dose**	**PK sampling**	**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/kg Altuvoct High dose cohort: 65 IU/kg Advate, then 65 IU/kg Altuvoct	Predose and 0.17, 0.5, 1, 3, 6, 9, 24, 48, 72, 96, 120, 168, 240 hours post-injection +288, 336 hours for high dose	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 Altuvoct Cohort 2: 65 IU/kg Altuvoct	Day 1: Predose, 0.5, 3, 24, 48, 72, 120 hours post-injection Day 8 and Day 15: Predose Day 22: Predose, 0.5, 3, 24, 48, 72,120, 168, 240, and 336 hours post-injection	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 Altuvoct	Predose and 0.17, 0.5, 1, 6, 24, 48, 72, 96, 120, 168, 240, 288, 336 hours post-injection	Completed
Efficacy and safety studies in patients with severe haemophilia A					
Safety, efficacy, and PK in patients	EFC16293 (XTEND-1) Phase 3	159 (133 in Arm A, 26 in Arm B)	Arm A (prophylaxis): 52 weeks 50 IU/kg Altuvoct once weekly Arm B: 26 weeks 50 IU/kg Altuvoct (on	Day 1 (baseline): predose and 0.25, 3, 24, 72, 168 hours	Completed

≥12 years of age			demand), then 26 weeks 50 IU/kg Altuvoct once weekly (prophylaxis)	post-injection (Arm A and B) Day 1 (baseline) and Week 26 visits: predose and 0.25, 3, 24, 72, 168, 240, and 336 hours post-injection (Arm A sequential subgroup) Peak and trough at Week 4, Week 13, Week 39, and Week 52 visits: predose*b* and 0.25 hours post-injection (All participants)	
Safety, efficacy, and PK in patients <12 years of age	EFC16295 (XTEND-kids) Phase 3	74 (38 in <6 years of age cohort, 36 in 6 to <12 years age cohort)[a]	52 weeks 50 IU/kg Altuvoct once weekly	Day 1 (Baseline): predose and 0.25, 3, 24, 72, 168 hours post-injection (PK-subgroup) Peak and trough at Week 4, Week 13, Week 26, Week 39, and Week 52 visits: predose and 0.25 hours post-injection (All participants)	Completed
Long-term	LTS16294	218 (176 in Arm A, 37	Up to 4 years	Day 1 (baseline):	Ongoing[c]

safety and efficacy in patients ≥12 years of age	(XTEND-ed) Phase 3	in Arm B, 5 in Arm C)[a]	50 IU/kg Altuvoct once weekly	predose and 0.25, 3, 24, 72, 168 hours post-injection (Arm B and C) Day 1 (baseline) and Week 26 visits: predose and 0.25, 3, 24, 72, 168, 240, and 336 hours post-injection (Arm B sequential subgroup) Peak and trough at Week 4, Week 13, Week 39, and Week 52 visits: predose*b* and 0.25 hours post-injection (All participants)	

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.] Interim results included in the current submission.
[c.] FVIII activity listing is included only for Arm C in the current submission.

A Phase 1 study investigating PK and initial tolerability in patients with Type 2N and 3 von Willebrand disease is completed. No PK data of this study is included in this submission.
In addition, population PK analyses were conducted using pooled data from Phase 1/2a and Phase 3 studies.

Pharmacokinetics

Analytical methods

Bioanalytical assays employed for the Altuvoct clinical studies

Assay purpose	Assay type	Analyte	Assay standard	LLOQ	Within-run accuracy Between-run accuracy[b]	Within-run precision Between-run precision	Clinical studies
One-stage clotting (OSC) assays							
Screening	OSC	Plasma FVIII activity	Plasma standard[a]	0.005 IU/mL	NA 92.0% to 105.0%	4.1% to 11.6% 0.7% to 6.5%	All BIVV001 studies (242HA101, 242HA102, EFC16293, EFC16295, LTS16294, PKM16978, PKM17085)
PK	OSC	Advate FVIII activity	Plasma standard[a]	0.005 IU/mL	NA 101.6% to 116.0%	3.7% to 8.6% 3.0% to 6.9%	242HA101, 242HA102, PKM17085
PK	OSC	Adynovi/ Adynovate FVIII activity	Plasma standard[a]	0.006 IU/mL	81.2% to 120.0% 87.9% to 119.3%	0.0% to 18.7% 3.6% to 10.1%	PKM17085
PK	OSC	BIVV001 FVIII activity	BIVV001 self-standard	0.010 IU/mL	97.4% to 132.0% 101.7% to 119.0%	0.2% to 11.5% 3.6% to 7.7%	242HA101, 242HA102
PK	OSC	BIVV001 FVIII activity	Plasma standard[a]	0.010 IU/mL	82.7% to 121.6% 90.0% to 114.6%	0.9% to 17.6% 3.4% to 9.7%	EFC16293, EFC16295, LTS16294, PKM16978, PKM17085
Chromogenic substrate (CS) assays							
Screening and PK	CS	Plasma FVIII activity and Advate FVIII activity	Plasma standard[a]	0.008 IU/mL	90.3% to 144.5% 102.5% to 110.4%	2.9% to 22.7% 5.0% to 19.4%	242HA101, 242HA102
PK	CS	BIVV001 FVIII activity	BIVV001 self-standard	0.010 IU/mL	89.4% to 116.5% 92.8% to 111.3%	0.5 to 9.6% 1.8 to 6.3%	242HA101, 242HA102
PK	CS	BIVV001 FVIII activity	Plasma standard[a]	0.033 IU/mL	89.8% to 111.3% 94.3% to 109.1%	0.8% to 6.9% 2.4% to 6.1%	EFC16293, EFC16295, LTS16294
Nijmegen-modified Bethesda assay (neutralizing ADAs against FVIII)							
Immunogenicity	OSC	FVIII Inhibitors	Plasma standard[a]	0.6 BU/mL	78.9% to 108.0% 90.6% to 99.0%[b]	9.4% to 10.2% 5.1% to 9.9%	All BIVV001 studies (242HA101, 242HA102, EFC16293, EFC16295, LTS16294, PKM16978, PKM17085)
BIVV001 ADA assay							
Immunogenicity	ELISA	ADAs	NA	10.635 ng/mL	NA NA	Screening: 0.9% to 33.8% Confirmation: 0.2% to 10.7% for BIVV001; 0.0% to 22.7% for Advate Screening: 7.5% to 14.6% Confirmation: 0.4% to 9.2% for BIVV001; 0.4% to 22.4% for Advate	All BIVV001 studies (242HA101, 242HA102, EFC16293, EFC16295, LTS16294, PKM16978, PKM17085)

Abbreviations: ADA = anti-drug antibody; CS = chromogenic substrate; ELISA = enzyme-linked immunosorbent assay; FVIII = coagulation factor VIII; LLOQ = lower limit of quantitation; NA = Not available; OSC = one-stage clotting; PK = pharmacokinetic; BIVV001 = Altuvoct
Advate is a recombinant full length FVIII (rFVIII) product; Adynovi/Adynovate is a PEGylated full length rFVIII product.
a Plasma standard calibrated against World Health Organisation (WHO) International Standard
b Accuracy recovery (% of theoretical value)

FVIII activity assays

Activated partial thromboplastin time (aPTT)-based one-stage clotting (OSC) assay

The OSC assay measures the activity of the intrinsic and common pathways of coagulation. In principle, this assay measures the formation of tenase complex, conversion of prothrombin to thrombin and the subsequent formation of the fibrin clot using an artificial intrinsic pathway

trigger (aPTT activator). Since FVIII is an important cofactor in the intrinsic pathway, the aPTT based OSC assays are used extensively to measure the FVIII activity of plasma samples from patients treated with replacement FVIII products in the clinical setting.

The OSC assay is used as the primary assay for measuring FVIII activity in the Altuvoct clinical development program. All Altuvoct clinical studies (Phase 1, Phase 1/2a and Phase 3) utilised a Clinical Laboratory Improvement Amendments (CLIA)-validated FVIII OSC assay with Actin® FSL as activator at Esoterix Inc. (now Labcorp). The lower limit of quantitation (LLOQ) of OSC assays is typically 0.5% or 1% of normal FVIII activity. This is near the minimum therapeutic threshold of FVIII activity (1% of normal), below which the risk of spontaneous bleeding increases significantly.

FVIII OSC assay was validated using Altuvoct product-specific self-standard for analysing samples from Phase 1/2a studies (242HA101 and 242HA102). Subsequently, the FVIII OSC assay was validated with WHO plasma standard for Phase 3 studies and Phase 1 studies (PKM17085 and PKM16978). Despite the change of assay standard, these two OSC assays are very similar, and results are comparable.

Two stage chromogenic substrate (CS) assay
An alternate method for determining plasma FVIII activity is the two stage CS assay. The CS assay quantifies FVIIIa-mediated conversion of FX to FXa in the presence of trace amounts of thrombin and excess FIXa, FX, Ca2+, and phospholipids. In the first stage, FVIII in a diluted plasma sample is quantitatively activated by thrombin into FVIIIa. With addition of FIXa, FX, phospholipids, and calcium, FVIIIa acts as a cofactor for FIXa to convert FX to FXa. In the second stage, FXa hydrolyses the chromogenic substrate, and the color intensity of the resulting product (p-nitroaniline released enzymatically) is directly proportional to the amount of FXa, which in turn is proportional to the amount of FVIII in the plasma sample. Similar to the OSC assay, the CS assay is also used to monitor the activity of FVIII replacement therapy.

All Altuvoct clinical studies (Phase 1, Phase 1/2a, and Phase 3) except for PKM17085 employed a CLIA-validated FVIII CS assay using BIOPHEN™ FVIII:C kit at Esoterix (Labcorp) in addition to the primary OSC assay for assessment of FVIII activity levels.

For FVIII activity measurement, significant discrepancies between the CS assay and aPTT-based OSC assay have been observed for some recombinant FVIII products. This is also the case for Altuvoct assays based on plasma standard, where the FVIII activity measured by CS assay was approximately 2.5-fold higher compared to aPTT-based OSC assay.

Field study: laboratory assay variability on the assessment of Altuvoct FVIII activity (Module 5.3.1.4 PMH0205)
In addition to the FVIII activity assessments in clinical study samples, the Sponsor performed a blinded, international, multicentre (13 countries, 35 laboratories) field study to evaluate the FVIII activity assay performance of Altuvoct in global clinical hemostasis laboratories, where a variety of aPTT and chromogenic reagents and different instruments were used for measuring Altuvoct and Advate activity in spiked plasma samples in a blinded manner.

Congenital FVIII-deficient plasma was spiked with either Altuvoct or a marketed rFVIII product (Advate) to 0.80, 0.20, or 0.05 IU/mL, based on labeled potency. Advate served as a control in gauging assay performance across the laboratories and reagents. For Altuvoct, labeled potency

was assigned using OSC assay with Actin FSL reagent. Hemostasis laboratories tested the spiked samples in their in-house FVIII assays using plasma FVIII standard and common, commercially available reagents and/or kits. All laboratories used their routine testing procedures. The majority of laboratories tested spiked samples using both OSC and CS assays.

The results of the study showed reagent-specific assay variabilities for Altuvoct when assessed with OSC assay (n=51), with a progressively higher variability at lower FVIII concentrations. However, no specific trend with any particular class of aPTT activators (ie, ellagic acid, kaolin, or silica) was observed. For Altuvoct, use of Actin FSL (n=7) as reagent resulted in reliable assessments across all activity levels within ±25% of assigned nominal value. However, when Actin FS (n=10) was used as a reagent, an over-recovery of activity by approximately 2.5-fold was observed across all 3 activity levels. Use of SynthASil (n=15) showed ~30% under-recovery with respect to the nominal potency.

A reagent-correlated variability was also observed for Advate but was less pronounced and within the acceptable range of ±25% for most OSC reagents tested.

For most CS assays kits (n=42), an over-recovery of FVIII activity in Altuvoct-spiked samples by approximately 2 to 3-fold (ie, 200% to 300%) was observed consistently across the three activity levels. This over-recovery was expected based on previous nonclinical and clinical data showing that OSC assay using Actin FSL (Altuvoct potency assignment reagent), displays approximately 2.5-fold lower molar specific activity compared to results from a panel of CS. Compared to the OSC assays, the CS assays displayed low inter assay variability for Altuvoct spiked plasma samples. Some assay variability was also observed for Advate samples when tested in different CS assays, but to a lesser extent than for Altuvoct.

The intra-lab variability was comparable for the two FVIII products in both OSC and CS assays, however, for the OSC assays the inter-assay variability was higher for Altuvoct compared to Advate.

Immunogenicity assays

FVIII inhibitor assay (Nijmegen-modified Bethesda assay)

The FVIII inhibitor assays measure the decrease of FVIII activity in a mixture of an exogenous source of the clotting factor (eg, normal pooled plasma) and the patient plasma containing the putative FVIII inhibitor. The method includes a pre-heating step to inactivate any remaining FVIII in the putative inhibitor plasma sample. A reference measurement is performed with the same method substituting the patient plasma with a control plasma sample that does not contain a FVIII inhibitor. After a standardised incubation time, residual FVIII activities in the assay mixtures are measured by aPTT based OSC assay. The residual FVIII activity is defined as the relative percentage of FVIII activity of the test mixture compared with the control mixture. The Nijmegen-modified Bethesda assay is recommended by the International Society on Thrombosis and Haemostasis (ISTH) as the reference method for FVIII inhibitor testing. One Nijmegen Bethesda Unit (BU) is defined as the amount of inhibitor that results in a decrease of 50% FVIII activity in the test sample (16).

Anti-drug antibody assay

In addition to FVIII inhibitors (neutralising ADAs), an immune response to Altuvoct may result in the generation of non-neutralising ADAs. Both types of ADAs can be evaluated by an enzyme-linked immunosorbent assay (ELISA) that detects immunoglobulins in serum or plasma that bind

specifically to the drug. The ADA assay used in the Altuvoct clinical studies employs a bridging format with an ELISA readout designed to detect all immunoglobulins reacting with Altuvoct, including potential antibodies that are targeted specifically to different components of the molecule: FVIII, Fc, XTEN polypeptide, or D'D3.

The applicant provided individual validation reports for the bioanalytical assays which were used to measure FVIII activity and immunogenicity. The assays were generally acceptable in terms of adequate accuracy and precision. There were significant differences between the aPTT-based OSC assay and CS assay, where the FVIII activity measured by CS assay was approximately 2.5-fold higher compared to OSC assay. These differences have been addressed in the SmPC. The results of the field study comparing different aPTT reagents indicated approximately 2.5-fold higher factor VIII activity levels when using Actin-FS instead of Actin-FSL in the one-stage clotting assay and approximately 30% lower results when using SynthASil. The influence of the reagents on the laboratory monitoring of FVIII replacement therapy has been addressed in the SmPC. The OSC assays were validated using Altuvoct product-specific self-standard for phase 1/2 studies and subsequently using a WHO standard for phase 3, however the two applied OSC assays were very similar, and results were comparable despite the change in the assay standard. The assay results included in the final PK analysis were the OSC data.

Absorption
Altuvoct is administered intravenously, thus no specific data on absorption are presented. In the Phase 3 study EFC16293 the mean incremental recovery (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
Altuvoct 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 below).

Altuvoct 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

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 two mechanisms:

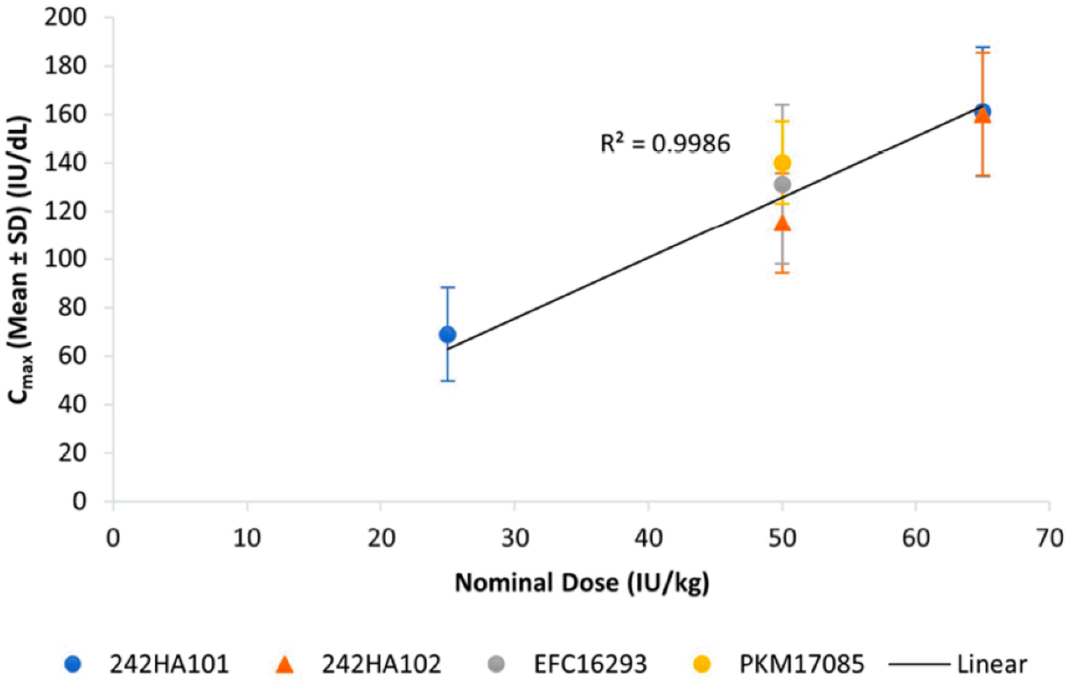
i. Recycling through FcRn and VWF-independent clearance, both of which would reduce the clearance and prolong the half-life compared to other FVIII products.

ii. The presence of two XTEN polypeptides further reduces the clearance.

Thus, Altuvoct clearance (0.503 mL/h/kg) was lower compared to Advate (3.26 mL/h/kg) (Standard half-life (SHL) product) and Adynovi (1.86 mL/h/kg) (Extended half-life (EHL) product), resulting in a half-life of Altuvoct (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 Altuvoct CL was 0.553 mL/h/kg and half-life was 48.4 hours in a typical patient (POH0731).

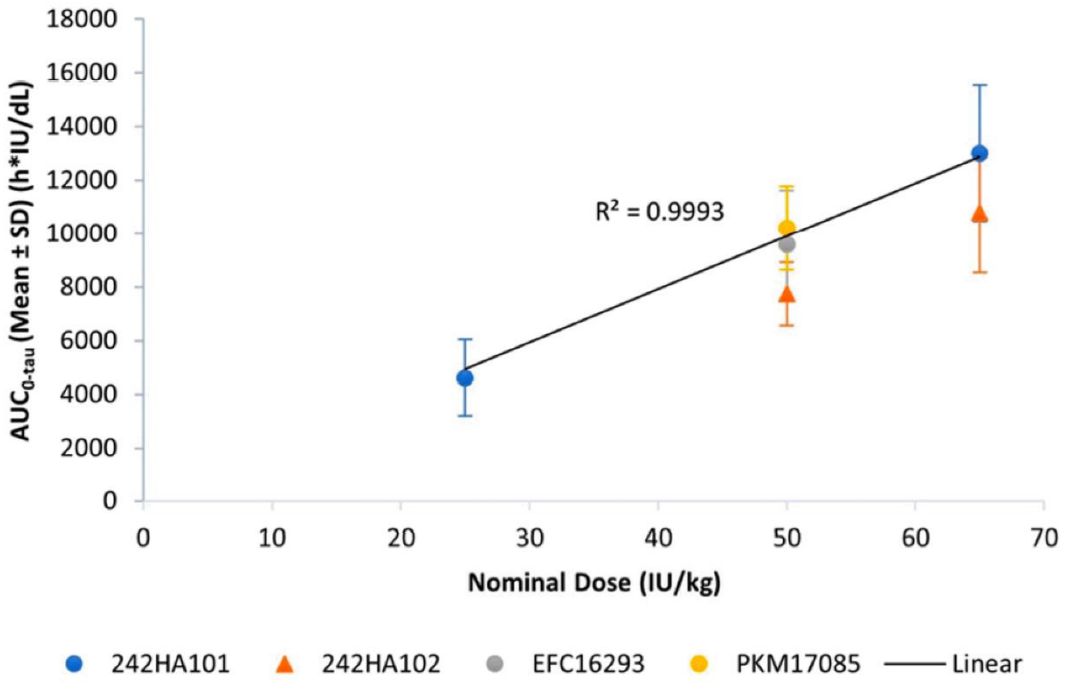
Dose proportionality and time dependencies
Following a single dose of Altuvoct, the CL and Vss were independent of dose between 25 and 65 IU/kg Altuvoct (Table below). Dose-proportionality was observed for Cmax and AUC0-tau between 25 and 65 IU/kg of Altuvoct (Figures below).

Altuvoct Cmax by dose in patients with haemophilia A after a single (or first) dose



Cmax = maximum FVIII activity at Day 1; SD = standard deviation.

Altuvoct 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

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

Once-weekly dosing of Altuvoct 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 below), indicating that steady state was achieved after the first dose.

Summary of Altuvoct 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 242HA101
In this Phase 1/2a, open-label, dose-escalation, multicentre study including adult male PTPs (≥150 EDs) 18 to 65 years of age with severe haemophilia A, participants (n=7 in the low dose cohort, n=9 in the high dose cohort) received a single IV dose of 25 IU/kg or 65 IU/kg of Advate in the low and high dose cohorts, respectively, followed by a washout period and a single IV dose of 25 IU/kg or 65 IU/kg of Altuvoct in the low and high dose cohorts, respectively.

The FVIII activity declined slowly following Altuvoct treatment, with a geometric mean half-life of 37.61 hours at 25 IU/kg and 42.54 hours at 65 IU/kg. Compared to Advate treatment, half-life was longer (p value <0.001) following Altuvoct treatment by 4.13-fold at 25 IU/kg, and 3.24-fold at 65 IU/kg. The IR of Altuvoct was consistent across doses. Advate and Altuvoct exposure was generally dose proportional.

Study 242HA102
This was a Phase 1/2a, open-label, single center study to evaluate the safety, tolerability, and PK of 4 once-weekly doses of 50 IU/kg (Cohort 1) or 65 IU/kg (Cohort 2) Altuvoct in adult male PTPs (≥150 EDs) 18 to 65 years of age with severe haemophilia A.

Following Altuvoct once-weekly dosing at 50 IU/kg and 65 IU/kg, the mean half-life values on Day 22 were 41.63 hours and 37.59 hours, respectively. The Cmaxss and AUC0-tau values on Day 22 were similar to those on Day 1, indicating weekly dosing of 50 or 65 IU/kg resulted in minimal accumulation. The steady state was achieved by Day 22 with 4 weekly doses of 50 and 65 IU/kg.

Study PKM17085
This was a Phase 1, open-label, single center, 3 period fixed sequence crossover study to characterise the PK of FVIII products: Altuvoct, 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 Altuvoct (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 below). Compared with Advate and Adynovi, a single 50 IU/kg dose of Altuvoct 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).

PKM17085: Summary of PK parameters for baseline-corrected FVIII activity following a single dose of Advate, Adynovi, and Altuvoct 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, multicentre study investigated efficacy, safety and PK of Altuvoct 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 Altuvoct 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 (ie, abbreviated and sequential PK subgroups); FVIII activity levels remained in the mild haemophilia range at the end of the weekly dosing interval (Figure below). 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 Altuvoct was 47.6 hours 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 postdose) 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).

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

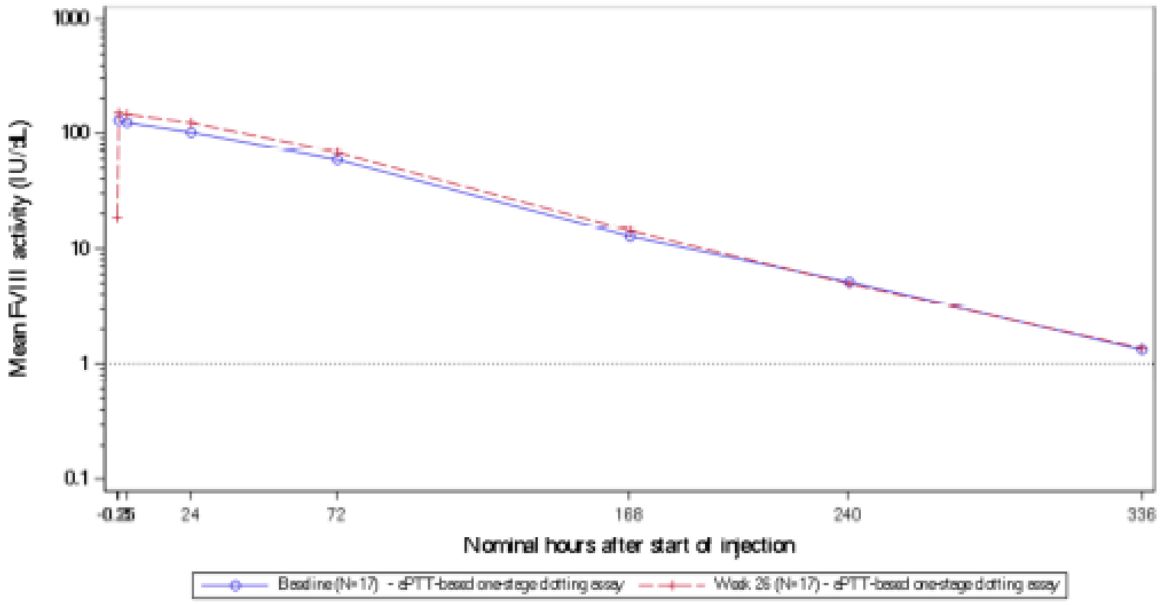
	C_{max} (IU/dL)	IR (IU/dL per IU/kg)	$AUC_{0\text{-}tau}$ (h*IU/dL)	$DN\_AUC_{0\text{-}tau}$ (h*kg*IU/dL/IU)	CL (mL/h/kg)	V_{ss} (mL/kg)	$t_{1/2z}$ (h)	MRT (h)
n	159	159	153[a]	153[a]	153[a]	153[a]	159	153[a]
Mean	131	2.60	9600	191	0.508	31.7	47.6	63.2
SD	33.0	0.648	2010	39.9	0.124	7.44	8.86	9.70

AUC0-tau = area under the activity-time curve over the dosing interval; CL = clearance; Cmax = maximum FVIII activity; DN_AUC0-tau = dosenormalised 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 Altuvoct for 26 weeks (Figure below).

EFC16293: Semilog 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.

Mean C_{trough} observed at steady state was 18.5 IU/dL (Table below), further demonstrating that Altuvoct maintained high sustained FVIII activity levels with 50 IU/kg once-weekly regimen. After 26 weeks of once-weekly 50 IU/kg Altuvoct 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).

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[a]
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

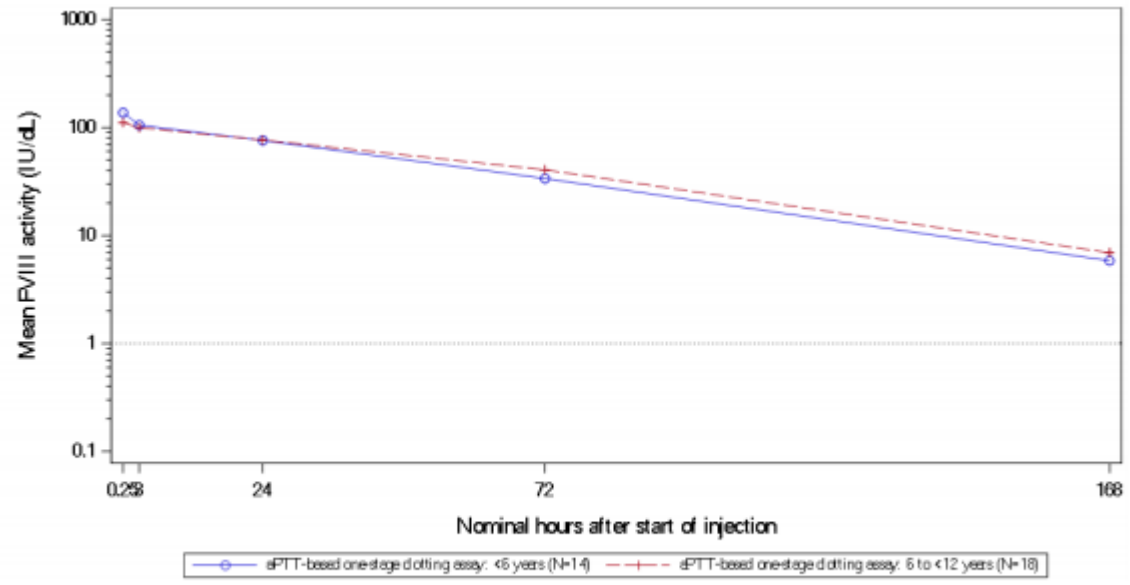
AI = accumulation index (AI is computed as AUCDay183/AUCDay1 ratio); AUC0-tau = area under the activity-time curve over the dosing interval; CLss = total clearance at steady state; Cmaxss = maximum FVIII activity at steady state; Ctrough = trough activity; DN_AUC0-tau = dose normalized area under the 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 Altuvoct was 43.6 (6.50) hours similar to what was observed with the OSC assay (ie, 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.

Study EFC16295 (XTEND-kids)
This is a Phase 3, single-arm, open-label study which is ongoing at the time of the dossier preparation. The study aims to determine, the safety, efficacy and PK of Altuvoct administered as once-weekly prophylactic treatment in previously treated paediatric participants <12 years of age with severe haemophilia A. The study comprises <6 years and 6 to <12 years of cohorts, where participants received Altuvoct at a dose of 50 IU/kg IV once weekly for 52 weeks.
A 50 IU/kg dose of Altuvoct resulted in high sustained FVIII activity levels in the normal to near-normal range (>40 IU/dL) for 2 to 3 days and remained in the mild haemophilia range at the end of the weekly dosing interval.

EFC16295: Semilog plot of mean baseline-corrected FVIII activity over time by age cohort on Day 1 based on OSC assay – PK Analysis Set



Note: Based upon a data cutoff date of 24 January 2022.
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.

The half-life and AUC0-tau were slightly lower in participants <6 years as compared to participants 6 to <12 years. This was attributed to a higher CL (approx. 10%) on average in patients <6 years of age as compared to participants between the age of 6 to 12 years.

Study LTS16294 (XTEND-ed) (ongoing)
It is a Phase 3 study that is ongoing at the time of the dossier preparation. No PK or immunogenicity data have been provided.

Special populations
Gender
The impact of sex on Altuvoct 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 popPK 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 popPK 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).

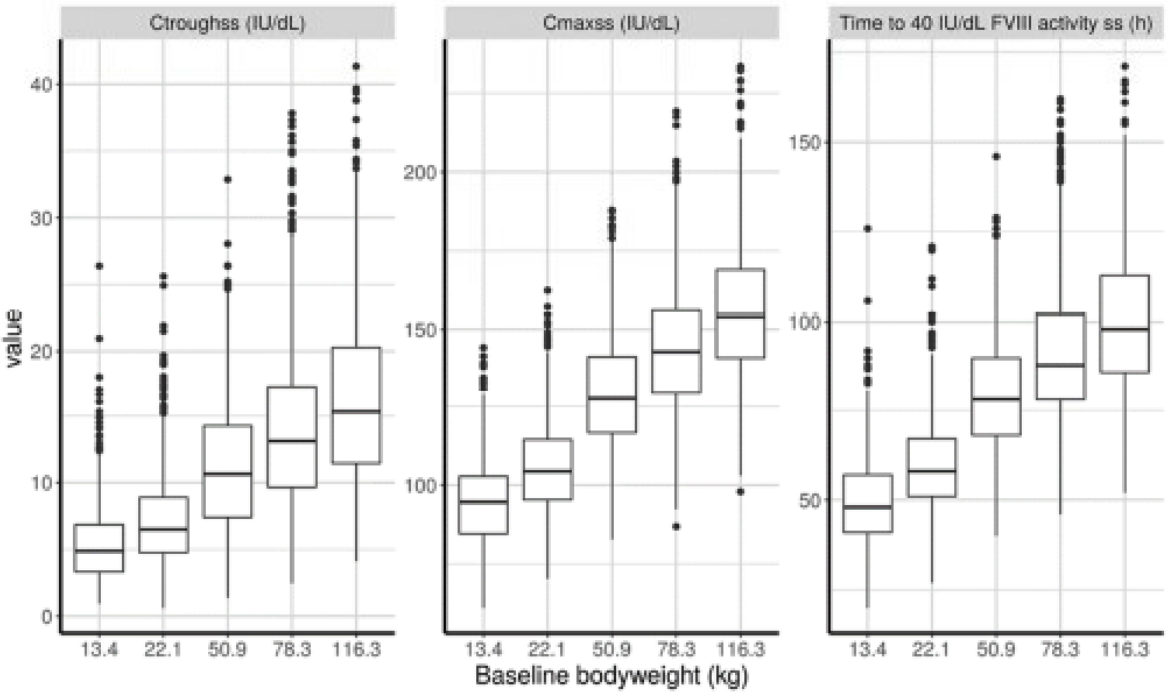
These simulations demonstrated that Asian race was a statistically significant PK covariate, with higher FVIII activity in Asians compared to non-Asians. However, there were no unique patterns or trends identified in reported TEAEs for Asian participants in the pivotal Phase 3 study EFC16293, confirming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

Weight

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

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.

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)



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 at any visit in each BMI category versus those of the entire study population were: 29 (26.6% vs 41.8%) for underweight or normal weight (BMI <25 kg/m^2), 48 (44.0% vs 38.6%) for overweight (BMI ≥25 to <30 kg/m^2), and 31 (28.4% vs 19.6%) for obese (BMI ≥30 kg/m^2). Of the 60 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. More specifically, the mean (SD) simulated time above 150 IU/dL at steady state was 5.57 (7.2) hours for adults in the upper range of body weight (116.3 kg), 2.65 (5.06) hours in the middle range, and 0.624 (2.15) hours in the low range of 50.9 kg. Thus, post-dose peak FVIII activity levels >150 IU/dL and >200 IU/dL were observed more frequently in patients with BMI values in the overweight to obese range.

Evaluating data of study EFC10295 by BMI category (WHO definitions for children), of the 38 participants with a peak FVIII activity level >150 IU/dL, 21 (55%) were underweight or of normal weight, 9 (24%) were overweight, and 8 (21%) were obese. Most of these 38 participants (33, 86.8%) recorded a peak FVIII activity level >150 IU/dL at ≤2 visits. For the 5 patients with a high peak at 3-5 visits, 1 was of normal weight and 4 were obese. A total of 13 (34%) participants had a peak FVIII activity level >200 IU/dL at ≥1 study visit: 10 of these participants were of normal weight, 1 was overweight, and 2 were obese. These results suggest a slight trend for having higher post-dose peak FVIII activity levels in children with higher BMI. 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 these of participants <65 years of age.

Children

Results from the Noncompartmental analysis (NCA) across various age groups indicated that there was an increase in clearance with decreasing age (Table below), 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.

Pharmacokinetic parameters for baseline-corrected FVIII activity following a single dose of Altuvoct 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)
$AUC_{0-\infty}$ (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 above). After the first 50 IU/kg dose of Altuvoct, 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, Altuvoct 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 Altuvoct 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 Altuvoct is being evaluated in the ongoing PKM16978 study.

The applicant has carried out a PBPK analysis with the aim to predict Altuvoct PK in paediatric patients (0 to <2, ≥2 to <6 and ≥6 to <12 years age groups) with severe haemophilia A. A PBPK model was first developed for Eloctate, antihaemophilic FVIII Fc fusion protein. The model was qualified using observed adult and paediatric data for Eloctate and then adapted for building the PBPK model for Altuvoct. The adult PK data were used to refine the PBPK model for Altuvoct by incorporating distribution and clearance mechanisms. After validating the PBPK model using observed adult Altuvoct PK data, the final model was used to simulate PK profiles for paediatric patients of various age groups by taking ontogeny into account.

The clinical studies which were used for Eloctate and Altuvoct model validation are shown in the following table. No data for paediatric patients <2 years old were used in model validation of Eloctate.

Eloctate and BIVV001 clinical studies used for model qualification

Study Drug	Study No.	Patient Population	Age (years)	Dose (IU/kg)	Subject number	Study design
Eloctate	998HA101	Adult	23 to 61	25	6	Eloctate single IV dose on Day 1
				65	10	
	8HA02PED	Pediatric	2 to 12	50	>24 for each age group	Pre-study followed by twice weekly prophylactic treatment of Eloctate (Use first 50 IU/kg IV Dose with PK assessment as the dataset)
BIVV001	242HA101	Adult	19 to 63	25	6	BIVV001 single IV dose on Day 1
				65	8	
	242HA102	Adult	24 to 58	50	9	BIVV001 repeated IV dose weekly
				65	14	

The default paediatric population module in Simcyp was used to incorporate paediatric-related changes including ontogeny factors. Additional paediatric ontogeny profiles from the minimal PBPK model for mAbs implemented in the Simcyp biologic module were adapted for building the paediatric model for Altuvoct. In addition, the effects of age on the neonatal Fc receptor (FcRn) abundance and vascular reflection fraction were incorporated in the PBPK model based on the literature data. As it can be seen in the following graphs, the ontogeny input parameter (i.e., FcRn expression, modulation factor) are highly dependent on age and weight. Moreover, no FcRn expression results for infants (i.e., <1 year of age) have been provided.

Thus, the fact that the PBPK model for Eloctate has not been validated using clinical data from paediatric patients <2 years of age, prevents it from being able to be used to simulate exposure of Eloctate or BIV001to paediatric patients <2 years of age, as its credibility has not been demonstrated.

Relationship between the estimated FcRn concentration (μmol/l) and body weight in various paediatric age groups.

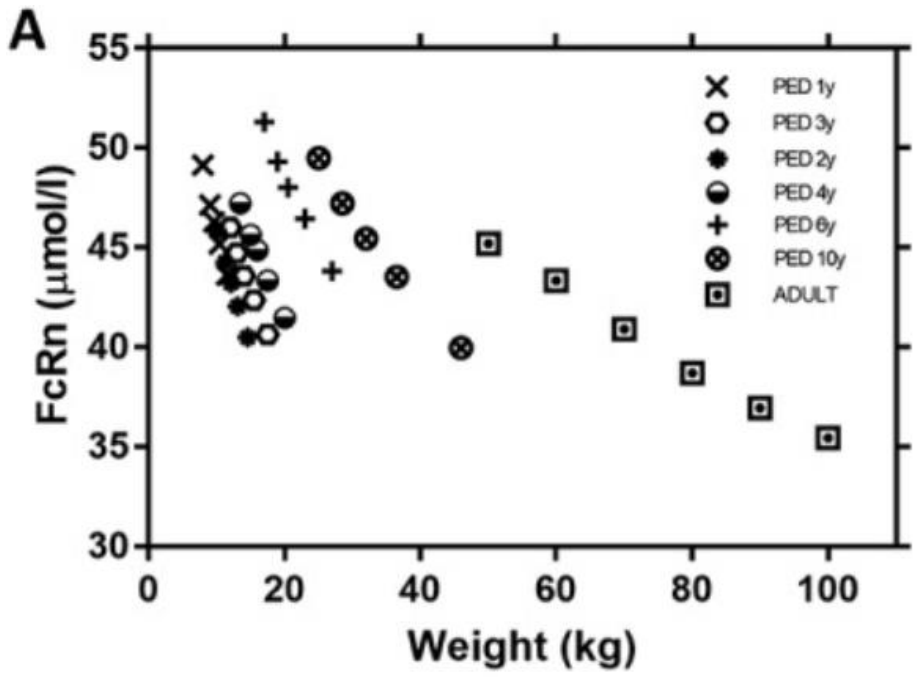
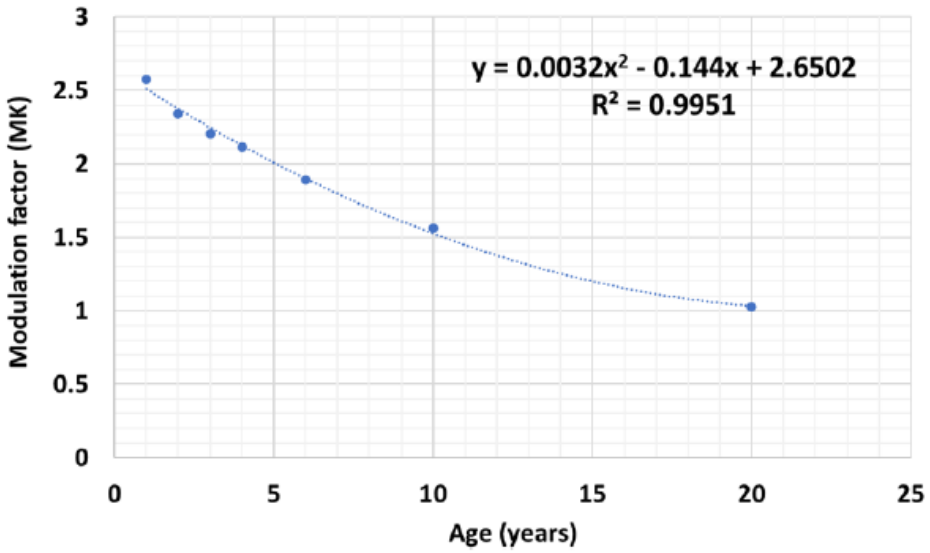


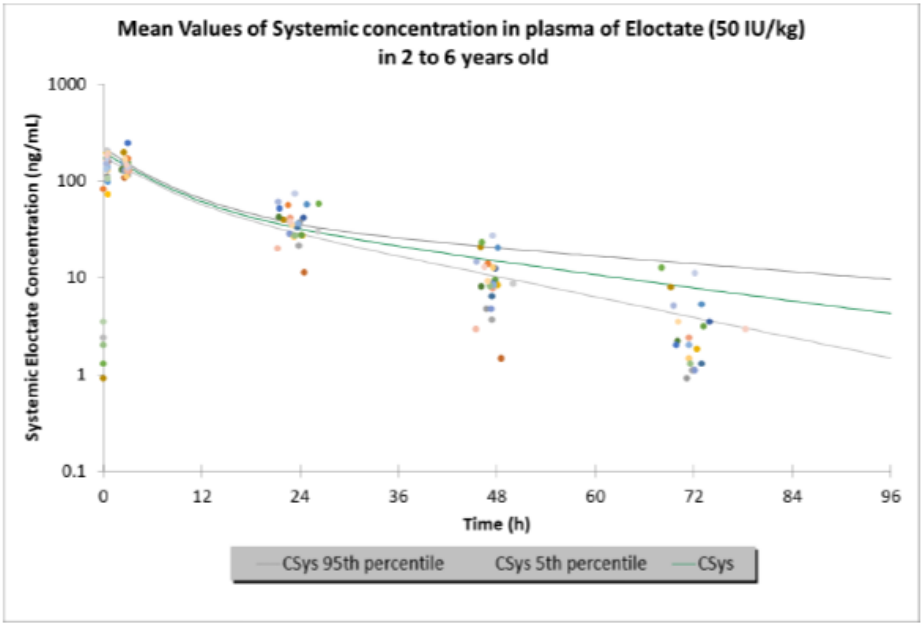
Figure 3 - Modulation factor (MK) of extravasation rate of the median participants.



Note: Figure was digitized and re-plotted from Hardiansyah et al.'s manuscript (Figure 5a) (14). The trendline for each age group was fitted by a quadratic function using Excel Microsoft 365.

Moreover, the model validation/qualification results that have been provided for Eloctate paediatric model do not appear to capture the variability or terminal half-life, with several observed points outside the 5 to 95th percentiles (the graph plasma concentration of Eloctate in 2 to 6 years old is given below).

Observed (Study 8HA02PED) and predicted mean plasma concentrations (with 5th to 95th percentile) of Eloctate in paediatric participants at ≥2 to <6 years following an IV dose of Eloctate at 50 IU/kg

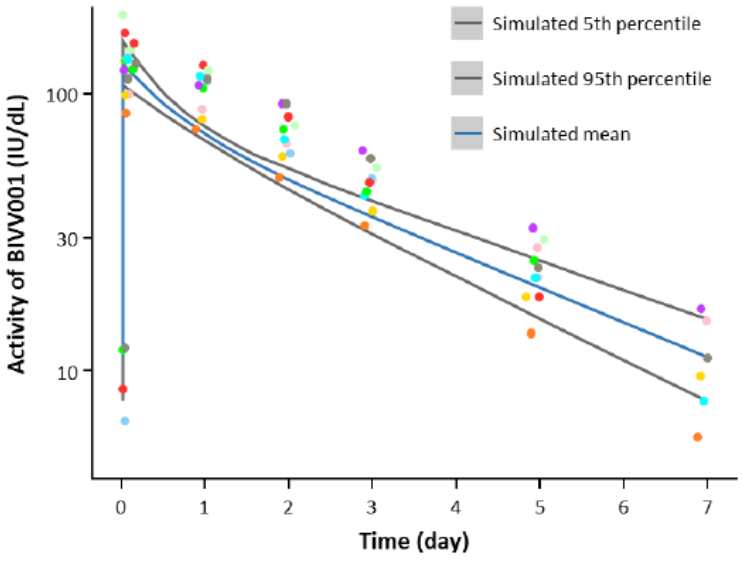


Note: Unit of Eloctate concentration = ng/ml

In addition, the PBPK model for Electorate overpredicted exposure for paediatric patients ≥2 to <6 years, while it underpredicted exposure for paediatric patients ≥6 to 12 years. This can be attributed to the different FcRn expression curves for these age groups (as seen in the graph from Hardiansyah et al. 2018).

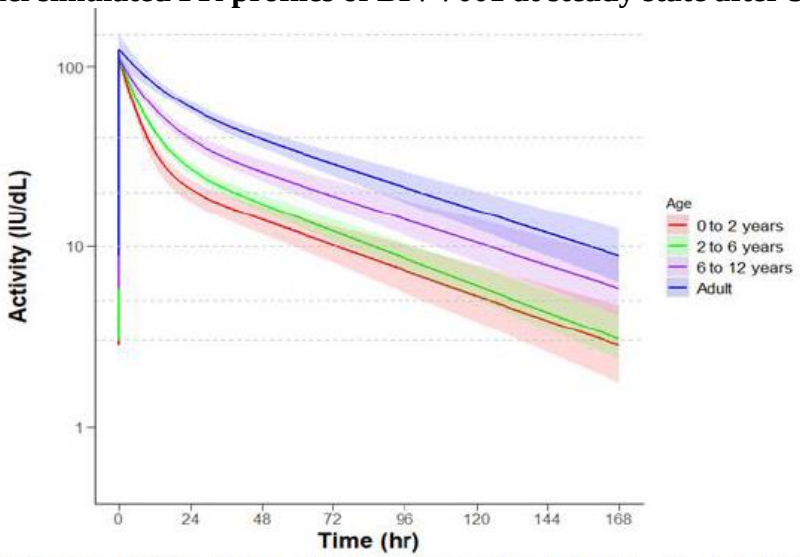
Also, the Altuvoct model does not capture well variability in activity of Altuvoct.

Observed (Study 242HA102, data obtained from one-state clotting assay) and predicted FVIII activity level (with 5th and 95th percentile) of BIVV001 in adults following repeated IV dose of BIVV001 at 50 IU/kg at day 22



The simulated of FVIII activity profiles and parameters for repeat-dose Altuvoct at Day 22 in paediatric populations aged 0 to <2 years, ≥2 to <6 years, ≥6 to 12 years, and adults are shown in the following graph. The 50 IU/kg IV QW regimen for Altuvoct is predicted to maintain sustained FVIII activity levels (>10%) for 2-5 days and achieve mean FVIII activity levels between 2.6-5.6 IU/dL at trough.

PBPK model simulated PK profiles of BIVV001 at steady state after 50 IU/kg QW



Note: PBPK model predicted PK profile by specific age groups and doses. The simulated PK profiles reflects the FVIII activity measured by chromogenic assay. Solid lines represent mean response; shaded regions represent 90% prediction intervals; horizontal dashed lines (from the top) represent concentrations of 150 IU/dL, 40 IU/dL, 20 IU/dL, 10 IU/dL, 5 IU/dL and 3 IU/dL.

Overall, the PBPK analysis to predict Altuvoct PK in paediatric patients with severe Haemophilia A is considered acceptable to justify the paediatric dosing in paediatric patients ≥ 2 years of age.

However, due to the lack of validation of the Eloctate PBPK model with clinical data from paediatric patients < 2 years of age as well as the lack of sufficient knowledge on ontogeny parameters (i.e., FcRn expression, modulation factor) for paediatric patients <2 years old, the PBPK model is not considered sufficient to support PK/dose selection of Altuvoct to paediatric patients < 2 years old. This is reflected in the approved indication:
Treatment and prophylaxis of bleeding in patients 2 years and above with severe or moderate haemophilia A (≤ 5% endogenous plasma factor VIII activity).

Pharmacodynamics
No dedicated PD studies were conducted but data on the episode of bleeds were obtained in the Phase 3 study EFC16293 and correlated to FVIII activity (PK).

Primary Pharmacodynamics and 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 (1). 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 Altuvoct 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 Altuvoct, further confirming the benefit of higher sustained FVIII levels.

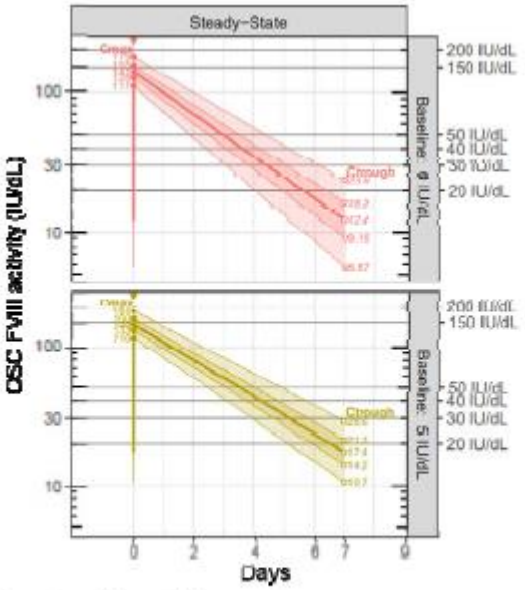
Based on the RTTE model simulations for a typical patient, the probability of zero bleeds in 1 year with Altuvoct 50 IU/kg once-weekly regimen was predicted to be 71% (95% CI: 50%-83%), indicating a low risk of bleed for Altuvoct. The probability of first bleed in 1 year with Altuvoct 50 IU/kg once-weekly 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).

Summary
The applicant did not conduct dedicated PD studies but data on the episode of bleeds were obtained in the Phase 3 study EFC16293 and correlated to FVIII activity (PK). The mechanism of action as replacement therapy for factor VIII is agreed.

Clinical studies were only conducted in patients with severe Haemophilia A (FVIII < 1%).
PK simulation of steady-state FVIII activity in patients with moderate haemophilia A (5 IU/dL) and severe haemophilia A (0 IU/dL) receiving weekly prophylaxis with efanesoctocog alfa (50 IU/kg) indicate that their VIII activity profiles over time are comparable (Figure 1). The proportions of patients having FVIII activity >150 IU/dL after dosing are similar for moderate and severe haemophilia A (Figure 2). These results do not indicate a relevant risk of over-exposure in patients with moderate haemophilia A.

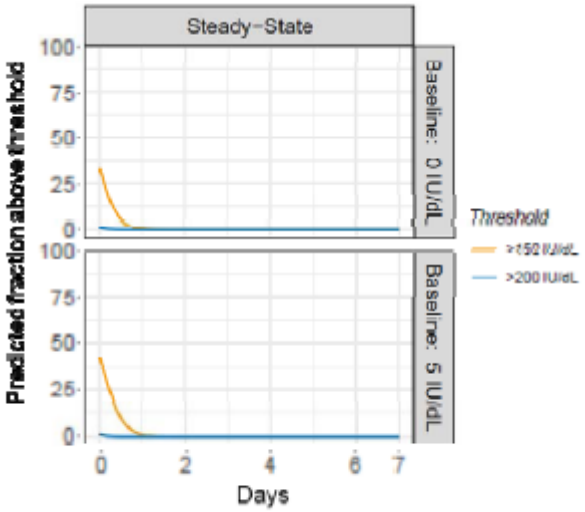
The simulations provided by the Applicant provides assurance that overexposure is unlikely in subjects with moderate haemophilia A (5 IU/dL) and the percentage fraction above threshold is comparable with subjects with severe haemophilia A (0 IU/dL), therefore there is no clinical pharmacology objections against the use of efanesoctocog alfa (50 IU/kg) in subjects with moderate haemophilia A.

Simulations of factor VIII activity at steady-state (50 IU/kg once weekly) in patients with severe (baseline: 0 IU/dL) and moderate (baseline: 5 IU/dL) haemophilia



Lines represent the 5%, 25%, median, 75% and 95% percentiles.
Source: Simulated Efanesoctocog Alfa (BIVV001) Factor VIII (FVIII) Activity Levels In Adolescents and Adults of 12 Years and Above With Mild or Moderate Haemophilia, A. Facius, ThinkQ2, 2023, Appendix 1 (Figure 2.2).

Predicted percent of subjects above thresholds



Source: Simulated Efanesoctocog Alfa (BIVV001) Factor VIII (FVIII) Activity Levels In Adolescents and Adults of 12 Years and Above With Mild or Moderate Haemophilia, A. Facius, ThinkQ2, 2023, Appendix 1 (Figure 2.5).

Immunogenicity

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 titer in the post screening/baseline period).

For each ADA positive participant, the ADA response was classified in the following categories:

- Persistent ADA response (defined by an ADA response duration greater or equal than 16 weeks).
- Transient ADA response (defined by an ADA response duration less than 16 weeks and the last sample of the post screening/baseline period neither being treatment-induced nor treatment-boosted).
- Indeterminate ADA response (defined by treatment-induced or treatment-boosted ADAs that are neither persistent nor transient).

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		23	3	0	0	0
LTS16294*		/	/	/	/	/
242HA101		15	0	0	0	0
242HA102		23	0	1	0	0**
PKM17085		13	2	1	0	1

*Data not available
**One participant in the 65 IU/kg cohort was tested positive for ADAs at the Day 50 (EOS) visit, follow-up unclear.

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 Altuvoct (VWF D'D3, FVIII, IgG1 Fc, and XTEN polypeptides).

PK exposure parameters at steady state obtained from popPK posthoc analysis were compared between the 4 ADA positive participants and ADA negative participants (Table below). 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.

ADA impact on Altuvoct PK parameters at steady state in Study EFC16293

	SUBJID	C_{min} (IU/dL)	C_{max} (IU/dL)	AUC (IU.h/dL)
ADA negative	N	149	149	149
	Mean (SD)	15.2 (6.05)	145 (22.6)	9595 (1939)
ADA positive treatment-emergent	016293-032-0136-00002	22.4	189	13100
	016293-032-0137-00001	7.27	146	7770
	016293-380-0401-00003	7.84	143	7820
	016293-032-0139-00504	11.4	115	7530

ADA: Anti-drug antibody. AUC: area under the activity time curve. Cmin: minimum FVIII activity. Cmax: minimum FVIII activity. N: number.
PK: pharmacokinetics. SD: standard deviation.

Altuvoct has a low potential for immunogenicity with only 4 Altuvoct-treated patients developing treatment-emergent anti-drug antibodies (ADAs) in XTEND-1, which were transient. The applicant presented data which indicate that there is no impact of ADAs on FVIII PK exposure (Cmin, Cmax and AUC).

Overall Clinical Pharmacology Summary
For Altuvoct bioanalytical methods, the applicant provided individual validation reports for the bioanalytical assays which were used to measure FVIII activity and immunogenicity. The assays were generally acceptable in terms of adequate accuracy and precision. The differences between bioanalytical methods in terms of sensitivity are addressed in the SmPC and the applicant recommended to use a validated one-stage clotting assay to determine plasma factor VIII activity of Altuvoct considering that this assay was used throughout the clinical development with an Actin-FSL-based one-stage clotting assay. The applicant's recommendation is acceptable.

Altuvoct is administered as an IV injection. The incremental recovery (IR) of Altuvoct, a key factor to characterise the PK of clotting factors, was comparable to the IR of other approved FVIII products (e.g., Advate, Adynovi). As it is typical for fusion proteins, Altuvoct exhibits a limited volume of distribution (Vss: 31.3-38.3 ml/kg fir dose 25-65 IU/kg). A similar Vss was predicted by the popPK analysis in typical patients. Altuvoct exhibits a long half-life (more than twice the half-life of FVIII products with standard half-life). Such an extended half-life is attributed to the structure of Altuvoct (rFVIIIFc-VWF-XTEN). Therefore, Altuvoct exhibited a lower clearance (0.503 ml/h/kg) and markedly longer half-life compared to other approved FVIII products. From the pop PK model, the Altuvoct CL was 0.553 mL/h/kg and half-life was 48.4 hours in a typical patient. Dose-proportionality was observed for Cmax and AUC0-tau between 25 and 65 IU/kg of Altuvoct. Minimal accumulation was observed upon multiple dosing.

Altuvoct has a low potential for immunogenicity with only 4 Altuvoct-treated patients developed treatment-emergent anti-drug antibodies (ADAs) which were transient. The applicant presented a data which indicates that there is no impact of ADAs on FVIII PK exposure (Cmin, Cmax and AUC).

The applicant has carried out a PBPK analysis with the aim to predict Altuvoct PK in paediatric patients (0 to <2, ≥2 to <6 and ≥6 to <12 years age groups) with severe Haemophilia A. The PBPK analysis is considered acceptable to justify the paediatric dosing in paediatric patients ≥ 2 years of age. However, due to the lack of validation of the Eloctate PBPK model with clinical data from paediatric patients < 2 years of age as well as the lack of sufficient knowledge on ontogeny parameters (i.e., FcRn expression, modulation factor) for paediatric patients <2 years old, the PBPK model is not considered sufficient to support PK/dose selection of Altuvoct to paediatric patients < 2 years old.

PK simulations provided by the Applicant provide assurance that overexposure is unlikely in subjects with moderate haemophilia A (5 IU/dL) and the percentage fraction above threshold is comparable with subjects with severe haemophilia A (0 IU/dL), therefore there is no clinical pharmacology objections against the use of efanesoctocog alfa (50 IU/kg) in subjects with moderate haemophilia A.

Clinical Efficacy and Safety

Main clinical study

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

The study was conducted in compliance with International Council for Harmonisation Good Clinical Practice.

Study objectives and efficacy endpoints are summarised:

Objectives	Endpoints
Primary	
• To evaluate the efficacy of BIVV001 as a prophylaxis treatment	• Annualized bleeding rate (ABR) in Arm A
Secondary	
Efficacy objectives	
• To evaluate the efficacy of BIVV001 as a prophylaxis treatment	• Intra-patient 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 **(key secondary endpoint)** • ABR by type and location for prophylaxis treatment per study arm • ABR for all bleeding episodes (including untreated bleeding episodes) for prophylaxis treatment per study arm • Intra-patient 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
• To evaluate the efficacy of BIVV001 in the treatment of bleeding episodes	• 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 International Society on Thrombosis and Haemostasis (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
• To evaluate BIVV001 consumption for the prevention and treatment of bleeding episodes	• Total annualized BIVV001 consumption per participant per study arm and treatment regimen
• To evaluate the effect of BIVV001 prophylaxis on 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

Objectives	Endpoints
	• Annualized Joint Bleeding Rate (AJBR) per study arm and treatment regimen
	• Target joint resolution at Week 52, based on ISTH criteria in Arm A
• To evaluate the effect of BIVV001 prophylaxis on Quality of Life (QoL) outcomes	• 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 from baseline to Week 52 in Arm A
	• Changes in PROMIS SF Physical Function (≥18 years old) measures from baseline to Week 52 in Arm A
• To evaluate the efficacy of BIVV001 for perioperative management	• 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
Safety objective	
• To evaluate the safety and tolerability of BIVV001 treatment	• The occurrence of adverse events (AEs) and serious adverse events (SAEs)
	• The occurrence of clinically significant changes from baseline in physical examination, vital signs, and laboratory tests
	• Development of inhibitors (neutralizing antibodies directed against factor VIII [FVIII]) as determined via the Nijmegen modified Bethesda assay
	• The occurrence of embolic and thrombotic events
PK objective	
• To assess the PK of BIVV001 based on the one-stage activated partial thromboplastin time (aPTT) and two-stage chromogenic FVIII activity assays	• PK parameters including, but not limited to, maximum activity (C_{max}), elimination half-life ($t_{1/2}$), total clearance (CL), total clearance at steady state (CLss), accumulation index (AI), area under the activity time curve (AUC), volume of distribution at steady state (Vss), mean residence time (MRT), incremental recovery (IR), trough activity (C_{trough}), time above predefined FVIII activity levels
Exploratory	
• To evaluate joint-health structural outcomes via ultrasound using the Joint Activity and Damage	• Changes in anatomical structural joint health outcomes via the JADE and/or HEAD-US protocol

Objectives	Endpoints
Exam (JADE) protocol and/or Hemophilia 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)	for ultrasound imaging from baseline to Week 52 in a subpopulation at selected sites in Arm A • Changes in PRO measures and physical activity per study arm and treatment regimen - PROMIS-SF Physical Function (≥18 years old) or PROMIS Pediatric-SF Physical Activity (<18 years old - Haem-A-QoL (≥17 years old) or Haemo-QoL (<17 years old) total score and subscale scores - PROMIS-SF Pain Interference (≥18 years old) or PROMIS Pediatric-SF Pain Interference (<18 years old) - EQ-5D-5L - Treatment Satisfaction Questionnaire for Medications (TSQM-9) - Patient Global Impression of Severity (PGIS) (activity component) - PGIS (joint component) - Change in physical activity measures (ActiGraph Activity Monitor) - Hemophilia Activities List (HAL) (≥18 years old) or pedHAL (<18 years old) • Change in HJHS total score and domain score (eg, swelling and strength) in Arm B by treatment regimen • Patient Global Impression of Change (PGIC) at Week 26 and Week 52 per study arm and treatment regimen • Patient Preference at Week 52 per study arm and treatment regimen • Exit interview at Week 52 (or at subsequent follow-up visit).

For the primary objective & endpoint, the study is essentially a single-arm trial.

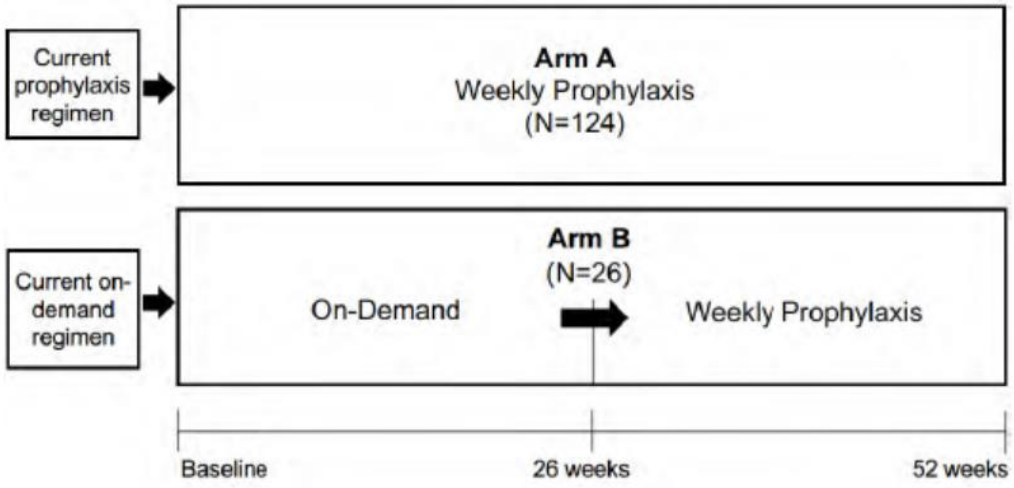
There are very many secondary and other objectives / endpoints that are descriptive in nature and that do not have an internal control arm to refer against.

Aspects of study design
A Phase III, open-label, multi-national, multi-centre study of the safety, efficacy, and PK of IV Altuvoct in previously treated patients ≥12 years of age with severe haemophilia A (defined as <1 IU/dL [<1%] endogenous FVIII or a documented genotype known to produce severe haemophilia A).

150 participants were planned to be enrolled and treated with Altuvoct.

The study comprised 2 arms:

Graphical study Design



Arm A included participants who were on a prophylaxis treatment regimen with FVIII prior to the study.

124 participants were planned to be enrolled in Arm A including at least 75 participants with at least 6 months of participation in Study 242HA201 / OBS16221 prior to baseline.

Arm B included participants who were on an on-demand treatment regimen prior to the study. 26 participants were planned to be enrolled in Arm B.

The study consisted of:

- An up to 8-week screening period
- An open-label treatment period of a maximum of 52 weeks
- A 2- to 3-week safety follow-up period (only applicable for participants who did not continue in the open-label extension study).

Surgery subgroup
Participants from either arm who underwent major surgery after the first dose of study drug were included in the surgery subgroup. A minimum of 10 major surgeries in at least 5 patients was targeted to assess the control and prevention of bleeding during use of Altuvoct in the surgical setting.

Participants were eligible to have major surgery performed with Altuvoct if they had at least 6 exposure days. Major surgery was defined as any invasive operative procedure that required any of the following:

- Opening into a major body cavity (eg abdomen, thorax, skull)
- Operation on a joint
- Removal of an organ
- Dental extraction of any molar teeth or ≥3 non-molar teeth
- Operative alteration of normal anatomy
- Crossing of a mesenchymal barrier (e.g. pleura, peritoneum, dura)

All patients were to receive a preoperative loading dose of 50 IU/kg prior to the surgical procedure. If needed, the dose level of Altuvoct was to be adjusted to aim for a FVIII activity level of at least 100% and maintained during the surgery according to WFH Guidelines.

Post-operatively, FVIII activity levels were to be maintained at recommended levels and duration according to WFH Guidelines.

Additional doses of 30 or 50 IU/kg every 2 to 3 days could be administered depending on the desired FVIII activity levels and the severity of the procedure.

Exit interviews
Qualitative semi-structured patient experience interviews were conducted in a subset of consenting participants from selected countries within 6 months after the Week 52 visit and before the end-of-study was declared. Because all eligible participants at the selected clinical sites were recruited in an unbiased, objective manner, it was anticipated that the overall interview study sample would be reasonably representative of the overall clinical trial sample.

Aspects of statistics
The study was open-label and without randomisation or blinding.
The primary efficacy analysis will be based on the Full Analysis Set.
The key secondary efficacy analysis will include participants in Arm A who have at least 6 months of historical data on prophylaxis treatment from observational Study 242HA201/OBS16221.

Because poor quality or adherence to the protocol can introduce bias towards the alternative hypothesis in a non-inferiority analysis, the key secondary efficacy analysis will be based on the Per Protocol Set. In order to minimise potential selection bias for the key secondary efficacy analysis, sites who participate in observational Study 242HA201/OBS16221 are expected to enrol qualified participants into this Phase 3 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 will be targeted to enrol in Arm A before additional participants from the observational study are enrolled in Arm A. Additional sites that are not participating in the observational study may enrol participants directly into this Phase 3 study.

Study teams conducted data reviews while the study was ongoing. However, to minimise potential operational biases the Sponsor's access to aggregated efficacy and PK data was restricted.

The company complied with guideline EMA/CHMP/BPWP/144533/2009 rev 2.

Trial product is administered at site attendance; the comparison to self-administration is considered to confer advantage to study outcomes.

See statistical conclusion at the end of this report.

Population

Inclusion criteria

- Previously treated patients with severe haemophilia A (defined as <1 IU/dL [<1%] endogenous FVIII or a documented genotype known to produce severe haemophilia A), aged 12 years or older.
- Participants in Arm B (on-demand regimen) had to have at least 12 episode of bleeds in the previous 12 months or at least 6 episode of bleeds in the previous 6 months prior to study enrolment.

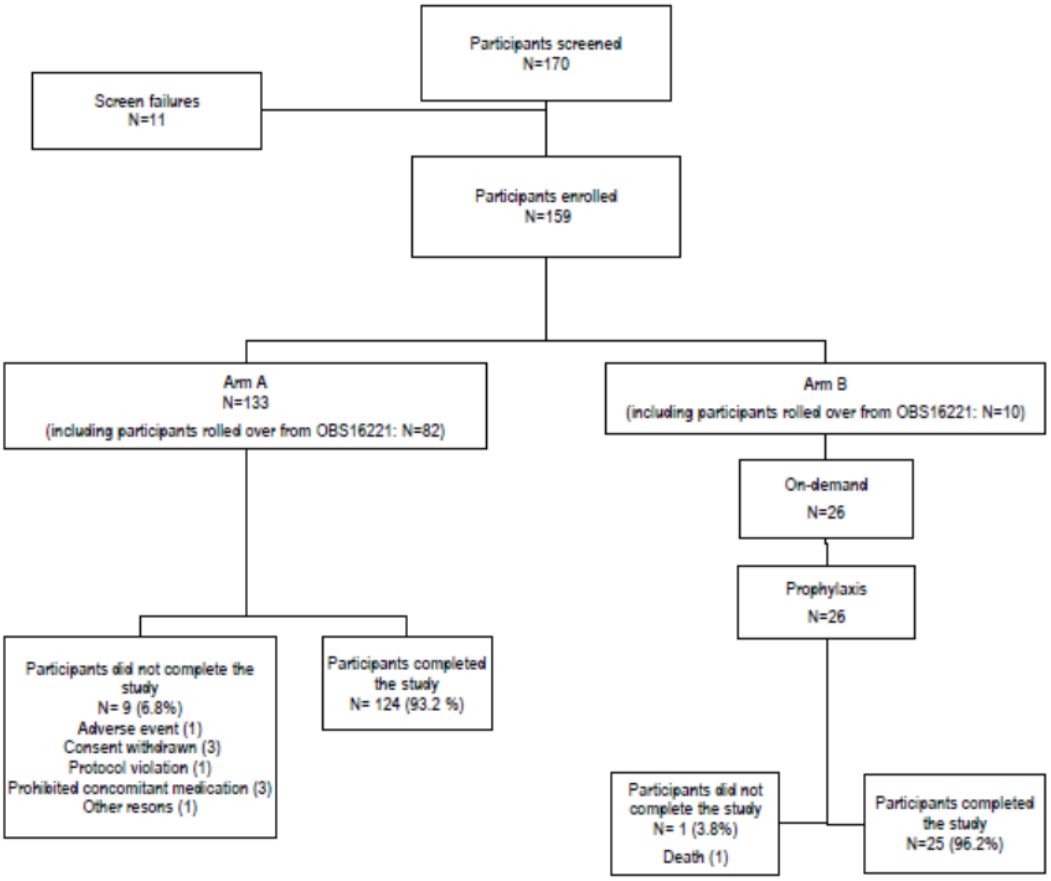
Previous treatment for haemophilia A (prophylaxis or on-demand regimen) was defined as any treatment with any recombinant and/or plasma derived FVIII product, or cryoprecipitate for at least 150 exposure days

Exclusion criteria

- Participants with a history of a positive inhibitor test or with a positive inhibitor test result at Screening were excluded.

- Disposition is summarised in the following diagram:

Participant disposition



170 participants were screened and 159 were enrolled: 133 in Arm A and 26 in Arm B. All the participants received at least one dose of Altuvoct.

149 (93.7%) participants completed the study and 10 (6.3%) prematurely discontinued. The most frequently reported reasons for study discontinuation were the use of prohibited concomitant medication and consent withdrawn (3 [1.9%] participants, each).

1 person died: “pancreas cancer with multiple metastatic nodules in liver”, considered unrelated to study product.

Demographic data

A summary of demographic and baseline characteristics is provided in the Table below:

	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)
Ethnicity, n (%)					
Number	132	26	26	13	158
Hispanic or Latino	12 (9.1)	13 (50.0)	13 (50.0)	1 (7.7)	25 (15.8)
Not Hispanic or Latino	112 (84.8)	13 (50.0)	13 (50.0)	9 (69.2)	125 (79.1)
Not reported due to confidentiality regulations	8 (6.1)	0	0	3 (23.1)	8 (5.1)
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)

	Arm A	Arm B			
	Prophylaxis (N=133)	On-demand (N=26)	Prophylaxis (N=26)	Surgery Subgroup (N=13)	Overall (N=159)
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.
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

Baseline disease characteristics.
The median and mean (SD) age at start of first prophylaxis was 1.0 and 3.6 (6.0) years for participants in Arm A.

For 25 of 26 participants in Arm B who were on on-demand treatment for at least 150 exposure days before study entry, an age at start of first prophylaxis was reported (median of 3.0 and mean [SD] of 10.8 [15.1] years) indicating these participants had been on prophylaxis treatment earlier in life.

All participants had at least 150 prior exposure days to FVIII.
Most (125 [78.6%]) had no family history of a FVIII inhibitor.

The mean (SD) number of episode of bleeds reported during the 12 months prior to the study was 3.2 (5.4) in Arm A (pre-study on prophylaxis regimen) and 35.7 (22.2) in Arm B (pre-study on-demand treatment).

44 (36.1%) participants in Arm A and 0 participant in Arm B reported no bleeds during the 12 months prior to the study.

In Arm B, almost all the participants had more than 5 bleeds during the 12 months prior to the study with 16 (69.6%) participants reporting more than 20 bleeds.

No participants in Arm B had fewer than 4 bleeds during the 12 months prior to the study.

The mean number of joint bleeds reported in the 12 months prior to the study was 2.3 (4.5) in Arm A and 27.4 (18.6) in Arm B. Of these joint bleeds, the mean number of spontaneous joint

bleeds was 1.3 (2.5) in Arm A and 20.9 (14.2) in Arm B and the mean number of traumatic joint bleeds was 1.1 (2.5) in Arm A and 7.2 (8.1) in Arm B.

At baseline, of the 133 participants in Arm A, 26 (19.5%) participants reported at least 1 target joint, with a total of 80 reported target joints. Of the 26 participants in Arm B, 23 participants reported at least 1 target joint at baseline.

Medical history
Subjects reported on haemophilic arthropathy (85 [53.5%] participants), hepatitis C (41 [25.8%] participants), hypertension (33 [20.8%] participants), HIV infection (21 [13.2%] participants) and knee arthroplasty (18 [11.3%] participants).

At study entry, 20 (12.6%), 19 (11.9%), and 57 (35.8%) of participants had positive HIV, hepatitis B and hepatitis C status, respectively.

Study participants had been exposed to different haemophilia treatments; of the 159 participants enrolled, 134 (84.3%) participants were on a prophylaxis regimen prior to study entry and 25 (15.7%) were on an on-demand treatment regimen.

Most participants (129 [81.6%]) were on a stable haemophilia treatment regimen for longer than 12 months prior to study entry.

Concomitant medications
The most frequently used concomitant medication was paracetamol in 65 (40.9%) participants, tozinameran (a covid vaccine) in 57 (35.8%) participants and celecoxib in 25 (15.7%) participants.

Medication for haemophilia-related pain was taken by 115 (72.3%) participants.

Intervention
Participants in Arm A were to receive Altuvoct at a dose of 50 IU/kg IV once weekly on a prophylaxis treatment regimen for up to 52 weeks.

Participants in Arm B were to receive Altuvoct as:

- On-demand regimen: Participants in Arm B received Altuvoct at a dose of 50 IU/kg IV as on-demand treatment of episode of bleeds for the first 26 weeks

followed by

- Prophylaxis regimen: Participants in Arm B switched to receive Altuvoct at a dose of 50 IU/kg IV once weekly as a prophylaxis treatment regimen for another 26 weeks.

During the scheduled study visits, 50 IU/kg Altuvoct was delivered via a slow push IV injection of 8 ±2 minutes (rate of administration determined by the participant's comfort level).
Overall, 96.9% of the participants were compliant to both the dosing and the dosing interval: 98.5% in Arm A and 88.5% in Arm B.

Comparator
Study OBS16221 was a global, multicentre, prospective study of up to 12 months' duration conducted in participants ≥12 years of age with severe haemophilia A who were receiving a marketed FVIII product; the aim of this study was to collect retrospective data from participants'

medical records as well as prospective clinical data (eg annualised rate of bleeding, haemophilia joint health score, patient-reported outcome measures of general health-related and disease-specific quality of life etc.) in order to enhance knowledge on the current care and treatment of severe haemophilia A.

Data from Study OBS16221 were used to perform an intra-participant comparison of ABR between weekly prophylactic treatment with Altuvoct and pre-study prophylactic treatment with a marketed FVIII product.

The study employed external comparator(s).

The schedule of assessments is shown on the following pages:

Schedule of Activities (SOA)

Table 1 - Overall schedule of activities from screening to safety follow-up call or visit

Tests and assessments	Screening[a,b] (Week -8 to Day 1)	Baseline[b] BIVV001 Day 1	Week 4[c] ±7 days	Week 13[c] ±7 days	Week 26[c,d] ±7 days	Week 39[c] ±7days	Week 52/ EOS/ET[c] ±7 days	Unscheduled visit[e]	Safety follow-up call or visit[f]
Informed consent[g]	X								
Assessment of eligibility	X	X							
Demographics[h]	X								
Weight	X	X	X	X	X	X	X		
Height	X								
Medical, surgical, and hemophilia history[i]	X								
FVIII activity (1-stage aPTT and chromogenic assays)[j,k]	X								
Genotype[i]		X							
In-clinic BIVV001 dosing[l]		X (applicable to both Arm A and Arm B)	X (applicable to Arm A only)	X (applicable to Arm A only)	X	X	X		
Safety									
Physical exam	X	X	X		X		X	X	
Vital signs[m]	X	X	X		X		X	X	
Pregnancy testing[n]	X	X		X	X	X	X		
HIV, HBV, and HCV status[o]	X								

Tests and assessments	Screening[a,b] (Week -8 to Day 1)	Baseline[b] BIVV001 Day 1	Week 4[c] ±7 days	Week 13[c] ±7 days	Week 26[c,d] ±7 days	Week 39[c] ±7days	Week 52/ EOS/ET[c] ±7 days	Unscheduled visit[e]	Safety follow-up call or visit[f]
CD4 count, viral load[p]	X								
Hematology[q]	X	X	X	X	X	X	X		
Clinical chemistry[r]	X	X	X	X	X	X	X		
von Willebrand Comprehensive Panel[s]	X	X	X	X	X	X	X		
Nijmegen-modified Bethesda assay (inhibitor assay)[k]	X	X	X	X	X	X	X		
Anti-rFVIIIFc-VWF-XTEN Antibody (ADA)[k]	X	X	X	X	X	X	X		
Adverse event/serious adverse event recording[t]	<<ongoing; monitor and record at all visits>>								
Prior and concomitant medications and concomitant therapies and procedures[u]	<<ongoing; monitor and record at all visits>>								
Monthly telephone call[v]	<<ongoing; once per month>>								
Efficacy									
HJHS joint assessments[w]		X			X		X		
Investigator's target joint assessment		X							
Physician's global assessment of response to treatment (PGA)			X	X	X	X	X		

Tests and assessments	Screening[a,b] (Week -8 to Day 1)	Baseline[b] BIVV001 Day 1	Week 4[c] ±7 days	Week 13[c] ±7 days	Week 26[c,d] ±7 days	Week 39[c] ±7days	Week 52/ EOS/ET[c] ±7 days	Unscheduled visit[e]	Safety follow-up call or visit[f]
Investigator's assessment of participant's response to treatment of bleeding episodes at the study site[x]		<<ongoing >>							
Ultrasound joint assessments[y]		X					X		
Serum and plasma samples[z] (optional)	X	X	X	X	X	X	X		
Electronic patient diary (ePD) training / administration/ review	X	X	<<ongoing >>						
Participant's completion of ePD including at-home dosing, bleeding episodes, and assessment of response to bleeding episodes[aa]		<<ongoing >>							
Pharmacokinetics									
Abbreviated pharmacokinetic Sampling[bb]		X							
Sequential pharmacokinetic sampling[cc]		X			X				
FVIII peak and trough sampling[dd]			X Arm A only	X Arm A only	X	X	X		
Participant-Reported Outcomes									
PROMIS Assessments[ee]		X			X		X		
Haem-A-QoL (≥17 years old) or –Haemo-QoL (<17 years old)		X			X		X		

Tests and assessments	Screening[a,b] (Week -8 to Day 1)	Baseline[b] BIVV001 Day 1	Week 4[c] ±7 days	Week 13[c] ±7 days	Week 26[c,d] ±7 days	Week 39[c] ±7days	Week 52/ EOS/ET[c] ±7 days	Unscheduled visit[e]	Safety follow-up call or visit[f]
HAL (≥18 years old) or pedHAL (<18 years old)		X			X		X		
TSQM		X			X		X		
Patient Global Impression of Severity (activity and joint)[ff]		X			X		X		
Patient Global Impression of Change					X		X		
EQ-5D-5L		X			X		X		
Treatment Preference Survey[gg]							X		
Physical Activity Monitor (ActiGraph Activity Monitor))[hh]	X	X	X	X	X	X	X		
Healthcare Resource Utilization		X			X		X		

BIVV001 = rFVIIIFc-VWF-XTEN (recombinant coagulation factor VIII Fc - von Willebrand factor - XTEN fusion protein), BU = Bethesda units, FVIII = Factor VIII, HBV = hepatitis B virus, HCV = hepatitis C virus, HIV = human immunodeficiency virus, HJHS=Hemophilia Joint Health Score HAL=Hemophilia Activities List, pedHAL=Pediatric Hemophilia Activities List, TSQM=Treatment Satisfaction Questionnaire for Medications, PGIC=Patient Global Impression of Change, PGIS=Patient Global Impression of Severity

a Screening may be accomplished over the course of more than 1 study visit if needed. The Screening Period is up to 8 weeks before Baseline

b Washout prior to the Screening tests of FVIII activity and inhibitor and prior to BIVV001 Day 1 dose administration is at least 96 hours (4 days) if the participant is receiving a conventional FVIII product and at least 120 hours (5 days) if current treatment is with an EHL FVIII product. For participants treated with an EHL FVIII product, the washout period may be extended at the discretion of the Investigator based on individual PK data and clinical phenotype. Separate samples for anti-rFVIIIFc-VWF-XTEN antibody (ADA) testing will be collected at the same timepoint when any samples are collected for inhibitor testing (including samples for suspected inhibitor and confirmatory inhibitor tests).

c Participants (except those in Sequential PK Arm) should schedule their study visits to be 7 ±1 day after the previous prophylactic dose of BIVV001.

d At this visit, participants in Arm B (on-demand treatment) switch to prophylaxis. Participants in the Sequential PK arm should schedule their Week 26 study visit to be 7 (+2) days after the previous prophylactic dose of BIVV001.

e Unscheduled visits may be necessary during the study to repeat any blood sampling if required, or at the discretion of the Investigator. If a participant has an unscheduled visit, the Investigator will record data as appropriate based on the purpose of the visit.

f This call or visit will occur 2 to 3 weeks after the last dose of BIVV001, unless the participant enrolls in the open-label extension study.

g Informed consent from the participant or the participant's legal guardian MUST be obtained prior to any study-related procedures, including washout of current FVIII therapy specifically for entry into the study, or the country's local regulations. Participant assent must also be obtained where applicable (according to the study site's geographic region).

h Demographics include sex, race, ethnicity, and date of birth (year of birth only), as permitted by local regulations. Race and ethnicity will be collected for reasons described in Section 4.5

i Includes hemophilia history assessment of disease severity, blood type, and Rh factor if not previously documented. For Repeat Screening Visit, update with any changes since original Screening Visit.

j Collection of samples for genotype analysis (as permitted by local regulations and ethics committees) will be governed by a separate informed consent form (ICF). HLA genotype will not be needed if previously documented.

k Washout prior to the Screening tests of FVIII activity and inhibitor and prior to BIVV001 Day 1 dose administration is at least 96 hours (4 days) if the participant is receiving a conventional FVIII product and at least 120 hours (5 days) if current treatment is with an EHL FVIII product. In participants treated with an EHL FVIII product, the washout period may be extended at the discretion of the Investigator based on individual PK data and clinical phenotype. . Washout prior to all other scheduled inhibitor tests must be at least 7±1 days. Inhibitor and ADA samples will be collected prior to BIVV001 dosing. Separate samples for anti-rFVIIIFc-VWF-XTEN antibody (ADA) testing will be collected at the same timepoint when any samples are collected for inhibitor testing (including samples for suspected inhibitor and confirmatory inhibitor tests). All inhibitor assays, including the assay for the Screening Visit and any confirmatory assays, will be performed by the central laboratory using the Nijmegen-modified Bethesda assay. If a Nijmegen-modified Bethesda assay result returns as ≥0.6 BU/mL, a separate sample must be collected and tested for confirmation of inhibitor development within 2 to 4 weeks. Testing for potential ADA formation will be performed at a central laboratory using a validated rFVIIIFc-VWF-XTEN-specific ADA assay. Confirmed positive samples will be further characterized for antibodies specific to FVIII, Fc, D'D3, or XTEN.

l Participants in Arm A will have BIVV001 doses given at each applicable scheduled visit. Participants in Arm B will have BIVV001 doses at visits Day 1, Weeks 26, 39, and 52. BIVV001 will be delivered via a slow push IV injection of 8 min ± 2 minutes, at a rate of administration determined by the participant's comfort level. Injection start and stop time will be recorded in the eCRF. Other doses may be self/caregiver administered at home (or in clinic) (Table 3)

m Vital signs include blood pressure, pulse rate, respiratory rate, and temperature (°C). Vital signs should be taken after the participant has been resting supine for 5 minutes. Vital signs will be measured pre-injection and 30 (±15 minutes) from the start of injection at clinic visits. Vital signs should also be taken at any unscheduled visit.

n Applicable to female participants only. A serum pregnancy test should be performed at screening. For all other time points, serum or urine pregnancy testing may be performed at the discretion of the Investigator. If a urine test cannot be confirmed as negative (eg, an ambiguous result), a serum pregnancy test is required. In such cases, the participant must be excluded from further participation if the serum pregnancy result is positive.

o For participants who have been historically negative, assess HIV, HBV, and HCV status with central laboratory test.

p For participants known to be HIV antibody positive, CD4 count and viral load tests must be performed at the central laboratory if results are not available from within 26 weeks prior to screening.

q Hematology parameters include red blood cell (RBC) count, white blood cell (WBC) count and differential, platelet count, hemoglobin (Hgb), and hematocrit (Hct). Blood samples for hematology analysis will be collected prior to BIVV001 dosing.

r Clinical chemistry parameters include alanine aminotransferase (ALT), aspartate aminotransferase (AST), alkaline phosphatase (ALP), gamma glutamyl transferase (GGT), bilirubin, blood urea nitrogen (BUN), creatinine, glucose, total protein, sodium, potassium, and chloride. Blood samples for clinical chemistry analysis will be collected prior to BIVV001 dosing.

s The Von Willebrand comprehensive panel (includes assessments of von Willebrand Factor [VWF] ristocetin cofactor activity and VWF antigen). Blood samples for analysis of Von Willebrand comprehensive panel will be collected prior to any BIVV001 dosing.

t Adverse events (AEs) and serious adverse events (SAEs) occurring after signing of the informed consent form (ICF) through the Safety Follow-Up Call or Visit will be recorded on the case report form (CRF).

u Prior and concomitant medications from up to 30 days prior to Screening and concomitant therapies and procedures from signing of ICF through the Safety Follow-Up Call or Visit will be recorded on the CRF.

v In addition to scheduled clinic visits, telephone calls are planned approximately once a month for the site staff to check on each participant's status. During the monthly telephone call, the participant's parent/caregiver will also be reminded about the requirement for timely ePD data entry, and assessments of "spontaneous" and "traumatic" bleeding episodes will be noted.

w Investigator will examine each participant's joints per the Haemophilia Joint Health Score (HJHS). At baseline, the Investigator will assess the presence of any target joints according to ISTH criteria.

x For bleeding episodes treated at the study sites, the Investigator will contact the participant approximately 72 hours from the time the BIVV001 injection was administered to treat the bleeding episode and record the participant's assessment of response to BIVV001 treatment on the eCRF using a 4-point bleeding response scale. For bleeding episodes that are treated at home, participants will record response to bleeding episodes in the ePD.

y Anatomical structural joint-health assessment via ultrasound imaging per Joint Tissue Activity and Damage Examination (JADE) protocol and/or Hemophilia Early Arthropathy Detection with Ultrasound (HEAD-US) in a subpopulation of participants from Arm A at selected sites.

z Samples will be collected prior to any BIVV001 dosing and will be archived by the central laboratory (if required) for future research, eg., immunology assays, further coagulation assays, or clarification of any clinical or laboratory AE, etc. This is optional and participants will sign an additional consent for this research.

aa Participants will record all bleeding episodes in the ePD beginning at Baseline. Assessment of response to bleeding episodes using a 4-point bleeding response scale. The participant should record response approximately 72 hours from the time the first BIVV001 injection was administered to treat the bleeding episode, unless treatment of the bleed was administered in the clinic. In that case, the investigator will report the participant's response to treatment via the eCRF.

bb All participants (except those in the sequential PK subgroup of Arm A) will undergo abbreviated PK sampling after the first dose of BIVV001 (Baseline). See abbreviated PK sampling details in Table 2.

cc Participants in the sequential PK subgroup (n=16) will undergo more extensive PK sampling at Baseline and again at Week 26. See sequential PK sampling details as described in Table 3.

dd Peak and trough sample only (collected within 30 min prior to rFVIIIFc-VWF-XTEN dosing and 15 min ± 3 min post injection. This trough sample should be collected at the same time point as the trough inhibitor and anti-drug antibody (ADA) samples taken predose (Table 2).

ee PROMIS Assessments to include Pain Intensity, Pain Interference (PROMIS-SF Pain Interference ≥18 years old or PROMIS Pediatric-SF Pain Interference <18 years old), and Physical Function (PROMIS-SF Physical Function ≥18 years old or PROMIS Pediatric-SF Physical Activity <18 years old). See Section 8.1.2.

ff Patient Global Impression of Severity (PGIS) assessment will include a single question on patient perception of activity and a single question on patient perception of joint health. See Section 8.1.2.

gg Treatment preference survey will consist of 2 questions on patient preference and a single question on Patient Global Impression of Change (PGIC). See Section 8.1.2.

hh Where available, assessments of physical activity (PA) will be done by using a triaxial medical grade accelerometer (ActiGraph Activity Monitor) worn on the nondominant wrist. Device to be worn daily for 7 consecutive days corresponding to scheduled visits. Refer to Section 8.1.3

It is noted that the study employs 10 clinical outcome assessment tools, most of which are patient-reported, as well as an electronic diary for patients and physician-reported outcome assessments; this is considered to represent a substantial burden to patients and to be highly likely to result in missing data.

Outcomes

The primary objective of the study was to evaluate the efficacy of Altuvoct weekly prophylaxis as estimated by the mean annualised bleed rate.

To note that the applicant has conducted a complex statistical analysis of outcomes. Refer to the statistical conclusion at the end of this report.

In the full analysis set, a total of 86 episode of bleeds were treated with Altuvoct in 133 participants who had an efficacy period in Arm A. The mean (SD) duration of the efficacy period was 47.55 (8.77) weeks. Total participant-years followed was 121.2.

The median (Q1; Q3) annualised bleed rate was 0.00. The mean annualised bleed rate [model-based] was 0.71.

In Arm A, 86 (64.7%) participants having no episode of bleeds during the study. An extract of the table is shown below.

Summary of annualized bleeding rates - Full Analysis Set

	Arm A
	Prophylaxis (N=133)
Annualized bleeding rate (ABR)	
Number	133
Mean (SD)	0.71 (1.43)
Median	0.00
Q1 ; Q3	0.00 ; 1.04
Min ; Max	0.0 ; 11.0
0	86 (64.7)
>0-5	45 (33.8)
>5-10	1 (0.8)
>10-20	1 (0.8)
>20	0

The ideal would be zero bleeds during the study period; no bleeds recorded in 65% of subjects during the study period of (median) 50 weeks is considered modest efficacy; up to 11 annualised bleeds is considered still not without clinical consequence.

The key secondary endpoint of the applicant is:
Intra-patient comparison of annualised bleed rate during them Altuvoct weekly prophylaxis treatment period versus the historical prophylaxis annualised bleed rate for participants in Arm A who participated in Study 242HA201/OBS16221, an observational study of pre-study standard of care prophylaxis treatment with marketed FVIII products (also referred to as "historical prophylaxis").

Participants who had an efficacy period ≥26 weeks in study EFC16293 and had an observation period ≥26 weeks in study OBS16221 were included for the analysis.

An intra-patient comparison is considered as an external (historical) control. Further, those subjects who participated in study OBS16221 were selected. From a clinical perspective, the approach of the applicant is regarded in a general sense only.

Results are summarised in the extract of the table, below:

Key secondary endpoint (hierarchical testing procedure)		Arm A	
Intra-participant comparison of ABR between BIVV001 prophylaxis and pre-study FVIII prophylaxis: non-inferiority analysis based on PPS	Comparison groups	Historical prophylaxis (OBS16221) (N=77)	BIVV001 prophylaxis (EFC16293) (N=77)
	Mean ABR (95% CI) [b]	2.99 (2.03; 4.42)	0.69 (0.43; 1.12)
	Mean difference (95% CI) [b]		-2.30 (-3.49; -1.11)
Intra-participant comparison of ABR between BIVV001 prophylaxis and pre-study FVIII prophylaxis: superiority analysis based on FAS	Comparison groups	Historical Prophylaxis (OBS16221) (N=78)	BIVV001 Prophylaxis (EFC16293) (N=78)
	Mean ABR (95% CI) [b]	2.96 (2.00; 4.37)	0.69 (0.43; 1.11)
	Rate ratio (95% CI) [b]		0.23 (0.13; 0.42)
	p-value (superiority) [c]		<0.0001

A comparison of data obtained during a clinical study and data obtained during 'usual care' is not considered to be a fair comparison; bias would favour the clinical study data.

Data are noted yet from a clinical perspective, the approach of the applicant is regarded in a general sense only.

The applicant also submits extensive comparisons between Altuvoct and the historical comparison for the full analysis set and the per protocol set; data are noted in a general sense only.

Refer to the statistical conclusion at the end of this report.

Annualised bleed rate by type of bleed is shown in the table below:

Type of bleed	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 spontaneous bleeding episodes	33	197	5
Total number of traumatic bleeding episodes	45	62	2
Total number of unknown bleeding episodes	8	9	1
Spontaneous			
Participant-level			
Number	133	26	26
Mean (SD)	0.29 (0.73)	15.87 (9.28)	0.45 (1.13)
Median	0.00	16.69	0.00
Q1 ; Q3	0.00 ; 0.00	8.64 ; 23.76	0.00 ; 0.00
Min ; Max	0.0 ; 4.7	0.0 ; 31.3	0.0 ; 4.1
0	107 (80.5)	1 (3.8)	22 (84.6)
>0-5	26 (19.5)	4 (15.4)	4 (15.4)
>5-10	0	2 (7.7)	0
>10-20	0	12 (46.2)	0
>20	0	7 (26.9)	0
Population-level, model based[a]			
Mean (95% CI)	0.27 (0.18; 0.41)	15.83 (12.27; 20.43)	0.44 (0.16; 1.20)
Traumatic			
Participant-level			
Number	133	26	26
Mean (SD)	0.36 (0.83)	4.82 (6.31)	0.15 (0.78)
Median	0.00	3.95	0.00
Q1 ; Q3	0.00 ; 0.00	0.00 ; 6.48	0.00 ; 0.00
Min ; Max	0.0 ; 5.5	0.0 ; 24.9	0.0 ; 4.0
0	103 (77.4)	8 (30.8)	25 (96.2)
>0-5	29 (21.8)	10 (38.5)	1 (3.8)
>5-10	1 (0.8)	6 (23.1)	0
>10-20	0	0	0
>20	0	2 (7.7)	0
Population-level, model based[a]			
Mean (95% CI)	0.37 (0.25; 0.54)	4.85 (3.04; 7.74)	0.17 (0.01; 1.89)

Type of bleed	Arm A	Arm B	
	Prophylaxis (N=133)	On-demand (N=26)	Prophylaxis (N=26)

Unknown type			
Participant-level			
Number	133	26	26
Mean (SD)	0.06 (0.48)	0.73 (1.78)	0.09 (0.44)
Median	0.00	0.00	0.00
Q1 ; Q3	0.00 ; 0.00	0.00 ; 0.00	0.00 ; 0.00
Min ; Max	0.0 ; 5.2	0.0 ; 6.3	0.0 ; 2.2
0	129 (97.0)	21 (80.8)	25 (96.2)
>0-5	3 (2.3)	3 (11.5)	1 (3.8)
>5-10	1 (0.8)	2 (7.7)	0
>10-20	0	0	0
>20	0	0	0
Population-level, model based[a]			
Mean (95% CI)	0.07 (0.02; 0.24)	0.73 (0.26; 2.01)	0.09 (0.01; 0.62)

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.

Those on prophylaxis experienced less bleeds than those on on-demand regimen.

For those on prophylaxis in arm A, subjects experienced: up to 5 spontaneous annualised bleeds; up to 10 traumatic annualised bleeds; and up to 10 annualised bleeds of 'unknown character'.

For those on on-demand treatment in arm B, subjects experienced: up to 31.3 spontaneous annualised bleeds; up to 24.9 traumatic annualised bleeds; and up to 6.3 annualised bleeds of 'unknown character'.

For those on prophylaxis in arm B, subjects experienced: up to 5 spontaneous annualised bleeds; up to 5 traumatic annualised bleeds; and up to 5 annualised bleeds of 'unknown character' (data are similar to those found in arm A).

In view of the claimed half-life of (about) 40hrs and the once per week administration posology, the applicant provided a summary of episode of bleeds by time since last prophylactic or on demand dose of efanesoctocog alfa.

In Arm A, the number of overall episode of bleeds on days 1-4 and days 5-7 after last prophylactic dose were similar (39 vs 36). Approximately two-thirds of the episode of bleeds that occurred during days 1-4 were traumatic bleeds (25/39, 64.1%), whereas during days 5-7 an equal number of spontaneous and traumatic bleeds occurred (18 each). For the 8 episode of bleeds of unknown type, the onset time was unknown.

A summary for Arm B is also provided.

The applicant described a different pattern of bleed for days 1-4 (two thirds were traumatic) versus days 5-7 (equal number of traumatic and spontaneous). The higher proportion of spontaneous bleeds in days 5-7 suggests that the product may not be able to provide such blanket protection over the course of 1 week following administration of product.

Annualised bleed rate by location is shown in the table below:

Location of bleed	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 at joint	61	219	7
Total number of treated bleeding episodes at muscle	25	27	0
Total number of treated bleeding episodes at internal	7	5	0
Total number of treated bleeding episodes at skin/mucosa	15	18	1
Total number of treated bleeding episodes at unknown location	0	1	0
Joint			
Participant-level			
Number	133	26	26
Mean (SD)	0.52 (1.09)	17.45 (7.31)	0.61 (1.33)
Median	0.00	18.42	0.00
Q1 ; Q3	0.00 ; 1.02	10.80 ; 23.90	0.00 ; 0.00
Min ; Max	0.0 ; 6.2	4.1 ; 30.4	0.0 ; 4.1
0	96 (72.2)	0	21 (80.8)
>0-5	35 (26.3)	1 (3.8)	5 (19.2)
>5-10	2 (1.5)	3 (11.5)	0
>10-20	0	13 (50.0)	0
>20	0	9 (34.6)	0
Population-level, model based[a]			
Mean (95% CI)	0.51 (0.36; 0.72)	17.48 (14.88; 20.54)	0.62 (0.25; 1.52)

Location of bleed	Arm A	Arm B	
	Prophylaxis (N=133)	On-demand (N=26)	Prophylaxis (N=26)
Muscle			
Participant-level			
Number	133	26	26
Mean (SD)	0.20 (0.93)	2.20 (3.28)	0.00 (0.00)
Median	0.00	0.00	0.00
Q1 ; Q3	0.00 ; 0.00	0.00 ; 4.15	0.00 ; 0.00
Min ; Max	0.0 ; 7.7	0.0 ; 13.0	0.0 ; 0.0
0	121 (91.0)	14 (53.8)	26 (100)
>0-5	10 (7.5)	8 (30.8)	0
>5-10	2 (1.5)	3 (11.5)	0
>10-20	0	1 (3.8)	0
>20	0	0	0
Population-level, model based[a]			
Mean (95% CI)	0.21 (0.10; 0.44)	2.18 (1.20; 3.98)	NC#
Internal			
Participant-level			
Number	133	26	26
Mean (SD)	0.05 (0.26)	0.40 (1.67)	0.00 (0.00)
Median	0.00	0.00	0.00
Q1 ; Q3	0.00 ; 0.00	0.00 ; 0.00	0.00 ; 0.00
Min ; Max	0.0 ; 2.0	0.0 ; 8.3	0.0 ; 0.0
0	127 (95.5)	24 (92.3)	26 (100)
>0-5	6 (4.5)	1 (3.8)	0
>5-10	0	1 (3.8)	0
>10-20	0	0	0
>20	0	0	0
Population-level, model based[a]			
Mean (95% CI)	0.06 (0.02; 0.13)	0.40 (0.06; 2.66)	NC#
Skin/mucosa			
Participant-level			
Number	133	26	26
Mean (SD)	0.12 (0.62)	1.45 (2.05)	0.08 (0.41)
Median	0.00	0.00	0.00
Q1 ; Q3	0.00 ; 0.00	0.00 ; 2.09	0.00 ; 0.00
Min ; Max	0.0 ; 6.2	0.0 ; 6.5	0.0 ; 2.1
0	125 (94.0)	15 (57.7)	25 (96.2)
>0-5	7 (5.3)	9 (34.6)	1 (3.8)
>5-10	1 (0.8)	2 (7.7)	0
>10-20	0	0	0

Location of bleed	Arm A	Arm B	
	Prophylaxis (N=133)	On-demand (N=26)	Prophylaxis (N=26)
>20	0	0	0
Population-level, model based[a]			
Mean (95% CI)	0.12 (0.05; 0.29)	1.44 (0.83; 2.52)	NC#
Unknown location			
Participant-level			
Number	133	26	26
Mean (SD)	0.00 (0.00)	0.08 (0.41)	0.00 (0.00)
Median	0.00	0.00	0.00
Q1 ; Q3	0.00 ; 0.00	0.00 ; 0.00	0.00 ; 0.00
Min ; Max	0.0 ; 0.0	0.0 ; 2.1	0.0 ; 0.0
0	133 (100)	25 (96.2)	26 (100)
>0-5	0	1 (3.8)	0
>5-10	0	0	0
>10-20	0	0	0
>20	0	0	0
Population-level, model based[a]			
Mean (95% CI)	NC#	0.08 (0.01; 0.57)	NC#

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.

#:The parameter cannot be estimated due to too few bleedings occurring in the category and regimen.

For 26 participants in Arm B the efficacy of 50 IU/kg once weekly Altuvoct prophylaxis in terms of annualised bleed rate was compared to on-demand treatment with Altuvoct. The total number of participant-years followed was 12.5 with on-demand treatment and 11.4 with prophylaxis treatment in Arm B. Results are shown in the following table:

Intra-patient comparison of annualised bleeding rates: BIVV001 prophylaxis versus on-demand in Arm B – Full Analysis Set

	Arm B	
	On-demand (N=26)	Prophylaxis (N=26)
Number of participants with an efficacy period	26	26
Total number of treated bleeding episodes	268	8
Total participant-years followed	12.5	11.4
Duration of efficacy period (weeks)		
Number	26	26
Mean (SD)	25.12 (1.07)	22.89 (6.00)
Median	25.00	25.08

Q1 ; Q3	24.72 ; 25.02	22.07 ; 27.06
Min ; Max	23.9 ; 29.3	1.1 ; 27.1
Annualized bleeding rate (ABR)		
Number	26	26
Mean (SD)	21.42 (7.41)	0.69 (1.35)
Median	21.13	0.00
Q1 ; Q3	15.12 ; 27.13	0.00 ; 0.00
Min ; Max	8.3 ; 33.4	0.0 ; 4.1
0	0	20 (76.9)
>0-5	0	6 (23.1)
>5-10	1 (3.8)	0
>10-20	10 (38.5)	0
>20	15 (57.7)	0
Negative Binomial regression model [a]		
Mean ABR (95% CI)	21.41 (18.81; 24.36)	0.70 (0.33; 1.48)
Rate ratio (95% CI)		0.03 (0.02; 0.07)
p-value (superiority) [b]		<.0001

Note:
1: Summaries are based on treated bleeds.
2: Percentages are based on the number of participants in each treatment regimen of Arm B 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).
a Estimated using a repeated negative binomial model with treatment (BIVV001 prophylaxis vs historical prophylaxis) as covariate.
b P-value relates to paired rate ratio (BIVV001 prophylaxis/on-demand) >=0.5.

Percentage of participants who maintained FVIII activity levels above prespecified levels during the study is summarised in the following table:

	Arm A: Prophylaxis (N=133)
n (%)	**Pre-dose (trough)**
Number of participants with at least one non-missing post-baseline result	131
Number of participants with all trough samples that are within 168 ±5 hours from the previous dose	103
Achieving trough FVIII activity levels above[a]	
>1%	103 (100)
>5%	102 (99.0)
>10%	86 (83.5)
>15%	42 (40.8)
>20%	18 (17.5)

Note: Percentages are based on the number of participants with all trough samples that are within 168 ±5 hours from the previous dose.
a Achieving trough FVIII activity levels above x% are based on the average trough samples (i.e., nominal 168 hour time point) from each scheduled visit (Week 4, Week 13, Week 26, Week 39, Week 52/EOS/ET) using the aPTT-based one-stage clotting assay. Participants with trough samples that are outside 168 +/-5 hours from the previous dose will be excluded from this analysis.

There appears to be much variability in the PK of the current product with most showing <15% activity at trough measurement.

Data of the table are consistent with a serum half-life of product of (about) 40hrs.

To note that factor VIII has a population half-life of (about) 12hrs in serum; the range is of the order 6hr to 24hr.

Number of injections and dose of Altuvoct to treat a episode of bleeds

362 bleeds were treated with Altuvoct; all but 1 of the episode of bleeds (99.7%) were controlled with ≤2 injections of Altuvoct, with 96.7% controlled by 1 injection, as summarised:

	Arm A	Arm B		
	Prophylaxis (N=133)	On-Demand (N=26)	Prophylaxis (N=26)	Overall (N=159)
Number of participants with an efficacy period	133	26	26	159
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
1	81 (94.2)	261 (97.4)	8 (100)	350 (96.7)
>1	5 (5.8)	7 (2.6)	0	12 (3.3)
<=2	85 (98.8)	268 (100)	8 (100)	361 (99.7)
>2	1 (1.2)	0	0	1 (0.3)
Per subject [b]				
Number [c]	47	26	6	73
Mean (SD)	1.0 (0.1)	1.0 (0.1)	1.0 (0.0)	1.0 (0.1)
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 ; 2	1 ; 1	1 ; 1	1 ; 2
1-<2	47 (100)	26 (100)	6 (100)	73 (100)
2-<3	0	0	0	0
3-<4	0	0	0	0
>=4	0	0	0	0

	Arm A	Arm B		
	Prophylaxis (N=133)	On-Demand (N=26)	Prophylaxis (N=26)	Overall (N=159)
1-<2	47 (100)	26 (100)	6 (100)	73 (100)
>=2	0	0	0	0

Note:
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.
b The number of injections required to resolve each bleeding episode is averaged across all bleeding episodes per participant.
c Number = number of participants with at least 1 treated bleeding episode. Percentages are based on this number.

In the main, episode of bleeding with managed with 2 or less injections; there is one instance of 3 injections being needed.

There appears little, if any, difference between the on-demand and prophylaxis regimens with regards to number of injections needed to treat a bleed.

Assessment of participants' response to Altuvoct treatment of episode of bleeds

Participants assessed the response to each injection of Altuvoct for treating a bleed using a 4-point scale of excellent, good, moderate and none based on ISTH standardised definitions in haemophilia.

Overall, across the 2 treatment arms, 375 injections of Altuvoct were given to treat 362 episode of bleeds during the efficacy period. Of these injections, 334 were evaluated for response with the majority (94.9%) 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.

Summary of participant's assessment of response to BIVV001 treatment of episode of bleeds – 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
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)
First injection for each bleeding episode				
Based on injections with an evaluation				
Number[a]	72	254	6	332
Excellent or Good	59 (81.9)	250 (98.4)	6 (100)	315 (94.9)
Excellent	39 (54.2)	194 (76.4)	5 (83.3)	238 (71.7)
Good	20 (27.8)	56 (22.0)	1 (16.7)	77 (23.2)
Moderate	10 (13.9)	4 (1.6)	0	14 (4.2)
None	3 (4.2)	0	0	3 (0.9)

	Arm A	Arm B		
n(%)	Prophylaxis (N=133)	On-demand (N=26)	Prophylaxis (N=26)	Overall (N=159)

Based on all injections				
Number[b]	86	268	8	362
Excellent or Good	59 (68.6)	250 (93.3)	6 (75.0)	315 (87.0)
Excellent	39 (45.3)	194 (72.4)	5 (62.5)	238 (65.7)
Good	20 (23.3)	56 (20.9)	1 (12.5)	77 (21.3)
Moderate	10 (11.6)	4 (1.5)	0	14 (3.9)
None	3 (3.5)	0	0	3 (0.8)
Response not provided	14 (16.3)	14 (5.2)	2 (25.0)	30 (8.3)

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

Although responses are described in the main as "excellent" or "good" or "moderate", it is noted that response was "not provided" in up to 25% instances within each grouping i.e. there is much uncertainty in what is the opinion of subjects.

Physician's global assessment of participant's response to Altuvoct treatment [based on a 4-point response scale] are summarised:

16.2.6 Efficacy response data
16.2.6.4 All other secondary endpoints
16.2.6.4.13 Summary of physician's global assessment of the participant's response to the BIVV001 treatment

	Arm A	Arm B	
	Prophylaxis (N=133)	On-demand (N=26)	Prophylaxis (N=26)
Total responses			
Number[b]	622	77	44
Excellent	595 (95.7)	74 (96.1)	41 (93.2)
Effective	27 (4.3)	3 (3.9)	3 (6.8)

Note: 1: Assessments during major surgical/rehabilitation periods are excluded.
[a]Percentages are based on the number of participants with non-missing observations at the respective visit.
[b]Percentage for total responses throughout the study will be based on the total number of assessments across all visits, including those at unscheduled visits; multiple responses per participant are counted.

Physician's global assessment of about 95% responses being 'effective' is noted within the context of an open-label, unblinded study lacking an internal control.

Target joint resolution

A target joint was defined as a major joint into which ≥3 spontaneous episode of bleeds occurred in a consecutive 6-month period. Resolution was achieved when ≤2 bleeds occurred into that joint during 12 months of continuous exposure. At baseline, 26 participants in Arm A reported a total of 80 target joints.

Results are summarised for arm A:

Summary of target joint resolution based on spontaneous bleeds – Full Analysis Set

n (%)	Arm A
	Prophylaxis (N=133)
Participants with target joints at baseline[a]	26
Participants with at least 12 months continuous exposure	14
Participants with ≥1 target joints resolved[b]	14 (100)
Total number of target joints at baseline[a]	80
Total number of target joints from participants with at least 12 months continuous exposure	45
Total number of target joints resolved[b]	45 (100)
Number of spontaneous bleeds in target joints resolved[c]	
0	44 (97.8)
1	1 (2.2)
2	0

Note:
1: The analysis includes only target joints with at least 12 months continuous exposure (defined as treatment regimen period ≥52 weeks). Target joints on which surgery (major or minor) was performed on or before the end of the participant's 12 months of exposure will be censored.

a A target joint at baseline is defined as a major joint with ≥3 spontaneous bleeding episodes in a consecutive 6 month period prior to entry to the study, captured at baseline.

b A target joint resolved is defined as ≤2 spontaneous bleeds into that joint during 12 months of continuous exposure. Percentage is calculated out of Participants with at least 12 months continuous exposure.

c Percentage is calculated out of total number of joints from participants with at least 12 months continuous exposure.

'Target joint' analysis is based on a subgroup of 26 subjects; the applicant only reports on those 14 subjects with 12 months exposure.

Reported outcome tools.

The applicant employed numerous reported-outcome tools.

It is considered that data do not convince on difference between status on Altuvoct versus status on previous medicinal product. Data are viewed in a general sense only.

<u>Surgery endpoints</u>
Minor surgery is defined as any invasive operative procedure in which only skin, mucous membranes, or superficial connective tissue is manipulated and does not meet the criteria for major surgery (eg dental extraction of <3 non-molar teeth). Minor surgical procedures may be performed at a local health care provider institution.

Major surgery is defined as any invasive operative procedure that requires any of the following:

- Opening into a major body cavity (eg, abdomen, thorax, skull)
- Operation on a joint
- Removal of an organ
- Dental extraction of any molar teeth or ≥3 non-molar teeth
- Operative alteration of normal anatomy
- Crossing of a mesenchymal barrier (e.g. pleura, peritoneum, dura)

It is recommended that any elective non-dental major surgery be performed at a study site, when possible.

14 major surgeries were performed in 13 participants. Of the 13 participants, 1 was in Arm B and all the other participants were in Arm A. One participant underwent 2 major surgeries (hip replacement on Day 37 and neurolysis of the ulnar nerve on Day 164).
In 2 of the 13 participants, both in Arm A, major surgeries (osteosynthesis of right tibia in Participant No. 016293-056-0161-00503 and coronary artery bypass in Participant No. 016293-840-0917-00501) took place after the last Altuvoct dosing and are thus not taken into account in the assessments of major surgeries.

Investigators' / Surgeons' assessment of participant's haemostatic response to Altuvoct treatment
The Investigators'/Surgeons' assessment of the participant's haemostatic response to Altuvoct treatment was collected 24 hours post-surgery based on the ISTH 4-point response scale of excellent, good, fair, and poor. Outcomes are shown:

	Surgery subgroup (N=13)
Number of major surgeries	12
Assessment of response, n (%)	
Excellent or Good	12 (100)
Excellent (=1)	12 (100)
Good (=2)	0
Fair (=3)	0
Poor/none (=4)	0
Number	12
Mean (SD)	1.0 (0.0)
Median	1.0
Q1 ; Q3	1.0 ; 1.0
Min ; Max	1 ; 1

Note:
1: Percentages are based on the number of major surgeries with assessments.:
2: The analysis in the table body is based on the major surgeries conducted during the treatment regimen, excluding the surgeries conducted after the last BIVV001 dosing. Those excluded major surgeries are counted in the capital N in the header.

Investigators'/Surgeons' assessment of the participant's haemostatic response to Altuvoct was available in all 12 major surgeries that occurred while the participant was on Altuvoct regimen. Haemostatic response was rated as excellent by the Investigators/Surgeons for all 12 major surgeries.

Estimated blood loss for major surgery
The mean (SD) estimated blood loss was 143.33 (189.38) mL during major surgery. Of the 6 participants for whom information was reported, 1 had no blood loss and 5 had estimated blood loss ranging between 10 mL (removal of device from left elbow) to 500 mL (hip replacement). The mean postoperative blood loss (ie, from the day following the end of surgery to the date of hospital discharge) was 65.56 (132.01) mL. Of the 9 participants for whom information was reported, 6 had no postoperative blood loss and 3 had postoperative blood loss of 90.0 mL (total knee replacement), 100.0 mL (removal of osteosynthesis material) and 400.0 mL (hip replacement), respectively.
Number and type of blood component transfusions for major surgery

No participants required transfusion during the surgical period

Summary of clinical efficacy

Design

Study XTEND-1 is considered a composite of two single arm studies with external controls.

Conduct

There were 158 male and 1 female subject; mean age 35yrs (range 12 – 72 yrs); 61% White, 18% Asian; median weight 78kg; median body mass index 25.7kg/m2. Baseline characteristics and medical history were typical of a population with haemophilia A.

133 subjects in arm A were administered Altuvoct 50 IU/kg once weekly intravenously as prophylaxis for up to 52 weeks (124 subjects completed the study); 26 subjects in arm B were administered Altuvoct 50 IU/kg intravenously on demand for 26 months and then transferred to weekly prophylaxis up to 52 weeks (25 subjects completed the study).

Outcomes and analysis

For those on prophylaxis in arm A, subjects experienced: up to 5 spontaneous annualised bleeds; up to 10 traumatic annualised bleeds; and up to 10 annualised bleeds of 'unknown character'.
For those on on-demand treatment in arm B, subjects experienced: up to 31.3 spontaneous annualised bleeds; up to 24.9 traumatic annualised bleeds; and up to 6.3 annualised bleeds of 'unknown character'.

For the 133 subjects in arm A (prophylaxis): the mean (SD) annualised bleed rate was 0.71 (1.43); the mean (SD) annualised spontaneous bleed rate was 0.29 (0.73); the mean (SD) annualised traumatic bleed rate was 0.36 (0.83).

For the 26 subjects in arm B during the on-demand phase: the mean (SD) annualised spontaneous bleed rate was 15.87 (9.28); the mean (SD) annualised traumatic bleed rate was 4.82 (6.31).
For the 26 subjects in arm B during the prophylaxis phase: the mean (SD) annualised spontaneous bleed rate was 0.45 (1.13); the mean (SD) annualised traumatic bleed rate was 0.15 (0.78).

Bleed rates during the on-demand phase are notably higher than the prophylaxis phase, as may be expected.

Episodes of bleeding were in joints, muscles, skin, 'internal' and unknown; the pattern is as expected for subjects with haemophilia A. Those on prophylaxis had less episodes of bleeding compared to those "on demand". In the main, episodes of bleeding were managed with 2 or less injections of the current product. Subjects considered responses to be excellent, good or moderate (though it is noted that about 25% subjects did not return results on this). The attending physician reported responses as excellent in about 95% instances.

The applicant reports on 12 major surgeries; outcome is reported as 'excellent'; none of the subjects needed transfusion.

The applicant reports on numerous outcome tools (patient- and clinician- driven); the reports appear to be presented on the basis of available-case analysis. Information from the various outcome tools - the Haemophilia Joint Health Score, Haem-A-QoL and PROMIS and EQ-5D-L

tools - show that some subjects fare better and some fare worse over the course of the study. Not all subjects returned data. Data from these tools is regarded in a general sense. Exit interviews showed that subjects were "quite or very satisfied with Altuvoct".

Conclusions on clinical efficacy
It may be concurred that Altuvoct bears efficacy yet, in the ideal situation where subjects do not experience bleeds (over the course of the study), up to 11 annualised bleeds were reported and 65% of subjects recorded 'no bleeds' during the study period of (median) 50 weeks.

In the pivotal study EFC16293 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 with severe haemophilia A.

Clinical safety
Exposure
All 159 participants included in the study received at least one dose of Altuvoct. 152 (95.6%) participants were treated for at least 39 weeks.

Of the 159 participants who received at least 1 dose of Altuvoct, 115 (72.3%) had 50 or more exposure days.

The mean (SD) duration of Altuvoct dosing (calculated from the date and time of the first Altuvoct dose to the end date and time of the last treatment regimen in the study) was 49.64 (8.34) weeks overall.

The mean (SD) total number of exposure days was 48.4 (10.5) in the overall population. Data are summarised in the following table:

	Arm A	Arm B		
	Prophylaxis (N=133)	On-demand (N=26)	Prophylaxis (N=26)	Overall (N=159)
Total exposure days (EDs)[a] , n (%)				
<5	2 (1.5)	0	1 (3.8)	2 (1.3)
5-<10	0	7 (26.9)	0	0
10-<25	3 (2.3)	19 (73.1)	8 (30.8)	5 (3.1)
25-<50	13 (9.8)	0	17 (65.4)	37 (23.3)
>=50	115 (86.5)	0	0	115 (72.3)
At least 5 exposure days	131 (98.5)	26 (100)	25 (96.2)	157 (98.7)
At least 10 exposure days	131 (98.5)	19 (73.1)	25 (96.2)	157 (98.7)
At least 25 exposure days	128 (96.2)	0	17 (65.4)	152 (95.6)
At least 50 exposure days	115 (86.5)	0	0	115 (72.3)
Number	133	26	26	159
Mean (SD)	50.9 (9.1)	11.9 (4.3)	23.8 (6.1)	48.4 (10.5)
Median	53.0	12.0	26.0	53.0
Min ; Max	2 ; 63	5 ; 21	2 ; 28	2 ; 63
Total number of injections per participant				
Overall				
Number	133	26	26	159
Mean (SD)	51.1 (9.2)	12.0 (4.2)	23.9 (6.0)	48.6 (10.6)
Median	53.0	12.0	26.0	53.0
Min ; Max	2 ; 63	5 ; 21	2 ; 28	2 ; 63
For Prophylaxis [b]				
Number	133	26	26	159
Mean (SD)	50.0 (9.0)	1.0 (0.0)	22.2 (7.9)	45.6 (13.3)
Median	52.0	1.0	25.5	52.0
Min ; Max	2 ; 62	1 ; 1	1 ; 28	2 ; 62

	Arm A	Arm B		
	Prophylaxis (N=133)	On-demand (N=26)	Prophylaxis (N=26)	Overall (N=159)
For Spontaneous bleed				
Number	133	26	26	159
Mean (SD)	0.3 (0.7)	7.7 (4.3)	0.2 (0.5)	1.5 (3.4)
Median	0.0	8.0	0.0	0.0
Min ; Max	0 ; 5	1 ; 15	0 ; 2	0 ; 17
For Traumatic bleed				
Number	133	26	26	159
Mean (SD)	0.3 (0.7)	2.4 (3.4)	0.1 (0.4)	0.7 (1.7)
Median	0.0	2.0	0.0	0.0
Min ; Max	0 ; 4	0 ; 15	0 ; 2	0 ; 15
For Follow-up injection after initial treatment of a bleed				
Number	133	26	26	159
Mean (SD)	0.1 (0.7)	0.6 (1.1)	0.0 (0.2)	0.2 (0.8)
Median	0.0	0.0	0.0	0.0
Min ; Max	0 ; 8	0 ; 4	0 ; 1	0 ; 8
For Surgical				
Number	133	26	26	159
Mean (SD)	0.3 (1.1)	0.2 (0.6)	0.5 (2.4)	0.4 (1.5)
Median	0.0	0.0	0.0	0.0
Min ; Max	0 ; 9	0 ; 3	0 ; 12	0 ; 15
For Other				
Number	133	26	26	159
Mean (SD)	0.1 (0.3)	0.2 (0.5)	0.8 (2.8)	0.2 (1.2)
Median	0.0	0.0	0.0	0.0
Min ; Max	0 ; 2	0 ; 2	0 ; 13	0 ; 13

Note:

1: Percentages are based on the number of participants in the Safety 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 An exposure day is a 24-hour period in which one or more BIVV001 injections are given. All injections over the study course are counted. The count from the overall column is the summation of exposure days from Arm A and Arm B overall i.e., the total exposure days are based on the final treatment regimen that patients arrive at, thus, the overall count might not be equal to the summation of the count from columns of treatment arm and regimen.

b Baseline injection for PK is counted in prophylaxis block.

72% subjects had ≥50 exposure days; 96% had at least 25 exposure days; the mean number of exposure days was 48 days; the mean number of injections was 48, mean 46 injections for prophylaxis, up to 17 injections for spontaneous bleed, up to 15 injections for traumatic bleed, up to 8 injections as follow-up after initial injection, up to 15 injections for management around time of surgery. Most experience described is in prophylaxis.

Prophylactic dose and dosing interval

The mean (SD) average dosing interval was 7.01 (0.26) days. Data are summarised:

	Arm A	Arm B	
	Prophylaxis (N=133)	Prophylaxis (N=26)	Overall (N=159)
Number of participants with an efficacy period	133	26	159
Average weekly dose (IU/kg)[a]			
Number	132	23	155
Mean (SD)	51.33 (2.24)	51.00 (1.32)	51.28 (2.13)
Median	51.33	50.85	51.21
Q1 ; Q3	50.43 ; 52.05	50.31 ; 51.63	50.33 ; 52.01
Min ; Max	38.1 ; 61.8	48.6 ; 54.9	38.1 ; 61.8
Average dosing interval (days)[b]			
Number	132	23	155
Mean (SD)	7.01 (0.28)	7.01 (0.09)	7.01 (0.26)
Median	7.00	7.00	7.00
Q1 ; Q3	6.96 ; 7.01	6.98 ; 7.00	6.97 ; 7.01
Min ; Max	6.0 ; 9.4	6.9 ; 7.3	6.0 ; 9.4

Note:

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 period of PK evaluations, surgery/rehabilitation (minor and major), and large injection intervals (>28 days).

a The average weekly dose is the total IU/kg of all prophylactic doses extrapolated to a weekly amount.

b Average dosing interval is the sum of days in all eligible dosing intervals divided by the number of eligible intervals. Eligible intervals are prophylactic dosing intervals that are not separated by a bleeding episode or surgical/rehabilitation period.

Compliance

Overall, 96.9% of the participants were compliant to both the dosing and the dosing interval: 98.5% in Arm A and 88.5% in Arm B.

Overall, 100.0% of the electronic patient diary records (injections or bleeds) were entered within 7 days of the event as requested by the protocol.

Adverse events

Of the 159 participants in the Safety Analysis Set, 123 (77.4%) experienced a total of 394 treatment emergent adverse events (Table below).

Overview summary of treatment-emergent adverse events – Safety Analysis Set

	Arm A	Arm B			
n (%)	Prophylaxis (N=133)	On-demand (N=26)	Prophylaxis (N=26)	Surgery subgroup[a] (N=13)	Overall (N=159)
Total number of TEAEs	358	22	11	3	394
Participants with at least one TEAE	108 (81.2)	12 (46.2)	8 (30.8)	1 (7.7)	123 (77.4)
Participants with at least one related TEAE	8 (6.0)	0	0	0	8 (5.0)
Total number of TESAEs	16	2	0	0	18
Participants with at least one TESAE	13 (9.8)	2 (7.7)	0	0	15 (9.4)
Participants with at least one related TESAE	1 (0.8)	0	0	0	1 (0.6)
Total number of TEAESIs	1	0	1	0	2
Participants with at least one TEAESI	1 (0.8)	0	1 (3.8)	0	2 (1.3)
Participants with at least one related TEAESI	0	0	0	0	0

TEAEs leading to death	0	1 (3.8)	0	0	1 (0.6)
TEAEs leading to treatment discontinuation	2 (1.5)	0	0	0	2 (1.3)

Note

1: Percentages are based on the number of participants in the Safety 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.

3: AEs with missing causality assessment are included in the related TEAE, TESAE, or TEAESI.

a Includes AEs occurring during a major surgical/rehabilitation period. But AEs which occur on the day of the major surgical/rehabilitation period starts will be included in the columns treatment arm and regimen, they will not be included in the column of surgery subgroup.

Abbreviations: TESAE = treatment-emergent serious adverse event; TEAESI = treatment emergent adverse events of special interest; TEAE = treatment-emergent adverse event; AE = adverse event.

Deaths

Death was reported in 1 participant, in Arm B. The participant (No. 016293-032-0137-00004) died on Day 217 of pancreatic carcinoma metastatic, that was reported on Day 173 and assessed by the Investigator as not related to Altuvoct.

Serious adverse events

Of the 159 participants in the Safety Analysis Set, 15 (9.4%) experienced a total of 18 treatment emergent adverse events.

- One treatment emergent adverse event of CD4 lymphocytes decreased in a participant with a history of HIV was assessed by the Investigator as related to Altuvoct and resulted in discontinuation of study drug.
- Another treatment emergent adverse event of combined tibia-fibula fracture also resulted in discontinuation of study drug due to use of another FVIII product (prohibited medication).
- One treatment emergent adverse event of pancreatic carcinoma metastatic had a fatal outcome.
- Other treatment emergent adverse events were considered not related to study drug.

The treatment emergent adverse events were reported in 9 different system-organ-classes; there is not a particular pattern; it may be concurred that most were not related to study drug.

There were 2 treatment discontinuations, as described above.

There were not any symptomatic overdoses; 2 subjects recorded asymptomatic overdoses of 86.8, 93.5 and 140 IUkg i.e. 3 occasions; none of the episodes was reported as serious or resulted in a change of dose.

Adverse events of special interest

There were not any reports of inhibitor development to FVIII during the study.
There were not any reports of Grade 3 or greater allergic reactions or anaphylaxis in association with Altuvoct administration during the study.
There were not any reports of embolic and thrombotic events during the study.
Two pregnancies in female partners of male participants were reported during the study; one has delivered uneventfully; one is on-going.

Laboratory safety
There were no clinically meaningful patterns or trends observed in the mean actual value or mean change from baseline over time in any clinical chemistry or haematology parameter (including von Willebrand ristocetin cofactor activity or von Willebrand factor antigen).

Vital signs
There were no clinically meaningful patterns or trends observed in the mean actual value or mean change from baseline over time in any of the vital sign parameters.

Summary of clinical safety
159 subjects were enrolled in the study and received at least one dose of Altuvoct; these subjects were included in the Safety Analysis Set.

154/159 subjects were treated for at least 26 weeks and 98/159 subjects were treated for at least 52 weeks.

The mean total number of exposure days per subject was 48.4 (range: 2 to 63) and 115/159 subjects were exposed to the current product for least 50 exposure days.

The mean (SD) annualised Altuvoct consumption per subject during the efficacy period was 3131.75 (4113.19) IU/kg for subjects in Arm A, 1135.32 (404.94) IU/kg for subjects in Arm B with on-demand treatment and 2751.54 (88.26) IU/kg after the subject switched to prophylaxis treatment

The applicant reports on 12 major surgery procedures in 11 subjects; subjects were administered a single loading dose of the current product prior to surgery; surgical procedures were completed without untoward incident.

123/159 subjects reported a treatment emergent adverse event; most such events were reported as mild in severity and not related to the current product.

Inhibiting antibodies to FVIII activity of the current product were not detected; there were not any reports of serious allergic reaction, anaphylaxis or vascular thrombotic events.

The total number of subjects, however, is small with limited exposure (albeit 52 weeks yet subjects may be exposed to this product life-long); knowledge of aspects of safety may be pursued via the risk management plan.

Main clinical study
Study title: A Phase 3 open-label, multicentre study of the safety, efficacy, and pharmacokinetics of intravenous recombinant coagulation Factor VIII Fc-von Willebrand Factor-XTEN fusion protein (rFVIIIFc-VWF-XTEN; Altuvoct) in previously treated paediatric patients <12 years of age with severe haemophilia A

The applicant states that the study was conducted in compliance with International Council for Harmonisation Good Clinical Practice.

Study objectives and efficacy endpoints are summarised:

Objectives	Endpoints
Primary	
• To evaluate the safety of BIVV001 in previously treated pediatric participants with hemophilia A	• The occurrence of inhibitor development (neutralizing antibodies directed against FVIII as determined via the Nijmegen-modified Bethesda assay)
Secondary	
• To evaluate the efficacy of BIVV001 as a prophylaxis treatment	• Annualized bleeding rate (ABR) (for treated bleeding episodes) • ABR (for treated bleeding episodes) by type and location • ABR for all bleeding episodes (including untreated bleeding episodes) • Percentage of participants who maintain FVIII activity levels over 1%, 3%, 5%, 10%, 15%, and 20% at Day 7
• To evaluate the efficacy of BIVV001 in the treatment of bleeding episodes	• Number of injections and dose of BIVV001 to treat a bleeding episode • Percentage of bleeding episodes treated with a single injection of BIVV001 • Assessment of response to BIVV001 treatment of individual bleeding episodes based on the International Society on Thrombosis and Haemostasis (ISTH) 4-point response scale • Physician's global assessment (PGA) of participant's response to BIVV001 treatment based on a 4-point response scale
• To evaluate BIVV001 consumption for prevention and treatment of bleeding episodes	• Total annualized BIVV001 consumption per participant
• To evaluate the effect of BIVV001 prophylaxis on joint health outcomes	• Annualized joint bleeding rate (AJBR) • Target joint resolution at Week 52, based on ISTH criteria • Change from Baseline to Week 52 in total score and domain scores (eg, swelling and strength) assessed by the Hemophilia Joint Health Score (HJHS)
• To evaluate the effect of BIVV001 prophylaxis on Quality of Life (QoL) outcomes	• Changes in Haemophilia Quality of Life Questionnaire for Children (Haemo-QoL) total score and physical health domain score from baseline to Week 52 (≥4 years old) and via parent proxy version (≥4 years old)
• To evaluate the efficacy of BIVV001 for perioperative management	• 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

Objectives	Endpoints
• To evaluate the safety and tolerability of BIVV001 treatment	• The occurrence of adverse events (AEs) and serious adverse events (SAEs) • The occurrence of clinically significant changes from baseline in physical examination, vital signs, and laboratory tests • The occurrence of embolic and thrombotic events
• To assess the PK of BIVV001 based on the one-stage activated partial thromboplastin time (aPTT) and two-stage chromogenic FVIII activity assays	• PK parameters including, but not limited to, maximum activity (C_{max}), elimination half-life ($t_{1/2}$), total clearance (CL), total clearance at steady state (CL_{ss}), volume of distribution at steady state (V_{ss}), area under the activity time curve (AUC), dose-normalized area under the activity-time curve (DNAUC), mean residence time (MRT), incremental recovery (IR), trough activity (C_{trough}), time above predefined FVIII activity levels
Exploratory	
• To assess the impact of BIVV001 treatment on caregiver- and/or patient-reported clinical outcome assessments measurements and health resource utilization	• Changes in PROMIS-SF (Patient-Reported Outcomes Measurement Information System Short Form) Physical Function measures from Baseline to Week 52 (≥8 years old) and via parent proxy version (≥5 years old) • Changes in PROMIS Pain Intensity measures from Baseline to Week 52 (≥8 years old) and via parent proxy version (≥5 years old) • Changes in PROMIS Pediatric-SF Pain Interference measures from Baseline to Week 52 (≥8 years old) and via parent proxy version (≥5 years old) • Changes in EuroQoL 5-dimension 5-level Youth (EQ-5D-Y) from Baseline to Week 52 (≥8 years old) and via parent proxy version (4-7 years old) • Caregiver interviews at Week 52 (or subsequent post-study follow-up visit) • Changes in healthcare resource utilization and productivity

The primary objective was to evaluate safety in the target population of previously treated paediatric subjects with severe haemophilia A.

The very many secondary and exploratory objectives are noted.

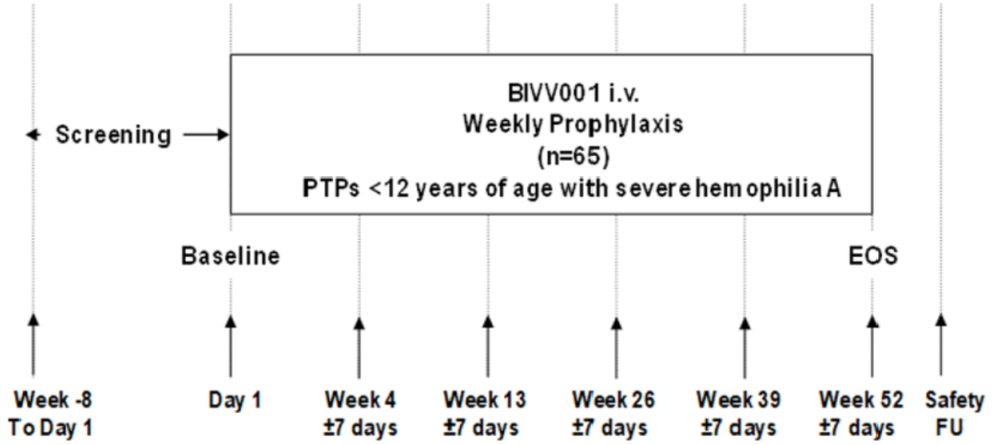
Aspects of study design
A multinational, multi-centre, single-arm, open-label, pivotal study.

The main objective of the study is to evaluate safety of IV administered Altuvoct in previously treated patients <12 years of age with severe haemophilia A (defined as <1 IU/dL [<1%] endogenous FVIII or a documented genotype known to produce severe haemophilia A).
The applicant also obtained data on efficacy and PK.

The study comprised 2 age cohorts of children (<6 years and 6 to <12 years); participants were to receive Altuvoct at a dose of 50 IU/kg IV once weekly for 52 weeks.

The study consisted of:
- Up to 8-week screening period;
- A 52-week open-label treatment period;
- A 2- to 3-week safety follow-up period only for participants who did not enter the open-label extension study.

The study design is summarised in the following figure (dates refer to the schedule of events):



EOS: end of study; FU: follow-up; IV: intravenous; PTP: previously treated patient.
Safety FU: The safety follow-up call or visit occurred 2 to 3 weeks after the last dose of BIVV001, unless the participant was enrolled in the open-label extension study.

Aspects of statistics
The study was single-arm, open-label and with no randomisation or blinding.
Study teams conducted data reviews while the study was ongoing.

Study design is noted without additional comment at this stage.

Statistical Conclusion
The Application is mainly supported by Phase 3 study EFC16293, an open-label, multicentre study of Efanesoctocog alfa in previously treated patients ≥ 12 years of age with severe haemophilia A. The study included two treatment arms, Arm A (N=133) receiving weekly prophylaxis doses for 52 weeks, and Arm B (N=26) receiving on-demand treatment for 26 weeks followed by 26 weeks of weekly prophylaxis. No concurrent control arms were included in the study, instead, a subset of patients from Arm A who had received prior prophylaxis for 6 months were rolled over from a previous observational study, allowing intra-patient comparisons (N=77).

Haemophilia A is a rare disease and therefore some flexibility can be awarded in terms of sample size and study design. The applicant did not address the request for appropriate justification of the success threshold and non-inferiority margin pre-specified for study EFC16293, explaining only that these had been agreed with other regulatory authorities (EMA and FDA) following scientific advice. The FDA correspondence referred to in the applicant's response has not been provided in the initial submission or responses, only EMA correspondence was provided. The latter includes a follow-up scientific advice letter where disagreement over the choice and justification of the ABR success threshold is expressed.

The lack of proper justification can be considered of limited relevance in this particular case, considering the upper bounds of the 95% Confidence Intervals for the two endpoints are well below the threshold/margin, the issue was not further pursued.

The absence of pre-defined success criteria for the paediatric study was also not explained, however due to the relevant magnitude of effect this was also not further pursued.

Even in the absence of mutually agreed success criteria, the results from EFC16293 and EFC16295 show that prophylaxis with efanesoctocog alfa provides effective and clinically meaningful prevention of bleeding events.

The statistical methodology and analysis populations used in the primary and key secondary endpoints are broadly acceptable, however, some additional issues were highlighted, including negative impact on study integrity from late protocol and SAP changes, and possible bias in the intra-patient comparison for the secondary endpoints in Arm A. As for the patient reported outcomes (other secondary endpoints), the analysis using MMRM is not considered to be conservative, and the Applicant did not adequately address the issues raised by the International Recognition Procedure parent regulator. However, as the PROs and its analysis are of limited interest, as they are not considered sufficiently robust to be relied upon, the issues are not further pursued.

The efficacy results for the primary and key secondary endpoints are considered to be substantially positive. However, since no concurrent control arm was included, and multiplicity adjustments were made at a late stage, the value of inferential statistics in this study is limited, and its results should be interpreted very carefully.

A paediatric single arm safety and efficacy study in patients <12 years of age with severe haemophilia A (EFC16295) was also included in the application. For this study statistical analyses were descriptive in nature, with no formal sample size calculation or hypothesis testing, and it is therefore only supportive in nature.

Population

Inclusion criteria

- Participants enrolled in this study were previously treated patients with severe haemophilia A (defined as <1 IU/dL [<1%] endogenous FVIII or a documented genotype known to produce severe haemophilia A) aged younger than 12 years.

Previous treatment of haemophilia A (prophylaxis or on-demand) was defined as any recombinant and/or plasma-derived FVIII replacement product, or cryoprecipitate for at least 150 exposure days for patients aged 6 to <12 years and for at least 50 exposure days for patients aged <6 years.

Exclusion criteria

- Participants with a history of a positive inhibitor test or with a positive inhibitor result at Screening.

Disposition

79 participants were screened for the study; 5 (6.3%) were screen failures: 3 had a history of inhibitor development to FVIII and 2 did not meet the criterion to understand the purpose and risks of the study. 74 subjects were enrolled; disposition of these subjects is summarised in the table below:

n (%)	Age cohort <6 years (N=38)	6 to <12 years (N=36)	Overall (N=74)
Number of participants			
Full Analysis Set [a]	38 (100)	36 (100)	74 (100)
Participants with an efficacy period [b]	38 (100)	36 (100)	74 (100)
Safety Analysis Set [c]	38 (100)	36 (100)	74 (100)
Per-protocol Set [d]	38 (100)	36 (100)	74 (100)
PK Analysis Set [e]	19 (50.0)	18 (50.0)	37 (50.0)
Surgery subgroup [f]	2 (5.3)	0	2 (2.7)
Number of major surgeries	2	0	2
Participants with at least one minor surgery	3 (7.9)	5 (13.9)	8 (10.8)
Number of minor surgeries	3	6	9
COVID19 non-impacted population [#]	38 (100)	36 (100)	74 (100)
Completion status			
Completed	36 (94.7)	36 (100)	72 (97.3)
Discontinued	2 (5.3)	0	2 (2.7)
Adverse event	0	0	0
Lost to Follow-Up	0	0	0
Protocol violation	0	0	0
Death	0	0	0
Consent withdrawn	0	0	0
Inability/Unwillingness to comply with protocol	0	0	0
Prohibited concomitant medications due to medical need as determined by investigator	0	0	0
Investigator decision	0	0	0
Withdrawal Criteria	0	0	0
Other	2 (5.3)	0	2 (2.7)

Note 1: Percentages are based on the number of participants in the All-Enrolled Analysis Set.

[a] All participants who received at least one dose of study drug. [b] FAS participants with at least 2 prophylactic injections.

[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 undergone major surgery after the first dose of study drug.

[#]Participants are without any major deviation related to COVID19.

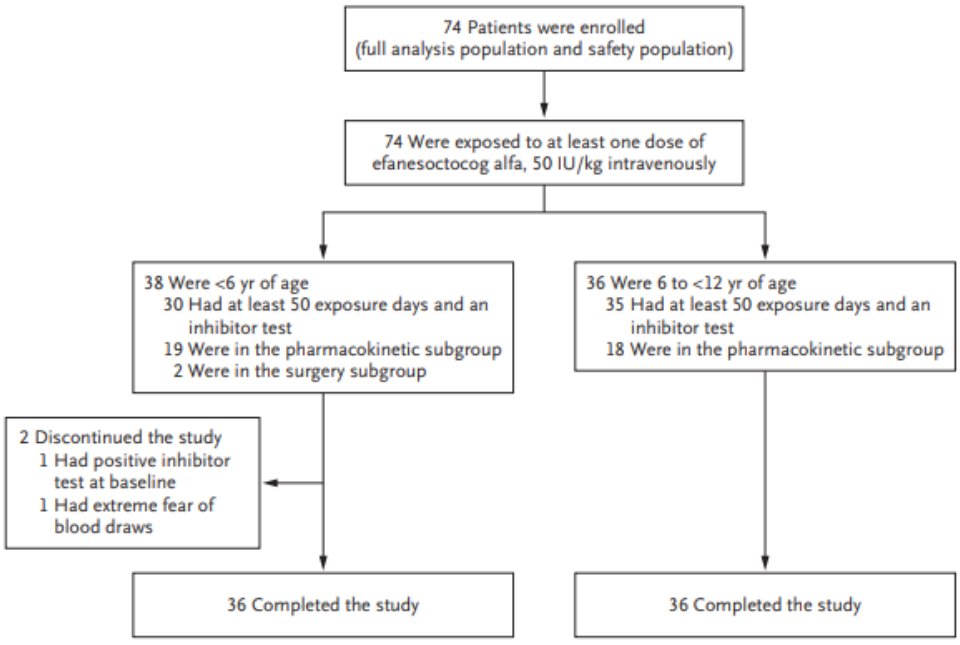


Figure 1. Patient Disposition and Exposure.

Patients younger than 6 years of age and those 6 to younger than 12 years of age may have been included in multiple subgroups. One patient younger than 6 years of age had a positive test for factor VIII inhibitor at baseline. However, the positive result was returned after the patient had initiated efanesoctocog alfa prophylaxis, and the patient was subsequently withdrawn from the study after receiving three doses.

Demographics and baseline characteristics are provided in the table below.

	Age cohort			
	<6 years (N=38)	6 to <12 years (N=36)	Surgery subgroup (N=2)	Overall (N=74)
Age (years)[a]				
Number	38	36	2	74
Mean (SD)	3.69 (1.21)	8.42 (2.08)	4.50 (0.71)	5.99 (2.91)
Median	4.00	8.00	4.50	5.00
Min ; Max	1.4 ; 5.0	6.0 ; 11.0	4.0 ; 5.0	1.4 ; 11.0
Sex, n (%)				
Male	38 (100)	36 (100)	2 (100)	74 (100)
Female	0	0	0	0

Ethnicity, n (%)				
Hispanic or Latino	2 (5.3)	1 (2.8)	0	3 (4.1)
Not Hispanic or Latino	36 (94.7)	33 (91.7)	2 (100)	69 (93.2)
Not Reported	0	2 (5.6)	0	2 (2.7)
Race, n (%)				
White	30 (78.9)	25 (69.4)	2 (100)	55 (74.3)
Black or African American	1 (2.6)	2 (5.6)	0	3 (4.1)
Asian	4 (10.5)	4 (11.1)	0	8 (10.8)
Not Reported	0	4 (11.1)	0	4 (5.4)
Other	3 (7.9)	1 (2.8)	0	4 (5.4)
Region[b], n (%)				
Asia/Pacific	11 (28.9)	8 (22.2)	1 (50.0)	19 (25.7)
Europe	7 (18.4)	20 (55.6)	0	27 (36.5)
North America	20 (52.6)	8 (22.2)	1 (50.0)	28 (37.8)
Weight (kg)				
Number	38	36	2	74
Mean (SD)	17.93 (3.53)	35.79 (12.86)	19.80 (0.14)	26.62 (12.90)
Median	18.00	32.85	19.80	22.05
Min ; Max	11.4 ; 25.7	17.2 ; 66.5	19.7 ; 19.9	11.4 ; 66.5
Body Mass Index(BMI) (kg/m2)				
Number	38	36	2	74
Mean (SD)	16.62 (1.73)	18.83 (3.90)	16.66 (1.52)	17.70 (3.17)
Median	16.41	18.22	16.66	16.89
Min ; Max	13.9 ; 21.5	13.2 ; 31.0	15.6 ; 17.7	13.2 ; 31.0

Note 1: Percentages are based on the number of participants with non-missing data in the Full Analysis Set.

2: Participants who have undergone major surgeries are presented in the surgery subgroup column in addition to in the age cohort columns. Each participant is counted only once in the overall column.

a Age = Age at time of informed consent.

b Europe includes Belgium, France, Germany, Hungary, Italy, Netherlands, Spain, Sweden, Switzerland, Ireland, and the United Kingdom. North America includes Canada, and the United States. Asia/Pacific includes Australia, Turkey, and Taiwan.

Baseline disease characteristics

71 (95.9%) of the 74 enrolled participants had a historical documented FVIII activity level below 1% and the remaining 3 participants had FVIII levels below 1% at screening visit and a documented genotype known to produce severe haemophilia A.

The mean (SD) age at diagnosis was 0.50 (0.80) years, ranging from 0 to 4 years.
57 [77.0%]) did not have a family history of an inhibitor.

None of the participants tested positive for HIV, hepatitis B or hepatitis C.

Overall, the mean (SD) age at the start of first prophylactic treatment was 1.0 (1.0) year (range from 0 to 5): 60 (81.1%) participants had prior exposure to recombinant FVIII and 14 (18.9%) participants to plasma-derived FVIII.

All but one of the participants were on prophylactic treatment with FVIII replacement prior to study entry (one in the 6 - 12yr cohort was on-demand). 50 [67.6%] participants) were on a stable pre-study prophylactic regimen for longer than 12 months prior to enrolment. A variety of FVIII products are described.

Medical history

Arthropathy was reported in 3 (4.1%) participants, joint instability in 2 (2.7%) participants, and 1 (1.4%) participant each reported haemophilic arthropathy, synovitis, arthralgia, haemarthrosis, muscle hematoma and growth retardation.

The most frequently used prior medication was paracetamol; sodium chloride and heparin use was reported as related to central venous catheter issues (access or infection).

The most frequently used concomitant medications (>10% of participants) were paracetamol in 42 (56.8%) participants, tranexamic acid in 13 (17.6%) participants, sodium chloride and amoxicillin (9 [12.2%] participants, each), and tozinameran (covid-19 vaccine) in 8 (10.8%) participants.

Medication for haemophilia-related pain was taken by 6 (8.1%) participants within 14 days prior to study visits overall

Intervention
The study intervention is outlined in the table below:

Intervention label	Prophylaxis
Intervention name	rFVIIIFc-VWF-XTEN (BIVV001)
Type	Drug
Dose formulation	Lyophilized powder in a sterile vial that requires reconstitution with sterile water for Injection (diluent)
Unit dose strengths	250, 500, 1000, 2000 IU per vial
Dosage level	50 IU/Kg every week
Route of administration	Intravenous
Use	Experimental
IMP or NIMP	IMP
Packaging and labeling	Study intervention was provided in vials. Each vial was labeled as required per country requirement
Current/Former name or alias	Not applicable

Altuvoct was delivered via a slow push IV injection at a rate of administration determined by the participant's comfort level and taking into account minimum injection duration per vial as per protocol.

Overall, 94.6% of the participants were compliant with both the dosing and the dosing interval. Treatment of episode of bleeds with Altuvoct during prophylaxis and dosing during minor or major surgeries is summarised in the table below:

Indication	Dosage	Frequency
Prophylaxis	50 IU/kg	Once weekly
Bleeding episode	50 IU/kg	Single dose for all bleeding episodes. Additional and adjusted doses only after consultation with the Investigator: If a bleeding episode does not improve, additional doses of 30 or 50 IU/kg every 2 to 3 days may be considered. For minor/moderate bleeding episodes within 2 to 3 days of a recent prophylactic dose, a 30 IU/kg dose may also be used.
Minor surgery	50 IU/kg	Single dose prior to surgery
Major surgery, only allowed after 6 EDs	50 IU/kg	Additional doses of 30 or 50 IU/kg every 2 to 3 days may be administered.

Minor and major surgeries were defined in the study protocol

Comparator

The study was a single-arm study; there is not a comparator.

The schedule of activities is summarised:

Tests and assessments	Screening[a, b] (Week -8 to Day 1)	Baseline[b] BIVV001 Day 1	Week 4[c] ±7 days	Week 13[c] ±7 days	Week 26[c] ±7 days	Week 39[c] ±7days	Week 52 ±7 days EOS/ET[c]	Unscheduled visit[d]	Safety follow-up call or visit[e]
Informed consent[f]	X								
Assessment of eligibility	X	X							
Demographics[g]	X								
Weight	X	X	X	X	X	X	X		
Height	X				X		X		
Medical, surgical, and hemophilia history[h]	X								
FVIII activity (1-stage aPTT assay)[i]	X								
Genotype[j]				X					
In-clinic BIVV001 dosing[k]		X	X	X	X	X	X		
Safety									
Physical exam	X	X	X		X		X	X	
Vital signs[l]	X	X	X		X		X	X	
HIV, HBV, and HCV status[m]	X								
CD4 count, viral load[n]	X								
Hematology[o]	X	X	X	X	X	X	X		
Coagulation parameters[p]		X			X		X		
Clinical chemistry[q]	X	X	X	X	X	X	X		

Tests and assessments	Screening[a, b] (Week -8 to Day 1)	Baseline[b] BIVV001 Day 1	Week 4[c] ±7 days	Week 13[c] ±7 days	Week 26[c] ±7 days	Week 39[c] ±7days	Week 52 ±7 days EOS/ET[c]	Unscheduled visit[d]	Safety follow-up call or visit[e]
von Willebrand Comprehensive Panel[f]		X	X	X	X	X	X		
Nijmegen-modified Bethesda assay (inhibitor assay)[j]	X	X	X	X	X	X	X		
Anti-rFVIIIFc-VWF-XTEN Antibody (ADA)[j]	X	X	X	X	X	X	X		
Adverse event/serious adverse event recording[s]	<<ongoing; monitor and record at all visits>>								
Prior and concomitant medications and concomitant therapies and procedures[t]	<<ongoing; monitor and record at all visits>>								
Monthly telephone call[u]	<<ongoing; once per month, after Week 4>>								
Efficacy									
HJHS joint assessments (≥4 years old)[v]		X			X		X		
Investigator's target joint assessment		X							
Physician's global assessment of response to treatment (PGA)				X			X		
Investigator's assessment of participant's response to treatment of bleeding episodes at the study site[w]		<<ongoing>>							
Left-over serum and plasma samples material preserved for future research[x] (optional)	X	X	X	X	X	X	X		
Electronic patient diary (ePD) training/administration/review[y]	X	X	<<ongoing>>						

Tests and assessments	Screening[a, b] (Week -8 to Day 1)	Baseline[b] BIVV001 Day 1	Week 4[c] ±7 days	Week 13[c] ±7 days	Week 26[c] ±7 days	Week 39[c] ±7days	Week 52 ±7 days EOS/ET[c]	Unscheduled visit[d]	Safety follow-up call or visit[e]
Caregiver completion of ePD including at-home dosing, bleeding episodes, and assessment of response to bleeding episodes[z]		<<ongoing>>							
Pharmacokinetics									
Pharmacokinetic sampling[aa]		X (for participants in the PK subgroup)							
FVIII peak and trough sampling[bb]		X (for participants not in the PK subgroup)	X	X	X	X	X		
Caregiver- and/or Patient-Reported Clinical Outcome Assessments (COA)									
PROMIS-SF Assessments[cc]		X			X		X		
Haemo-QoL[dd]		X			X		X		
EQ-5D-Y[ee]		X			X		X		
Caregiver interviews (only in selected countries)							X (or subsequent post-study follow-up visit)		
Healthcare Resource Utilization		X			X		X		

Abbreviations: AE = Adverse event; ADA = anti-drug antibody; ALP = alkaline phosphatase; ALT = alanine aminotransferase; aPTT = activated partial thromboplastin assay; AST = aspartate aminotransferase; BIVV001 = rFVIIIFc-VWF-XTEN (recombinant coagulation Factor VIII Fc - von Willebrand factor - XTEN fusion protein); BU = Bethesda units; BUN = blood urea nitrogen; COA = clinical outcome assessment; eCRF = electronic Case Report Form; EOS = End of study; ePD = electronic patient diary; EQ-5D-Y = EuroQoL-Youth; ET = early termination; FVIII = Factor VIII; GGT = gamma glutamyl transferase; HBV = hepatitis B virus; Hct=hematocrit; HCV = hepatitis C virus; Hgb = hemoglobin; HIV = human immunodeficiency virus; HJHS = Hemophilia Joint Health Score; HLA = Human leukocyte antigen; ICF = informed consent form; ISTH=International Society on Thrombosis and Haemostasis; PGA = Physician's Global Assessment; PK = pharmacokinetics; PROMIS = Patient-Reported Outcomes Measurement Information System; RBC = red blood cell; SAE = serious adverse events; VWF = von Willebrand; WBC = white blood cell.

a Washout prior to the Screening inhibitor test is at least 48 hours to obtain interpretable test results. Screening may be accomplished over the course of more than 1 study visit if needed. The Screening Period is up to 8 weeks before Baseline. Individuals who do not meet the criteria for participation in this study (screen failure) may be rescreened twice maximum. Individuals who rescreen will sign the informed consent form (ICF) again and repeat all screening assessments.

b Washout prior to BIVV001 Day 1 dose administration is at least 96 hours (4 days) for 6 to <12 years participants and at least 72 hours (3 days) for <6 years participants. The washout period prior to Day 1 BIV001 dose administration may be modified at the discretion of the Investigator based on individual PK data and clinical phenotype in consultation with the medical monitor. Separate samples for anti-rFVIIIFc-VWF-XTEN antibody testing will be collected at the same timepoint when any samples are collected for inhibitor testing (including samples for suspected inhibitor and confirmatory inhibitor tests).

c Participants should schedule their study visits to be 7 ±1 day after the previous prophylactic dose of BIVV001.

d Unscheduled visits may be necessary during the study to repeat any blood sampling if required, or at the discretion of the Investigator. If a participant has an unscheduled visit, the Investigator will record data as appropriate based on the purpose of the visit. Vital signs should be taken after the participant has been resting supine for 5 minutes. If BIVV001 is being administered at an unscheduled visit, vital signs will be measured pre-injection and 30 (+/-15) minutes from the start of injection. If an unscheduled visit occurs only for purposes of prophylactic administration of BIVV001, collection of physical exam and vital sign data is not required.

e This call or visit will occur 2 to 3 weeks after the last dose of BIVV001, unless the participant enrolls in the open-label extension study.

f Informed consent from the participant's legal guardian MUST be obtained prior to any study-related procedures, including washout of current FVIII therapy specifically for entry into the study. Participant assent must also be obtained where applicable (according to the study site's local regulations).

g Demographics include sex, race, ethnicity, and date of birth (year of birth only), as permitted by local regulations. Race and ethnicity will be collected for reasons described in Section 10.1.4

h Includes hemophilia history assessment of disease severity, blood type, and Rh factor if not previously documented. For Repeat Screening Visit, update with any changes since original Screening Visit.

i Collection of samples for genotype analysis (as permitted by local regulations and ethics committees) will be governed by a separate ICF. Human leukocyte antigen (HLA) genotype will not be needed if previously documented. If blood volume is limiting, this assessment may be performed at a subsequent visit. The participant's parent/legal guardian may provide consent in order to receive this testing at any time during the Treatment Period.

j Washout prior to scheduled visits other than screening and baseline should be at least 7 ±1 days. Inhibitor and anti-drug antibody (ADA) samples will be collected prior to BIVV001 dosing. Separate samples for ADA testing will be collected at the same time point when any samples are collected for inhibitor testing (including samples for suspected inhibitor and confirmatory inhibitor tests). All inhibitor assays, including the assay for the Screening Visit and any confirmatory assays, will be performed by the central laboratory using the Nijmegen-modified Bethesda assay. If a Nijmegen-modified Bethesda assay result returns as ≥0.6 Bethesda units (BU)/mL, a separate sample must be collected and tested for confirmation of inhibitor development within 2 to 4 weeks. Testing for potential ADA formation will be performed at a central laboratory using a validated rFVIIIFc-VWF-XTEN- specific ADA assay. Confirmed positive samples will be further characterized for antibodies specific to FVIII, Fc, D'D3, or XTEN.

k Participants will have BIVV001 doses given at each applicable scheduled visit delivered via a slow push intravenous injection at a rate of administration recommended in the protocol (Section 6.1.2) and determined by the participant's comfort level. Injection start and stop time will be recorded in the electronic Case Report Form (eCRF). Other doses may be self/caregiver administered at home (or in clinic).

l Vital signs include blood pressure, pulse rate, respiratory rate, and oral, tympanic, axillary or temporal temperature (°C). Vital signs should be taken after the participant has been resting supine for 5 minutes. Vital signs will be measured pre-injection and 30 (±15) minutes from the start of injection at clinic visits.

m For participants who have been historically negative, viral testing will be performed at a central laboratory. Human immunodeficiency virus (HIV) tests will include HIV-1 antibodies, HIV-2 antibodies and HIV-1 p24 antigen. Hepatitis B virus (HBV) tests will include HBV surface antigen, anti-HBV surface antibody and anti-HBV core antibody. Hepatitis C virus (HCV) tests will include anti-HCV antibodies.

n For participants known to be HIV antibody positive, CD4 count and viral load tests must be performed at the central laboratory if results are not available from within 26 weeks prior to screening.

o Hematology parameters include red blood cell (RBC) count, white blood cell (WBC) count and differential, platelet count, hemoglobin (Hgb), and hematocrit (Hct). Blood samples for hematology analysis will be collected prior to BIVV001 dosing.

p Coagulation parameters include activated partial thromboplastin time (aPTT).

q Clinical chemistry parameters include alanine aminotransferase (ALT), aspartate aminotransferase (AST), alkaline phosphatase (ALP), gamma glutamyl transferase (GGT), bilirubin, blood urea nitrogen (BUN), creatinine, nonfasting glucose, total protein, sodium, potassium, and chloride. Blood samples for clinical chemistry analysis will be collected prior to BIVV001 dosing.

r The von Willebrand (VWF) comprehensive panel includes assessments of von Willebrand Factor ristocetin cofactor activity and VWF antigen. Blood samples for analysis of VWF comprehensive panel will be collected prior to any BIVV001 dosing.

s Adverse events (AEs) and serious adverse events (SAEs) occurring after signing of the ICF through the Safety Follow-Up Call or Visit will be recorded on the eCRF.

t Prior medications from up to 30 days prior to Screening and concomitant therapies and procedures from signing of ICF through the Safety Follow-Up Call or Visit will be recorded on the eCRF. Pain medication related to Hemophilia and administered within 2 weeks prior to the visit will be recorded on the eCRF.

u In addition to scheduled clinic visits, telephone calls are planned approximately once a month, after Week 4, for the site staff to check on each participant's status. During the monthly telephone call, the participant's parent/caregiver will also be reminded about the requirement for timely ePD data entry, and assessments of "spontaneous" and "traumatic" bleeding episodes will be noted.

v Investigator will examine each participant's joints per the Haemophilia Joint Health Score (HJHS). At baseline, the Investigator will assess the presence of any target joints according to the International Society on Thrombosis and Haemostasis (ISTH) criteria.

w For bleeding episodes initially treated at the study sites, the Investigator will contact the caregiver approximately 72 hours from the time the BIVV001 injection was administered to treat the bleeding episode at the study site and record the caregiver's assessment of response to BIVV001 treatment on the eCRF using a 4-point bleeding response scale. For bleeding episodes that are treated at home, caregivers will record response to bleeding episodes in the ePD.

x Samples will be collected prior to any BIVV001 dosing and will be archived by the central laboratory (if required) for future research, eg, immunology assays, further coagulation assays, or clarification of any clinical or laboratory AE, etc. This is optional and participants/caregivers will sign an additional consent for this research.

y At the screening visit, caregivers will be shown and trained on the ePD device to ensure understanding of obligation to enter data during the trial. Devices will be given to caregivers at the baseline visit.

z Caregivers will record all bleeding episodes in the ePD beginning at Baseline. Assessment of response to bleeding episodes will be performed using a 4-point bleeding response scale. The caregiver should record response approximately 72 hours from the time the first BIVV001 injection was administered to treat the bleeding episode, unless treatment of the bleed was administered in the clinic. In that case, the investigator will report the caregiver's response to treatment via the eCRF.

aa The first 12 participants in each age cohort will undergo PK sampling after the first dose of BIVV001 (Baseline). Thereafter, PK sampling at Baseline will be optional. See PK sampling details in Table 2.

bb Trough and peak samples are collected within 30 minutes prior to rFVIIIFc-VWF-XTEN dosing and 15 (±3) minutes post-injection, respectively. This trough sample should be collected at the same time point as the trough inhibitor and ADA samples taken predose.

cc Patient-Reported Outcomes Measurement Information System (PROMIS) Assessments to include Pain Intensity, Pain Interference (PROMIS Pediatric-SF Pain Interference <18 years old), and Physical Function (PROMIS Pediatric-SF Physical Activity <18 years old). The PROMIS instruments will be administered to participants ≥8 years old and to parent proxy for participants aged 5-12 years.

dd The Haemo-QoL children version will be administered to participants ≥4 years old and the parent will be administered a parent proxy version (≥4 years old).

ee The EQ-5D-Y children version will be administered to participants ≥8 years old and the parent version will be administered to parent proxy (for participants 4-7 years old).

Outcomes
The primary outcome was related to safety, described in the safety section of this report.

Secondary outcomes
Annualised rates of bleeding are summarised in the following table:

	Age cohort		
	<6 years (N=38)	6 to <12 years (N=36)	Overall (N=74)
Number of participants with an efficacy period	38	36	74
Total number of treated bleeding episodes	17	47	64
Total participant-years followed	35.4	35.2	70.6
Duration of efficacy period (weeks)			
Number	38	36	74
Mean (SD)	48.67 (8.49)	51.01 (3.47)	49.81 (6.61)
Median	50.79	51.22	51.08
Q1 ; Q3	49.08 ; 52.07	51.06 ; 52.08	50.09 ; 52.07
Min ; Max	1.1 ; 55.1	32.4 ; 54.1	1.1 ; 55.1
Annualized bleeding rate (ABR)			
Number	38	36	74
Mean (SD)	0.46 (0.70)	1.32 (3.66)	0.88 (2.62)
Median	0.00	0.00	0.00
Q1 ; Q3	0.00 ; 1.00	0.00 ; 1.51	0.00 ; 1.02
Min ; Max	0.0 ; 3.1	0.0 ; 21.4	0.0 ; 21.4
0	24 (63.2)	23 (63.9)	47 (63.5)
>0-5	14 (36.8)	11 (30.6)	25 (33.8)
>5-10	0	1 (2.8)	1 (1.4)
>10-20	0	0	0
>20	0	1 (2.8)	1 (1.4)
ABR, model based[a]			
Mean (95% CI)	0.48 (0.30; 0.77)	1.33 (0.64; 2.76)	0.89 (0.56; 1.42)

Note 1: Summaries are based on treated bleeds.
2: Percentages are based on the number of participants with an evaluable efficacy period.
3: The efficacy period reflects the sum of all intervals of time during which participants are treated with BIVV001 excluding periods of PK evaluations, surgery/rehabilitation (minor and major), and large injection intervals (>28 days).
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.

With a median duration for exposure to product of 51 weeks, 64% of subjects reported zero bleeds. This is similar to the figure reported in the accompanying study on subjects >12yrs and is considered to be modest.

It is noted that one subject had more than 5 annualised bleeds and one subject had more than 20 annualised bleeds.

Data on spontaneous and traumatic bleeds are summarised:

Type of bleed	Age cohort <6 years (N=38)	Age cohort 6 to <12 years (N=36)	Overall (N=74)
Number of participants with an efficacy period	38	36	74
Total number of spontaneous bleeding episodes	6	5	11
Total number of traumatic bleeding episodes	10	21	31
Total number of unknown bleeding episodes	1	21	22
Spontaneous			
Participant-level			
Number	38	36	74
Mean (SD)	0.16 (0.38)	0.14 (0.49)	0.15 (0.44)
Median	0.00	0.00	0.00
Q1 ; Q3	0.00 ; 0.00	0.00 ; 0.00	0.00 ; 0.00
Min ; Max	0.0 ; 1.1	0.0 ; 2.0	0.0 ; 2.0
0	32 (84.2)	33 (91.7)	65 (87.8)
>0-5	6 (15.8)	3 (8.3)	9 (12.2)
>5-10	0	0	0
>10-20	0	0	0
>20	0	0	0
Population-level, model based[a]			
Mean (95% CI)	0.17 (0.08; 0.38)	0.14 (0.04; 0.53)	0.16 (0.08; 0.30)
Traumatic			
Participant-level			
Number	38	36	74
Mean (SD)	0.27 (0.56)	0.59 (1.15)	0.42 (0.91)
Median	0.00	0.00	0.00
Q1 ; Q3	0.00 ; 0.00	0.00 ; 0.98	0.00 ; 0.96
Min ; Max	0.0 ; 2.1	0.0 ; 5.1	0.0 ; 5.1
0	30 (78.9)	25 (69.4)	55 (74.3)
>0-5	8 (21.1)	10 (27.8)	18 (24.3)
>5-10	0	1 (2.8)	1 (1.4)
>10-20	0	0	0
>20	0	0	0
Population-level, model based[a]			
Mean (95% CI)	0.28 (0.14; 0.55)	0.59 (0.31; 1.14)	0.44 (0.27; 0.70)

Type of bleed	Age cohort <6 years (N=38)	Age cohort 6 to <12 years (N=36)	Overall (N=74)

Unknown type			
Participant-level			
Number	38	36	74
Mean (SD)	0.03 (0.17)	0.59 (3.05)	0.30 (2.14)
Median	0.00	0.00	0.00
Q1 ; Q3	0.00 ; 0.00	0.00 ; 0.00	0.00 ; 0.00
Min ; Max	0.0 ; 1.0	0.0 ; 18.3	0.0 ; 18.3
0	37 (97.4)	32 (88.9)	69 (93.2)
>0-5	1 (2.6)	3 (8.3)	4 (5.4)
>5-10	0	0	0
>10-20	0	1 (2.8)	1 (1.4)
>20	0	0	0
Population-level, model based[a]			
Mean (95% CI)	0.03 (0.00; 0.20)	0.59 (0.12; 3.02)	0.31 (0.07; 1.25)

Note 1: Summaries are based on treated bleeds.
2: Percentages are based on the number of participants with an evaluable efficacy period.
3: The efficacy period reflects the sum of all intervals of time during which participants are treated with BIVV001 excluding periods of PK evaluations, surgery/rehabilitation (minor and major), and large injection intervals (>28 days).
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.

In the overall population, there were 11 spontaneous episode of bleeds, 31 traumatic episode of bleeds and 22 episode of bleeds of unknown type.

A summary of episode of bleeds, by time since last prophylactic dose of efanesoctocog alfa was also provided.

	Total bleeds N=64	Spontaneous bleeds N=11	Traumatic bleeds N=31	Unknown bleeds N=22
Age group (years) : Age <6, N	17	6	10	1
Onset since prophylactic dose, n (%)				
n	17	6	10	1
Days 1-4	10 (58.8)	4 (66.7)	6 (60.0)	0
Days 5-7	5 (29.4)	2 (33.3)	3 (30.0)	0
Days >7	1 (5.9)	0	1 (10.0)	0
N/A	0	0	0	0
Unknown	1 (5.9)	0	0	1 (100)

Bleeds with unknown onset time are counted as Unknown, these are bleeds that are counted as new bleeds due to being treated more than 72 hours after last treatment of the bleed. Bleeds occuring before the first prophylactic dose in the study are classified as N/A. Only bleeds and doses that are within the efficacy periods are evaluated.

	Total bleeds N=64	Spontaneous bleeds N=11	Traumatic bleeds N=31	Unknown bleeds N=22
Age group (years) : Age 6 to <12, N	47	5	21	21
Onset since prophylactic dose, n (%)				
n	47	5	21	21
Days 1-4	11 (23.4)	2 (40.0)	9 (42.9)	0
Days 5-7	14 (29.8)	3 (60.0)	11 (52.4)	0
Days >7	1 (2.1)	0	0	1 (4.8)
N/A	1 (2.1)	0	1 (4.8)	0
Unknown	20 (42.6)	0	0	20 (95.2)

Bleeds with unknown onset time are counted as Unknown, these are bleeds that are counted as new bleeds due to being treated more than 72 hours after last treatment of the bleed. Bleeds occuring before the first prophylactic dose in the study are classified as N/A. Only bleeds and doses that are within the efficacy periods are evaluated.

	Total bleeds N=64	Spontaneous bleeds N=11	Traumatic bleeds N=31	Unknown bleeds N=22
Age group (years) : Overall, N	64	11	31	22
Onset since prophylactic dose, n (%)				
n	64	11	31	22
Days 1-4	21 (32.8)	6 (54.5)	15 (48.4)	0
Days 5-7	19 (29.7)	5 (45.5)	14 (45.2)	0
Days >7	2 (3.1)	0	1 (3.2)	1 (4.5)
N/A	1 (1.6)	0	1 (3.2)	0
Unknown	21 (32.8)	0	0	21 (95.5)

Bleeds with unknown onset time are counted as Unknown, these are bleeds that are counted as new bleeds due to being treated more than 72 hours after last treatment of the bleed. Bleeds occuring before the first prophylactic dose in the study are classified as N/A. Only bleeds and doses that are within the efficacy periods are evaluated.

Across the two age cohorts, the numbers of overall episode of bleeds on days 1-4 and days 5-7 after last prophylactic dose were similar (21 vs 19). Among these, the percentage of traumatic bleeds was similar during days 1-4 (15/21, 71.4%) and days 5-7 (14/19, 73.7%). In participants <6 years old, 10/17 (58.8%) episode of bleeds occurred on days 1-4 after the last prophylactic dose. The percentage of traumatic episode of bleeds was the same during days 1-4 and days 5-7 (60% each).

In participants 6 to <12 years old, 11/47 (23.4%) episode of bleeds occurred on days 1-4 after the last prophylactic dose. The percentage of traumatic episode of bleeds was similar during days 1-4 and days 5-7 (9/11, 81.8% vs 11/14, 78.6%). For 20/21 (95.2%) episode of bleeds of unknown type in this age cohort, the time of onset was unknown.

Data on location of bleed are summarised in the following table:

	Age cohort		
Location of bleed	**<6 years (N=38)**	**6 to <12 years (N=36)**	**Overall (N=74)**
Number of participants with an efficacy period	38	36	74
Total number of treated bleeding episodes at joint	7	35	42
Total number of treated bleeding episodes at muscle	1	6	7
Total number of treated bleeding episodes at internal	3	2	5
Total number of treated bleeding episodes at skin/mucosa	6	9	15
Total number of treated bleeding episodes at unknown location	0	0	0
Joint			
Participant-level			
Number	38	36	74
Mean (SD)	0.19 (0.63)	0.99 (3.62)	0.58 (2.57)
Median	0.00	0.00	0.00
Q1 ; Q3	0.00 ; 0.00	0.00 ; 0.48	0.00 ; 0.00
Min ; Max	0.0 ; 3.1	0.0 ; 21.4	0.0 ; 21.4
0	34 (89.5)	27 (75.0)	61 (82.4)
>0-5	4 (10.5)	8 (22.2)	12 (16.2)
>5-10	0	0	0
>10-20	0	0	0
>20	0	1 (2.8)	1 (1.4)

Location of bleed	Age cohort <6 years (N=38)	Age cohort 6 to <12 years (N=36)	Overall (N=74)
Population-level, model based[a]			
Mean (95% CI)	0.19 (0.06; 0.62)	0.99 (0.38; 2.60)	0.59 (0.27; 1.28)
Muscle			
Participant-level			
Number	38	36	74
Mean (SD)	0.03 (0.16)	0.17 (0.51)	0.09 (0.38)
Median	0.00	0.00	0.00
Q1 ; Q3	0.00 ; 0.00	0.00 ; 0.00	0.00 ; 0.00
Min ; Max	0.0 ; 1.0	0.0 ; 2.0	0.0 ; 2.0
0	37 (97.4)	32 (88.9)	69 (93.2)
>0-5	1 (2.6)	4 (11.1)	5 (6.8)
>5-10	0	0	0
>10-20	0	0	0
>20	0	0	0
Population-level, model based[a]			
Mean (95% CI)	0.03 (0.00; 0.20)	0.17 (0.06; 0.50)	0.10 (0.04; 0.26)
Internal			
Participant-level			
Number	38	36	74
Mean (SD)	0.08 (0.28)	0.06 (0.35)	0.07 (0.31)
Median	0.00	0.00	0.00
Q1 ; Q3	0.00 ; 0.00	0.00 ; 0.00	0.00 ; 0.00
Min ; Max	0.0 ; 1.0	0.0 ; 2.1	0.0 ; 2.1
0	35 (92.1)	35 (97.2)	70 (94.6)
>0-5	3 (7.9)	1 (2.8)	4 (5.4)
>5-10	0	0	0
>10-20	0	0	0
>20	0	0	0
Population-level, model based[a]			
Mean (95% CI)	0.08 (0.03; 0.26)	0.06 (0.00; 0.75)	0.07 (0.02; 0.20)
Skin/mucosa			
Participant-level			
Number	38	36	74
Mean (SD)	0.16 (0.38)	0.25 (0.60)	0.21 (0.50)
Median	0.00	0.00	0.00
Q1 ; Q3	0.00 ; 0.00	0.00 ; 0.00	0.00 ; 0.00
Min ; Max	0.0 ; 1.1	0.0 ; 2.0	0.0 ; 2.0

Location of bleed	Age cohort <6 years (N=38)	Age cohort 6 to <12 years (N=36)	Overall (N=74)
0	32 (84.2)	30 (83.3)	62 (83.8)
>0-5	6 (15.8)	6 (16.7)	12 (16.2)
>5-10	0	0	0
>10-20	0	0	0
>20	0	0	0
Population-level, model based[a]			
Mean (95% CI)	0.17 (0.08; 0.38)	0.25 (0.11; 0.59)	0.21 (0.12; 0.37)
Unknown location			
Participant-level			
Number	38	36	74
Mean (SD)	0.00 (0.00)	0.00 (0.00)	0.00 (0.00)
Median	0.00	0.00	0.00
Q1 ; Q3	0.00 ; 0.00	0.00 ; 0.00	0.00 ; 0.00
Min ; Max	0.0 ; 0.0	0.0 ; 0.0	0.0 ; 0.0
0	38 (100)	36 (100)	74 (100)
>0-5	0	0	0
>5-10	0	0	0
>10-20	0	0	0
>20	0	0	0
Population-level, model based[a]			
Mean (95% CI)	NC#	NC#	NC#

Note 1: Summaries are based on treated bleeds.

2: Percentages are based on the number of participants 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).

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.

#:The parameter cannot be estimated due to too few bleedings occurring in the category.

One participant in older cohort had 21 treated bleeds as per analysis, 18 of which were unconfirmed resulting from intensive consolidation therapy

Data refer to treated bleeds. In the overall population, there were 42 joint bleeds, 7 muscle bleeds, 5 internal bleeds and 15 bleeds into skin or mucosae i.e. 69 bleeds in total.

<u>Annualised bleed rate for all episode of bleeds</u>
The estimated mean annualised bleed rate based on all episode of bleeds (treated and untreated) was 2.82 (95% CI: 1.79 to 4.42). The observed median (Q1; Q3) was 0.49 (0.00; 2.05).

Forty-seven out of 74 (63.5%) participants had an annualised bleed rate of 0.

3 participants had an annualised bleed rate >20. Of these 3 participants:
One participant had a high number of 21 treated bleeds, 18 of which were unconfirmed; this participant did not receive Altuvoct weekly prophylaxis treatment for an extended period of time.

One participant in the <6 years of age cohort had 38 untreated bleeds including 29 skin and mucosal bleeds and 9 muscle bleeds (mainly arms and legs).
One participant in the 6 to <12 years of age cohort had 29 untreated bleeds including 22 nose bleeds and 7 oral mucosal bleeds.

Percentage of participants who maintain FVIII activity levels

Data are summarised in the following table:

n (%)	Age Cohort		
	<6 years (N=38) Pre-dose (trough)	6 to <12 years (N=36) Pre-dose (trough)	Overall (N=74) Pre-dose (trough)
Number of participants with at least one non-missing post-baseline result	37	36	73
Number of participants with all trough samples that are within 168 ±5 hours from the previous dose	32	29	61
Achieving trough FVIII activity levels above[a]			
>1%	32 (100)	29 (100)	61 (100)
>3%	32 (100)	29 (100)	61 (100)
>5%	24 (75.0)	29 (100)	53 (86.9)
>10%	6 (18.8)	15 (51.7)	21 (34.4)
>15%	3 (9.4)	2 (6.9)	5 (8.2)
>20%	1 (3.1)	2 (6.9)	3 (4.9)

Note 1: Percentages are based on the number of participants with all trough samples that are within 168 ±5 hours from the previous dose.

a Achieving trough FVIII activity levels above x% are based on the average trough samples (i.e., nominal 168 hour time point) from each scheduled visit (Week 4, Week 13, Week 26, Week 39, Week 52/EOS/ET) using the aPTT-based one-stage clotting assay.

Participants with trough samples that are outside 168 ±5 hours from the previous dose will be excluded from this analysis.

Number of injections and dose of Altuvoct to treat of episode of bleeds
Data are summarised in the table below:

	Age cohort		
	<6 years (N=38)	6 to <12 years (N=36)	Overall (N=74)
Number of participants with an efficacy period	38	36	74
Per bleeding episode			
Number [a]	17	47	64
Mean (SD)	1.12 (0.33)	1.30 (0.69)	1.25 (0.62)
Median	1.00	1.00	1.00
Q1 ; Q3	1.00 ; 1.00	1.00 ; 1.00	1.00 ; 1.00
Min ; Max	1.0 ; 2.0	1.0 ; 4.0	1.0 ; 4.0
1	15 (88.2)	37 (78.7)	52 (81.3)
2	2 (11.8)	8 (17.0)	10 (15.6)
3	0	0	0
4	0	2 (4.3)	2 (3.1)
>4	0	0	0
1	15 (88.2)	37 (78.7)	52 (81.3)
>1	2 (11.8)	10 (21.3)	12 (18.8)
<=2	17 (100)	45 (95.7)	62 (96.9)
>2	0	2 (4.3)	2 (3.1)
Per participant [b]			
Number [c]	14	13	27
Mean (SD)	1.11 (0.29)	1.05 (0.18)	1.08 (0.24)
Median	1.00	1.00	1.00
Q1 ; Q3	1.00 ; 1.00	1.00 ; 1.00	1.00 ; 1.00
Min ; Max	1.0 ; 2.0	1.0 ; 1.7	1.0 ; 2.0
1-<2	13 (92.9)	13 (100)	26 (96.3)
2-<3	1 (7.1)	0	1 (3.7)
3-<4	0	0	0
>=4	0	0	0
1-<2	13 (92.9)	13 (100)	26 (96.3)
>=2	1 (7.1)	0	1 (3.7)

Note 1: The efficacy period reflects the sum of all intervals of time during which participants are treated with BIVV001 excluding periods of PK evaluations, surgery/rehabilitation (minor and major), and large injection intervals (>28 days).

[a] Number = total number of treated bleeding episodes. Percentages are based on this number.

[b] The number of injections required to resolve each bleeding episode is averaged across all bleeding episodes per participant.

[c] Number = number of participants with at least 1 treated bleeding episode. Percentages are based on this number.

One participant in in the older cohort had 21 treated bleeds as per analysis, 18 of which were unconfirmed resulting from intensive consolidation therapy: 11 required 1 injection, 8 required 2 injections and 2 required 4 injections for bleed resolution.

Assessment of participants' response to Altuvoct treatment of episode of bleeds
Participants (or caregivers) provided an assessment of response to the first injection of Altuvoct for treating a bleed using a 4-point scale of excellent, good, moderate and none, based on the International Society on Thrombosis and Haemostasis definitions for haemophilia. The assessment (using table below) should be performed about 72 hours after the initial treatment for the episode of bleeds.

ISTH assessment of treatment of acute bleeds

Excellent	Complete pain relief within 8 h and/or complete resolution of signs of bleeding after the initial injection and not requiring any further replacement therapy for relief of persistent symptoms and signs in the same joint within 72 h
Good	Significant pain relief and/or improvement in signs of bleeding within approximately 8 h after a single injection, but requiring more than one dose of replacement therapy within 72 h for complete resolution
Moderate	Modest pain relief and/or improvement in signs of bleeding within approximately 8 h after the initial injection and requiring more than one injection within 72 h but without complete resolution
None	No or minimal improvement, or condition worsens, within approximately 8 h after the initial injection

Data are summarised:

Summary of participant's assessment of response to BIVV001 treatment of episode of bleeds – Full Analysis Set

	Age cohort		
n(%)	**<6 years (N=38)**	**6 to <12 years (N=36)**	**Overall (N=74)**
Number of participants with an efficacy period	38	36	74
Each injection			
Based on injections with an evaluation			
Number[a]	16	25	41
Excellent or Good	15 (93.8)	25 (100.0)	40 (97.6)
Excellent	14 (87.5)	22 (88.0)	36 (87.8)
Good	1 (6.3)	3 (12.0)	4 (9.8)
Moderate	1 (6.3)	0	1 (2.4)
None	0	0	0
Based on all injections			
Number[b]	19	61	80

	Age cohort		
n(%)	**<6 years (N=38)**	**6 to <12 years (N=36)**	**Overall (N=74)**

Excellent or Good	15 (78.9)	25 (41.0)	40 (50.0)
Excellent	14 (73.7)	22 (36.1)	36 (45.0)
Good	1 (5.3)	3 (4.9)	4 (5.0)
Moderate	1 (5.3)	0	1 (1.3)
None	0	0	0
Response not provided	3 (15.8)	36 (59.0)	39 (48.8)
First injection for each bleeding episode			
Based on injections with an evaluation			
Number[a]	16	24	40
Excellent or Good	15 (93.8)	24 (100.0)	39 (97.5)
Excellent	14 (87.5)	22 (91.7)	36 (90.0)
Good	1 (6.3)	2 (8.3)	3 (7.5)
Moderate	1 (6.3)	0	1 (2.5)
None	0	0	0
Based on all injections			
Number[b]	17	47	64
Excellent or Good	15 (88.2)	24 (51.1)	39 (60.9)
Excellent	14 (82.4)	22 (46.8)	36 (56.3)
Good	1 (5.9)	2 (4.3)	3 (4.7)
Moderate	1 (5.9)	0	1 (1.6)
None	0	0	0
Response not provided	1 (5.9)	23 (48.9)	24 (37.5)

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 excluding periods of PK evaluations, surgery/rehabilitation (minor and major), and large injection intervals (>28 days).

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.

Responses are mostly rated at 'excellent' or 'good' yet 49% injections did not return a response; absent response was most notable in those aged 6 to 12yrs (non-response in 59% in this age group).

Data are noted yet the high percentage of 'not provided' is considered to affect interpretation of data.

Physician's global assessment of participant's response to Altuvoct treatment

The Physician's global assessment is an assessment of the participant's response to treatment using a 4-point response scale (Table below).

Excellent	• Bleeding episodes responded to fewer than or the usual number of injections or less than or the usual dose of FVIII, **OR** • The rate of breakthrough bleeding during prophylaxis was less than or equal to that usually observed.
Effective	• Most bleeding episodes responded to the same number of injections and dose, but some required more injections or higher doses, **OR** • There was a minor increase in the rate of breakthrough bleeding.
Partially effective	• Bleeding episodes most often required more injections and/or higher doses than expected, **OR** • Adequate breakthrough bleeding prevention during prophylaxis required more frequent injections and/or higher doses.
Ineffective	• Routine failure to control hemostasis or hemostatic control required additional agents.

Overall, the physician's global assessment of the participant's response to their Altuvoct treatment was excellent for 96.6% of all visits and effective for 1.4% of the visits. Data are summarised:

16.2.6 Efficacy response data
16.2.6.1 Efficacy of BIVV001 in the treatment of bleeding episodes
16.2.6.1.14 Summary of physician's global assessment of the participant's response to the BIVV001 treatment

	Age Cohort		
	<6 years (N=38)	6 to <12 (N=36)	Overall (N=74)
Total responses [a]			
Number[b]	74	73	147
Excellent	71 (95.9)	71 (97.3)	142 (96.6)
Effective	0	2 (2.7)	2 (1.4)
Partially effective	0	0	0
Ineffective	3 (4.1)	0	3 (2.0)

Note: 1: Assessments during major surgical/rehabilitation periods are excluded.
[a]Percentages are based on the number of participants with non-missing observations at the respective visit.
[b]Percentage for total responses throughout the study will be based on the total number of assessments across all visits, including those at unscheduled visits; multiple responses per participant are counted.

The global assessments of the physicians are noted within the context of an open-label, unblinded study lacking an internal control.

Target joint resolution

A target joint was defined as a major joint into which ≥3 spontaneous episode of bleeds occurred in a consecutive 6-month period. Resolution was achieved when ≤2 bleeds occurred into that joint during 12 months of continuous exposure.

There were 2 participants at baseline reporting a total of 3 target joints, one participant in the <6 years of age cohort and one in the 6 to <12 years of age cohort.

Data are summarised:

Summary of target joint resolution based on spontaneous bleeds – Full Analysis Set

n (%)	<6 years (N=38)	6 to <12 years (N=36)	Overall (N=74)
Participants with target joints at baseline[a]	1	1	2
Participants with at least 12 months continuous exposure	0	1	1
Participants with ≥1 target joints resolved[b]	0	1 (100)	1 (100)
Total number of target joints at baseline[a]	1	2	3
Total number of target joints from participants with at least 12 months continuous exposure	0	2	2
Total number of target joints resolved[c]	0	2 (100)	2 (100)
Number of spontaneous bleeds in target joints resolved[c]			
0	0	2 (100)	2 (100)
1	0	0	0
2	0	0	0

Note 1: The analysis includes only target joints with at least 12 months continuous exposure (defined as treatment regimen period >=52 weeks). Target joints on which surgery (major or minor) was performed on or before the end of the participant's 12 months of exposure will be censored.
[a]A target joint at baseline is defined as a major joint with >=3 spontaneous bleeding episodes in a consecutive 6 month period prior to entry to the study, captured at baseline.
[b]A target joint resolved is defined as <=2 spontaneous bleeds into that joint during 12 months of continuous exposure. Percentage is calculated out of participants with at least 12 months continuous exposure.
[c]Percentage is calculated out of total number of joints from participants with at least 12 months continuous exposure.

Reported outcome tools.

The applicant employed numerous reported-outcome tools; these are assessed below.

Surgery outcome assessments:

Surgeries

Two major surgeries were performed in two participants, both in the <6 years of age cohort. These involved dental restoration including one tooth extraction in one and circumcision in the other. The FVIII activity level on the day of surgery (pre-dose sample) was 32.7% for one participant and 59.5% for the other participant. The dosing of Altuvoct in the surgical treatment period was initiated with one preoperative (loading) dose of 61.9 IU/kg and 60.4 IU/kg, respectively. Two days after the surgery, a second dose of 37.1 IU/kg was administered in the participant who underwent dental surgery. Both participants subsequently resumed a once-weekly prophylactic Altuvoct dosing of 50 IU/kg during the peri-operative period.

The Investigators' / Surgeons' assessment of the participant's haemostatic response to Altuvoct treatment was collected 24 hours post-surgery based on the International Society on Thrombosis and Haemostasis 4-point response scale of excellent, good, fair and poor (see Table below).

Excellent	Intraoperative and postoperative blood loss similar (within 10%) to the non-hemophilic patient with no extra (unplanned) doses of FVIII/FIX/"bypassing agents" needed and blood component transfusions are similar to the non-hemophilic patient
Good	Intraoperative and/or postoperative blood loss slightly increased over expectation for the non-hemophilic patient (between 10% and 25% of expected), but the difference is judged by the involved surgeon/anesthetist/relevant healthcare professional to be clinically insignificant as evidenced by no extra (unplanned) doses of FVIII/FIX/"bypassing agents" needed and blood component transfusions are similar to the non-hemophilic patient
Fair	Intraoperative and/or postoperative blood loss increased over expectation (25%-50%) for the non-hemophilic patient and additional treatment is needed such as extra (unplanned) doses of FVIII/FIX/"bypassing agents" or increased blood component use (within two-fold) of the anticipated transfusion requirement
Poor	Significant intraoperative and/or postoperative blood loss that is substantially increased over expectation (>50%) for the non-hemophilic patient, requires intervention, and is not explained by a surgical/medical issue other than hemophilia, unexpected hypotension or unexpected transfer to an Intensive Care Unit due to bleeding or substantially increased blood component use (>2 fold) of the anticipated transfusion requirement

Investigator'/Surgeon's assessment of the participant's haemostatic response to Altuvoct was rated as excellent for both; the two participants did not receive any other FVIII treatment or blood components for the surgery. During the surgery of circumcision, an estimated blood loss of 50 mL was reported and 10 mL after the surgery on the same day.

In addition, 9 minor surgeries were reported during the study, involving one port replacement, one port removal and one esophagogastroduodenoscopy in the <6 years of age cohort, and in the 6 to <12 years of age cohort, 2 dental extractions, one port revision, one port replacement each in one participant and two gastroscopy exams in another participant. A preoperative loading dose of Altuvoct was sufficient to maintain haemostasis during surgery.

Summary of clinical efficacy

Design

Study XTEND-Kids was a single-arm study without controls.

Conduct

74 subjects were enrolled; all were male; 74% White, 11% Asian; age range 1.4 to 11yrs; weight range from 11.4kg to 66.5kg. Baseline characteristics and medical history were typical of a population with haemophilia A at this age.

Subjects were administered Altuvoct 50 IU/kg once weekly intravenously as prophylaxis for up to 52 week. Overall, 94.6% of the participants were compliant with both the dosing and the dosing interval.

Outcomes and analysis

In the overall population, there were 42 joint bleeds, 7 muscle bleeds, 5 internal bleeds and 15 bleeds into skin or mucosae i.e. 69 bleeds in total.

The mean (SD) annualised bleed rate was 0.88 (2.62); the mean (SD) annualised spontaneous bleed rate was 0.15 (0.44); the mean (SD) annualised traumatic bleed rate was 0.42 (0.91). Most bleeds were treated with one injection. Participants reported response to injection as excellent or good. Physicians reported on responses as 'excellent'.

Two surgeries are reported on; subjects were administered the current product and had essentially uneventful surgical procedures.

The applicant reports on numerous outcome tools (patient-, clinician- and observer-driven); the reports appear to be presented on the basis of available-case analysis. Data from these tools is regarded in a general sense: change scores show negative and positive changes over the course of the study i.e. some fare better and some fare worse.

Overall conclusions on clinical efficacy

It may be concurred that Altuvoct bears efficacy.
64% of subjects reported zero bleeds over the course of the study.
Overall, 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 children with severe haemophilia A.

Clinical safety

Exposure

Exposure is summarised in the following table:

	Age cohort		
	<6 years (N=38)	6 to <12 years (N=36)	Overall (N=74)
Total exposure days (EDs)[a], n (%)			
<5	1 (2.6)	0	1 (1.4)
5-<10	0	0	0
10-<25	0	0	0
25-<50	6 (15.8)	1 (2.8)	7 (9.5)
>=50	31 (81.6)	35 (97.2)	66 (89.2)
At least 5 exposure days	37 (97.4)	36 (100)	73 (98.6)
At least 10 exposure days	37 (97.4)	36 (100)	73 (98.6)
At least 25 exposure days	37 (97.4)	36 (100)	73 (98.6)
At least 50 exposure days	31 (81.6)	35 (97.2)	66 (89.2)
Number	38	36	74
Mean (SD)	51.2 (8.6)	53.9 (4.9)	52.5 (7.2)
Median	53.0	54.0	53.0
Min ; Max	3 ; 57	33 ; 72	3 ; 72
Total number of injections per participant			
Overall			
Number	38	36	74
Mean (SD)	51.3 (8.7)	54.1 (5.2)	52.6 (7.3)
Median	53.0	54.0	53.0
Min ; Max	3 ; 58	33 ; 74	3 ; 74
For Prophylaxis			
Number	38	36	74
Mean (SD)	50.2 (8.5)	51.9 (4.3)	51.1 (6.8)
Median	52.0	53.0	53.0
Min ; Max	3 ; 56	32 ; 57	3 ; 57
For Spontaneous bleed			
Number	38	36	74
Mean (SD)	0.2 (0.4)	0.2 (0.5)	0.2 (0.4)
Median	0.0	0.0	0.0
Min ; Max	0 ; 1	0 ; 2	0 ; 2
For Traumatic bleed			
Number	38	36	74
Mean (SD)	0.3 (0.6)	0.6 (1.1)	0.4 (0.9)
Median	0.0	0.0	0.0
Min ; Max	0 ; 2	0 ; 5	0 ; 5

	Age cohort		
	<6 years (N=38)	6 to <12 years (N=36)	Overall (N=74)
For Follow-up injection after initial treatment of a bleed			
Number	38	36	74
Mean (SD)	0.1 (0.3)	0.9 (5.2)	0.5 (3.6)
Median	0.0	0.0	0.0
Min ; Max	0 ; 1	0 ; 31	0 ; 31
For Surgical			
Number	38	36	74
Mean (SD)	0.1 (0.4)	0.3 (1.0)	0.2 (0.8)
Median	0.0	0.0	0.0
Min ; Max	0 ; 2	0 ; 6	0 ; 6
For injections with other reason			
Number	38	36	74
Mean (SD)	0.4 (2.0)	0.2 (0.6)	0.3 (1.5)
Median	0.0	0.0	0.0
Min ; Max	0 ; 12	0 ; 3	0 ; 12

Note 1: Percentages are based on the number of participants in the Safety Analysis Set.

a An exposure day is a 24-hour period in which one or more BIVV001 injections are given.All injections over the study course are counted.

One participant in the older cohort received an intensive consolidation therapy resulting in 33 BIVV001 injections including 31 follow-up injections after initial treatment of the two traumatic bleeds with good and excellent hemostatic response. This participant had a total of 74 injections and 72 EDs during the study.

Of the 74 participants who received at least 1 dose of Altuvoct, 66 (89.2%) achieved 50 or more exposure days, with 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.

All 74 participants included in the study received at least one dose of Altuvoct. There were 73 (98.6%) participants treated for at least 39 weeks and 56 (75.7%) participants treated for at least 52 weeks.

The mean (SD) duration of Altuvoct dosing (calculated from the date and time of the first Altuvoct dose to the end date and time of the last treatment regimen in the study) was 51.08 (6.15) weeks overall, 49.80 (8.40) weeks in the <6 years of age cohort, and 52.43 (0.85) weeks in the 6 to <12 years of age cohort.

The prophylactic dose and prophylactic injection interval are summarised in the table below.

	Age cohort		
	<6 years (N=38)	6 to <12 years (N=36)	Overall (N=74)
Number of participants with an efficacy period	38	36	74
Average weekly dose (IU/kg)[a]			
Number	38	36	74
Mean (SD)	56.74 (5.14)	53.23 (2.00)	55.03 (4.29)
Median	55.33	53.06	54.17
Q1 ; Q3	53.19 ; 57.90	51.98 ; 54.86	52.32 ; 56.27
Min ; Max	51.2 ; 75.1	49.6 ; 57.4	49.6 ; 75.1
Average dosing interval (days)[b]			
Number	38	36	74
Mean (SD)	7.00 (0.09)	7.00 (0.08)	7.00 (0.08)
Median	7.00	7.00	7.00
Q1 ; Q3	6.98 ; 7.01	6.98 ; 7.00	6.98 ; 7.01
Min ; Max	6.8 ; 7.3	6.9 ; 7.3	6.8 ; 7.3

Note 1: The efficacy period reflects the sum of all intervals of time during which participants are treated with BIVV001, excluding periods of PK evaluations, surgery/rehabilitation (minor and major), and large injection intervals (>28 days).

a The average weekly dose is the total IU/kg of all prophylactic doses extrapolated to a weekly amount.

b Average dosing interval is the sum of days in all eligible dosing intervals divided by the number of eligible intervals. Eligible intervals are prophylactic dosing intervals that are not separated by the PK assessment, a bleeding episode, or surgical/rehabilitation period.

Two outlying average weekly doses of 72.23 and 75.1 IU/kg corresponded to two participants in the <6 years of age cohort with several injections entered in the electronic diary incorrectly; additional training in the use of the electronic diary was provided and the weekly dose in the subsequent entries was consistently close to 50 IU/kg.

The mean (SD) dosing compliance rate (defined as the number of doses taken within 80% to 125% of the Altuvoct study dose [50 IU/kg] out of the total number of doses taken) was 97.39% (9.34).

The mean (SD) dosing interval compliance rate (defined as number of prophylactic doses taken within 36 hours of the Altuvoct study dosing interval [7 days] out of total number of intervals) was 97.98% (3.65).

Annualised Altuvoct consumption

The total consumption of Altuvoct corresponds to the sum of doses of Altuvoct received as part of the prophylaxis treatment, and if any, of the doses of Altuvoct for the treatment of episode of bleeds.

The mean (SD) annualised Altuvoct consumption per participant during the efficacy period was 3003.24 (394.01) IU/kg.

The mean (SD) and median annualised Altuvoct consumption were 3115.57 (488.64) IU/kg and 2986.26 IU/kg, respectively, for participants in the <6 years of age cohort, and 2884.67 (207.88) IU/kg and 2837.09 IU/kg, respectively, for participants in the 6 to <12 years of age cohort.

Adverse events (AEs)
Of the 74 participants in the Safety Analysis Set, 62 (83.8%) experienced a total of 255 treatment emergent adverse events:

33 (86.8%) participants in the <6 years of age cohort experienced 146 treatment emergent adverse events and 29 (80.6%) participants in the 6 to <12 years of age cohort experienced 108 treatment emergent adverse events.

Data are summarised:

n (%)	Age cohort			
	<6 years (N=38)	6 to <12 years (N=36)	Surgical/rehab. period - Surgery subgroup[a] (N=2)	Overall (N=74)
Total number of TEAEs	146	108	1	255
Participants with at least one TEAE	33 (86.8)	29 (80.6)	1 (50.0)	62 (83.8)
Participants with at least one related TEAE	3 (7.9)	0	0	3 (4.1)
Total number of TESAEs	6	4	0	10
Participants with at least one TESAE	5 (13.2)	4 (11.1)	0	9 (12.2)
Participants with at least one related TESAE	0	0	0	0
Total number of TEAESIs	1	0	0	1
Participants with at least one TEAESI	1 (2.6)	0	0	1 (1.4)
Participants with at least one related TEAESI	0	0	0	0
TEAEs leading to death	0	0	0	0
TEAEs leading to treatment discontinuation	0	0	0	0

Note 1: Percentages are based on the number of participants in the Safety Analysis Set.
2: AEs with missing causality assessment are included in the related TEAE, related TESAE or related TEAESI.
a Includes AEs emergent during the major surgical/rehabilitation period; these AEs are excluded from each age cohort column but are included in the overall column. Each participant is counted only once in the overall column.
Abbreviations: TEAESI = treatment-emergent adverse event with special interest; TESAE = treatment-emergent serious adverse event; TEAE = treatment-emergent adverse event; AE = adverse event.

Most treatment emergent adverse events were assessed by the Investigator as not related to Altuvoct.

5 treatment emergent adverse events were assessed by the Investigator as related to Altuvoct in 3 participants, all in the <6 years age cohort. Related treatment emergent adverse events 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). None were assessed as serious or resulted in treatment discontinuation of Altuvoct.

Deaths
There were not any deaths reported during the study

Serious adverse events
Of the 74 participants in the Safety Analysis Set, 9 (12.2%) experienced a total of 10 treatment emergent serious adverse events: 5 (13.2%) participants aged <6 years and 4 (11.1%) aged 6 to <12 years. All treatment emergent serious adverse events were assessed by the Investigator as not related to Altuvoct, no action was taken with Altuvoct and the outcomes were reported as recovered / resolved.

Discontinuations
No participants discontinued Altuvoct treatment due to a treatment emergent adverse event during the study.

Adverse events of special interest
There were not any adverse events of special interest of symptomatic overdose reported during the study.

There were not any reports of inhibitor development to FVIII during the study.

An event of "hives around eyes, mouth, face, and chest" was reported in a 2-year-old participant after "eating chocolate". This participant had no history of allergies at Baseline. The participant was treated with 2 doses of intramuscular epinephrine, oral dexamethasone and oral cetirizine after which the event resolved. The Investigator assessed the event as non-serious and not related to Altuvoct. There was no action taken with Altuvoct and no report of recurrence on continued Altuvoct treatment.

There were not any reports of embolic and thrombotic events during the study.

Laboratory safety
There were not any clinically meaningful patterns or trends observed in the mean actual value or mean change from baseline over time in any clinical chemistry or haematology (including a Von Willebrand factor comprehensive panel: VWF antigen and VWF ristocetin cofactor activity assays) parameter.

Vital signs
There were not any clinically meaningful patterns or trends observed in the mean actual value or mean change from baseline over time in vital sign parameters in either age cohort.

Physical examination findings
There were not any abnormal physical examination findings reported as a treatment emergent adverse event during the study.

Asymptomatic overdose
Two events of asymptomatic overdoses with Altuvoct were reported in one participant aged <6 years and one participant aged 6 to <12 years, respectively; both had administered two doses in quick succession. None of the overdoses were assessed by the Investigator as serious or resulted in a Altuvoct dose change.

Summary of clinical safety
Exposure
All 74 subjects in the study received at least one dose of Altuvoct and were included in the Safety Analysis Set.

73/74 subjects were exposed to the current product for at least 39 weeks and 56/74 subjects were exposed to the current product for at least 52 weeks.

The mean (SD) total number of exposure days per subject was 52.5 (7.2); 66/74 subjects reached at least 50 exposure days.

The mean (SD) annualised Altuvoct consumption per participant during the efficacy period was 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.

Two surgeries took place without untoward outcome.

62/74 subjects had at least one treatment-emergent adverse event; most such events were reported as mild and not related to the current product.

There were not any reports of serious allergy or anaphylaxis or thrombo-embolic events. Treatment emergent anti-drug antibody responses were not observed in 73 evaluable subjects; all subjects tested negative for anti-drug antibodies during the on-treatment phase. The total number of subjects, however, is small with limited exposure (albeit 52 weeks yet subjects may be exposed to this product life-long); knowledge of aspects of safety may be pursued via a risk management plan.

Overall conclusions on clinical safety

Overall and at this stage of product development, it is considered that aspects of safety would not give rise to undue concern. The pooled data are described in the corresponding European Public Assessment Report (EPAR).

Benefit-risk assessment

Summary of favourable effects

Study XTEND-1:

For those on prophylaxis in arm A, subjects experienced: up to 5 spontaneous annualised bleeds; up to 10 traumatic annualised bleeds; and up to 10 annualised bleeds of ‘unknown character’.

For those on on-demand treatment in arm B, subjects experienced: up to 31.3 spontaneous annualised bleeds; up to 24.9 traumatic annualised bleeds; and up to 6.3 annualised bleeds of ‘unknown character’.

For the 133 subjects in arm A (prophylaxis): the mean (SD) annualised bleed rate was 0.71 (1.43); the mean (SD) annualised spontaneous bleed rate was 0.29 (0.73); the mean (SD) annualised traumatic bleed rate was 0.36 (0.83).

For the 26 subjects in arm B during the on-demand phase: the mean (SD) annualised spontaneous bleed rate was 15.87 (9.28); the mean (SD) annualised traumatic bleed rate was 4.82 (6.31).

For the 26 subjects in arm B during the prophylaxis phase: the mean (SD) annualised spontaneous bleed rate was 0.45 (1.13); the mean (SD) annualised traumatic bleed rate was 0.15 (0.78).

The applicant reports on 12 major surgeries; outcome is reported as 'excellent'; none of the subjects needed transfusion.

Study XTEND-Kids

In the overall population, there were 42 joint bleeds, 7 muscle bleeds, 5 internal bleeds and 15 bleeds into skin or mucosae i.e. 69 bleeds in total.

The mean (SD) annualised bleed rate was 0.88 (2.62); the mean (SD) annualised spontaneous bleed rate was 0.15 (0.44); the mean (SD) annualised traumatic bleed rate was 0.42 (0.91).

Most bleeds were treated with one injection. Participants reported response to injection as excellent or good. Physicians reported on responses as 'excellent'.

Two surgeries are reported on; subjects were administered the current product and had essentially uneventful surgical procedures.

Uncertainties and limitations about favourable effects

In the context of the rarity of the targeted disease, studies were conducted on a small number of subjects over a short time frame of (about) 52 weeks (considered short because subjects may be exposed to product life-long) in line 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). Durability of efficacy is therefore to be established.

The applicant reports on numerous outcome tools (patient-, clinician- and observer-driven); the reports appear to be presented on the basis of available-case analysis; the applicant does not appear to have submitted evidence of validation for most of the tools or that these tools have retained psychometric properties across the multi-national, multi-lingual settings of the trial. Data from these tools is regarded in a general sense: change scores show negative and positive changes over the course of the study i.e. some fare better and some fare worse.

The applicant has conducted studies only in those with severe haemophilia A (and not the moderate or mild forms). The prolonged half-life of the current product and proposed posology raised concern over use in the mild and moderate forms of haemophilia A; MHRA accepted the PK modelling exercise of the applicant to extend the indication to those with moderate haemophilia A but not the mild form. In addition, based on PK considerations, the indication has been restricted to those ≥2yrs age.

Summary of unfavourable effects

Treatment-emergent adverse events were mostly 'mild' and not considered related to the current product. There were not any reports of serious allergy or anaphylaxis or thrombo-embolic events. Treatment emergent anti-drug antibody responses were not found. It is considered that aspects of safety would not give rise to particular concern at this stage. The pooled data are described in the corresponding EPAR.

Uncertainties and limitations about unfavourable effects

In the context of the rarity of the targeted disease, the total number of subjects in studies, however, is small with limited exposure (albeit 52 weeks yet subjects may be exposed to this product life-long); Additional long-term data are needed and will be collected in three category 3 trials

Benefit-risk assessment and discussion

Importance of favourable and unfavourable effects

Zero bleeds would be ideal in an ideal situation; about 65% subjects achieved this in the time frames of the current studies. Unfavourable effects may be managed clinically. The prospect of zero (clinically evident) bleeds or much reduced number of bleeds is considered to be more important than the described unfavourable effects.

Balance of benefits and risks

Potential for benefit is considered to outweigh risk in subjects studied in the submitted trials.

Conclusions

The applicant has conducted studies only in those with severe haemophilia A (and not the moderate or mild forms) in line with the requirements laid down in the guideline on the clinical investigation of recombinant and human plasma-derived factor VIII products (EMA/CHMP/BPWP/144533/2009 rev 2). The prolonged half-life of the current product and proposed posology raised concern over use in the mild and moderate forms of haemophilia A; the applicant was able to justify use in moderate form of haemophilia A based on a PK modelling exercise; MHRA found that the PK model did not convince on use of product in mild haemophilia A; the applicant has accepted to not pursue the indication for mild haemophilia A.

Too few subjects in the clinical studies were <2yrs age to allay concerns over use in those subjects <2yrs. The applicant has accepted (and this stage) to not pursue the indication for those subjects with haemophilia A who are <2yrs age.

The benefit-risk profile may be considered positive in those with severe or moderate haemophilia A (≤5% endogenous plasma factor VIII activity) and who are ≥2yrs age.

For all of these points the indication has been restricted, as described.

Recommendation

A positive recommendation may be made for Altuvoct in the claimed indication of "Treatment and prophylaxis of bleeding in patients 2 years and above with severe or moderate haemophilia A (≤5% endogenous plasma factor VIII activity)".

The grant of marketing authorisations was recommended.

VI. RISK MANAGEMENT PLAN (RMP)

The applicant has submitted an RMP, in accordance with the requirements of Regulation 182 of The Human Medicines Regulation 2012, as amended. In addition to routine pharmacovigilance and risk minimisation measures, additional pharmacovigilance activities have been proposed (see table below for the risk minimisation measures and pharmacovigilance activities for all safety concerns):

Important identified risk: Inhibitor development to FVIII	
Evidence for linking the risk to the medicine	Inhibitors are an established, potential complication of factor replacement therapy in hemophilia and occur in approximately 25% to 30% of all PUPs with severe hemophilia A. The risk of inhibitor development is considered maximal during the first 20-30 EDs to FVIII [46]. Inhibitor development in previously treated patients is a rare event with an estimated incidence of 2 per 1000 person years [48].
Risk factors and risk groups	The causes of inhibitor development to FVIII are not known. However, elevated risk has been associated with periods of peak FVIII treatment, surgery, family history of inhibitors, and FVIII genetic mutations including large deletions, nonsense mutations and intron 22 inversion [6, 55, 56].
Risk minimization measures	**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. SmPC section 4.8: Information about the risk of inhibitor development in patients with hemophilia A treated with factor VIII, including with efanesoctocog alfa. PL section 2.0: Information how to detect early signs and symptoms of inhibitor development. Legal status: Prescription only medicine. **Additional risk minimization measures:** None
Additional pharmacovigilance activities	**Additional pharmacovigilance activities:** 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. See section II.C of this summary for an overview of the post-authorization development plan.
Important potential risk: Serious vascular thromboembolic events	
Evidence for linking the risk to the medicine	In the literature, thromboembolic events reported in hemophilia A patients treated with FVIII replacement products are rare. The risk of vascular thromboembolic events with the use rFVIII products, has not been established. Published reports of vascular thrombotic adverse events in patients with hemophilia A and recombinant FVIII replacement occur in the setting of pre-existing risk factors, e.g. cardiovascular risk factors and indwelling central venous catheters.

Important potential risk: Serious vascular thromboembolic events (cont'd)	
Risk factors and risk groups	Patients with pre-existing risk factors (e.g. cardiovascular risk factors, indwelling central venous catheters) for thromboembolism. Cardiovascular risk factors are more likely to occur with advancing age. Cardiovascular risk factors include hyperlipidemia, smoking, diabetes, hypertension, obesity for arterial thrombotic events. For venous thrombotic events, risk factors include trauma or fractures, surgery, immobilization, hormonal therapy, pregnancy, hypercoagulability and advancing age.
Risk minimization measures	**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. Legal status: Prescription only medicine. **Additional risk minimization measures**: None
Additional pharmacovigilance activities	**Additional pharmacovigilance activities:** 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. See section II.C of this summary for an overview of the post-authorization development plan.
Important missing information: Safety in previously untreated patients	
Risk minimization measures	**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 on how to detect early signs and symptoms of inhibitor development. Legal status: Prescription only medicine. **Additional risk minimization measures**: None
Additional pharmacovigilance activities	**Additional pharmacovigilance activities:** Observational Registry Study in Previously Untreated Patients (PUPs) with Hemophilia A (ATHN). The PedNet Hemophilia Registry Data collection in PUPs. See section II.C of this summary for an overview of the post-authorization development plan .

Missing information: Long term use	
Risk minimization measures	**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. Legal status: Prescription only medicine. **Additional risk minimization measures:** None
Additional pharmacovigilance activities	Additional pharmacovigilance activities: Long-term safety and efficacy of BIVV001 in previously treated patients with Hemophilia A (LTS16294) See section II.C of this summary for an overview of the post-authorization development plan.
Missing information: Safety in elderly patients ≥ 65 years of age	
Risk minimization measures	**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. Legal status: Prescription only medicine. **Additional risk minimization measures:** None
Additional pharmacovigilance activities	Additional pharmacovigilance activities: Long-term safety and efficacy of BIVV001 in previously treated patients with Hemophilia A (LTS16294) See section II.C of this summary for an overview of the post-authorization development plan.

This is acceptable.

VII. USER CONSULTATION

A full colour mock-up of the Patient Information Leaflet (PIL) was provided with the application in accordance with legal requirements, including user consultation.

VIII. OVERALL CONCLUSION, BENEFIT/RISK AND RECOMMENDATION

The quality of the products is acceptable. The non-clinical and clinical data submitted have shown the positive benefit/risk of these products in the treatment and prophylaxis of bleeding in patients with haemophilia A (congenital factor VIII deficiency).

The Summaries of Product Characteristics (SmPCs), Patient Information Leaflet (PIL) and labelling are satisfactory.

In accordance with legal requirements, the current approved UK versions of the SmPCs and PIL for these products are available on the MHRA website.

TABLE OF CONTENT OF THE PAR UPDATE

Steps taken after the initial procedure with an influence on the Public Assessment Report (non-safety variations of clinical significance).

Please note that only non-safety variations of clinical significance are recorded below and in the annexes to this PAR. The assessment of safety variations, where significant changes are made, are recorded on the MHRA website or European Medicines Agency (EMA) website. Minor changes to the marketing authorisation are recorded in the current SmPCs and/or PIL available on the MHRA website.

Application type	**Scope**	**Product information affected**	**Date of grant**	**Outcome**	**Assessment report attached Y/N**