Summary Basis for Regulatory Action

Date:	February 21, 2023
From:	Zuben Sauna, PhD, Review Committee Chair, CBER/OTAT/DPPT/HB
BLA STN:	BLA 125771/0
Applicant:	Bioverativ Therapeutics, Inc.
Submission Receipt Date:	June 30, 2022
Action Due Date:	February 28, 2023
Proper Name:	antihemophilic factor (recombinant), Fc-VWF-XTEN fusion protein-ehtl
Proprietary Name:	ALTUVIIIO
Indication:	For use in adults and children with Hemophilia A (congenital Factor VIII deficiency) for: (1) Routine prophylaxis to reduce the frequency of bleeding episodes; (2) On-demand treatment and control of bleeding episodes; (3) Perioperative management of bleeding.

Recommended Action: The Review Committee recommends approval of this product.

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Director, Office of Tissues and Advanced Therapies

Discipline Reviews	Reviewer / Consultant - Office/Division
CMC • CMC Product (Product Office and OCBQ/DBSQC) • Facilities review (OCBQ/DMPQ) • Establishment Inspection Report (OCBQ/DMPQ and Product Office) • QC, Test Methods, Product Quality (OCBQ/DBSQC)	Zuben Sauna, PhD, CBER/OTAT/DPPT Daniel Lagasse, PhD, CBER/OTAT/DPPT Gregory Price, PhD, CBER/OCBQ/DMPQ Ritu Agarwal, PhD, CBER/OCBQ/DBSQC Marie Anderson, PhD, CBER/OCBQ/DBSQC Seth Schulte, MS, CBER/OCBQ/DBSQC Tao Pan, PhD, CBER/OCBQ/DBSQC Noel Baichoo, PhD, CBER/OCBQ/DBSQC Parmesh Dutt, PhD, CBER/OCBQ/DBSQC
Clinical • Clinical (Product Office) • Postmarketing safety Pharmacovigilance review (OBPV/DE) • BIMO	Megha Kaushal, MD, CBER/OTAT/DCEPT Mary Rubin, MD, CBER/OBPV/DPV Haecin Chun, MS, CBER/OCBQ/BIMO
Statistical • Clinical data (OBPV/DB) • Non-clinical data	Jiang Hu, PhD, CBER/OBPV
Non-clinical/Pharmacology/Toxicology • Toxicology (Product Office) • Developmental toxicology (Product Office) • Animal pharmacology	Melek Sunay, PhD, CBER/OTAT/DCEPT
Clinical Pharmacology	Xiaofei Wang, PhD, CBER/OTAT/DCEPT
Labeling • Promotional (OCBQ/APLB)	Kristine Khuc, PharmD, CBER, OCBQ, DCM, APLB Oluchi Elekwachi, PharmD, MPH, CBER/OCBQ/DCM/APLB
Other Review(s) not captured above categories, for example: • Consults • Devices • Software • Human Factors • FONSI	Ye Xiong, PhD, CDER/OTS/OCP Youwei Bi, PhD, CDER/OTS/OCP Manuela Grimstein, PhD, CDER/OTS/OCP Yuching Yang, PhD, CDER/OTS/OCP Jian Liu, PhD, CDER/OTS/OCP Sarah Stothers, RN, MSN, MPH CDER/OND/ODES Coleen Little, PharmD, CDER/OSE/OMEPRM Millie Shah, PharmD, CDER/OSE/OMEPRM Alan Stevens, PhD, CDRH/OPEQ/OHTIII

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1. Introduction

Bioverativ has submitted an original Biologics License Application (BLA) to seek U.S. licensure for antihemophilic factor (recombinant), Fc-VWF-XTEN fusion protein-ehtl. The applicant uses the International Nonproprietary Name, efanesoctocog alfa, as well as the abbreviation, BIVV001. The proprietary name of the U.S. marketed product will be ALTUVIIIO. ALTUVIIIO is a lyophilized powder available in seven nominal strengths of 250, 500, 750, 1000, 2000, 3000 or 4000 international units (IU)/vial of recombinant Factor VIII (rFVIII) potency. The product is reconstituted with 3 mL of sterile water for injection for intravenous administration.

The active ingredient of ALTUVIIIO is a recombinant fusion protein consisting of a single-chain B-domain-deleted (BDD) human Factor VIII (FVIII) covalently linked to the

human Von Willebrand Factor (VWF) D'D3 domain via the human immunoglobulin G1 Fc domain and 2 XTEN polypeptides [unstructured polypeptides consisting of repeats of six amino acids (glycine, alanine, proline, threonine, serine, glutamic acid)]. The ALTUVIIIO protein has a molecular weight of approximately 312 kDa and is expressed as two polypeptide chains [chain 1: FVIII-XTEN-Fc (b) (4) and chain 2: VWF-XTEN-Fc (b) (4)

The applicant designed ALTUVIIIO to function as a recombinant extended half-life (EHL) FVIII product. The IgG1 Fc, VWF D'D3, and XTEN polypeptide portions of the ALTUVIIIO molecule were included to extend the half-life of the FVIII molecule in circulation. Please see *Section 3a. (Product Quality)* for a detailed description of the role each of these moieties plays in extending the half-life of FVIII.

The ALTUVIIIO Drug Substance (DS) and Drug Product (DP) are manufactured at the (b) (4)
Chemistry, Manufacturing, and Control (CMC) reviewers concluded that the applicant has adequately characterized the physiochemical, biochemical, and *in vitro* function properties of ALTUVIIIO, and provided documented evidence that the commercial manufacturing process consistently results in ALTUVIIIO with the intended identity and biological function. In addition to the biological activity of the FVIII, half-life extension of ALTUVIIIO is dependent on binding of the Fc moiety to the neonatal Fc receptor (FcRn) and the abrogation of the binding of FVIII to VWF by the D'D3 domain. Thus, the CMC reviewers suggested that the applicant develop suitable functional assays to evaluate these interactions. The applicant assessed ALTUVIIIO human IgG1 Fc domain binding to FcRn, the integrity of the VWF D'D3 domain, and the intramolecular shielding of FVIII-endogenous VWF interactions. The XTEN linkers are unstructured polypeptides with no known molecular interactions that can be measured in a functional assay.

The CMC reviewers noted limitations in the overall DS and DP release strategy that will be addressed through postmarketing commitments.

This document summarizes the basis for regular approval of ALTUVIIIO. A Phase 3 clinical trial and an ongoing Phase 3 clinical trial provide the primary evidence of safety and effectiveness for the treatment of adult, adolescent, and pediatric patients with Hemophilia A. Our recommendation for approval is based on the reduction in annualized bleeding rate (ABR) demonstrated in both Phase 3 clinical trials. No neutralizing antibodies were reported following administration of ALTUVIIIO. The risks of ALTUVIIIO include thrombosis and allergic reactions, which are expected for this class of products.

The applicant has provided substantial evidence of effectiveness and safety based on these adequate and well controlled clinical trials, supported by the clinical investigation and preclinical studies. The review team recommends regular approval of this BLA with CMC Postmarketing Commitments (PMCs) listed in Section 11.c of this document.

The proposed indication is for use in adults and children with hemophilia A (congenital Factor VIII deficiency) for:
- Routine prophylaxis to reduce the frequency of bleeding episodes
- On-demand treatment and control of bleeding episodes
- Perioperative management of bleeding

2. Background

Hemophilia A (HA) is an X-linked congenital bleeding disorder caused by a deficiency of functional FVIII which manifests as bleeding episodes. It is the most common of the severe inherited coagulopathies, with an incidence of approximately 1 in 10,000 births, with approximately 20,000 affected males in the United States. The relationship of bleeding severity correlates with clotting factor level. Patients with <0.01 IU/ mL or <1% of functional FVIII are categorized as having severe HA. Moderate severity HA and mild severity HA are characterized by clotting factor levels of 1-5% and 5 to <40%, respectively.

The severity of bleeding manifestations in hemophilia generally correlates with the degree of the clotting factor deficiency and can be acutely life-threatening. Joint bleeding is the most frequent bleeding manifestation in children and adults. Repeated bleeding into the joints is debilitating and causes development of target joints from inflammation due to prior bleeding. To prevent joint destruction, the standard of care in patients with severe HA is primary prophylaxis with infusions of FVIII.

These regular infusions are initiated at the time of the first bleeding episode in a joint or earlier aiming to prevent joint damage. However, inhibitory antibodies to infused FVIII products develop in a substantial percentage of patients treated with either plasma-derived or recombinant FVIII (rFVIII) products, which may complicate treatment with FVIII.

Currently, there are over ten licensed rFVIII products, some of which are full-length and others that are BDD products. These products are indicated for adults and children with HA for the control and prevention of bleeding episodes, perioperative management, and routine prophylaxis to reduce the frequency of bleeding episodes and the risk of joint damage.

ALTUVIIIO is a VWF-independent extended half-life FVIII product that maintains high sustained factor levels for most of the dosing interval which can control bleeds as well as reduce the frequency of bleeding episodes. Weekly administration of this product can reduce the treatment burden for patients with HA.

Table 1. Regulatory History

Regulatory Events / Milestones	Date
1. IND submission	May 10, 2017
2. Fast Track designation granted	February 5, 2021
3. Orphan Drug designation granted	August 3, 2017
4. Breakthrough Therapy designation granted	May 13, 2022
5. Pre-BLA meeting	April 22, 2022
6. BLA 125771/0 submission	June 30, 2022
7. BLA filed	August 26, 2022

Regulatory Events / Milestones	Date
8. Mid-Cycle communication	October 26, 2022
9. Late-Cycle meeting	December 19, 2022
10. Action Due Date	February 28, 2023

3. Chemistry Manufacturing and Controls (CMC)

a. Product Quality

Description

ALTUVIIIO is provided as a sterile, nonpyrogenic, preservative-free, white to slightly yellow lyophilized powder. Prior to intravenous (IV) infusion, the product is reconstituted with 3 mL sterile water for injection (sWFI) as diluent. After reconstitution, the solution appears as a clear and colorless liquid, free of visible particles and contains the following excipients: 10 mM histidine, 250 mM arginine hydrochloride, 5 mM calcium chloride dihydrate, 5% w/v sucrose and 0.05% w/v polysorbate 80. ALTUVIIIO is available in single-dose vials containing the labelled amount of FVIII activity, expressed in IU. Each vial contains, nominally, 250, 500, 750, 1000, 2000, 3000 or 4000 IU. The potency of ALTUVIIIO is assigned using a validated one-stage clotting activity (aPTT) assay calibrated against the World Health Organization (WHO) international standard for blood coagulation factor VIII concentrate.

The applicant designed ALTUVIIIO to function as a recombinant extended half-life (EHL) FVIII product. The IgG1 Fc, VWF D'D3, and XTEN polypeptide portions of the ALTUVIIIO molecule were included to extend the half-life of the FVIII molecule in circulation. The dimeric IgG1 Fc domain binds to the neonatal Fc receptor (FcRn), shuttling the ALTUVIIIO fusion protein into a naturally occurring protein recycling pathway and avoiding lysosomal catabolism. The VWF D'D3 domain prevents ALTUVIIIO from binding to endogenous VWF, thus circumventing the normal formation of a FVIII and VWF noncovalent complex in circulation, which limits the half-life to (b) (4) (b) (4) The XTEN polypeptides function by altering the ALTUVIIIO hydrodynamic radius, thus reducing rates of clearance and degradation and improving pharmacokinetic properties. The bioengineering strategies result in ALTUVIIIO having a prolonged plasma half-life of (b) (4) Currently marketed EHL FVIII products have an average plasma half-life of (b) (4)

Analytical Characterization

Analytical characterization of ALTUVIIIO was carried out to determine whether the active ingredient (b) (4) has the expected (i) primary amino acid sequence, disulfide bonds, and secondary and higher order structure; (b) (4) (b) (4) Additional characterization studies evaluated the kinetics of (b) (4) the structure and function of size variants, and the impact of metal binding on structure and function.

(b) (4)

In addition to the biological activity of the FVIII, half-life extension of ALTUVIIIO is dependent on binding of the Fc moiety to the neonatal Fc receptor (FcRn) and the abrogation of the binding of FVIII to VWF by the D'D3 domain. Thus, the CMC reviewers suggested that the applicant develop suitable functional assays to evaluate these interactions. The applicant assessed ALTUVIIIO human IgG1 Fc domain binding to FcRn using a (b) (4) was used to assess the integrity of the VWF D'D3 domain and the D'D3 binding assay measures (b) (4) of FVIII-endogenous VWF interactions. The XTEN linkers are unstructured polypeptides with no known molecular interactions that can be measured in a functional assay.

CMC reviewers concluded that the applicant has adequately characterized the physiochemical, biochemical, and *in vitro* function properties of ALTUVIIIO, and that the applicant has provided documented evidence that the commercial manufacturing process consistently results in ALTUVIIIO with the intended identity and biological function.

Impurities
Adequate removal of product and process-related impurities by the commercial manufacturing process was demonstrated during process development and process validation. The clearance of impurities to levels substantially lower than established permitted daily exposure (PDE) limits supports a clear safety margin. Compounds for which a PDE limit is not established were considered safe if clinical studies presented no adverse events.

Product-related impurities: The product-related impurities measured by the applicant were (b) (4) (b) (4) are routinely measured during ALTUVIIIO (b) (4) using a (b) (4) (b) (4) and DP release testing using a (b) (4) .

A strategy for evaluating all plausible (b) (4) species due to Fc-Fc interactions was not provided. However, the CMC reviewers determined the potential formation of product-related (b) (4) species (such as FVIII-XTEN-Fc chains or VWF-XTEN-Fc chains dimerizing via the Fc domain) poses minimal risk to product purity, given the ALTUVIIIO purification and control testing schemes. For example, the (b) (4) (b) (4) would clear VWF-XTEN-Fc chain dimers, which would not contain a FVIII moiety. Moreover, product-related (b) (4) species would also be identified through routine batch monitoring using the (b) (4) due to the substantial molecular weight changes compared to the heterodimeric ALTUVIIIO product.

Process-related impurities: The process-related impurities evaluated in ALTUVIIIO included host cell DNA, (b) (4) (b) (4) The applicant demonstrated that clearance of host cell DNA is appropriately controlled through process design; residual host cell DNA testing is not required for ALTUVIIIO (b) (4) release. Similarly, for all (b) (4) process performance qualification (PPQ) batches, the (b) (4) (b) (4) level was below the limit of quantitation. At-scale impurity clearance validation studies confirmed that (b) (4) manufacturing consistently clears this process-related impurity. As this critical quality attribute is appropriately controlled through process design, (b) (4) release testing is not required for ALTUVIIIO (b) (4) is introduced at a concentration of (b) (4) (b) (4) in the (b) (4) The applicant assessed whether residual levels of this process-related impurity would be present in the (b) (4) and therefore did not perform a quantitative analysis of the (b) (4) PPQ batches. For residual (b) (4) in ALTUVIIIO (b) (4), the applicant's safety assessment determined a (b) (4) LRV safety margin based on worst-case scenario calculations. Residual (b) (4) is routinely monitored immediately before the final (b) (4) as an in-process test with an action limit of (b) (4)

Microbial Contaminants: The potential microbial contaminants include bacterial endotoxin and viable microorganisms. Endotoxin is routinely measured as ALTUVIIIO (b) (4) release testing per a compendial test method and the release specification is (b) (4) (b) (4) Bioburden is also measured in all (b) (4) batches prior to release with the following release specifications: (b) (4)

The information provided related to ALTUVIIIO product- and process-related impurities is acceptable as submitted. The applicant performed safety assessments and testing of key in-process and (b) (4) samples for product- and process-related impurities for PPQ (b) (4) batches. The results of the impurities testing demonstrate that the Process (b) (4) (b) (4)

manufacturing process consistently clears impurities from ALTUVIIIO (b) (4) batches. The ALTUVIIIO Process (b) (4) (b) (4) manufacturing process adequately clears and controls the levels of product- and process-related impurities in the ALTUVIIIO (b) (4) material.

Drug Product Release Specification
The DP release specifications for ALTUVIIIO have been justified based on one of three approaches: (i) historical data of batches manufactured for clinical studies, (ii) statistical analyses, (iii) they are based on compendia. In the reviewer's estimation, these are standard approaches used for the justification of specifications. The reviewers also determined that the appropriate approach was applied to justify the individual analytical methods. The release specifications for the DP provided in the table below are considered adequate to confirm product quality and manufacturing consistency.

Test Attribute	Method	Release Acceptance Criteria	Stability Acceptance Criteria
Lyophilized Product, Appearance	Visual inspection	White to off-white cake or powder	White to off-white cake or powder
Solution, Color	Visual, (b) (4) (b) (4)	<Y4	<Y4
Solution, Clarity & degree of opalescence	(b) (4)	(b) (4)	(b) (4)
Solution, Visible Particulates in Injections	(b) (4)	Essentially free of particles	Essentially free of particles
(b) (4)	(b) (4)	(b) (4)	(b) (4)
(b) (4)	(b) (4)	(b) (4)	(b) (4)
Residual Moisture (%)	(b) (4)	(b) (4)	(b) (4)
Reconstitution Time (seconds)	Visual	(b) (4)	(b) (4)
Identity	One-Stage Clotting Assay (aPTT)	Meets Biological Activity Specification	Not tested
Identity	Non-Reduced SDS-PAGE	(b) (4)	(b) (4)
Biological Activity (IU/vial)	One-Stage Clotting Assay (aPTT)	(b) (4) of Target (IU/vial)	(b) (4) of Target (IU/vial)
(b) (4)	(b) (4)	(b) (4)	(b) (4)
Purity (%)	Non-Reduced SDS PAGE	(b) (4)	(b) (4)
(b) (4)	(b) (4)	(b) (4)	(b) (4)
(b) (4)	(b) (4)	(b) (4)	(b) (4)
Bacterial Endotoxin (EU/mL)	(b) (4)	250 IU/vial: (b) (4) 500 IU/vial: (b) (4) 750-4000 IU/vial: (b) (4)	
Sterility	(b) (4)	No Growth	Not tested
Container Closure Integrity	(b) (4)	Not tested	Pass
(b) (4)	(b) (4)	(b) (4)	(b) (4)

The CMC reviewers noted limitations in the overall (b) (4) DP release strategy compared to similar licensed products. Thus, the CMC reviewers obtained PMCs (see Section 11c) from the applicant to develop (b) (4) release specifications for: (b) (4)

Process Description
The ALTUVIIIO (b) (4) drug product (DP) manufacturing process involves the following steps:

Process	Manufacturing Process Steps
(b) (4)	
Drug Product	(b) (4) (b) (4) (b) (4) (b) (4) 17) In-line sterile filtration 18) Aseptic vial filling and partial stoppering 19) Lyophilization 20) Capping 21) Visual Inspection 22) Bulk Packaging and Storage.

(b) (4)

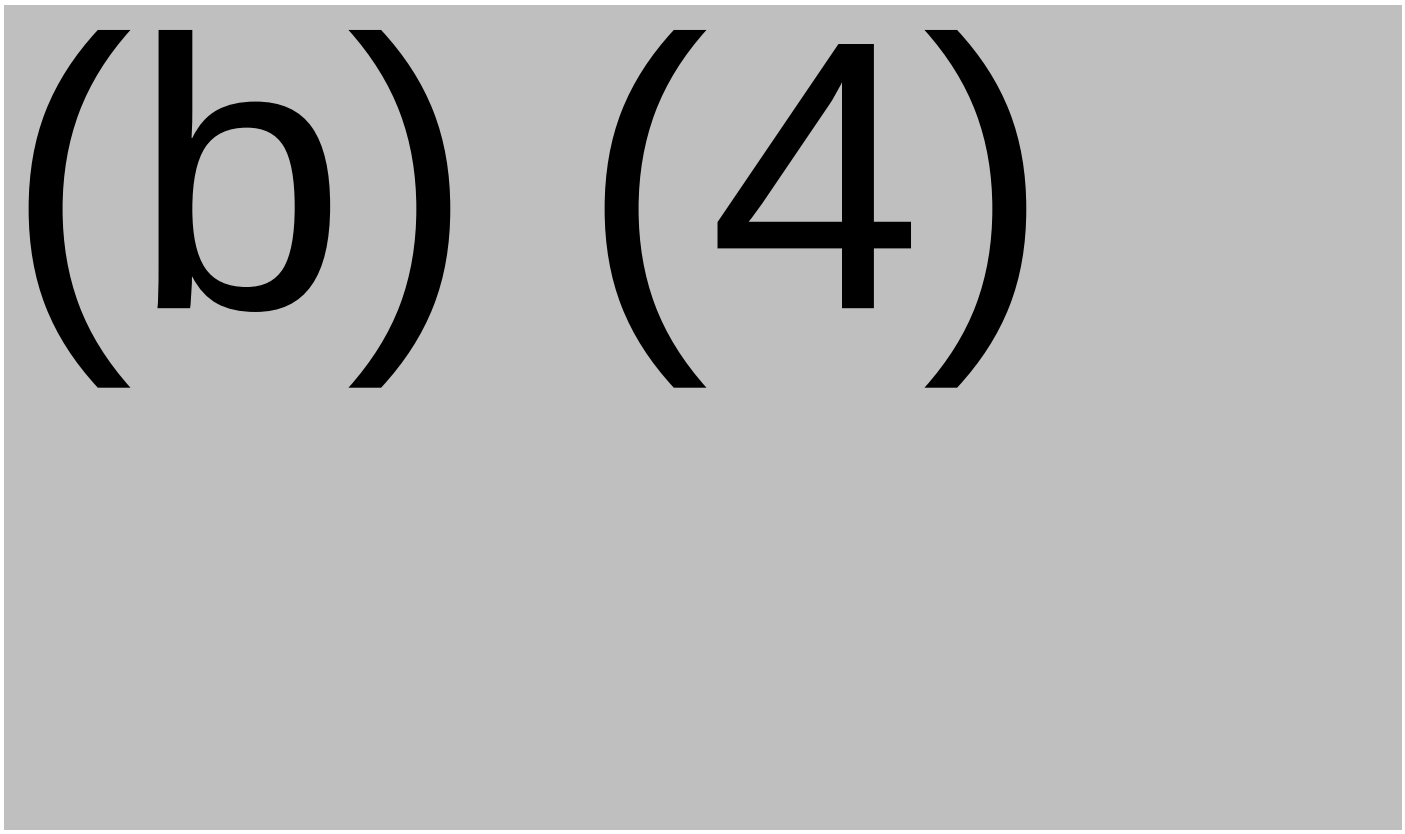
(b) (4)

Vials are filled and the sterilized stoppers are set on the vials and then lyophilized. The filled vials are stoppered and capped under controlled aseptic conditions, and visually inspected. Final vials are then packaged and stored at 2 to 8°C (+5°C ± 3°C) until they are shipped.

Critical process steps, parameters, and their control
The critical control parameters for the ALTUVIIIO manufacturing process are adequate. The acceptance criteria and/or action limits are based on historical data and manufacturing experience can assure product quality.

The following process parameters were deemed critical during the manufacture of ALTUVIIIO:

(b) (4)



The CMC reviewers noted that the applicant did not provide information on (b) (4) manufacturing mixing validation studies. Mixing validation is important because of the large scale (b) (4) bioreactors and a mixing study is especially needed to ensure proper mixing of (b) (4) Thus, the CMC reviewers requested the applicant to provide mixing studies for (b) (4) manufacturing operations. In response to our information request, the applicant provided TR-MS-050942, a performance qualification report for mixing steps in the (b) (4) The results in this report demonstrated that mixing validation studies were adequately executed.

Process validation

(b) (4)

Full-scale conformance lots were manufactured to demonstrate that the ALTUVIIIO manufacturing process is robust and reproducible, can be maintained within established parameters, and consistently produces product meeting all predetermined in-process limits, release specifications and quality attributes. No substantive changes were made in the manufacturing process, facilities and equipment between batches used in the

Phase III clinical trials and conformance batches. (b) (4) DP from the conformance lots were placed on real-time and accelerated stability programs.

Conformance lots manufacture
The applicant provided batch analysis results for (b) (4) ALTUVIIIO (b) (4) batches manufactured in 2016 at the (b) (4) site. The (b) (4) batches were used for toxicological and clinical studies. Batch analysis results for (b) (4) batches manufactured using (b) (4) were also provided. These (b) (4) batches were manufactured between 2017 and 2021 at the (b) (4) site and were used for clinical, stability, and PPQ studies. The ALTUVIIIO (b) (4) batch numbers and dates of manufacture of the commercial conformance lots are provided below:

(b) (4)

The applicant provided batch analysis results for the (b) (4) (b) (4) ALTUVIIO DP batch (b) (4) manufactured in 2017 and used in Phase 1 clinical studies. The applicant also provided batch analysis data for (b) (4) DP batches (b) (4) (b) (4) manufactured using (b) (4) at the (b) (4) site between 2018 and 2021. The ALTUVIIIO DP batch numbers and dates of manufacture of the commercial conformance lots are provided below:

DP Lot No.	Manufacturing Date	Site of Manufacture	Drug Substance Source	Nominal Vial Strength	Lot Size, # Vials	Use
(b) (4)				250 IU	(b) (4)	PPQ/ Commercial/ Stability
				1000 IU		PPQ/ Commercial/ Stability
				4000 IU		PPQ/ Commercial/ Stability

Viral Testing Controls and Clearance
applicant based the control of adventitious agents on ICH Q5A guidelines. The safety plan includes facility/procedural controls, absence of animal-derived raw materials (animal-derived products are neither a part of the DP nor are they used in the manufacture of ALTUVIIIO), cell bank testing, testing unprocessed bulk harvest samples, and viral clearance studies. The ALTUVIIIO (b) (4) manufacturing process was

evaluated for the clearance of adventitious viral agents using samples from representative at-scale batches (b) (4) In addition, the following five downstream manufacturing unit operations were evaluated for viral clearance using (b) (4) . In these studies, a panel of model viruses were used to determine the log reduction of virus (LRV) for each of the purification steps. (b) (4) model viruses (b) (4) were selected based on differences in size, resistance to physio-chemical impacts, genome type, and envelope coat. The (b) (4) (b) (4) while maintaining other process parameters within (b) (4) manufacturing ranges. The applicant determined the sample virus titer by (b) (4) (b) (4) assay. These studies are summarized below:

(b) (4)

Taken together, these data provide evidence that the process for manufacturing ALTUVIIIO includes the control of adventitious agents ensuring product safety.

Stability

The stability program for ALTUVIIIO DP followed ICH Guidelines and includes long-term, accelerated, stress, temperature cycling, and photostability studies. The shelf-life of the DP is justified by real-time stability data under long-term storage conditions. The proposed shelf life for ALTUVIIIO DP is 48 months from the date of manufacture when stored at 5 ± 3°C in primary packaging and secondary packaging. Within this period of 48 months, the DP may be stored for up to 6 months at room temperature (not to exceed 30 °C).

The applicant also provided real-time stability data for DS batches stored under long-term storage conditions for up to (b) (4) . Based on these studies the shelf-life of ALTUVIIIO DS is (b) (4) under long-term storage conditions (b) (4) in (b) (4) Moreover, the applicant has demonstrated that the in-process and DS release and stability testing methods can detect ALTUVIIIO DS product quality changes in the event of manufacturing process or storage condition excursions.

Comparability Protocol
The applicant provided a comparability protocol (CP) proposing to add (b) (4) at the (b) (4) (b) (4) site as an alternative ALTUVIIIO DP manufacturer for all dosage strengths. As part of establishing the DP manufacturing process on (b) (4) of the (b) (4) site, the applicant proposed manufacturing changes and provided a risk-based impact assessment for each proposed change. The applicant also proposed a reduced reporting category of Changes Being Effected 30 (CBE-30) for a future manufacturing supplement. The CMC reviewers concluded that in the aggregate the proposed manufacturing changes constitute a major change with the potential to impact the safety and efficacy of the product and recommended that the proposed manufacturing changes be reported in a Prior Approval Supplement (PAS). In STN 125771/0.34 (received 10 February 2023), the applicant agreed and changed the CP reporting category to a PAS.

b. Testing Specifications

The analytical methods and their validations and/or qualifications reviewed for the ALTUVIIIO drug substance and drug product were found to be adequate for their intended use.

c. CBER Lot Release

Under the provision described in 60 FR 63048-63049 publication (8 December 1995), routine lot-to-lot release by CBER is not required for ALTUVIIIO because it is a well-characterized therapeutic recombinant product. Thus, ALTUVIIIO is not subject to CBER Lot Release.

d. Facilities Review / Inspection

Facility information and data provided in the BLA were reviewed by CBER and found to be sufficient and acceptable. The facilities involved in the manufacture of ALTUVIIIO and inspectional histories are listed in the table below.

Name/Address	FEI number	DUNS number	Inspection/ Waiver	Justification /Results
(b) (4)			Waived	CDER (b) (4) VAI*
			Pre-License Inspection	CBER/DMPQ* (b) (4) VAI
			Waived	ORA* (b) (4) NAI*
			Waived	ORA (b) (4) NAI
			Waived	ORA (b) (4) NAI
			Waived	CDER (b) (4) VAI
			Waived	CDER (b) (4) VAI
			Waived	ORA (b) (4) NAI
			Waived	MRA* and reviewed by ORA (b) (4) VAI

*DMPQ: Division of Manufacturing and Product Quality; ORA: Office of Regulatory Affairs; VAI: Voluntary Action Indicated; NAI: No Action Indicated; MRA: Mutual Recognition Agreement

CDER conducted a pre-license inspection (PLI) of the drug substance manufacturer, (b) (4) in (b) (4) All 483 issues were resolved, and the inspection was classified as VAI.

DMPQ conducted a PLI of the drug product manufacturer (b) (4) in (b) (4) and issued a Form FDA 483 at the end of the inspection. The firm has responded to all the observations, and the corrective actions were reviewed and found to be adequate. All inspectional issues were resolved, and the inspection was classified as voluntary action indicated (VAI).

ORA performed a surveillance inspection of the (b) (4) (b) (4) manufacturing facility in (b) (4) No Form FDA 483 was issued, and the inspection was classified as NAI.

ORA performed a pre-approval inspection (PAI) of the (b) (4) facility in (b) (4) No Form FDA 483 was issued, and the inspection was classified as NAI.

ORA performed a surveillance inspection of (b) (4) in (b) (4) (b) (4) No Form FDA 483 was issued, and the inspection was classified as NAI.

CDER conducted a pre-approval inspection (PAI) of (b) (4) (b) (4) in (b) (4) All 483 issues were resolved, and the inspection was classified as VAI.

CDER conducted a pre-approval inspection (PAI) of (b) (4) (b) (4) in (b) (4) All 483 issues were resolved, and the inspection was classified as VAI.

ORA performed a surveillance inspection of the (b) (4) facility in (b) (4) No Form FDA 483 was issued, and the inspection was classified as NAI.

A Mutual Recognition Agreement (MRA) GMP inspection of the (b) (4) facility was conducted in (b) (4) The inspection was reviewed by ORA and classified as VAI.

e. Container/Closure System

The lyophilized drug product is filled into (b) (4) clear glass vials (b) (4) which are stoppered with 20 mm (b) (4) chlorobutyl rubber stoppers (b) (4) and sealed with 20 mm colored aluminum seals with (b) (4) (b) (4) (b) (4) performed the container closure integrity testing at the (b) (4) employing the (b) (4) container closure integrity test method; all acceptance criteria were met.

The sterile water for injection is filled into (b) (4) glass syringe barrels (b) (4) with bromobutyl rubber plunger stoppers (b) (4) (b) (4) and tamper proof tip caps (b) (4) (b) (4) performed the container closure integrity testing at the (b) (4) facility, employing the (b) (4) all acceptance criteria were met.

f. Environmental Assessment

The BLA includes a request for categorical exclusion from an Environmental Assessment under 21 CFR 25.31. The FDA concluded that this request is justified, and no extraordinary circumstances exist that would require an environmental assessment.

4. Nonclinical Pharmacology/Toxicology

The *in vitro* clotting activity of ALTUVIIIO in human plasma samples obtained from FVIII-depleted plasma or hemophilia A patients was determined by measurement of aPTT levels. *In vivo* pharmacodynamics (PD) were evaluated by single intravenous (IV) administration of ALTUVIIIO™ (37.5 to 150 IU/kg) in hemophilia A mice following tail clip injury. Results demonstrated a dose-dependent reduction in bleeding times and blood loss similar to those seen in mice injected with Advate®, a full-length recombinant FVIII, that was used as a comparator.

Prophylactic activity was assessed in hemophilia A mice that received a single IV administration of ALTUVIIIO (1.5-100 IU/kg) 72 hours prior to tail vein transection (TVT) compared to IV administered Advate® 24 hours prior to TVT. Based on the occurrence of spontaneous re-bleeding during the 24 hours post-TVT, ALTUVIIIO displayed a 3-fold prolongation of prophylactic activity relative to Advate® at all dose levels evaluated. This correlated with a 3-fold longer half-life ($T_{1/2}$) of ALTUVIIIO compared to Advate®. Comparable survival protection, measured as effective dose 50 (ED50; dose level that corresponded to 50% survival in animals 24 hours following TVT), was observed for ALTUVIIIO (7 IU/kg) and Advate® (9 IU/kg).

Pharmacokinetic and toxicokinetic assessments were performed following single and repeat IV administration of ALTUVIIIO in hemophilia A mice, (b) (4) rats, and (b) (4) monkeys. Systemic exposure levels after a single administration of ALTUVIIIO in mice, rats and monkeys showed dose-dependent proportional increases in maximum concentration and area under the concentration-time curve. The terminal half-life of ALTUVIIIO, which reflects the exposure and clearance of the fusion protein in plasma, was approximately (b) (4) in mice and monkeys, and approximately (b) (4) in rats. Overall, the $T_{1/2}$ of ALTUVIIIO was approximately 3-fold longer than Advate®.

A repeat-dose IV toxicity study in healthy adult (b) (4) rats administered 5, 250, and 750 IU/kg ALTUVIIIO every 3 days for 4 weeks did not result in any adverse findings, and no evidence of thrombus formation was observed. The no observed adverse effect level (NOAEL) was the maximum dose level administered, 750 IU/kg/dose, which is 15-fold higher than the maximum recommended prophylactic clinical dose level of ALTUVIIIO (50 IU/kg once weekly).

A repeat-dose IV toxicity study in healthy (b) (4) monkeys administered 25, 75, 250, 750 IU/kg ALTUVIIIO every 4 days for 4 weeks showed increased aPTT values likely due to acquired hemophilia resulting from the development of anti-drug antibodies (ADAs) to ALTUVIIIO. ADA-induced acquired hemophilia resulted in the death of one monkey on Day 30 due to excess bleeding following blood sample collection. There were no other adverse findings directly attributed to the pharmacologic activity/intended mechanism of ALTUVIIIO.

A hemocompatibility study was conducted to evaluate the effect of ALTUVIIIO on hemolysis and plasma flocculation (turbidity) of human blood. Whole blood samples were collected from 3 healthy male and 3 healthy female human subjects. No hemolytic

effect or flocculation was observed following *in vitro* treatment of human whole blood with ALTUVIIIO at 0.41, 1.2 and 4.1 µg/mL.

Genotoxicity, carcinogenicity, and developmental and reproductive toxicity studies were not conducted with ALTUVIIIO. This is acceptable based on the product and its nonclinical safety profile.

5. Clinical Pharmacology

The Pharmacokinetic (PK) profile of ALTUVIIIO was characterized in adult and pediatric previously treated patients (PTPs) with severe hemophilia A across six clinical studies. ALTUVIIIO was administered IV as a single dose (25 and 65 IU/kg) or repeated doses for 4 weeks with a 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.

To support its application, the applicant conducted population PK and population PK/pharmacodynamic (PD) analysis to evaluate the relationship between FVIII activity and bleed hazard. Physiologically based PK (PBPK) modeling was used to understand the effect of age ontogeny on ALTUVIIIO PK profile and to further support pediatric dose selection of ALTUVIIIO.

FVIII activity in the PK samples was measured by two assays: activated partial thromboplastin time (aPTT)-based one-stage clotting assay (OSC) and (b) (4) chromogenic (CS) assay. The OSC assay was also used for ALTUVIIIO potency assignment and was the primary PK assay to support dose selection. The OSC assay was primarily used to assess the PK of ALTUVIIIO.

General PK Profile: after IV injection, the PK profile of ALTUVIIIO exhibited a shallow distribution phase followed by a linear, and non-saturable elimination phase with a long half-life compared to other approved FVIII products. The mean terminal plasma half-life of ALTUVIIIO was about 3.8- and 2.7-fold times the half-life of Advate (an approved FVIII product with standard half-life) and Adynovi (an approved FVIII product with extended half-life), respectively.

Dose proportionality: dose proportionality was observed for Cmax and AUC with doses ranging from 25 IU/kg to 65 IU/kg.

Steady State: weekly dosing of 50 IU/kg of ALTUVIIIO showed minimal accumulation. With once weekly dose at 50 IU/kg, BIVV001 provided FVIII activity in the normal to near-normal range (> 40 IU/dL) for 3 to 4 days and > 10 IU/dL at the end of the weekly dosing interval in adults and adolescents. Once weekly dose of ALTUVIIIO at 50 IU/kg provided FVIII activity in the normal to near-normal range (> 40 IU/dL) for 2 to 3 days, >10 IU/dL for approximately 6 to 7 days, and in the mild hemophilia range (>5 IU/dL) at the end of the weekly dosing interval in both cohorts of children <12 years of age.

Intrinsic Factors Impacting ALTUVIIIO *PK Profiles (PK in Special Populations):* Body weight was a statistically significant covariate on both clearance (CL) and volume of distribution (V). Younger children (< 12 years) with lower body weight had higher weight-normalized clearance, shorter half-life and lower Ctrough levels of FVIII activity at steady state compared to adults and adolescents. In addition to body weight, Asian race was the only covariate that impacted the PK of ALTUVIIIO, with a higher Cmaxss, Ctrough, and time to 40 IU/dL FVIII activity in the Asian population compared to the non-Asian population. The PK differences between Asian and non-Asian population were not clinically meaningful. Other covariates (VWF antigen levels, hematocrit, blood type, and HCV/HIV status) had no impact on ALTUVIIIO PK profiles.

PK/PD Relationships: The relationship between FVIII activity level and bleeding prevention (clinical efficacy outcome) was evaluated using a repeated time-to-event (RTTE) model. Based on FVIII PK/PD analyses, the risk of bleeding is negatively correlated with FVIII activity. Once weekly 50 IU/kg ALTUVIIIO provided factor VIII activity levels that were associated with a low bleed risk.

Adults and Adolescents: The probability of zero bleeds in 1 year with ALTUVIIIO 50 IU/kg once-weekly regimen was predicted to be 71% (95% CI: 50%-83%) in adults and adolescents, indicating a low risk of bleed for ALTUVIIIO.

Pediatrics < 12 years: the probability of first bleed in 1 year was predicted to be 45% [95% CI: 39%-50%] and 48% [95% CI: 42%-54%] for pediatrics 6-<12 years and <6 years, respectively. The predicted ABRs in pediatrics 6-<12 years and <6 years treated with 50 IU/kg ALTUVIIIO once weekly were 0.97 and 1.28, respectively. Despite the lower exposure, the interim efficacy results of the ongoing XTEND-Kids study showed that pediatric subjects with severe hemophilia treated with ALTUVIIIO had a comparable annual bleeding rate (ABR) to that observed in adults and adolescents despite a lower FVIII activity.

Above results indicate that the proposed dosing regimen of ALTUVIIIO (50 IU/kg once weekly) is acceptable.

Immunogenicity: ALTUVIIIO showed a low immunogenic potential in previously treated patients (PTPs) with hemophilia A. FVIII Inhibitor antibody development was not detected in any of the five clinical studies, and the incidence of treatment-emergent anti-drug antibodies (ADAs) was low: 4 of 277 (2.2%) BIVV001-treated subjects developed transient ADAs. Factor VIII activity profiles of the 4 subjects with treatment-emergent (TE) ADAs in Study EFC16293 overlapped with the factor VIII activity profiles of the ADA-negative profiles, and their PK parameters were comparable to the mean of ADA-negative subjects. No apparent differences with respect to bleeding episodes and the PD response after ALTUVIIIO treatment were observed in the 4 subjects with treatment-emergent ADAs compared to ADA-negative subjects. Available data indicates that there is no evident impact of ADAs on FVIII PK and clinical outcomes.

6. Clinical/Statistical

The clinical review team's recommendation for regular approval of ALTUVIIIO for the treatment of Hemophilia A for use in adults and children with Hemophilia A (HA) for

routine prophylaxis treatment to reduce the frequency of bleeding episodes, on-demand treatment and control of bleeding episodes, and perioperative management of bleeding episodes is based on 2 clinical studies, Study EFC 16293 and Study EFC16295.

a. Clinical Program

Study EFC 16293 was a multicenter, open-label, study designed to evaluate the PK, safety, and efficacy of ALTUVIIIO for prophylaxis and treatment of bleeds, and surgeries in previously treated adults and adolescents (≥12 years of age) with severe hemophilia A (congenital FVIII deficiency). The study was divided into two parts: Part A evaluated subjects that were on a prior routine prophylaxis regimen and Part B evaluated subjects that were on a prior on-demand regimen.

Part A enrolled 133 subjects that received ALTUVIIIO weekly for prophylaxis treatment for up to 52 weeks. Subjects who completed at least 26 weeks of prophylaxis therapy were efficacy-evaluable (N=128). Efficacy was based on annualized bleeding rate (ABR). The mean ABR for all bleeds was 1.11 (95% CI: 0.83, 1.48) and median (Q1, Q3) ABR for all bleeds was 0 (0, 1.2). An intra-subject comparison (N = 78) between mean ABR during on-study prophylaxis with ALTUVIIIO and that during pre-ALTUVIIIO administration Baseline FVIII prophylaxis yielded a reduction in ABRs for treated bleeds (pre- ALTUVIIIO administration Baseline: 3.0 (2, 4.4) vs. post-ALTUVIIIO administration: 0.7 (0.4; 1.1)

Part B enrolled 26 subjects who were on an on-demand regimen prior to the study. Subjects received ALTUVIIIO on demand for the first 26 weeks and then weekly prophylaxis for another 26 weeks. The mean (95 %CI) ABR for all bleeds during prophylaxis was 0.9 (0.4, 1.8) compared to 22.2 (19.4, 25.4) while receiving on-demand therapy. The median ABR (Q1, Q3) for all bleeds was 0 (0, 1.9) compared to 21.1(16.8, 27.1) while receiving on-demand therapy.

Perioperative management of hemostatic response was evaluated in 13 major surgical procedures in subjects who were treated with ALTUVIIIO for surgical hemostasis. Thirteen major surgeries (in 11 adults and adolescents and 1 child) were evaluated for hemostatic response. Treatment with ALTUVIIIO provided good or excellent hemostatic control in all major surgeries.

Study EFC16295 was a multicenter, open-label, study to evaluate the PK, safety, and efficacy of treatment with ALTUVIIIO for prophylaxis and treatment of bleeds in previously treated pediatric subjects (<12 years of age) with severe Hemophilia A.

This study is ongoing, and the interim analysis was provided for review in support of the pediatric indication, which was agreed upon at the pre-BLA meeting. There were 67 subjects <12 years of age who were treated with ALTUVIIIO. Subjects with an efficacy period of at least 26 weeks were evaluable; there were 23 evaluable subjects. These subjects were administered ALTUVIIIO weekly and had a mean treated ABR of 0.54 (95% CI: 0.23, 1.26) and median ABR (Q1, Q3) of 0 (0, 1.3) compared to a pre-ALTUVIIIO administration Baseline mean treated ABR (SD) of 1.7 (2.1) and median of

1.0 (0; 8). For all bleeds (treated and not treated), the mean ABR was 3.6 (95% CI: 1.6, 8.4) and the median (Q1, Q3) ABR was 0 (0, 4.5).

The basis of FDA's conclusion of substantial evidence of effectiveness comes from the adult and pediatric adequate and well controlled trials with clinically meaningful benefit in ABR during the efficacy evaluable period. Therefore, the evidence supports regular approval for ALTUVIIIO.

b. Bioresearch Monitoring (BIMO) – Clinical/Statistical/Pharmacovigilance

BIMO inspections were issued for three foreign and one domestic clinical study sites that participated in the conduct of Study EFC16293. The inspections did not reveal problems that impact the data submitted in this Biologics License Application (BLA).

c. Pediatrics

This application is exempt from Pediatric Research Equity Act (PREA) because it is intended for a biologic product for which orphan designation has been granted. The results of the interim analysis from Study EFC16295 provide persuasive evidence of clinical benefit in the pediatric population (see Section 6a above).

d. Other Special Populations

The efficacy of ALTUVIIIO has not been studied in any other special populations.

7. Safety and Pharmacovigilance

The safety of ALTUVIIIO was evaluated in a total of 126 previously treated patients (PTPs) with severe hemophilia A [159 adult and adolescent (12-17 years) and 67 pediatric subjects (<12 years of age)]. The safety dataset included all subjects who received at least one dose of ALTUVIIIO. There were no deaths related to ALTUVIIIO. The most frequent adverse reactions were headache (33 subjects), arthralgia (26 subjects), and back pain (nine subjects). There were no anaphylactic or allergic reactions. No subject developed neutralizing antibodies to FVIII. Fourteen subjects developed transient anti-drug antibodies to different moieties of the product with no clinical consequence. There were three subjects, with pre-existing risk factors, who developed thrombosis during the extension study. This risk will be conveyed in the US Prescribing Information (PI). Although not reported in the clinical trials, the class effect risks of FVIII inhibitory antibodies and allergic reactions will be conveyed in the PI.

Review of the clinical data found no safety concern that would necessitate a Risk Evaluation and Mitigation Strategy (REMS), a postmarketing commitment (PMC) or a required postmarketing (PMR) study that is specifically designed to evaluate safety as a primary endpoint. The applicant plans a postapproval voluntary study to assess safety of use of ALTUVIIIO in previously untreated patients (PUPs), and there is an ongoing long-term follow-up study of clinical trial participants. For 3 years following approval, the

applicant will be required to conduct enhanced pharmacovigilance for thromboembolic events (TEEs), with expedited reporting of all TEEs (regardless of seriousness) and sponsor assessment for TEEs (based on cumulative and interval safety data) in periodic safety reports.

For all other adverse events, the applicant will conduct routine pharmacovigilance. Postmarketing adverse experiences should be reported to CBER in accordance with 21 CFR 600.80. Routine surveillance includes 15-day expedited reports for serious, unlabeled/unexpected adverse events, and quarterly periodic safety reports for 3 years and annually thereafter. Distribution reports should be provided to CBER in accordance with 21 CFR 600.81.

8. Labeling

The proposed proprietary name, ALTUVIIIO, was reviewed by the Advertising and Promotional Labeling Branch (APLB) on September 9, 2022 and was found acceptable. CBER communicated the acceptability of the proprietary name to the applicant on September 27, 2022. The proper name suffix, -ehtl, was designated on January 9, 2023, making (antihemophilic factor (recombinant), Fc-VWF-XTEN fusion protein-ehtl) the proper name.

The Advertising and Promotional Labeling Branch (APLB) reviewed the proposed prescribing information, patient package insert, instructions for use, package and container labels on January 6, 2023, and found them acceptable from a promotional and comprehension perspective.

9. Advisory Committee Meeting

An advisory committee meeting was not convened because initial review of the application did not raise concerns or identify controversial issues that would benefit from an advisory committee discussion.

10. Other Relevant Regulatory Issues

ALTUVIIIO has received Orphan Drug Designation, Fast Track Designation, and Breakthrough Therapy Designation and this submission was reviewed under priority review.

11. Recommendations and Benefit/Risk Assessment

a. Recommended Regulatory Action

The applicant has provided substantial evidence of effectiveness based on two adequate and well controlled clinical trials with supportive evidence from the initial clinical investigations and preclinical studies. The applicant has provided compelling evidence of a clinically meaningful benefit in Annualized Bleed Rates in adults, adolescents, and children.

The applicant has met the statutory requirements for regulatory approval and the review team recommends regular approval of ALTUVIIIO, for the treatment of adults and

children with Hemophilia A (Congenital Factor VIII deficiency) for: Routine Prophylaxis to reduce the frequency of bleeding episodes; On-Demand treatment and control of bleeding episodes; and Perioperative management of bleeding.

b. Benefit/Risk Assessment

ALTUVIIIO has demonstrated a clinically meaningful benefit in reduction of ABRs for routine prophylaxis, and has demonstrated hemostatic efficacy with on-demand treatment of and prevention of spontaneous or traumatic bleeding in adults and children with Hemophilia A and in the perioperative setting for reduction of bleeding during surgery.

The most common adverse reactions were headache and joint pain. These events were mild and transient. No neutralizing antibodies were reported following administration of ALTUVIIIO. The risks of ALTUVIIIO include thrombosis and allergic reactions, which are expected for this class of products.

This application has provided substantial evidence of the safety and effectiveness of ALTUVIIIO in adults and children with severe Hemophilia A. The overall benefit-risk profile favors approval of ALTUVIIIO for use in adults and children with Hemophilia A for routine prophylaxis to reduce the frequency of bleeding episodes; On-Demand treatment and control of bleeding episodes; and Perioperative management of bleeding.

c. Recommendation for Postmarketing Activities

Clinical data raised no safety concern that would necessitate a Risk Evaluation and Mitigation Strategy (REMS) or a safety-related post-marketing requirement (PMR).

The pharmacovigilance plan includes: (1) an ongoing long-term follow-up study of clinical trial subjects, (2) a post-marketing study to characterize the safety profile in previously untreated patients (PUPs) including the risk of inhibitor development to FVIII, and (3) adverse event reporting in accordance with 21 CFR 600.80. In addition, enhanced pharmacovigilance for occurrence of thromboembolic events (TEEs) will be in place for 3 years following approval; this will include expedited adverse event reporting of all TEEs occurring with the use of ALTUVIIIO and the applicant's assessment and summary of TEEs in periodic safety reports.

In STN 125771/0.32 [received 08 February 2023], the applicant proposed four PMCs to:

(i) add an upper limit to the (b) (4) acceptance criteria in the DS specification
(ii) add a test for (b) (4) to the DS specification
(iii) develop a DS specification to control (b) (4)
(iv) include (b) (4) as an identification test for DS release.

For each PMC, the applicant committed to submit final reports and Module 3 updates by March 29, 2024 and implement DS lot testing starting with the 2024 DS campaign.

In STN 125771/0.34 [received 14 February 2023], the applicant proposed three PMCs to:

(i) develop and include a DS release specification to control (b) (4)
(ii) include DP release specifications for total protein and specific activity
(iii) develop and include DP release specifications to control for individual excipients (polysorbate 80, arginine, histidine, calcium, sucrose).

For the (b) (4) DS release specification PMC, the applicant committed to submit final reports and Module 3 updates by June 28, 2024, and implement DS lot testing starting with the Q3 2024 campaign batches.

For the total protein and specific activity DP release specification PMC, the applicant committed to submit final reports and Module 3 updates by March 29, 2024, and implement DP lot testing starting with the Q2 2024 campaign batches.

For the excipient DP release specification PMC, the applicant committed to submit final reports and Module 3 updates by June 28, 2024, and implement DP lot testing starting with the Q3 2024 campaign batches.