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BLA Clinical Review Memorandum

Application Type	Efficacy Supplement - Response to FDA Complete Response Letter
STN	125264/1670
CBER Received Date	November 13, 2019
PDUFA Goal Date	August 13, 2020 (Revised following a Major Amendment Decision)
Division / Office	DCEPT / OTAT
Priority Review (Yes/No)	No
Reviewer Name(s)	Najat Bouchkouj, MD
Review Completion Date / Stamped Date	August 12, 2020
Supervisory Concurrence	Tejashri Purohit-Sheth, MD
Applicant	Wyeth Pharmaceuticals
Established Name	Antihemophilic Factor (Recombinant), Plasma/Albumin Free
(Proposed) Trade Name	Xyntha [Moroctocog Alfa (AF-CC)]
Pharmacologic Class	Clotting factor replacement (Antihemophilic Factor VIII)
Formulation(s), including Adjuvants, etc.	Lyophilized powder in single-use vials and single-use prefilled dual-chamber syringes. Upon reconstitution, the product is a clear to slightly opalescent, colorless solution that contains sodium chloride, sucrose, Lhistidine, calcium chloride and Polysorbate 80
Dosage Form(s) and Route(s) of Administration	Intravenous infusion
Dosing Regimen	Adults and adolescents (≥12 years): The recommended starting regimen is 30 IU/kg of XYNTHA administered 3 times weekly. Children (<12 years): The recommended starting regimen is 25 IU/kg of XYNTHA administered every other day.
Proposed Indication(s) and Intended Population(s)	Routine prophylaxis to prevent or reduce the frequency of bleeding episodes in adults and children with hemophilia A
Recommended Indication(s) and Intended Population(s)	Routine prophylaxis to reduce the frequency of bleeding episodes in adults and children with hemophilia A
Orphan Designated (Yes/No)	No

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GLOSSARY

ABR	Annualized bleeding rate
AE	Adverse event
AF-CC	Albumin-free cell culture
ALT	Alaninine aminotransferase
BDDrFVIII	B-domain-deleted recombinant
BL	Biological License
BLA/sBLA	Biologics License Application (supplemental)
CBER	Center for Biologics Evaluation and Research
CHMP	Committee for Medicinal Products for Human Use
CI	Confidence interval
CL	Clearance
CO	Clinical Overview
CPMP	Committee for Proprietary Medicinal Products
CSR	Clinical study report
ED	Exposure day
EMA	European Medicine Agency
FDA	Food and Drug Administration
FVIII	Factor VIII
FVIII:C	Factor VIII concentration/Factor VIII activity in
GCP	Good Clinical Practice
IND	International New Drug
iPSP	Initial Pediatric Study Plan
IRB	Institutional Review Board
ITT	Intent-to-treat
IU	International unit
Kg	Kilogram
LETE	Less than expected therapeutic effect
MA	Major Amendment
max	Maximum
MeDRA	Medical Dictionary for Regulatory Activities
min	Minimum
mITT	Modified intent-to-treat
N	Number of subjects
n	Subset of population in each category.
NA	Not applicable
PADER	Periodic Adverse Drug Experience Report
PAS	Prior Approval Supplement
PK	Pharmacokinetic
PSUR	Periodic Safety Update Report
PTP	Previously treated patients
RP	Routine prophylaxis
SAE	Serious adverse event
SCE	Summary of Clinical Efficacy
SCP	Summary of Pharmacokinetics
SCS	Summary of Clinical Safety
SD	Standard deviation
SE	Standard error
STN	Submission Tracking Number
TEAE	Treatment-emergent adverse event
USPI	United States Package Insert

Xyntha Moroctocog alfa albumin-free cell culture (AF-CC)

1. EXECUTIVE SUMMARY

Xyntha is a recombinant antihemophilic Factor VIII (FVIII) product currently indicated in adults and children with hemophilia A for on-demand treatment (OD) and control of bleeding episodes and for perioperative management. This supplement is intended to add the routine prophylaxis indication. The Applicant was issued a Complete Response (CR) letter on October 13, 2017 because there was a concern regarding the high rate of factor VIII inhibitor development. This response to CR contains efficacy data to support the routine prophylaxis indication based on two clinical studies, 3082B2-310 [Study 310] and 3082B2-313 [Study 313]. The safety data were reviewed in prior safety labeling supplement STN 125264/1769 (Seq 0481), which was approved on 13 Aug 2019.

A total of 102 subjects were analyzed for efficacy across both studies to support the indication of routine prophylaxis. Study 310 consisted of two parts, a pharmacokinetics (PK) period which supported the initial approval, and a safety and efficacy period intended to characterize the efficacy response of prophylactic treatment compared to on-demand infusions of Xyntha. The efficacy analysis included 94 previously treated patients (PTPs) with severe or moderately severe hemophilia A who were 12 years of age or older. The mean (±SD) annualized bleed rate (ABR) for treated bleeds in all subjects was 3.9 (± 6.5) and median (min, max) ABR was 1.9 (0-42.1). The mean ABR for spontaneous and traumatic bleeds was 1.9 and 2.0, respectively. Among 18 adolescent subjects, eight (44%) had no bleeding episodes while on routine prophylaxis with Xyntha. The mean (±SD) ABR was 7.3 (± 10.9) and median (min, max) ABR was 3.1 (0-42.1). After excluding the one adolescent outlier who had an ABR of 44, the mean ABR becomes 5.2 in the adolescent subgroup. Subjects' mean and median prophylactic dose was 30 IU/kg three times weekly.

The primary objective of Study 313 was to demonstrate that Xyntha prophylaxis, at 25 IU/kg administered every other day (EOD), reduces the ABR relative to on-demand (OD) therapy in pediatric patients with severe or moderately severe hemophilia A. The primary efficacy analysis was based on eight subjects who received OD therapy followed by routine prophylaxis at a dose of 25 IU/kg EOD. Four of the eight subjects (50%) had no bleeding episodes while on routine prophylaxis with Xyntha. The mean (±SD) ABR for all subjects during the prophylaxis period was 1.5 (± 2.2) and median (min, max) ABR was 0.6 (0-6.2) compared to 47 (±32.2) and 34 (0-92.4) in the OD period.

Across all ages, 46 subjects (45%) had zero bleeds during the reporting period. There was an 89% reduction in ABR for subjects on routine prophylaxis compared to OD dosing.

The development of Factor VIII inhibitors with Xyntha was evaluated in 167 adult and pediatric PTPs with at least 50 exposure days (EDs) across four studies (Study 310, Study 313, and supportive studies Study 3315 and Study 4418). Four of 167 (2.4%) subjects developed Factor VIII inhibitors across all studies (Two in Study 310 and two in Study 313).

This submission triggers Pediatric Research Equity Act (PREA) and the Pediatric Equity Research Committee (PeRC) meeting was held on June 30, 2020. Post Marketing Requirements are considered fulfilled with the submission of this sBLA.

The overall benefit-risk profile of Xyntha is favorable and the clinical reviewer recommends approval of the sBLA for the new indication of: routine prophylaxis to reduce the frequency of bleeding episodes.

1.1 Demographic Information: Subgroup Demographics and Analysis Summary

All subjects were male. Among 94 subjects in the adult/adolescent study (310), 18 subjects (19%) were adolescents (12-16 years of age). The median age in Study 310 was 24 years of age (min-max: 12-60 yrs) and mean ± SD was (28 ± 12.8 yrs). The median age among the 51 subjects enrolled in the pediatric study, Study (313) was 4.4 years of age (min-max: 1.1-12.7 yrs) and mean ± SD was (4.3 ± 1.9 yrs). The predominant race represented in the studies was White and predominant ethnicity was Not Hispanic/Latino.

Reviewer comment: *Because the predilection for clinical bleeding is dependent on the degree of factor VIII deficiency, the impact of race and ethnicity related differences on efficacy are expected to be minimal. Therefore, it is reasonable to extrapolate from Whites and Not Hispanic/Latino to the other races and ethnic groups*

1.2 Patient Experience Data

None submitted.

Data Submitted in the Application

Check if Submitted	Type of Data	Section Where Discussed, if Applicable
☐	Patient-reported outcome	
☐	Observer-reported outcome	
☐	Clinician-reported outcome	
☐	Performance outcome	
☐	Patient-focused drug development meeting summary	
☐	FDA Patient Listening Session	
☐	Qualitative studies (e.g., individual patient/caregiver interviews, focus group interviews, expert interviews, Delphi Panel)	
☐	Observational survey studies	
☐	Natural history studies	
☐	Patient preference studies	
☐	Other: (please specify)	
☒	**If no patient experience data were submitted by Applicant, indicate here.**	
Check if Considered	**Type of Data**	**Section Where Discussed, if Applicable**
☐	Perspectives shared at patient stakeholder meeting	
☐	Patient-focused drug development meeting	
☐	FDA Patient Listening Session	

☐	Other stakeholder meeting summary report	
☐	Observational survey studies	
☐	Other: (please specify)	

2. CLINICAL AND REGULATORY BACKGROUND

2.1 Disease or Health-Related Condition(s) Studied

Hemophilia A (HA) is an X-linked congenital bleeding disorder caused by a deficiency of functional clotting factor VIII (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 severe with spontaneous bleeding into joints or muscles. Moderate severity and mild severity have clotting factor levels of 1-5% and 5 to<40%, respectively.

The average life expectancy is less than 20 years with quality of life severely limited by joint complications and intracranial hemorrhage. 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, making usual treatment with FVIII complicated. Prophylaxis has been shown to prevent complications later in life and to decrease the incidence of inhibitor formation.

2.2 Currently Available, Pharmacologically Unrelated Treatment(s)/Intervention(s) for the Proposed Indication(s)

Currently, there are several licensed rFVIII products some of which are full-length FVIII products and others that are beta domain deleted (BDD) products. These products are indicated for adults and children with HA for the control and prevention of bleeding episodes, and/or perioperative management, and/or routine prophylaxis to reduce the frequency of bleeding episodes and the risk of joint damage. In addition, Hemlibra (Emicizumab) is an FDA approved bispecific factor IXa- and factor X-directed antibody indicated for routine prophylaxis to prevent or reduce the frequency of bleeding episodes in adult and pediatric patients with HA with or without factor VIII inhibitors. The following table includes currently approved FVIII products:

Table 1: Approved FVIII Products

Product	Category	Full Length(FL) or B Domain Deleted (BDD)	Cell Expression	Year Approved
Recombinate	Recombinant	FL	CHO	1992
Kogenate	Recombinant	FL	BHK	1993
Refacto	Recombinant	BDD	CHO	2000
Advate	Recombinant Plasma/Albumin Free	FL	CHO	2003
Xyntha	Recombinant	BDD	CHO	2008

Product	Category	Full Length(FL) or B Domain Deleted (BDD)	Cell Expression	Year Approved
Novoeight	Recombinant	BDD	CHO	2013
Eloctate	Recombinant Fc Fusion Protein	BDD	HEK	2014
Obizur	Recombinant Porcine Sequence	BDD	BHK	2014
Nuwiq	Recombinant	BDD	HEK	2015
Adynovate	Recombinant 20kDA PEGylated	FL	CHO	2015
Afstyla	Recombinant Single Chain	BDD	CHO	2016
Kovaltry	Recombinant	FL	BHK	2016
JIVI	Recombinant 60kDA PEGylated	BDD	BHK	2018
Esperoct	Recombinant 40kDA PEGylated	BD truncated	CHO	2019

2.3 Safety and Efficacy of Pharmacologically Related Products

Inhibitor formation and pathogen transmission are the main safety concerns when treating HA patients with FVIII replacement therapy. FVIII concentrates derived from human plasma first became available in the 1960s. The high risk of viral transmission from human plasma donors, underscored by the human immunodeficiency virus (HIV) epidemic in the 1980s, led to the development of rFVIII products which became available in the 1990s. The rFVIII products are genetically engineered and manufactured from animal cell lines, thus minimizing the risk of transmission of human pathogens. Full-length and modified rFVIII have been produced in Chinese hamster ovary (CHO) or baby hamster kidney (BHK) cells. In addition to the risk of pathogen transmission, the development of neutralizing antibodies, or inhibitors, has been and remains the most concerning safety issue following the administration of FVIII concentrates. The etiology of the development of inhibitors is thought to be a host immune response triggered by non-human proteins contained in the final recombinant FVIII product. Purification steps in the manufacturing processes of successive generations of rFVIII aim to reduce both the transmission of pathogens and the development of inhibitors, which occurs in up to 30% of patients with severe Hemophilia A[1].

The development of inhibitors decreases the efficacy of replacement therapy, necessitates FVIII dosage increases and/or the use of “bypass” agents, increases the risk of unmanageable bleeding and increases cost of treatment (by 3-5 fold)[2]. The incidence of inhibitor development is approximately 30% in severe disease and less in mild or moderate disease. The highest incidence is in previously untreated patients with severe disease (reported incidence from 3-52%). Inhibitor development in previously treated patients who have not previously developed a FVIII inhibitor is less, reported as 0.9-4%. Potential risk factors for inhibitor development include genetic factors, such as

1 Gouw SC, van der Bom JG, Ljung R, et al. Factor VIII products and inhibitor development in severe hemophilia A. N Engl J Med. 2013;368:231-9.
2 Goudemand J.Treatment of patients with inhibitors: cost issues. Haemophilia 2013;5:397-491.

the type of FVIII gene mutation, human leukocyte antigen (HLA) type, polymorphisms in immune regulatory regions, family history of inhibitors and ethnic background as well as immunologic environment during early treatment and high intensity of treatment (either peak acute treatment or high overall treatment frequency).

2.4 Previous Human Experience with the Product (Including Foreign Experience)

Xyntha® (moroctocog alfa albumin-free cell culture [AF-CC]) is a recombinant antihemophilic Factor VIII (FVIII) product currently indicated in adults and children with hemophilia A for on-demand treatment and control of bleeding episodes and for perioperative management. Xyntha was first approved in the US on 21 February 2008.

2.5 Summary of Pre- and Post-submission Regulatory Activity Related to the Submission

30 Apr 2003 (STN 125080)	Initial BLA submission
18 Jun 2003	Wyeth was informed that the clinical trial (Study 310), may not support licensure as the study had failed its safety endpoint due to a high number of inhibitors.
23 Jan 2004	Wyeth withdrew the BLA
Jan – Jun 2005	Several telecons and correspondence relevant to the study design took place between the agency and the sponsor: Because of significant changes made to the product, the product was classified as a new product. FDA also agreed to the concept of use Bayesian statistical methods to evaluate safety.
21 Feb 2008	BLA Approval indicated for control and prevention of bleeding episodes and for surgical prophylaxis in patients with hemophilia A.
17 Oct 2014	Approval to include expansion of the indication to include all pediatric age groups.
25 Mar 2016	Proposed initial Pediatric Study Plan (iPSP) Study 310
7 June 2016	Agreed iPSP, reflecting edits requested by the FDA
13 Oct 2017	Complete Response Letter with the following deficiency: *"Currently, the high rate of inhibitor development with your product outweighs the potential benefits of Xyntha as prophylactic therapy. We recommend that you identify risk factors associated with inhibitor development with the administration of Xyntha. Please identify a patient population in whom the benefit risk profile is potentially favorable and prospectively study the safety and efficacy of Xyntha in this patient population."*
13 Aug 2019	Approval of supplemental BLA 125264/1769 to update the safety and on-demand efficacy information in the USPI based on the final study results from Study 313. In addition, the indication statement was updated to align with class labeling.

2.6 Other Relevant Background Information

N/A.

3. SUBMISSION QUALITY AND GOOD CLINICAL PRACTICES

3.1 Submission Quality and Completeness

The BLA was submitted electronically and formatted as an electronic Common Technical Document (eCTD) according to FDA guidance for electronic submission. This submission was not adequately organized to allow a complete clinical review in a timely manner to meet the action due date for this review cycle without unreasonable difficulty. Data sets from multiple prior submissions were referenced requiring need to navigate back and forth between prior and current submission. The updated data sets for Study 313 were submitted under STN 125264/1769 Seq 0481. The primary data sets for Study 310 were not provided and the Applicant referred FDA back to the original BLA submission, 125264/0 Seq 0373. However, the reviewer was not been able to locate the primary data sets for Study 310 in that submission. Datasets supporting Study 310 were only provided in "pooled datasets" under 125264/1769 Seq 0481. The pooled datasets included data from Study 310 and updated data from Study 313. After several information requests (IRs), the Applicant submitted new data sets for bleeding and exposure for Studies 310 and 313. A major amendment (MA) was required to review the substantial amount of clinical information related to efficacy provided in Amendments 1670/6-14.

3.2 Compliance With Good Clinical Practices And Submission Integrity

Several sites were inspected previously for the original BLA in 2008 for Study 310. Additional sites were evaluated in 2011 for Study 311 and in 2014 and 2017 for Study 313. Based on the history of previous inspections, the Bioresearch Monitoring (BIMO) did not issue any further clinical inspections for this supplement, which was reasonable. The final BIMO memo was issued in August 2017 under STN 125264/1670.

Of note, Site 010 in Poland was previously found to be non-good clinical practice (GCP)-compliant in 2014, therefore, the Applicant has excluded data from that site and data from this site were not used to support this submission.

3.3 Financial Disclosures

No financial disclosure forms were included in this submission because of no new investigators. Based on prior clinical review memos, the Applicant stated that none of the investigators disclosed a financial interest in this product.

4. SIGNIFICANT EFFICACY/SAFETY ISSUES RELATED TO OTHER REVIEW DISCIPLINES

4.1 Chemistry, Manufacturing, and Controls

No additional Chemistry, Manufacturing, and Controls **(**CMC) information was provided in this submission.

4.2 Assay Validation

N/A

4.3 Nonclinical Pharmacology/Toxicology

No additional Pharmacology/Toxicology information was provided in this submission.

4.4 Clinical Pharmacology

No additional clinical pharmacology information was provided in this submission.

4.5 Statistical

See Statistical Review Memo for complete review.

4.6 Pharmacovigilance

N/A

5. Sources of Clinical Data and Other Information Considered in the Review

5.1 Review Strategy

The clinical review focused on review of:

- The Applicant's response to clinical issues conveyed in the CRL
- The efficacy datasets (bleeding and exposure data) for Studies 310 and 313 supporting the indication of prophylaxis and proposed labeling changes

The clinical review did not focus on review of:

- The safety and updated on-demand data that were submitted under Amendment 1769 Seq 0481, because the data were already reviewed by the clinical reviewer and the supplement was approved on 13 August 2019.

To assess the efficacy of therapy, the ABR or number of bleeds per year, was derived for each subject for each treatment regimen by using the following formula: ABR = number of bleeds / (days on treatment regimen / 365.25). The applicant's ABR calculation included only the bleeds that required treatment with a FVIII replacement product during the time on treatment. Bleeds not requiring treatment were not included in their analyses. However, FDA analyzed both treated and non-treated bleeds.

5.2 BLA/IND Documents That Serve as the Basis for the Clinical Review

The review of this supplement was based primarily on the clinical data provided in sBLA 125264/1670.6-16.
125264/1769.0 Seq 0481
Of note, no datasets were provided in 125264/0 Seq 0373.

5.3 Table of Studies/Clinical Trials

The clinical development program for Xyntha in adult and pediatric subjects with HA consists of five completed studies (Study 310 [3082B2 310]; Study 311 [3082B2-311]; Study 313 [B1831001, 3082B2-313]; Study 3315 [3082B2-3315]; and Study 4418 [3082B2-4418]; See Table 2 below.

The completed ReFacto Study 3082A1-300-WW (Study 300) and completed ReFacto AF Study 3082B2-4432-WW (Study 4432) for both children and adults were included in this application to provide historical on-demand efficacy data that were pooled with on-demand efficacy data from Study 313 for comparison to routine prophylaxis data from Studies 310 and 313.

Table 2: Xyntha Clinical Development Program in Patients with Hemophilia A

Study #	Design	Population	< 17 years	> 17 years	Status Date
310	Phase 3, double-blind, randomized crossover PK period to assess BE of Xyntha and Advate, followed by open-label period to evaluate efficacy and safety for use in prophylaxis and on demand treatment of bleeding	Male PTPs ≥12 ≥ 150 EDs	18	76	Complete Nov 2016
311	Open-label multicenter study to assess efficacy and safety of xyntha in patients with hemophilia A undergoing elective major surgery	Male PTPs ≥12 ≥ 150 EDs	0	30	Complete Jun 2008
313	Phase 3, randomized, open-label, multi-center study to evaluate prophylaxis treatment and to characterize the efficacy, safety, and PK of Xyntha in in children with hemophilia A	Male PTPs <6 yrs[a] ≥ 20 EDs	50[d]	0	Complete Apr 2018
3315	Phase 3b/4, non-randomized, open label, prospective study to evaluate efficacy and safety of Xyntha in < 6 years of age in usual care settings	Male <6 yrs < 50 EDs	1	0	Terminated [b] Dec 2009
4418	Phase 4, post-marketing, non-randomized, evaluate the safety of Xyntha in subjects transitioning from ReFacto or other FVIII replacement to Xyntha in usual care setting	Male PTPs ≥12 >150 EDs	3	9	Terminated [c] Aug 2011

Abbreviations: ED=exposure day; FVIII=Factor VIII; PK=pharmacokinetics; PTPs=previously treated patients

a. Age increased to <16 years with amendment 10)
b. Study 3315 was terminated to not compete for enrollment with Study 313
c. Study 4418 was terminated due to administrative reasons and not due to any safety issues
d. One subject was enrolled but did not receive any study treatment and therefore was excluded from analysis

5.4 Consultations

None.

5.4.1 Advisory Committee (AC) Meeting (if applicable)

There were no controversial issues warranting an AC meeting.

5.4.2 External Consults/Collaborations

None.

5.5 Literature Reviewed (if applicable)

1. Gouw SC, van der Bom JG, Ljung R, et al. Factor VIII products and inhibitor development in severe hemophilia A. N Engl J Med. 2013;368:231-9.
2. Goudemand J.Treatment of patients with inhibitors: cost issues. Haemophilia 2013;5:397-491.

6. DISCUSSION OF INDIVIDUAL STUDIES/CLINICAL TRIALS

6.1 Trial #1

Study 310: A Randomized Two-way Blinded Crossover-Design Study to Establish the Bioequivalence of B-Domain Deleted Recombinant Factor VIII (BDDrFVIII, moroctocog alfa [AF-CC]) With a Full-Length Recombinant Factor VIII Preparation (FLrFVIII, Advate), Followed by an Open-Label Trial of the Safety and Efficacy of Xyntha in Previously Treated Patients With Hemophilia A.

Completed Phase 3, randomized, two-way blinded crossover bioequivalence study, followed by an open-label safety and efficacy study in male previously treated subjects >12 years of age with severe or moderately severe hemophilia A (FVIII:C <2%) and with ≥150 EDs to any FVIII product. Routine prophylaxis dosing with Xyntha was initiated using 30 ± 5 IU/kg 3 times a week for all subjects.

The primary data for this Phase 3 clinical trial were reviewed for the original BLA submission 125264/0. See the final clinical review memo dated 01 January 2008, authored by Nisha Jain, M.D., for the complete review which focused on the primary endpoint of PK data and bioequivalence to Advate.

6.1.1 Objectives (Primary, Secondary, etc.)

Primary Objectives

The primary safety objective of this study was to determine the incidence rate of FVIII inhibitors associated with the use of Xyntha in the study patient population. The primary efficacy objective of this study was to establish the bioequivalence of Xyntha and a full-length recombinant FVIII (Advate) using the one stage (OS) FVIII assay.

Secondary Objectives

- To characterize the PK of Xyntha in comparison to Advate and over time
- To characterize the efficacy of Xyntha in preventing and treating bleeding episodes during prophylaxis treatment
- To characterize the efficacy response of both prophylactic and on-demand infusions of Xyntha
- To characterize the rate of “Less than Expected Therapeutic Effect” (LETE) responses of Xyntha when used either prophylactically or for treatment of a bleeding episode (“on-demand”) or in the instance of low recovery
- To characterize the consumption of Xyntha (international units/kg) over time
- To characterize the adverse events
- To characterize the incidence of allergic reactions
- To characterize patient compliance with prescribed regimen(s)

6.1.2 Design Overview

The study consisted of 2 parts, a PK period and a safety and efficacy (SE) period. The SE period of the study was conducted as an open-label, multicenter trial of Xyntha in routine prophylaxis and on-demand therapy in at least 81 previously treated patients (PTPs) with severe or moderately severe hemophilia A. Patients received a defined prophylaxis regimen of Xyntha for a minimum of 50 exposure days (EDs) over 6 months. Xyntha was to be used exclusively for both prophylaxis and the treatment of any bleeds whether spontaneous or traumatic. Efficacy data were collected on the success of

prophylaxis and detailed data were collected on the response of bleeds to therapy with Xyntha. Safety data were collected on adverse events, especially the occurrence of FVIII inhibitors.

6.1.3 Population

Male patients ≥12 years of age with severe or moderately severe hemophilia A (FVIII activity in plasma [FVIII:C] < 2 %), who were previously treated with > 150 EDs to any FVIII product.

6.1.4 Study Treatments or Agents Mandated by the Protocol

Routine prophylactic dosing was initiated using the same dosing regimen at “step 1” (30 ± 5 IU/kg 3 times a week) for all patients. The dose was prescribed by the investigator based on the actual potency on the label of the test article used, and the patient's most recent actual body weight as measured during the study. Predefined “escape” criteria provided rules for dose escalation to higher intensity dosing regimens, initially to step 2 (45 ± 5 IU/kg 3 times a week), and then to more frequent or higher doses as determined by the investigator.

Escape criteria for escalating to a higher step (e.g., step 1 to step 2) were either:

- Two (2) spontaneous (atraumatic) bleeding episodes into major joints such as elbow, ankle or knee joint(s) or other target joints over a 4-week (28-day) period,

  or

- Three (3) or more spontaneous (atraumatic) bleeding episodes (e.g., 1 joint and 2 soft tissue or other site) over a 4-week (28-day) period.

In addition to routine prophylaxis, intermittent prophylaxis in the form of additional infusions of study drug was allowed if it was believed such treatment was required to prevent bleeding for an upcoming activity or procedure.

6.1.5 Directions for Use

The active ingredient in Xyntha, Antihemophilic Factor (Recombinant), also called coagulation factor VIII (FVIII), or moroctocog alfa, is a recombinant antihemophilic factor which is produced by recombinant DNA technology. Formulation is a lyophilized powder preparation, route of administration is intravenous, study regimen: 30 IU/kg; 30 + 5 IU/kg given 3 times per week.

6.1.6 Sites and Centers

Up to the data cut-off date (13 March 2007) the study was conducted at 24 active sites in 10 countries: Australia (1 site), Belgium (1 site), Finland (1 site), Germany (1 site), Hungary (1 site), Italy (1 site), New Zealand (2 sites), Poland (3 sites), Sweden (2 sites), and United States of America (11 sites).

6.1.7 Surveillance/Monitoring

Study schedule is summarized in Figure 1 below.

Figure 1: Surveillance and Monitoring on Study 310

Study Period	Screening	Crossover PK Period		Safety and Efficacy Period							
	Visit 1	Visit 2	Visit 3	Visit 4	Visit 5	Visit 6	Visit 7	Visit 8	Visit 9	Visit 10	Final Contact
Procedure	Screening[a]	PK1[e,g]	PK2[e,g]	Month 0 visit (Safety and Efficacy Day 1)	Month 1 visit (Safety and Efficacy Month 1± 1 week)	Month 2 visit (Safety and Efficacy Month 2 ± 1 week)	Month 3 visit (Safety and Efficacy Month 3 ± 1 week)	Month 4 visit (Safety and Efficacy Month 4 ± 1 week)	Month 5 visit (Safety and Efficacy Month 5 ± 1 week)	Month 6 visit (Safety and Efficacy Month 6 ± 1 week) and PK3[e,g,k]	
Consent/Assent	X										
Demographics	X										
Medical and Drug History	X										
Vital Signs	X			X	X		X			X	
Physical Exam	X			X	X		X			X	
Height	X										
Weight	X			X	X		X			X	
HIV 1&2 antibodies	X										
CD4	X									X	
Hepatitis Serology Panel[b]	X										
Serum Chemistry[i]	X									X	
Hematology[j]	X									X	
PT or INR	X										
Factor VIII:C[b]	X			X	X		X			X	
Factor VIII inhibitor[b]	X			X	X		X			X	
Enrollment and Randomization[d]	X										
Dispense Study Drug				X	X	X	X	X	X		

Study Period	Screening	Crossover PK Period		Safety and Efficacy Period							
	Visit 1	Visit 2	Visit 3	Visit 4	Visit 5	Visit 6	Visit 7	Visit 8	Visit 9	Visit 10	Final Contact
Procedure	Screening[a]	PK1[e,g]	PK2[e,g]	Month 0 visit (Safety and Efficacy Day 1)	Month 1 visit (Safety and Efficacy Month 1± 1 week)	Month 2 visit (Safety and Efficacy Month 2 ± 1 week)	Month 3 visit (Safety and Efficacy Month 3 ± 1 week)	Month 4 visit (Safety and Efficacy Month 4 ± 1 week)	Month 5 visit (Safety and Efficacy Month 5 ± 1 week)	Month 6 visit (Safety and Efficacy Month 6 ± 1 week) and PK3[e,g,k]	
Drug Accountability					X	X	X	X	X	X	
Efficacy Assessments					X	X	X	X	X	X	
Regimen Adjustment					X	X	X	X	X		
Adverse Event Collection	X	X	X	X	X	X	X	X	X	X	X
Patient Diary Collection					X	X	X	X	X	X	
Concomitant Medications	X	X	X	X	X	X	X	X	X	X	X
ELISA for Anti-FVIII[b], Anti-CHO[b]	X			X	X		X			X	
ELISA Anti- TNI.2[b]	X									X	
Pharmacokinetic Measurement on approximately 30 Patients[c]		X	X							X[k]	

Source: Study Protocol, Section 5.3.5

6.1.8 Endpoints and Criteria for Study Success

The primary safety objective of this study was to determine the incidence rate of FVIII inhibitors associated with the use of Xyntha in the study patient population. The primary

efficacy objective of this study was to establish the bioequivalence of Xyntha and a full-length recombinant FVIII (Advate) using the OS FVIII assay. Secondary objectives in this study were: to characterize the PK of Xyntha in comparison to Advate and over time, characterize the efficacy of Xyntha in preventing and treating bleeding episodes during prophylaxis treatment, characterize the efficacy response of both prophylactic and on-demand infusions of Xyntha, characterize the rate of "Less than Expected Therapeutic Effect" (LETE) responses of Xyntha when used either prophylactically or for treatment of a bleeding episode ("on-demand") or in the instance of low recovery, characterize the consumption of Xyntha (international units/kg) over time, characterize the adverse events, characterize the incidence of allergic reactions, and characterize patient compliance with prescribed regimen(s).

Factor VIII Inhibitors
For the purposes of this study a patient was considered to have developed a positive inhibitor after they had received study drug, if they had a titer of >0.6 Bethesda Units/mL in a sample assayed at the central laboratory using the Nijmegen assay. Positive Factor VIII inhibitors were further categorized as low titer or high titer. Low titer inhibitors were defined as those positive inhibitors with a titer of $\leq$5 Bethesda Units/mL in a sample assayed at the central laboratory using the Nijmegen assay. High titer inhibitors were defined as those positive inhibitors with a titer of > 5 Bethesda Units/mL assayed at the central laboratory using the Nijmegen assay. If an inhibitor resolved by the Nijmegen assay, at or before a patient's final assessment it was further classified as transient.

If a patient had a local laboratory assay that was considered positive by the investigator in spite of a negative central laboratory result, or the investigator considered the patient to have developed an inhibitor for other reasons based on clinical grounds, then the finding was to be reported in the manner of and recorded as a serious adverse event (SAE) rather than count as an inhibitor.

Investigators were required to report all confirmed inhibitors in the same expedited manner as outlined for SAEs (section 30.4). Reports or assays received by Wyeth which were suggestive of a Factor VIII inhibitor were to be confirmed by the study's central laboratory before communication with regulatory authorities. Confirmed inhibitors were to be reported to regulatory authorities in the same manner as unexpected, related serious adverse events. Patients who developed a confirmed inhibitor on the study were to be withdrawn from the study after completion of the procedures of Visit 10 and the final contact.

Stopping Rules and Inhibitor Formation
The Data Safety and Monitoring Board were to have a formalized process for reviewing inhibitor formation rates and under what circumstances an excess number of inhibitors would lead to a recommendation to halt the trial. As described below if 3 patients in the study develop de novo inhibitors, the trial was to be stopped by the sponsor. The sponsor could stop the trial for any reason; the reason for trial cessation was required to be documented.

6.1.9 Statistical Considerations & Statistical Analysis Plan

In general, all efficacy and safety endpoints were summarized with descriptive statistics as appropriate. Descriptive statistics were used to summarize demographic and baseline

data on the study population, as well as hemostatic efficacy, TEAEs and treatment-emergent hemophilia events, LETE, and annualized bleeding episodes.

Pharmacokinetic assessment methods: Blood samples for determination of FVIII activity were collected at study visits 2 and 3 (PK1 and PK2) and at the 6-month visit during the SE period of the study (PK3) at pre-specified times over 48 hours after the start of test article infusion. FVIII activity PK parameters for Xyntha and Advate® at the PK visits were derived using standard non-compartmental methods. The primary PK endpoints include the areas under the curve from zero to the last measurable concentration (AUCt), and from zero to infinity (AUC¥), and incremental recovery (K value, IU/dL per IU/kg). Secondary endpoints include maximum concentration (Cmax), terminal disposition half-life (t1/2), and in vivo recovery (%).

Efficacy assessment methods: for prophylaxis, the number of infusions, dose per infusion, number of bleeding episodes, and time between last infusion to start of a new bleed were assessed. In the on-demand setting, efficacy measurements were made based on the patient's assessment of response to on-demand treatment of bleeding episodes according to a 4-point rating scale (excellent, good, moderate, and no response) as well as Xyntha use (mean dose [IU/kg] and number of infusions per bleed). The assessment of response was made within approximately 8 hours after infusion or prior to the next infusion for the same bleeding episode. Instances of LETE in both the prophylaxis and on-demand setting were also assessed.

6.1.10 Study Population and Disposition

6.1.10.1 Populations Enrolled/Analyzed

All 94 subjects had ≥150 previous EDs to FVIII replacement products. Of the 94 subjects in the SE period of the trial, 74 (79%) subjects had at least one target joint identified (a target joint was defined as a major joint into which repeated bleeding occurred with clinical signs and/or symptoms of underlying target joint damage). One subject, patient (b) (6), was enrolled with a FVIII:C >2% at screening (3.63%), but remained in the study based on a subsequent on-study activity level of 0.0101 IU/mL assessed at the central laboratory after a wash-out of 114 hours. Two populations were evaluated in this trial, one to establish bioequivalence and the other population for safety and efficacy. The thirty-one subjects evaluated for bioequivalence were reviewed previously in the original BLA application (See clinical review memo dated 01 January 2008).

6.1.10.1.1 Demographics

All subjects (100%) enrolled in the study were male, with a median age of 24 years (mean 27.7 years; range, 12 to 60 years). Most subjects (81%) were 17 years of age or older and most were white (95%). See Table 3.

Table 3: Study 310 Demographics and Baseline Characteristics

Study 310	N=94
Age	
Mean	27.7
SD	12.8
Median	24
Min, Max	12, 60
Sex, n (%)	

Study 310	N=94
Male	94 (100)
Race, n (%)	
Other	5 (5)
White	89 (95)
Ethnicity, n (%)	
Hispanic or Latino	4 (5)
Non-Hispanic and non-Latino	90 (96)

Source: FDA analysis

6.1.10.1.2 Medical/Behavioral Characterization of the Enrolled Population
Of the 94 subjects in the SE period of the trial, 74 (79%) subjects had at least one target joint identified (a target joint was defined as a major joint into which repeated bleeding occurred with clinical signs and/or symptoms of underlying target joint damage).

6.1.10.1.3 Subject Disposition
Ninety-four (94) subjects enrolled and were treated with at least one dose of Xyntha in the study and were included in the intent to treat (ITT) population. Three subjects discontinued treatment early [(Subject (b) (6) (47 EDs), Subject (b) (6) (1 ED), and subject (b) (6) (17 EDs)]. Two additional subjects excluded from the efficacy-evaluable population completed the entire 6 months of the SE period of the study with fewer than 50 recorded EDs (Subject (b) (6) (47 EDs) did not achieve 50 EDs due to incomplete compliance with his prescribed treatment. Subject (b) (6) (29 EDs) lost some of his patient diaries and thus test article usage could not be provided for visits 8 through 10 (covering 3 months of study participation).

Therefore, 89 subjects accrued ≥50 EDs to Xyntha and thus were part of the efficacy-evaluable population for secondary efficacy objectives. The median time on study (from day of signing informed consent to day of last study contact) for all 94 subjects was 240.5 days, which included a median of 178 days on routine prophylaxis (from day of first routine prophylaxis dose to day of last study visit).

6.1.11 Efficacy Analyses

6.1.11.1 Analyses of Primary Endpoint(s)

The primary data for this Phase 3 clinical trial were reviewed for the original BLA submission 125264/0. See the final clinical review memo dated 01 January 2008, authored by Nisha Jain, M.D., for the complete review which focused on the primary endpoint of PK data and bioequivalence to Advate.

6.1.11.2 Analyses of Secondary Endpoints

All subjects began routine prophylaxis treatment at a dose of 30 IU/kg 3 times a week (as per protocol). Seven dose escalations were prescribed for 6 subjects during the course of the study, including two escalations for Subjects (b) (6) and single escalations for subjects (b) (6) .

Narratives for subjects who were prescribed one or more dose escalations:

1. **Subject** (b) (6):15 yo who was prescribed Xyntha 30 ± 5 IU/kg 3 times per week followed by escalation to 45 ± 5 IU/kg 3 times per week after meeting escape criterion B (3 spontaneous bleeds within 28 days in any location).
2. **Subject** (b) (6)**:** 15 yo who was prescribed Xyntha 30 ± 5 IU/kg 3 times per week followed by escalation to 45 ± 5 IU/kg 3 times per week after meeting escape criterion B
3. **Subject** (b) (6)**:** 25 yo who was prescribed Xyntha 30 ± 5 IU/kg 3 times per week followed by escalation to 45 ± 5 IU/kg 3 times per week after meeting escape criterion A (2 spontaneous bleeds within 28 days in a major joint). He subsequently escalated again to 45 ± 5 IU/kg QOD after meeting escape criterion B.
4. **Subject** (b) (6)**:** 24 yo who was prescribed Xyntha 30 ± 5 IU/kg 3 times per week followed by escalation to 40 ± 5 IU/kg 3 times per week after having a traumatic joint bleed for which he received 3 on-demand infusions in a week. His dose was escalated by the investigator in response to subject request due to pain.
5. **Subject** (b) (6)**:** 20 yo who was prescribed Xyntha 30 ± 5 IU/kg 3 times per week followed by escalation to 45 ± 5 IU/kg 3 times per week after meeting escape criterion A.
6. **Subject** (b) (6)**:** 17 yo who was prescribed Xyntha 30 ± 5 IU/kg 3 times per week followed by escalation to 45 ± 5 IU/kg 3 times per week after meeting escape criteria A and B.

Reviewer comment: *Based on subject diaries and CRFs, compliance with prescribed treatment regimens was excellent. Subjects who were outliers in terms of compliance, defined as an average dose >5 IU/kg discrepant from their prescribed dose, or an average frequency of prophylaxis dosing >20% discrepant from their weekly prescribed prophylactic frequency, were individually examined by the Applicant for efficacy. This analysis was generally uninformative due to the overall high compliance rates in the study population.*

Annualized Bleeding Rates in Prophylaxis Subjects

Treated bleeds:

Bleeding episodes that required treatment with FVIII and that occurred while the subject was on routine prophylaxis were considered in the calculation of the ABR as specified in the protocol. An ABR was calculated from each subject's data on bleeding, and these values were summarized for the study population as a whole.

Among all 94 subjects, 43 (46%) had no bleeding episodes while on routine prophylaxis with Xyntha. Of the 51 subjects with bleeds, 37 subjects had spontaneous bleeds, 38 subjects had traumatic bleeds and 24 subjects had both spontaneous and traumatic bleeds. Fifty-seven (57/94; 61%) subjects reported no spontaneous bleeding. Of these 57 subjects with no reported spontaneous bleeds, 14 subjects reported traumatic bleeds.

Reviewer comment: *In the updated bleeding datasets (IR310ZBE) which were submitted in May 2020, Subject* (b) (6) *(12 yo) had ABR of 0 and ABR duration period of 92 days when calculated by the Applicant. However, it was noted that the subject had two traumatic bleeds on Day 1 and Day 156 respectively. The subject was withdrawn from the study after 66 EDs due to transient low titer FVIII inhibitor. He had 38 EDs*

before the visit at which the inhibitor was detected and an additional 28 EDs after that visit and before he was withdrawn. Therefore, his ABR should be recalculated to 4.68.

When including Subject (b) (6) in ABR analysis, the mean (±SD) ABR for all subjects was 3.9 (± 6.5) and median (min, max) ABR was 1.9 (0-42.1). See Table 4.

The mean ABR was 1.9 and 2.0 for spontaneous and traumatic bleeds, respectively. The median ABR for spontaneous and traumatic bleeds individually was 0 for both types of bleeds.

Table 4: ABR For Treated Bleeds in All Subjects

N=94	ABR*	ABR#
Mean	3.88	3.93
SD	6.48	6.46
Median	1.92	1.93
Min	0.0	0.0
Max	42.14	42.14

*Excluding Subject (b) (6)
#Including Subject (b) (6)

ABR analysis by age group: adolescents vs. adults.
ABR in adolescents:
Among 18 adolescent subjects, eight (44%) had no bleeding episodes while on routine prophylaxis with Xyntha. When including Subject (b) (6), the mean (±SD) ABR was 7.3 (± 10.9) and median (min, max) ABR was 3.1 (0-42.1). See Table 5 below.

Table 5: ABR For Treated Bleeds in Adolescents

N=18	ABR*	ABR#
Mean	6.99	7.25
SD	11.10	10.98
Median	0.98	3.06
Min	0.0	0.0
Max	42.1	42.1

*Excluding Subject (b) (6)
#Including Subject (b) (6)

ABR in adults:
Among 76 adult subjects, the mean (±SD) ABR was 3.1 (± 4.6) and median (min, max) ABR was 1.9 (0-42.1). See Table 6 below.

Table 6: ABR For Treated Bleeds in Adults

N=76	ABR
Mean	3.12
SD	4.62

N=76	ABR
Median	1.92
Min	0.0
Max	42.1

Table 7 below provides ABRs for treated bleeds in Xyntha compared to other FDA approved FVIII products.

Table 7: ABR For Treated Bleeds Compared to Other FDA Approved FVIII Products

	Mean ABR (± SD)	Median ABR (IQR)
Eloctate	Adults: 2.88 Adolescents: 2.63	Overall: 1.6 (0-4.7) Adults: 1.44 Adolescents: 1.92
Kovaltry	Overall 3.87(± 5.21)	1.0 (0-5.0) (2xwk) 2.0 (3xwk)
Afstyla		Overall: 1.14 (0-4.2) 0.0 (2xwk) 1.53 (3xwk)
Nuwiq	2.28 (± 3.73)	0.9 (range: 0-14.7)
Adynovate	4.7 (± 8.6) Adolescents: 5.2	1.9 Adolescents: 2.1
Novoeight	5.62 (4.16-7.59)	3.1 (5.6) Adolescents: 4.4 (6.9)
Advate	6.24 Ext: 2.45 Adolescents: 5.48 Ext: 1.93	3.67 Ext: 1.39 Adolescents: 3.98 Ext: 1.57
Kogenate	2.0	0.0
Esperoct	3.0 (±4.7) Adolescents: 3.5 (± 3.9)	1.2 (0-4.3) 2.2 (0.9-4.7)
Xyntha **N=94 All** **N=18 Adolescents**	3.9 (± 6.5) 7.3 (± 10.98)	1.9 (0-44.2) 3.1

SD: standard deviation, (IQR): interquartile range, 25th and 75th percentiles, Rx: treatment, 2xwk: Twice weekly, 3xwk: three times

Reviewer comment*: Although mean and median ABRs in all 94 subjects fall within other approved FVIII products, the numbers for the adolescents age group are higher in comparison. The Reviewer asked the Applicant to provide an explanation to justify the high observed ABR in adolescents. The Applicant responded with the following rationale:*

- *The population of adolescents treated in study 310 was reflective of the other populations included in this BLA along with the hemophilia A population in general.*

- *Baseline FVIII activity levels and target joint status were not markedly different in any age group.*
- *Among adolescents, there were no perceptible differences in the population that bled versus those that did not bleed.*
- *Compliance in the adolescent populations was generally high and was determined in this study as having received ±5% of the prescribed dose. There were only 2 subjects whose factor intake was plus or minus 5% of the prescribed amount. Specifically:*
  - *One subject received greater than 5% of the prescribed dose and had an ABR of 21.4 (subject (b) (6))*
  - *One subject was 5% below the prescribed dose and had an ABR of 0.*
- *The pharmacokinetics of FVIII activity model predicated that FVIII activity for adolescents would be intermediate between adults and younger children.*
- *Across Studies 310 and 313, there was a trend toward a higher total mean ABR in the adolescent population studied compared to younger children and adults (7.32, 1.45 and 3.20 respectively). This trend was also present when assessing the ABR by etiology (spontaneous or traumatic): Spontaneous ABR 3.33, 0.6, and 1.63; traumatic ABR 3.99, 0.85, and 1.57 for adolescents, young children and adults, respectively.*
- *At an individual subject level, one **subject ((b) (6))** in the adolescent group had a mean ABR that was markedly higher (total ABR 44.15) than other adolescents and other age groups by a factor of ~2 and was the only subject in the adolescent group whose ABR worsened during the study period compared to 12 months prior to study participation, suggesting he may be an outlier. His ABR was 24 in the 12 months prior to the study (using a combination of on-demand treatment and prophylaxis). There was no clear defining reason for this discrepancy, specifically baseline hemophilia status/history, target joint status (none reported), compliance, and or/pattern of bleeds. The subject did require a dose increase during the study, but this did not appear to markedly improve the frequency of bleeding events. Taken together, it was reasonable to consider this subject may be an outlier with unusually high ABR despite compliance with treatment and may be impacting the calculations to some degree.*
- *ABR assessments were performed without this subject and showed that while the mean ABR for total (5.15 versus 1.45 and 3.20 in younger children and adults) and traumatic bleeds (3.52 versus 0.85 and 1.57 in younger children and adults) did not markedly change, the spontaneous ABR was now similar to that seen in the other age groups assessed (1.63 versus 0.6 and 1.63 in younger children and adults, respectively). This suggests that (1) this subject was an outlier impacting mean ABR calculations (note that median levels were similar for all age groups) (2) the mean rate of spontaneous bleeding events is similar across all age groups and (3) that this adolescent group studies tended to have higher rate of traumatic bleeding events.*
- *Traumatic bleeds by nature can be variable and certain situations can place one at increased risk of having a traumatic bleed. Adolescents tend to partake in higher-risk activities, including sports, that can potentially impact the overall ABR and traumatic ABR based on the cohort of participants that is enrolled in a study.*
- When excluding the outlier subject, 42 of 93 (45%) subjects reported no bleeding while on routine prophylaxis. The mean ABR for subjects during routine prophylaxis was 89% lower than the mean ABR for subjects during on-demand treatment.

- The Table below lists the ABRs in adolescents and adults when excluding the outlier Subject (b) (6)

Table 8: ABR in adolescents and adults excluding the outlier Subject (b) (6)

Age Category	Number of subjects	% Reduction from OD	Statistic	Treated Total Routine Prophylaxis ABR	Treated Spontaneous Routine Prophylaxis ABR	Treated Traumatic Routine Prophylaxis ABR
≥12 years	93	89%	Mean±SD	3.6±5.18	1.6±2.87	1.9±3.99
			Median (Min-Max)	1.9 (0.0-23.3)	0.0 (0.0-13.7)	0.0 (0.0-23.3)
12 to <17 years	17	89%	Mean±SD	5.2±6.90	1.6±2.94	3.5±5.77
			Median (Min-Max)	2.0 (0.0-21.4)	0.0 (0.0-11.6)	1.9 (0.0-19.6)
≥17 years	76	89%	Mean±SD	3.2±4.70	1.6±2.88	1.6±3.42
			Median (Min-Max)	1.9 (0.0-23.3)	0.0 (0.0-13.7)	0.0 (0.0-23.3)

Abbreviations: OD = on demand; ABR = annualized bleeding rate; SD = standard deviation, Min=minimum, Max=maximum.

The Review Team finds the Applicant's justification acceptable given that the relatively high ABR was mainly driven by the one outlier subject, and when excluding this subject from the analysis, the ABR becomes within the range of other approved FVIII products. In addition, the spontaneous ABRs significantly decreased; which may suggest higher physical activity in this subject leading to more traumatic bleeds. The ABRs in the label will represent all subjects treated in the study. A footnote will be included to describe the ABRs when excluding the one outlier subject.

All bleeds (treated and non-treated with Xyntha):

When including all bleeds in the analysis of ABR (treated and non-treated with Xyntha), 36 of 94 subject (38%) had no bleeding episodes while on routine prophylaxis.

including Subject (b) (6) in ABR analysis, the mean (±SD) ABR for all subjects was 4.4 (± 7.2) and median (min, max) ABR was 2.0 (0-50.2). See Table 7.

Table 9: ABR For All Bleeds (Treated and Non-Treated) in All Subjects

N=94	ABR*	ABR#
Mean	4.39	4.44
SD	7.17	7.16
Median	2.00	2.04
Min	0.0	0.0
Max	50.17	50.17

*Excluding Subject (b) (6)
#Including Subject (b) (6)

ABR analysis by age group: adolescents vs. adults.

ABR in adolescents:
Among 18 adolescent subjects, six (33%) had no bleeding episodes while on routine prophylaxis with Xyntha. When including Subject (b) (6), the mean (±SD) ABR was 8.4 (± 12.7) and median (min, max) ABR was 3.2 (0-50.2). See Table 8 below.

Table 10: ABR For All Bleeds (Treated and Non-Treated) in Adolescents

N=18	ABR*	ABR#
Mean	8.10	8.36
SD	12.86	12.73
Median	2.16	3.20
Min	0.0	0.0
Max	50.17	50.17

*Excluding Subject (b) (6)
#Including Subject (b) (6)

ABR in adults:
Among 76 adult subjects, 29 (38%) had no bleeding episodes. The mean (±SD) ABR was 3.5 (± 4.7) and median (min, max) ABR was 1.9 (0-50.2). See Table 9 below.

Table 11: ABR For All Bleeds (Treated and Non-Treated) in Adults

N=76	ABR
Mean	3.51
SD	4.71
Median	1.99
Min	0.0
Max	50.17

Reviewer comment*: As expected, mean ABRs increased when the analysis included all bleeds (treated and not treated). However, ABRs remain within the range of several other approved FVIII products.*

Reviewer comment: *Although ABR analysis utilizing all bleeds (treated and untreated) are generally performed by FDA Reviewers, the USPI of prior FDA approved FVIII products did not consistently include non-treated bleeds because these analyses are post-hoc analyses.*

Time from Previous Xyntha Infusion to New Bleeds During Prophylaxis
During routine prophylaxis with Xyntha, 180 bleeds occurred. Of these bleeds, 61% (110 of 180 bleeds) occurred ≤48 hours after the last dose of Xyntha and 39% (70 of 180 bleeds) occurred >48 hours after the last dose of Xyntha. The majority of bleeds reported to occur ≤48 hours after the last routine prophylaxis dose were traumatic (64 of 110 bleeds; 58%). In contrast, 42 of 70 bleeds (60%) reported to occur >48 hours after the last routine prophylaxis dose were spontaneous. The incidence of spontaneous bleeding that occurred after 48 hours following a dose of Xyntha is not unexpected, and

is consistent with a waning of the prophylactic effect of the most recent infusion as residual FVIII activity declines over time.

Less Than Expected Therapeutic Effect in the Prophylaxis Setting
LETE in the prophylaxis setting was defined as a spontaneous bleed within 48 hours after a regularly scheduled prophylactic dose (which was not used to treat a bleed) of study drug in the absence of confounding factors. Per protocol, LETE was based on investigator's assessment of a bleed. Investigators evaluated 50 spontaneous bleeds (including the 46 spontaneous bleeds that occurred during prophylaxis, were treated with test article, and an additional 4 bleeds during prophylaxis not treated with test article) in 29 subjects and determined that 22 of these bleeds represented LETE.

The Applicant's review of the database revealed that one event of LETE in one subject ((b) (6)) was incorrectly reported as such, based on the presence of a confounding factor. Three additional bleeds in three additional subjects ((b) (6)) should have been classified as LETE but investigators incorrectly reported the presence of a confounding factor. Finally, one subject ((b) (6)) for whom LETE was reported once actually experienced LETE twice, due to an investigator incorrectly identifying a confounding factor for the additional LETE-related bleed.

Thus, in total, 25 spontaneous bleeds during routine prophylaxis in 13 subjects met the predefined criteria to be considered LETE. The incidence rate of LETE during prophylaxis was 0.4% (25 events of LETE/6347 routine prophylactic infusions). Multiple events of LETE were identified for three subjects, including Subject (b) (6) (7 LETE events), Subject (b) (6) (6 LETE events) and Subject (b) (6) (2 LETE events). All other subjects for whom LETE was reported had one event of LETE, including Subjects (b) (6) .

Reviewer comment: *The incidence rate of LETE is acceptable and is within what is observed with similar products.*

Exposure to Xyntha:
Xyntha Dosing Summary for Routine Prophylaxis Treatment
The mean and median dose per infusion was 30 IU/Kg in the prophylaxis period. Mean and median of infusions per 30 days were 11.5 and 12 respectively.

Reviewer comment: *This dose supports the Applicant's proposed starting dosing regimen of 30 IU/Kg three times weekly.*

Xyntha Dosing Summary for On-Demand Treatment
The data for on-demand treatment were reviewed in sBLA 125264/1769 Seq 0481. See the clinical review memo dated 05 August 2019, authored by Helkha Peredo-Pinto, MD, MPH.

6.1.11.3 Subpopulation Analyses

N/A, as the study population was homogenous, no subgroup analyses were performed. Please see Section 6.1.11.2 for age based ABR analysis.

6.1.11.4 Dropouts and/or Discontinuations

Four (4) subjects discontinued treatment early, before completing 6 months of routine prophylaxis treatment during the SE period of the trial:

- Subject (b) (6) was discontinued after 47 EDs (110 days on routine prophylaxis) for non-elective surgery.
- Subject (b) (6) (1 ED) and Subject (b) (6) (17 EDs and 51 days on routine prophylaxis) were both withdrawn by the respective investigators due to non-compliance.
- Subject (b) (6) was withdrawn after 66 EDs (153 days on routine prophylaxis) due to the development of an inhibitor to FVIII. He had 38 EDs to Xyntha before the visit at which the inhibitor was detected and an additional 28 EDs after that visit and before he was withdrawn.

Of the 18 subjects who were 12 to <17 years of age, 16 completed the study. There were no subjects who discontinued from the study due to unsatisfactory response.

6.1.11.5 Exploratory and Post Hoc Analyses

N/A

6.1.12 Safety Analyses

6.1.12.1 Methods

All 94 treated subjects treated with at least 1 dose of Xyntha, comprising the ITT patient population, were included in the safety analysis. Transient low-titer inhibitors were detected in 2 of 94 subjects (2.1% of the study population) in this study (Subject (b) (6)). Across all studies, the rate of inhibitor development was 2.4% (4 of 167 subjects). The safety data were reviewed in sBLA 125264/1769 Seq 0481 and the label was updated accordingly. See the clinical review memo dated 05 August 2019, authored by Helkha Peredo-Pinto, MD, MPH.

6.1.13 Study Summary and Conclusions

Efficacy:

- All 94 subjects in the ITT population received Xyntha for routine prophylaxis or for intermittent prophylaxis (n=17) supplementing routine prophylaxis. Seven dose escalations were prescribed for six subjects over the course of the study.
- The mean (±SD) ABR for treated bleeds in all subjects was 3.9 (± 6.5) and median (min, max) ABR was 1.9 (0-42.1). The mean ABR for spontaneous and traumatic bleeds was 1.9 and 2.0; respectively.
- Among 18 adolescent subjects, eight (44%) had no bleeding episodes while on routine prophylaxis with Xyntha. The mean (±SD) ABR was 7.3 (± 10.9) and median (min, max) ABR was 3.1 (0-42.1).
- After excluding the one adolescent outlier who had ABR of 44, the mean ABR becomes 5.2 in the adolescent subgroup.
- Fifty-seven (57/94; 61%) subjects reported no spontaneous bleeding while on routine prophylaxis with Xyntha and 43 subjects (43/94; 46%) had no bleeding episodes of any type.
- The incidence rate of LETE during prophylaxis was 0.4%.

Safety:

- Two FVIII inhibitors were identified in the 94 subjects on this study.

6.2 Trial #2

Study 313: An Open Label Study to Evaluate Prophylaxis Treatment and to Characterize the Efficacy, Safety, and Pharmacokinetics of B-Domain Deleted Recombinant Factor VIII Albumin Free (Moroctocog alfa [AF-CC]) in Children with Hemophilia A.

This was a Phase 3, interventional, open-label study to evaluate prophylaxis treatment, and to characterize the efficacy, safety, and PK of FVIII:C after Xyntha administration in subjects younger than 6 years of age with moderately severe to severe hemophilia A (FVIII:C ≤2%) and with ≥20 prior exposure days (EDs) to FVIII products (≥50 EDs prior to Amendment 4). Amendment 10 raised the inclusion age to <16 years after the On-demand was enrolled.

Two interim analyses clinical study reports (CSRs) dated 07 November 2013 (data cut-off date of 31 December 2012) and 11 April 2016 (data cut-off date of 26 June 2015), presented analyses of selected data collected for approximately 4 and 7 years, respectively, after initiation of study enrollment. The first interim analysis CSR included OD therapy efficacy data collected for approximately 4 years after initiation of study enrollment and demonstrated that Xyntha was efficacious in the treatment of hemophilia A when used for the OD treatment of bleeding episodes in children under 6 years of age. The second interim analysis CSR included data on efficacy, and OD therapy compared with RP, collected for approximately 7 years after initiation of study enrollment.

As agreed previously with FDA, data for 15 subjects enrolled at non-GCP compliant Site 010 in Poland and reported in the sBLA filed on 20 December 2013 (Sequence #113) have not been included.

6.2.1 Objectives (Primary, Secondary, etc)

Primary Objective: To demonstrate that Xyntha routine prophylaxis (RP) reduces annualized bleeding rates (ABRs) relative to on demand (OD) therapy.

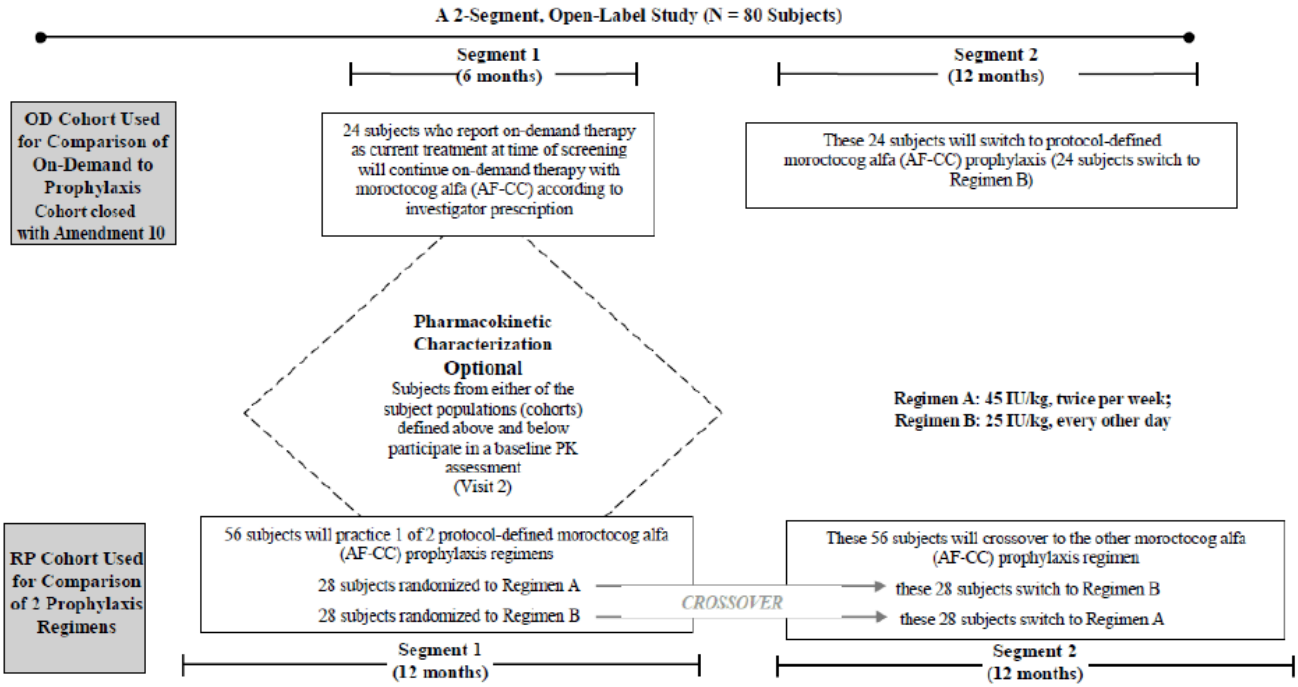
Secondary Objectives

- To assess the effect of a high-frequency (25±5 IU/kg, administered every other day) versus low-frequency (45±5 IU/kg, administered twice a week) dosing schedule on the efficacy of Xyntha prophylaxis;
- To characterize the PK of FVIII:C after administration of Xyntha in children younger than 6 years of age with hemophilia A;
- To describe Xyntha efficacy and safety in children, including characterization of the incidence of less than expected therapeutic effect (LETE).

6.2.2 Design Overview

The study was conducted in two 6 to 12-month segments. Two cohorts were enrolled: the OD cohort included subjects who practiced OD therapy for Segment 1 followed by RP therapy for Segment 2 and the RP cohort included subjects who practiced RP therapy for both segments. Segment 1 for the OD cohort was 12 months for subjects enrolled prior to Amendment 7, and 6 months in duration for subjects enrolled thereafter. For the RP subjects, each segment was 12 months in duration. The study design is shown in Figure 2.

Figure 2: Study 313 Design



Source: Protocol Amendment 10, Section 16.1.1.
OD cohort was closed at the time of Protocol Amendment 10.
Abbreviations: AF-CC=Albumin free cell culture; OD=on-demand; PK=pharmacokinetic; RP=routine prophylaxis.

6.2.3 Population

The study was originally planned to recruit approximately 72 pediatric subjects (<6 years) with moderately severe to severe hemophilia A (confirmed FVIII:C ≤2% by both the local laboratory and the central laboratory at screening) at approximately 40 sites. Then, with Amendment 10, because prophylaxis had replaced OD as the preferred standard of medical care, the OD cohort was closed. From this time, enrollment into the RP cohort continued with a planned target of 56 pediatric subjects aged 6 months to <16 years of age.

6.2.4 Study Treatments or Agents Mandated by the Protocol

The study was conducted in two 6 to 12-month segments. Two cohorts were enrolled:

- The OD cohort included subjects who practiced OD therapy for Segment 1 followed by RP therapy for Segment 2
- The RP cohort included subjects who practiced RP therapy for both segments. Segment 1 for the OD cohort was 12 months for subjects enrolled prior to Amendment 7, and 6 months in duration for subjects enrolled thereafter. For the RP subjects, each segment was 12 months in duration.

Randomization to RP was stratified by hemophilia A severity: FVIII:C <1% or 1-2% (according to central laboratory screening result). In Segment 1, RP subjects were randomly assigned to either:

- Regimen A: 45±5 IU/kg, administered BIW – low-frequency;
- Regimen B: 25±5 IU/kg, administered EOD – high-frequency.

For Regimen A, the interval between prophylactic infusions was 3 to 4 days and was not to exceed 4 days. For Regimen B, the interval between prophylactic infusions was to be approximately 48 hours. After completion of the first segment, all subjects crossed over to the alternate prophylactic regimen for Segment 2. Subjects who received OD therapy during Segment 1 were treated with prophylactic Regimen B (high-frequency). RP subjects who followed Regimen A in in Segment 2 and, conversely, RP subjects who followed Regimen B in Segment 1 followed Regimen A in Segment 2.

During prophylaxis (Segment 1 and/or Segment 2), a subject's treatment was escalated to a higher intensity prophylaxis regimen (45±5 IU/kg, administered EOD) if the following criteria justifying regimen escalation were met over a 4-week period in the absence of a confirmed inhibitor:

- the occurrence of 2 or more spontaneous joint bleeds, ***or***
- the occurrence of 3 or more spontaneous bleeds (consisting of joint bleeds, and/or significant soft tissue/muscle or other site bleeds).

Subjects who met dose escalation criteria while on this more intensive regimen could dose escalate to an even higher intensity regimen designated by the investigator. The subject was subsequently treated with the assigned regimen(s) until the respective 12-month period of prophylaxis with study drug was completed (Segment 1 or 2), inclusive of treatment time on all the prophylaxis regimens assigned during the respective study segment.

If a bleed occurred, subjects in either cohort were treated in an OD setting with study drug at a dose and frequency prescribed by each subject's treating physician.

6.2.5 Directions for Use

Xyntha, study drug, was supplied by the sponsor. Study drug was formulated as a sterile, nonpyrogenic, lyophilized powder preparation for IV injection. Diluent (0.9% NaCl) was provided in a syringe along with the study drug in the study drug kit. Study drug was administered as an IV infusion over several minutes after reconstitution of the lyophilized powder with diluent. If an indwelling catheter (e.g., Port-A-Cath®) was in place, it could be used for study drug infusions, when appropriate.

6.2.6 Sites and Centers

The study was conducted at 42 sites in 17 countries: Argentina (1 site), Austria (1 site), Colombia (1 site), Croatia (1 site), Germany (1 site), Italy (1 site), Jordan (1 site), Lebanon (1 site), Mexico (3 sites), New Zealand (1 site), Oman (1 site), Peru (1 site), Poland (1 site), Romania (1 site), Spain (1 site), Turkey (12 sites) and United States of America (13 sites). Twenty-one (21) of these sites (Sites 001, 002, 003, 005, 008, 018, 019, 022, 023 [United States of America], Site 013 [Spain], Site 016 [Germany], Site 24 [Italy], Sites 35, 037, 086, 9 and 040 [Mexico], Site 045 [Lebanon] and Site 078 [Peru]) were shipped study drug but did not enroll any subjects.

6.2.7 Surveillance/Monitoring

Study schedule assessments/monitoring are noted below.

Figure 3: Surveillance and Monitoring on Study 313 (On-Demand Cohort)

Study Procedures[a]	Screening[b]		SEGMENT 1 *(OD Treatment Phase)*						
Study Visit/Contact ID	1		2		3	4		5	6[d]
Study Interval[c]	Day –35 to –1		Day 1		Month 1 (±1wk)	Month 2 (±1wk)		Month 3 (±1wk)	Month 4.5 (±1wk)
Informed consent/assent	X	72-hour FVIII washout		72-hour FVIII washout			72-hour FVIII washout		
Demographics, medical history, hemophilia A information	X								
Physical examination[d]	X		X		X			X	
CD4 cell count	X								
PT or INR	X								
Hematology panel[e]	X		X[e]						
Serum chemistry[e]	X								
FVIII activity (FVIII:C)[f]	X[a, f]		X		X			X	
FVIII inhibitor[f]	X[a, f]		X		X			X	
Anti-FVIII antibody[f]	X[f]		X		X			X	
Anti-CHO antibody[f]	X[f]		X						
Anti-TN8.2 antibody[f]	X[f]		X						
Subject Diary[g]	X		X		X			X	
PK assessment[h]			X[h]						
Randomization to regimen[i]	X[i]								
Study drug dispensed			X		X			X	
Study drug accountability					X			X	
Telephone contact[j]						X			X
Concomitant medications[k]	COLLECTED at EACH VISIT/CONTACT								
Adverse events[k]	COLLECTED at EACH VISIT/CONTACT								

Study Procedures[a]		SEGMENT 2 *(RP Treatment Phase)*											Final Contact[m]
Study Visit/Contact ID		7	8		9	10		11	12		13	14		15	16
Study Interval[c]		Mo.6 (±1wk)	Mo.7.5 (±1wk)		Mo.9 (±1wk)	Mo.10.5 (±1wk)		Mo.12 (±1wk)	Mo.13.5 (±1wk)		Mo.15 (±1wk)	Mo.16.5 (±1wk)		Mo.18 (±1wk)	Mo.19 (+10 days)
Physical examination[d]	72-hour FVIII washout	X		72-hour FVIII washout	X		72-hour FVIII washout	X		72-hour FVIII washout	X		72-hour FVIII washout	X	
CD4 cell count														X	
Hematology panel[e]		X												X	
Serum chemistry[e]		X												X	
FVIII activity (FVIII:C)[f]		X			X			X			X			X	
FVIII inhibitor[f]		X			X			X			X			X	
Anti-FVIII antibody[f]		X			X			X			X			X	
Anti-CHO antibody[f]		X												X	
Anti-TN8.2 antibody[f]		X												X	
Subject Diary[g]		X			X			X			X			X	
Study drug dispensed		X			X			X			X				
Study drug accountability		X			X			X			X			X	
Telephone contact[j]			X			X			X			X			X
Concomitant medications[k]	COLLECTED at EACH VISIT/CONTACT														
Adverse events[k]	COLLECTED at EACH VISIT/CONTACT														

Source: Protocol Amendment 9, Section 16.1.1.

Abbreviations: AE=adverse event; CD4=cluster of differentiation 4; CHO=Chinese hamster ovary; FVIII=factor VIII; FVIII:C=factor VIII activity in plasma; ID=identification; INR=international normalized ratio; Mo=month; OD=on-demand; PK=pharmacokinetic; PT=prothrombin time; RP=routine prophylaxis; TN8.2=affinity ligand used in study drug purification process; Wk=week.

[a] All testing was performed by the central laboratory. The local laboratory also performed FVIII activity and FVIII inhibitor testing to confirm eligibility.

[b] Screening period. Interval starting from the signing of the consent/assent form and extending up to Visit 2 (Day 1). There were up to approximately 35 days in this interval (Day -35 to Day 1).

[c] Study day or month. Visits/contacts 3 (Month 1) through 15 (Month 18) were conducted within ± 1 week of indicated study month. Final Study Contact (Visit 16, Month 19) was conducted at least 28 days (+10 days) from Final Study Visit (Visit 15, Month 18).

[d] Included collection of vital signs and weight. Also included collection of height at Visits 1 (Screening) and 7 (Month 6) for the OD cohort only.

[e] For Visit 2 (Day 1), hematology panel was only collected for subjects participating in the PK assessment.

[f] Subjects observed a minimum 72-hour FVIII washout before sample collection. For screening purposes, subjects were instructed to return to the clinic following a 72-hour FVIII washout for this sample collection if the washout was not observed before the initial Screening Visit.

[g] Subject Diary dispensed and/or collected. Subject Diary was reviewed at each visit (information about AEs, concomitant medications, study compliance, study drug infusions and assessments, less than expected therapeutic effect, and dose escalation and/or changes, if applicable, was reviewed).
[h] Approximately 16 eligible subjects were to participate in a PK assessment (conducted at Visit 2, Day 1).
[i] Randomization occurred only after study eligibility criteria had been confirmed and documented. Subjects who reported OD therapy as their current treatment at the time of screening and who continued to practice OD therapy for 6 months during Segment 1 (as prescribed by the investigator), practiced protocol-defined prophylactic Regimen B for 12 months during Segment 2.
[j] Information about AEs, concomitant medications, dose escalation and/or changes, if applicable, and study compliance was collected during these contacts. This could have been conducted at appropriately scheduled clinic visits if preferred.
[k] Collected at each visit/contact from the time the consent/assent form was signed to the Final Study Contact.
[l] Segment 1 reduced to a 6 month period from 12 months as a result of Protocol Amendment 7.
[m] Visit 19, Month 24 for subjects before Amendment 7.

Figure 4: Surveillance and Monitoring on Study 313 (Routine Prophylaxis Cohort)

Study Procedures[a]	Screening[b]		SEGMENT 1 *(RP Treatment Phase)*												
Study Visit/Contact ID	1		2		3	4		5	6		7	8		9	10
Study Interval[c]	(Day –35 to –1)		Day 1		Mo.1 (±1wk)	Mo.2 (±1wk)		Mo.3 (±1wk)	Mo.4.5 (±1wk)		Mo.6 (±1wk)	Mo.7.5 (±1wk)		Mo.9 (±1wk)	Mo.10.5 (±1wk)
Informed consent/assent	X	72-hour FVIII washout		72-hour FVIII washout			72-hour FVIII washout			72-hour FVIII washout			72-hour FVIII washout		
Demographics, medical history, hemophilia A information	X														
Physical examination[d]	X		X		X			X			X			X	
CD4 cell count (HIV subjects only)	X														
PT or INR	X														
Hematology panel[e]	X		X[e]												
Serum chemistry[e]	X														
FVIII activity (FVIII:C)[f]	X[a, f]		X		X			X			X			X	
FVIII inhibitor[f]	X[a, f]		X		X			X			X			X	
Anti-FVIII antibody[f]	X[f]		X		X			X			X			X	
Anti-CHO antibody[f]	X[f]		X												
Anti-TN8.2 antibody[f]	X[f]		X												
Subject Diary[g]	X		X		X			X			X			X	
PK assessment[h] (Optional from Amendment 10)			X[h]												
Randomization to regimen[i]	X[i]														
Study drug dispensed			X		X			X			X			X	
Study drug accountability					X			X			X			X	
Telephone contact[l]						X			X			X			X
Concomitant medications[k]	COLLECTED at EACH VISIT/CONTACT														
Adverse events[k]	COLLECTED at EACH VISIT/CONTACT														

Study Procedures[a]Study Procedures[a]		SEGMENT 2 *(RP Treatment Phase)*												Final Contact
Study Visit/Contact ID		11	12		13	14		15	16		17	18		19	20
Study Interval[c]Study Interval[c]		Mo.12 (±1wk)	Mo.13.5 (±1wk)		Mo.15 (±1wk)	Mo.16.5 (±1wk)		Mo.18 (±1wk)	Mo.19.5 (±1wk)		Mo.21 (±1wk)	Mo.22.5 (±1wk)		Mo.24 (±1wk)	Mo.25 (+10 days)
Physical examination[d]	72-hour FVIII washout	X		72-hour FVIII washout	X		72-hour FVIII washout	X		72-hour FVIII washout	X		72-hour FVIII washout	X	
CD4 cell count														X	
Hematology panel[e]		X												X	
Serum chemistry[e]		X												X	
FVIII activity (FVIII:C)[f]		X			X			X			X			X	
FVIII inhibitor[f]		X			X			X			X			X	
Anti-FVIII antibody[f]		X			X			X			X			X	
Anti-CHO antibody[f]		X												X	
Anti-TN8.2 antibody[f]		X												X	
Subject Diary[g]		X			X			X			X			X	
Study drug dispensed		X			X			X			X				
Study drug accountability		X			X			X			X			X	
Telephone contact[j]			X			X			X			X			X
Concomitant medications[k]	COLLECTED at EACH VISIT/CONTACT														
Adverse events[k]	COLLECTED at EACH VISIT/CONTACT														

Source: Protocol Amendment 10, Section 16.1.1.

Abbreviations: AE=adverse event; CD4=cluster of differentiation 4; CHO=Chinese hamster ovary; FVIII=factor VIII; FVIII:C=factor VIII activity in plasma; ID=identification; INR=international normalized ratio; Mo=Month; PK=pharmacokinetic; PT=prothrombin time; RP=routine prophylaxis; TN8.2=affinity ligand used in study drug purification process; Wk=week.

[a] All testing was performed by the central laboratory. The local laboratory also performed FVIII activity and FVIII inhibitor testing to confirm eligibility.

[b] Screening period. Interval starting from the signing of the consent/assent form and extending up to Visit 2 (Day 1). There were up to approximately 35 days in this interval (Day -35 to Day -1).

[c] Study day or month. Visits/contacts 3 (Month 1) through 19 (Month 24) were conducted within ± 1 week of indicated study month. Final Study Contact (Visit 20, Month 25) was conducted at least 28 days (+10 days) from Final Study Visit (Visit 19, Month 24).

[d] Included collection of vital signs and weight. Also included collection of height at Visits 1 (Screening) and 11 (Month 12) for the RP cohort only.

[e] For Visit 2 (Day 1), hematology panel was only collected for subjects participating in the optional (from Amendment 10) PK assessment.

[f] Subjects observed a minimum 72-hour FVIII washout before sample collection. For screening purposes, subjects were instructed to return to the clinic following a 72-hour FVIII washout for this sample collection if the washout was not observed before the initial Screening Visit.

[g] Subject Diary dispensed and/or collected. Subject Diary was reviewed at each visit (information about AEs, concomitant medications, study compliance, study drug infusions and assessments, less than expected therapeutic effect, and dose escalation and/or changes, if applicable, was reviewed).

[h] Approximately 16 eligible subjects were to participate in a PK assessment (conducted at Visit 2, Day 1).

[i] Randomization occurred only after study eligibility criteria had been confirmed and documented. Only those subjects who practiced prophylaxis during both study segments were randomized to 1 of the 2 protocol-defined prophylaxis regimens to be followed for 12 months during Segment 1; these subjects then crossed over to the other protocol-defined prophylaxis regimen for 12 months during Segment 2.

[j] Information about AEs, concomitant medications, dose escalation and/or changes, if applicable, and study compliance was collected during these contacts. This could have been conducted at appropriately scheduled clinic visits if preferred.

[k] Collected at each visit/contact from the time the consent/assent form was signed to the Final Study Contact.

6.2.8 Endpoints and Criteria for Study Success

The primary efficacy endpoint is the ABR in subjects receiving routine prophylaxis compared with OD treatment. The number of bleeds for the ABR calculation included all bleeds requiring treatment with a FVIII replacement product during the time on treatment.

Reviewer comment: *Additional analysis of bleeds that did not require treatment was performed by the reviewer.*

Secondary efficacy endpoints include: ABR of the High- and Low frequency prophylaxis, PK characterization, safety assessments to include FVIII inhibitors, and other efficacy endpoints including number of infusions per bleed, assessment of the response of bleed to treatment, and the incidence of LTETE.

To assess the efficacy of RP and OD therapy, the ABR or number of bleeds per year, was derived for each subject for each treatment regimen by using the following formula: ABR = number of bleeds / (days on treatment regimen / 365.25)

6.2.9 Statistical Considerations & Statistical Analysis Plan

For the primary objective of demonstrating that Xyntha prophylaxis reduces the ABR relative to on-demand therapy, the null hypothesis is that prophylactic treatment does not reduce the ABR relative to on-demand treatment. The alternative hypothesis is that prophylactic therapy does reduce the ABR.

To test the hypothesis, an analysis of variance (ANOVA) was conducted to compare the mean ABR between subjects in the on-demand (segment 1) and prophylaxis (segment 2) treatment regimens. Only subjects who received on-demand therapy with Xyntha during segment 1, before starting the protocol-defined Xyntha prophylaxis in segment 2, will be included in this analysis. The ANOVA included factors for treatment regimen (study segment 1 or 2). The model also included a blocking factor for subjects to ensure that the comparison of ABRs from each treatment regimen is performed on a within subject basis. The p-value for treatment regimen calculated in ABR of the ITT population was used to test the null hypothesis; a p-value less than 0.05 will be considered significant.

Statistical Power and Sample Size Considerations

The sample size of this study is based on the statistical comparison between ABR in the on-demand versus prophylaxis treatment settings, and the statistical comparison between ABR for the high- versus low-frequency prophylaxis schedules; approximately 72 subjects were to be enrolled to permit these comparisons (24 OD and 48 RP subjects for each comparison, respectively). Of these 72 subjects, approximately 16 subjects were to undergo the PK assessment for the secondary objective of PK characterization.

6.2.10 Study Population and Disposition

6.2.10.1 Populations Enrolled/Analyzed

Study population and disposition are provided for the ITT population.

6.2.10.1.1 Demographics

All subjects were male. The mean ±SD age (range) was 4.65±1.99 years (1.1-12.7 years). The majority of subjects (84%) were aged between 2 and 6 years, were white (78%) and of non-Hispanic and non-Latino ethnicity (86%). The mean ±SD weight was 18.74±5.44 kg for all subjects. Similar characteristics were observed for the subjects in the RP and OD cohorts. All seven subjects with PK data available, and included in the PK analysis, were younger than 6 years of age. See Table 11 for details.

Table 12: Study 313 Demographics and Baseline Characteristics

Characteristic	**AB (N=18)**	**BA (N=24)**	**OD (N=9)**	**Total (N=51)**
Age Category				
Infant (1 month - <2 years)	1 (5.6)	2 (8.3)	0	3 (5.9)
Child (2 years - <6 years)	15 (83.3)	19 (79.2)	9 (100.0)	43 (84.3)
Child (6 years - <12 years)	1 (5.6)	3 (12.5)	0	4 (7.8)
Child (12 years - <16 years)	1 (5.6)	0	0	1 (2.0)

Sex, n (%)				
Male	18 (100.0)	24 (100.0)	9 (100.0)	51 (100.0)
Race, n (%)				
Other	5 (27.8)	5 (20.8)	1 (11.1)	11 (21.6)
White	13 (72.2)	19 (79.2)	8 (88.9)	40 (78.4)
Ethnicity, n (%)				
Hispanic or Latino	2 (11.1)	3 (12.5)	2 (22.2)	7 (13.7)
Non-Hispanic and Non-Latino	16 (88.9)	21 (87.5)	7 (77.8)	44 (86.3)
Weight (kg)				
N	18	24	9	51
Mean (SD)	17.81 (5.35)	19.28 (5.30)	19.19 (6.38)	18.74 (5.44)
Min, Max	11.5, 34.4	9.8, 28.0	13.3, 35.0	9.8, 35.0
Median	17.15	19.33	17.50	18.20

Abbreviations: AB=prophylaxis sequence received during Segments 1 and 2: the low- followed by the high-frequency dosing sequence; BA=prophylaxis sequence received during Segments 1 and 2: the high- followed by the low-frequency dosing sequence; ITT=intent to treat; kg=kilogram; min=minimum; max=maximum; n=number of observations; N=number of subjects in group; OD=on-demand cohort; SD=standard deviation.

6.2.10.1.2 Medical/Behavioral Characterization of the Enrolled Population

All subjects had severe HA (i.e., FVIII activity <1%) at screening. Most subjects had a life time exposure to FVIII of >50 days; Five subjects had between 20 and 50 prior EDs. The mean (±SD) total number of bleeds in the last 12 months was 9.1±14.3. A total of 20 (39%) subjects had a target joint involvement bleed. For the OD Cohort, the mean (±SD) baseline ABR was 15.8 ±6.6 and median (min, max) of 17 (3, 24). A total of 7 of 9 (78%) subjects had a target joint involvement bleed.

6.2.10.1.3 Subject Disposition

A total of 71 subjects (excluding Site 010 in Poland) were screened, and 51 subjects were enrolled into this study and included in the ITT population. A total of 50 subjects were included in the mITT population; one subject enrolled in the OD cohort did not receive any study drug. A total of 41 (80%) subjects completed the study and 10 (20%) subjects discontinued the study early; the most common reason for discontinuation was AE (9.8%).

6.2.11 Efficacy Analyses

6.2.11.1 Analyses of Primary Endpoint(s)

Annualized Bleeding Rates

The primary efficacy analyses were performed on the OD cohort (OD therapy in Segment 1 followed by RP regimen 25 IU/kg EOD) in Segment 2 as per protocol. The first month of prophylaxis regimen in Segment 2 was considered a washout period.

Treated bleeds:
Bleeding episodes that required treatment with Xyntha and that occurred while the subject was on routine prophylaxis were considered in the calculation of the ABR as specified in the protocol. An ABR was calculated from each subject's data on bleeding, and these values were summarized for the study population as a whole.

Among the eight treated subjects, four (50%) had no bleeding episodes while on routine prophylaxis with Xyntha. The mean (±SD) ABR for all subjects was 1.5 (± 2.2) and median (min, max) ABR was 0.6 (0-6.2) compared to 47 (±32.2) and 34 (0-92.4) in the OD period. See Table 12. When excluding the washout period, the mean ABR during the OD period was 52.9. Therefore, the mean ABR for subjects during routine prophylaxis was 97% lower than the mean ABR for subjects during on-demand treatment.

Table 13: ABR For Treated Bleeds in Study 313 (On-Demand Cohort)

N=8	ABR
Mean	1.45
SD	2.20
Median	0.56
Min	0.0
Max	6.17

During the RP-B (25 IU/kg EOD) regimen, mean (±SD) ABRs were similar for spontaneous bleeds (0.6±1.3 [median: 0.0]) and traumatic bleeds (0.8±1.3 [median: 0.0]). The mean ABR regardless of etiology was significantly lower during the RP-B (25 IU/kg EOD) regimen than for OD therapy.

All bleeds (treated and non-treated):
When including all bleeds in the analysis of ABR (treated and non-treated with Xyntha), The same four subjects (50%) had no bleeding episodes. The mean (±SD) ABR for all subjects was 1.9 (± 2.8) and median (min, max) ABR was 0.6 (0-6.4). See Table 13 below.

Table 14: ABR For All Bleeds (Treated and Non-Treated) in Study 313 (On-Demand Cohort)

N=8	ABR
Mean	1.85
SD	2.78
Median	0.56
Min	0.0
Max	6.40

6.2.11.2 Analyses of Secondary Endpoints

There were three subjects who were prescribed one or more dose escalations:

1. **Subject** (b) (6): 5 yo who was prescribed Xyntha 25 ± 5 IU/kg QOD followed by escalation to 45 ± 5 IU/kg QOD after experiencing 3 bleeding events in one week, though not meeting escape criteria. He remained on this dose for the

duration of the segment, but discontinued early when his parents declined to switch in the next segment to RP45 regimen due to subject's adverse experience with RP25.

2. **Subject** (b) (6)**:** 4 yo who was prescribed Xyntha 45 ± 5 IU/kg BIW followed by escalation to 45 ± 5 IU/kg QOD after meeting escape criterion A. He went on to follow RP25 regimen in segment 2 and completed the study.
3. **Subject** (b) (6)**:** 3 yo who was prescribed Xyntha 45 ± 5 IU/kg BIW followed by escalation to 45 ± 5 IU/kg QOD after meeting both escape criteria A and B.

Reviewer comment: *None of the above three subjects were among the OD Cohort.*

ABR for High vs. Low frequency prophylaxis regimen

Descriptive statistics are summarized in Table 14 for the subsets of subjects randomized to the AB and BA sequences.

Table 15: ABR for Routine Prophylaxis Cohort

ABR	Regimen A (RP45) (Number of Bleeds=106)	Regimen B (RP25) (Number Bleeds=75)
N	38	38
Mean (SD)	3.3 (5.3)	2.2 (4.1)
Min, Max	0.0, 24.6	0.0, 18.4
Median	1.1	1.0

Abbreviation: ABR=annualized bleed rate; Regimen A [45 IU/kg BIW] and Regimen B [25 IU/kg EOD]); OD=on-demand; RP25= routine prophylaxis 25 IU/kg; BIW=twice weekly; EOD=every other day; min=minimum; max=maximum; N=number of subjects with ABR data included for each regimen.

Reviewer comment: *The reviewer did not analyze the comparison between the two prophylaxis regimens because the Applicant is not seeking an indication for the routine prophylaxis regimen A (45 IU/kg BIW).*

Assessment of less-than expected therapeutic effect (LTETE)

No subject reported LETE in the OD setting. In the prophylaxis setting, seven subjects were identified as having spontaneous bleeding episodes within 48 hours after a regularly scheduled prophylaxis dose of study drug with no confounding factors. Five (10%) subjects had a bleeding episode during Regimen B and three (7%) subjects had a bleeding episode during Regimen A (one subject had a bleeding episode in both Regimen A and Regimen B).

Exposure to Xyntha:

Including subjects in the OD cohort, the mean (±SD) dose was 25.7±4.6 IU/kg with median (min, max) of 25 (11, 44). In the OD cohort during RP Regimen B (25 IU/kg EOD), two subjects received total doses which were outside their expected doses:

- One subject (b) (6) received a total dose of 3142 IU/kg which was below the expected dose of 4063 IU/kg and
- One subject (b) (6) who received a total dose of 5244 IU/Kg which was above the expected dose of 4288 IU/kg.

6.2.11.3 Subpopulation Analyses

N/A, as the study population was homogenous, no subgroup analyses were performed.

6.2.11.4 Dropouts and/or Discontinuations

A total of 71 subjects (excluding Site 010 in Poland) were screened, and 51 subjects were enrolled into this study and included in the ITT population. A total of 50 subjects were included in the mITT population; One subject enrolled in the OD cohort did not receive any study drug. A total of 41 (80%) subjects completed the study and 10 (20%) subjects discontinued the study early; the most common reason for discontinuation was AE (9.8%).

6.2.11.5 Exploratory and Post Hoc Analyses

N/A

6.2.12 Safety Analyses

6.2.12.1 Methods

Among 64 pediatric PTPs who were evaluated for immunogenicity, two subjects (3%) developed FVIII inhibitors. Across all studies, four of 167 subjects (2.4%) developed factor VIII inhibitors. The safety data for this clinical trial were reviewed in sBLA 125264/1769 Seq 0481 and the label was updated accordingly. See the clinical review memo dated 05 August 2019, authored by Helkha Peredo-Pinto, MD, MPH.

6.2.13 Study Summary and Conclusions

- The primary objective of this study was met: the prophylaxis regimen at a dose of 25 IU/kg EOD was more efficacious as measured by ABR than OD treatment.
- The mean (±SD) ABR for all subjects was 1.5 (± 2.2) and median (min, max) ABR was 0.6 (0-6.2) compared to 47 (±32.2) and 34 (0-92.4) in the OD period.
- Among the eight treated subjects in the OD Cohort, four (50%) had no bleeding episodes while on routine prophylaxis with Xyntha.
- ABR for prophylaxis at a dose of 45 IU/kg BIW was shown to be equivalent compared to a more frequently administered prophylaxis regimen (25 IU/kg EOD), satisfying a secondary objective. However, the Applicant is not seeking the less frequent dosing regimen.
- PK parameters observed in this study are similar to those observed in other studies of young patients (<6 years) with hemophilia A.
- Two of 64 subjects (3%) developed FVIII inhibitors.

9. ADDITIONAL CLINICAL ISSUES

9.1 Special Populations

9.1.3 Pediatric Use and PREA Considerations

This product triggers PREA as a new indication. The supplement was previously presented at PeRC on August 30, 2017 and at the time, the pediatric data supported an assessment. As discussed prior in the reveiw, the Applicant was issued a complete

response (CR) letter because of concern regarding high inhibitor rate. Safety is no longer an issue in the current sBLA submission. However, the Reviewer Team opted to present it again at PeRC to discuss efficacy results and the concern with high ABR in adolescents.

On June 30, 2020, PeRC agreed with the Reviewer's initial assessment that the high ABR in the adolescent age group, coupled with the small sample size in the younger age group (<6 years), and the absence of data from subjects in the 6-11 years of age make it challenging to approve the routine prophylaxis indication in children. PeRC noted that the benefit-risk profile does not support approving this product for the routine prophylaxis indication in the pediatric population. PeRC recommended that the failed trial outcome in adolescents is described in the label.

However, upon further analysis of the data and several IRs to the Applicant providing justification for the observed high ABR in adolescents, and when excluding the one outlier adolescent subject with extremely high ABR (mainly traumatic), the ABRs fall within the range of previously approved FVIII products.

Data from studies 310 and 313 cover pediatric subjects ages 2 to < 6 years (study 313) and 12 to < 17 years (study 310). Efficacy for pediatric patients, ages 0 to 2 years and 6 to < 12 years, are extrapolated / interpolated; respectively, from efficacy and PK observed for "neighboring" age cohorts as agreed previously with the Applicant. In general, the PK of exogenously administered FVIII products is age dependent. Younger children have lower incremental recovery, faster clearance, and shorter elimination half-lives than older children, adolescents, and adults. The currently approved package insert for Xyntha states that higher or more frequent dosing may be needed in pediatric patients.

Therefore, based on the Applicant's justification and further analyses of the ABR data, the review team recommends approval of the routine prophylaxis indication in all pediatric age groups. The PREA PMR is considered fulfilled with this sBLA.

10. CONCLUSIONS

Overall, Xyntha demonstrated efficacy in adults and children for routine prophylaxis. On-demand efficacy results and safety results were reviewed previously and were approved in prior labeling supplement. Development of FVIII inhibitors is communicated in the Warnings and Precautions Sections of the label.

The Reviewer recommend Xyntha to be approved for the following indication in adults and children: routine prophylaxis to reduce the frequency of bleeding episodes

11. RISK-BENEFIT CONSIDERATIONS AND RECOMMENDATIONS

11.1 Risk-Benefit Considerations

The risk of Xyntha was reviewed in prior sBLA 125264/1769 Seq 0481, and includes Factor VIII inhibitors development.

11.2 Risk-Benefit Summary and Assessment

The benefits of routine prophylaxis with Xyntha include: the reduction of total, spontaneous and traumatic bleeding in patients with Hemophilia A.

The risks of Xyntha include: FVIII inhibitory antibodies development. The risk of development of inhibitory antibodies is considered an expected adverse event.

The results from Studies 310 and 313 demonstrated that Xyntha is safe and effective in adults and children with hemophilia A. The median and mean ABRs were acceptable for the patient population and were overall comparable to other FDA approved FVIII products. Although the ABR was high in adolescents' subjects compared to adults and younger pediatric subjects, when excluding one outlier subject, the ABRs fall within the range of what has been approved for the treatment of Hemophilia A. Finally, the safety profile of Xyntha was similar to what is known and expected for this class of product. Thus, the benefit-risk profile of Xyntha is considered favorable.

11.3 Discussion of Regulatory Options

The available data support approval of the indication for routine prophylaxis for adults and children with hemophilia A.

11.4 Recommendations on Regulatory Actions

Approval for the routine prophylaxis indication is recommended for adults and children.

11.5 Labeling Review and Recommendations

The revised USPI was reviewed, commented, and revised by the appropriate discipline reviewers. The Advertising and Promotional Labeling Branch (APLB) reviewer conducted its review from a promotional and comprehension perspective. Labeling issues have successfully been resolved with the Applicant.

11.6 Recommendations on Postmarketing Actions

Routine pharmacovigilance is recommended.