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Application Type	BLA
STN	125264/1670.6
CBER Received Date	December 15, 2016 (original submission) November 13, 2019 (response to CR letter)
PDUFA Goal Date	August 13, 2020 (after major amendment)
Division / Office	OTAT
Committee Chair	Megan Zimmerman, M.D.
Clinical Reviewer(s)	Megan Zimmerman, M.D.
Project Manager	Jacqueline Glen, M.S.
Priority Review	Not applicable
Reviewer Name(s)	Boris Zaslavsky, Ph.D., Dr.Sc.
Review Completion Date / Stamped Date	
Supervisory Concurrence	Renée C. Rees, Ph.D. Team Leader, OBE/DB/TEB
	Boguang Zhen, Ph.D. Branch Chief, OBE/DB/TEB
Applicant	Wyeth Pharmaceuticals Inc.
Established Name	Antihemophilic Factor (Recombinant), Plasma/Albumin Free
(Proposed) Trade Name	Xyntha
Pharmacologic Class	
Formulation(s), including Adjuvants, etc	
Dosage Form(s) and Route(s) of Administration	
Dosing Regimen	28 IU/kg - 47 IU/kg per infusion
Indication(s) and Intended Population(s)	Extend current indication to routine prophylaxis treatment in children and adolescents <17 years of age and adults (≥17 years of age) with moderately severe to severe hemophilia A

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GLOSSARY

ABR	Annualized Bleeding Rate
BIW	Administered Twice Weekly
BU	Bethesda Unit
CRL	Complete Response Letter
CSR	Clinical Study Report
EOD	Every Other Day
FVIII:C	Factor VIII concentration/Factor VIII activity in plasma
GCP	Good Clinical Practice
ITT	Intent-to-Treat
IU	International Units
mITT	Modified Intent-to-Treat
OD	On-Demand
RP	Routine Prophylaxis
sBLA	Supplemental Biologics License Application

1. EXECUTIVE SUMMARY

Xyntha was licensed by the FDA in 2008 for the control and prevention of bleeding episodes and for perioperative management in adults with hemophilia A. In 2014, the indication was extended to children with hemophilia A. In December 2016, the applicant submitted supplemental BLA (sBLA) 125264/1670 to seek a new indication of routine prophylaxis (RP) in children and adults, supported by interim results from Study 313 and the results from completed study Study 310. The FDA issued a complete response letter (CRL) for safety and efficacy deficiencies for that sBLA. In response to the CRL the applicant submitted this amendment to the sBLA; it contains efficacy data to support the routine prophylaxis indication based on both completed clinical studies: Study 310 and Study 313. The safety data were reviewed in a prior labeling supplement sBLA 125264/1769, which was approved in August 2019.

Study 313 is a Phase 3, open-label, randomized, multi-center, interventional study in subjects (initially planned <6 years of age, later raised to <16 years of age) with moderately severe to severe hemophilia A. The study consists of two cohorts: one cohort evaluated the reduction of the annualized bleeding rate (ABR) in subjects initially treated on-demand (OD) followed by high-frequency RP dosing. The second cohort evaluates high- vs. low-frequency RP dosing.

The primary objective of this study was to demonstrate that Xyntha prophylaxis reduces annualized bleeding rates (ABRs) relative to on demand (OD) therapy. The analysis population for this objective consists of eight subjects ages <6 years at time of screening visit. The mean ABR (±standard error [SE]) for the OD cohort during the RP regimen (Regimen B [25 IU/kg EOD]) was 1.5 ± 2.2 (median = 0.6, range = 0, 6.2), and 47.0 ± 32.2 (median = 34.0, range = 0, 92.4) during the OD therapy. This is a 97% reduction in ABR. The model-based ABR mean estimate during the RP high frequency dosing regimen was 1.76 ± 0.798

and it was significantly lower (p=0.0040) than the OD therapy estimate of 47.02 ± 10.749.

For Study 310, the previously-reported results for the 94 subjects showed the mean ABR for all bleeds for all subjects was 3.9 (median 1.9, range 0 to 42.1); the mean ABR for subjects 12 to <17 years was 7.3 and 3.2 for subjects ≥ 17 years. Comparison to pre-specified age-specific OD historical controls yields an 84.2% reduction for adolescents and an 89.5% reduction for adults.
In an integrated analysis of subjects of all ages studied in Studies 313 and 310, the ABR was 88.68% lower for routine prophylaxis compared with the ABR for on-demand treatment alone. After excluding the one adolescent outlier who had ABR of 44, the mean ABR becomes 5.2 in the adolescent subgroup.

The statistical evidence supports approval of the proposed extension of the current indication to routine prophylaxis treatment in pediatric children (<12 years) and adolescents and adults (≥12 years of age) with moderately severe to severe hemophilia A to reduce frequency of bleeding episodes.

2. CLINICAL AND REGULATORY BACKGROUND

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

December 15, 2016: Applicant submitted sBLA 125264/1670 to extend the current indication for Xyntha to routine prophylaxis treatment in children and adolescents (<17 years of age) and adults with moderately severe to severe hemophilia A. This submission included the (second) interim results of Study 313 and the final study results of Study 310. It was reviewed by me (Statistical Review of sBLA 125264/1670, dated by October 13, 2017).

October 13, 2017: FDA issued a CRL for sBLA 125264/1670 with the following deficiency: “Currently, the high rate of inhibitor development with your product outweighs the potential benefits of Xyntha as prophylactic therapy. 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.”

October 5, 2018: Applicant submitted the final Clinical Study Report (CSR) for Study 313 to IND 10040.

February 8, 2019: Applicant submitted sBLA 125264/1769 to provide an update to the existing safety data and OD efficacy information in the US Prescribing Information (USPI) based on the final CSR for Study 313. The statistical evaluation of these updates is documented in Dr. Tingting Zhou’s review memo, dated August 7, 2019.

November 13, 2019: Applicant submitted amendment 125264/1670.6 in response to the outstanding October 2018 CRL.

March 25, 2020, Applicant submitted a major amendment to BLA 125264/1670.6, extending the PDUFA deadline three months to August 13, 2020. BLA 125264/1670 was supported by interim analyses from Study 313 and completed Study 310. This amendment contains efficacy data to support the routine prophylaxis indication based on two completed clinical studies 310 and 313.

3. SUBMISSION QUALITY AND GOOD CLINICAL PRACTICES

3.1 Submission Quality and Completeness

The submission was adequately organized for conducting a complete statistical review without unreasonable difficulty.

5. SOURCES OF CLINICAL DATA AND OTHER INFORMATION CONSIDERED IN THE REVIEW

5.1 Review Strategy

In support of the proposed routine prophylaxis indication and to address the deficiencies noted in the October 13, 2017 CRL (see Section 2.5), the applicant relies on data for pediatric subjects <17 years of age from Studies 310 and 313, and adult subjects ≥17 years of age from Study 310. Routine prophylaxis data in both these studies have been reviewed in previous submissions.

- 125264/1670.0: I evaluated the (second) interim clinical study report for Study 313 (dated April 11, 2016, data cutoff June 26, 2015) and the final clinical study report for Study 310 in my review memo dated October 13, 2017.
- 125264/1769: Tingting Zhou, Ph.D. evaluated the final clinical study report for Study 313 in her review memo dated August 7, 2019.

Rather than re-analyzing the same individual study data again, this current review takes the approach of referencing the previously reviewed results in the two sBLAs, when appropriate. An integrated efficacy analysis utilizing the data from the two final clinical study reports is presented in Section 7.

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

BLA 125264/1670.6
Module 1.14: Labeling, Sections 8.4 and 14
Module 2.5: Clinical Overview
Module 2.7.3: Summary of Clinical Efficacy
Module 2.7.4: Summary of Clinical Safety
Module 5.3.5.3: Study Report Body

BLA 125264/1670.12
Module 1.2: Cover letter

Module 5.3.5.2: Study Report of Uncontrol Clinical Studies
Module 5.3.5.3: Report of Analysis of Data from More than One Study

BLA 125264/1670.13
Module 1.2 Cover letter

BLA 125264/1670.14
Module 1.11.4 Response to FDA IR Information Request Dated 16 July 2020
Module 5.3.5.2: Study Report of Uncontrol Clinical Studies

BLA 125264/1670.15
Module 1.14.1.3 Draft Labeling Text

BLA 125264/1769.0
Module 2.5: Clinical Overview
Module 2.7.3: Summary of Clinical Efficacy
Module 2.7.4: Summary of Clinical Safety
Module 5.3.5.2: Study Report Body

5.3 Table of Studies/Clinical Trials

Table 1. Listing of Studies Supporting the Xyntha Routine Prophylaxis sBLA Submission

Study Number / Completion Date	Study Design	Subject Population	No. of Subjects Treated <17 Years of Age	No. of Subjects Treated ≥17 Years of Age
Study 310 (3082B2-310-WW) November 2006	Phase 3, double-blind, randomized crossover PK period to assess BE of Xyntha and Advate®, followed by an open-label period to evaluate efficacy and safety of Xyntha for use in prophylaxis and on-demand treatment of bleeding. Xyntha PK at 6 months was also evaluated for patients who completed PK period.	Male PTPs ≥12 years of age with severe to moderately severe hemophilia A (FVIII:C ≤1%) in PK period; FVIII:C ≤2% in the safety and efficacy period) and ≥150 EDs to any FVIII product	18	76
Study 313 (B1831001 or 3082B2-313-WW) 18 April 2018	A Phase 3, randomized open label study to evaluate prophylaxis treatment and to characterize the efficacy, safety, and pharmacokinetics of Xyntha administered in children with Hemophilia A	Male PTPs <6 years of age (age increased to <16 years with Amendment 10[b]) of age with severe to moderately severe hemophilia A (FVIII:C≤2%) and with ≥20 prior EDs to FVIII products.	50[c]	NA

b. Study Amendment 10 provided for closing the enrollment of subjects into the on-demand cohort and revised the protocol to include subjects at least 6 months to <16 years.
c. An additional 15 subjects were treated at Site 010 in Poland; data for these subjects are not in the analyses due to GCP violations.
“Source: Adapted from BLA 125264/1769; Clinical Overview, p.7”

6. DISCUSSION OF INDIVIDUAL STUDIES/CLINICAL TRIALS

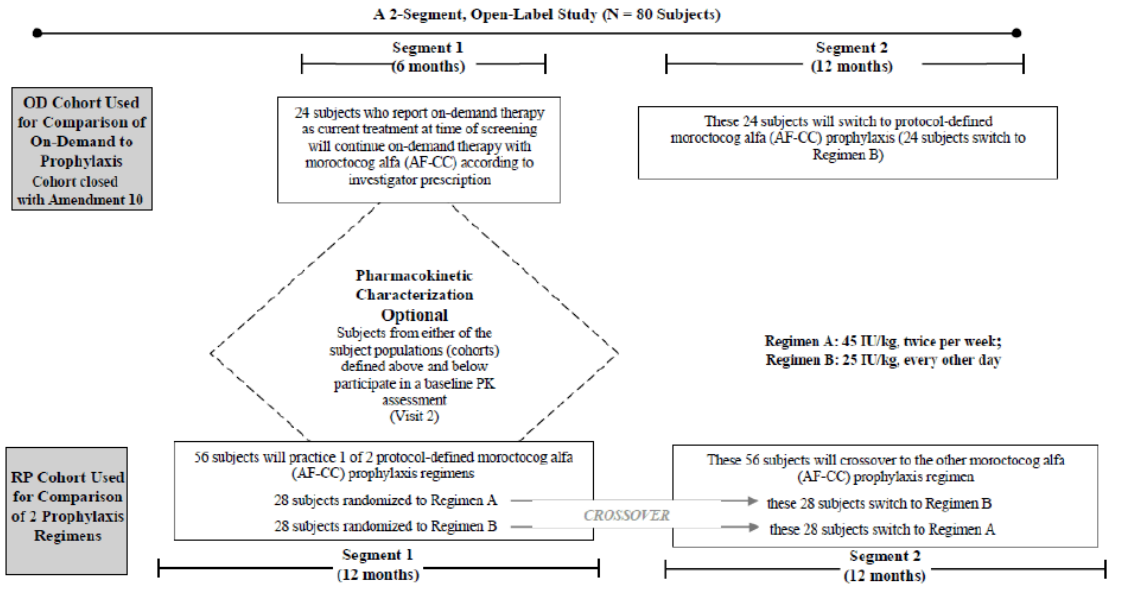
6.1 Trial #1

Study 313 (B1831001) is entitled “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.”

Please refer to the final statistical review memo for BLA 125264/1769 (Tingting Zhou, Ph.D., dated August 7, 2019) for a complete description of the study design and the enrolled subjects in the completed study. A summary is the following.

This was an open-label, multi-centered clinical trial that contains two cohorts: on-demand (OD) and routine prophylaxis (RP). The OD cohort is used for comparison of on-demand treatment to a high dose prophylaxis regimen (Regimen B, 25 IU/kg every other day). The RP cohort is used for comparison of two prophylaxis regimens (low-dose Regimen A at 45 IU/kg twice per week vs. the afore mentioned high-dose Regimen B). The study enrolled male subjects of age ≥6 months to <16 years with moderately severe to severe hemophilia A (FVIII:C <=2%) and negative to FVIII inhibitor. The study design is shown in Figure 1.

Figure 1. Study Overview



OD=on-demand; PK=pharmacokinetic; RP=routine prophylaxis. Regimen A: 45±5 IU/kg, administered twice weekly (BIW); Regimen B: 25±5 IU/kg, administered EOD.
“Source: BLA 125264/1670.6, Module 5.3.5.2. Final Clinical Study Report, Figure 1”

As the primary objective of the study is to demonstrate that routine prophylaxis reduces the ABR relative to OD therapy, this review focuses on the OD cohort only. Of the 9 subjects in the OD cohort, 7 (77.8%) subjects completed the study and 2 (22.2%) withdrew from the study. The eight subjects treated in the OD cohort for both the OD and RP regimen averaged 5 ± 1.1 years in age. Demographic and baseline characteristics of the ITT population are given in Table 2.

Table 2. Demographic and baseline characteristics of the ITT population

Characteristic	AB (N=18)	BA (N=24)	OD (N=9)	Total (N=51)
Age (years)				
Mean (SD)	4.73 (2.47)	4.62 (1.93)	4.54 (1.09)	4.65 (1.99)
Min, Max	1.1, 12.7	1.2, 9.6	2.4, 5.9	1.1, 12.7
Median	4.70	4.55	4.90	4.70
Age Category, n (%)				
Infant (1 month - <2	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	1 (5.6)	3 (12.5)	0	4 (7.8)
Child (12 years - <16	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)
Body Mass Index (BMI) (kg/m2)				
Mean (SD)	15.43 (1.49)	16.10 (1.54)	16.78 (4.62)	15.98 (2.34)
Min, Max	12.9, 18.9	13.6, 19.2	14.1, 28.9	12.9, 28.9
Median	15.41	16.00	15.33	15.67

"Source: Statistical Review BLA 125264/1769, Section 6.1.10.1.1 Demographics, Table 3"

6.1.11 Efficacy Analyses

6.1.11.1 Analyses of Primary Endpoint(s)

The mean ABR (±SE) for the OD cohort during the RP regimen (Regimen B [25 IU/kg EOD]) was 1.5 ± 2.2 (median = 0.6, range = 0, 6.2), and 47.0 ± 32.2 (median = 34.0, range = 0, 92.4) during the OD therapy (Table 3). This is a 97% reduction in ABR. Using a linear mixed-effects model, the ABR estimate was

1.76 ± 0.798, significantly lower (p=0.0040) than the estimate for the OD therapy of 47.02 ± 10.749.

Table 3. Annualized Bleed Rate for On-Demand Cohort (On-Demand Regimen and Prophylaxis 25 IU/kg Every Other Day Regimen) (ITT Population). (Subject Ages <6 Years at Time of Screening Visit.)

	Annualized Bleed Rate[a]			
Statistic	**On-Demand (Number of Bleeds=363)**	**Prophylaxis (Regimen B) (Number of Bleeds=10)**	**Difference[b]**	**Ratio**
ITT Population				
Descriptive Statistics				
N	9	8	8	
Mean (SD)	47.0 (32.2)	1.5 (2.2)	51.4 (30.4)	
Min, Max	0.0, 92.4	0.0, 6.2	10.1, 92.4	
Median	34.0	0.6	51.0	
Interquartile Range	24.8, 74.4	0.0, 2.2	26.9, 76.7	
Linear Mixed-Effects Model				
N	9	8	9	
Estimate	47.02	1.76	45.26	
Standard Error	10.749	0.798	11.320	
P-value[c] (95% CI)			0.0040 (19.16, 71.37)	
Students t-test				
N[d]	8	8	8	
P-value[e]			0.0020	
Ratio (95% CI)[f]				0.03 (0.00, 0.08)

All Site 010 subjects are excluded from the analysis.
Note: If a subject did not complete a regimen's treatment period, the days on regimen ended at the last study visit for that period. The first month of prophylaxis regimen in Segment 2 was considered a washout period.
Abbreviations: ABR=annualized bleed rate; CI=confidence interval; EOD=every other day; ITT=intent to treat; min=minimum; max=maximum; N=number of subjects with ABR data included for each regimen; OD=on-demand; Regimen B=RP25=routine prophylaxis 25 IU/kg EOD; SD=standard deviation.
a ABR=Number of bleeds / (Days on regimen/ 365.25).
b Difference=On-demand ABR minus prophylaxis ABR.
c P-value from mixed model ABR=Treatment with unstructured variance-covariance matrix for within subject measurement. Hemophilia Severity was not included in the model as planned because all enrolled subjects were severe.
d Only the eight subjects who were evaluated with both OD and RP dosing during the study are included in the paired t-test.
e P-value from paired t-test. Subjects must have had ABR data for both regimens to be included in the analyses.
f Ratio of the arithmetic means of the ABR for each segment (RP25 ABR / OD ABR) and 1-sided 95% CI for the ratio.

"Source: BLA 125264/1670.6, Module 5.3.5.2. Final Clinical Study Report, Table 10"

Reviewer Comments:

1. *In sBLA 125264/1670.6, the final clinical study report states the linear mixed model estimate for ABR for Regimen B is 1.76 ± 0.798 (Module 5.3.5.2. Final Clinical Study Report, Table 10, page 99). This estimate is shown above in Table 3. However, the interim clinical study report I reviewed in the original sBLA (125264/1670.0) reported ABR = 2.29 ± 1.043 (mixed model) for Regimen B on the same closed OD cohort (Module 5.3.5.2., Clinical Study Report, Table 8, page 195). The applicant explained the difference in ABRs is due to the fact that at the time of interim analysis, while enrollment into the OD cohort was closed (Study 313 Protocol Amendment 10, 30 November 2015), two subjects did not yet have complete data (BLA 125264/1670.13, Module 1.2 Cover letters, Response to FDA request for information dated 15 July 2020):*
   - *Subject* (b) (6) *had a Regimen B ABR of 5 bleeds in 272 days in segment 2 (ABR=6.7), while in the final CSR, he had 5 bleeds in 296 days (ABR=6.2)*
   - *Subject* (b) (6) *had a Regimen B ABR of 3 bleeds in 174 days in segment 2 (ABR= 6.3), while in the final CSR, he had 3 bleeds in 342 days (ABR=3.2)*
2. *Due to the differences in follow-up for the same two subjects, the (descriptive) mean ABR=1.5 ± 2.2* (median = 0.6, range = 0, 6.2) *reported in Table 3 above is also different from the corresponding mean of 1.9 ± 2.9* (median = 0.6, range = 0, 6.7) *reported in Table 5 of my review memo for sBLA 125264/1670.0.*

6.1.11.2 Analyses of Secondary Endpoints

Please see Dr. Tingting Zhou's statistical review memo for sBLA 125264/1769 for a complete review of the ABRs for RP cohort Regimens A and B.

In summary, the mean ABR ± SD was 3.3 ± 5.3 during Regimen A, and 2.2 ± 4.1 during Regimen B. The 90% 2-sided CI (0.03, 2.22) for the mean difference in ABRs for the two prophylaxis regimens demonstrated equivalence (the limits of the 90% CI fell wholly within the prospectively defined equivalence interval of [–3, 3] bleeds per year).

Reviewer Comment: The protocol/statistical analysis plan (SAP) initially specified an equivalence interval of (-4, 4) bleeds per year. However, Amendment 10 of the protocol and SAP version 5 changed the equivalence interval to (-3,3) bleeds per year.

6.1.11.3 Subpopulation Analyses

For the subjects in the efficacy analysis population that received on-demand therapy followed by prophylaxis (i.e., the OD cohort), no subgroup analysis of the

effect sex, race or age on efficacy was performed because all subjects were male, most were white, and all were <6 years of age.

6.1.11.4 Dropouts and/or Discontinuations

Of the 9 subjects in the OD cohort, 7 subjects completed the study and 2 withdrew from the study (subject (b) (6) was never dosed and subject (b) (6) was observed for 337 days).

6.1.12 Safety Analyses

Please refer to the final statistical review memo for BLA 125264/1769 (Tingting Zhou, Ph.D., dated August 7, 2019) for a review of the safety endpoints in the completed study. Of note, one subject had a confirmed positive test for FVIII inhibitors after receiving the first dose, yielding an inhibitor rate of 2.04% (1/49 subjects; 95% CI: 0. 05%, 10.85%).

7. INTEGRATED OVERVIEW OF EFFICACY

7.1 Indication #1

Routine prophylaxis to prevent or reduce the frequency of bleeding episodes in pediatric and adolescent subjects <17 years of age and adult subjects (≥17 years of age) with moderately severe to severe hemophilia A.

7.1.1 Methods of Integration

The applicant relies on data from two clinical studies (Study 313 and Study 310; see Table 1) to provide the efficacy support for the current sBLA submission.

Study 313 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 <16 years of age. The primary objective of the study was to demonstrate that routine prophylaxis (25 ± 5 IU/kg every other day) reduces ABR relative to on-demand treatment.

Study 310 was a Phase 3 study in subjects ≥12 years of age. The second part of the study consisted of an open-label single-arm safety and efficacy period for routine prophylaxis (30 ± 5 IU/kg 3 times per week) and on-demand treatment for any bleeding episodes.

7.1.2 Demographics and Baseline Characteristics

Both studies provide data on subjects who received both on-demand therapy and routine prophylaxis. Their demographic characteristics are shown in Table 4.

Table 4. Demographic Summary of Subjects Who Received XYNTHA in both a Routine Prophylaxis Treatment Regimen and On-Demand Treatment Regimen

	Study 310	Study 313
Age (years)		
N	94	8
Mean	27.7	5
Std. Dev.	12.8	1.1
Median	24	5
Min, Max	12, 60	2, 6
Age Category, n (%)		
< 12 years	0	8 (100.0%)
12 - 16 years	18 (19.1%)	0
17 - 65 years	76 (80.9%)	0
Sex, n(%)		
Male	94 (100.0%)	8 (100.0%)
Race, n(%)		
Asian	1 (1.1%)	0
Other: Arab.	1 (1.1%)	0
Other: Fijian Indian.	1 (1.1%)	0
Other: Mid Eastern Iranian.	1 (1.1%)	0
Other: Mixed race.	1 (1.1%)	1 (12.5%)
White	89 (94.7%)	7 (87.5 %)
Ethnic Origin, n(%)		
Hispanic or Latino	4 (4.3%)	2 (25.0 %)
Non-Hispanic and Non-Latino	90 (95.7%)	6 (75.0 %)
Weight(kg)		
N	94	8
Mean	72.7	20
Std. Dev.	16.1	6.6
Median	73.1	19
Min, Max	42.0, 120.3	13, 35
Height(cm)		
N	93	8
Mean	176.2	108
Std. Dev	7.7	6.9
Median	176.0	109
Min, Max	156.0,	94, 118

Abbreviations: Max=maximum; Min=minimum; Std. Dev.=standard deviation
"Sources: BLA 125264/1670.6, Module 2.7.4, Summary of Clinical Safety, link CSR on page 10, CSR-66997, Table 8; and BLA 125264/1670.14, Module 5.3.5.2: Response to FDA Information Request dated 16 July 2020."

7.1.4 Analysis of Primary Endpoint(s)

Across all age categories, the percentage of subjects with an ABR of zero during routine prophylaxis was approximately 45.1% (46/102 subjects). In subjects of all ages studied, the ABR was much lower (88.86%) for routine prophylaxis compared with the ABR for on-demand treatment alone. A summary of ABR comparison for routine prophylaxis vs OD control groups (all ages) is given in Table 5.

Table 5. Study 310 and 313 - All Ages Descriptive Statistics. Percentage Reduction in Mean ABR During Routine Prophylaxis Compared to Mean ABR During On-Demand

Statistic	OD ABR	RP ABR	% Reduction in ABR compared to OD
n	115	102	
Mean (SD)	34.36 (24.177)	3.83 (6.441)	88.86%
Median	29.59	1.92	
Min, Max	0.00, 137.98	0.00, 44.15	

"Source: BLA 125264/1670.6, Module 2.5 Clinical Overview, Xyntha (Antihemophilic Factor [Recombinant]), Table 2, page 14."

Reviewer Comments: *As noted in Section 5.1, the routine prophylaxis data in the Study 310 final clinical study report submitted in sBLA 125264/1670.0 were previously reviewed by me (statistical review memo dated October 13, 2017). Table 10 in that memo gives the total, spontaneous and traumatic mean ABR results for all ages (≥12 years; n=94). Table 11 provides the total ABR by age group (12 - <17 years and ≥17 years); these results are included in Table 6 below.*

The FDA observed that subject ((b) (6)*) in the adolescent group (12 - <17 years) had a mean routine prophylaxis ABR that was markedly higher (total ABR=44.15) than other adolescents and other age groups by a factor of ~2. ABR was calculated with and without this outlier (Table 6).*

Including the outlier, the treated total ABR mean±SD during prophylaxis for the 18 adolescents was 7.3±11.37 with median (min-max) of 3.0 (0.0-44.2). The spontaneous mean ABR was 3.3±7.73 with median of 0.0 (0.0-32.1). The traumatic mean ABR was 4.0±5.94 with median of 1.9 (0.0-19.6). The treated total mean ABR during prophylaxis for the 94 subjects aged ≥12 years was 4.0±6.64 with median of 1.9 (0.0-44.2). The spontaneous treated mean ABR was 2.0±4.25 with median of 0.0 (0.0-32.1). The traumatic mean ABR was 2.0±4.10 with median of 0.0 (0.0-23.3).

Excluding the outlier, ABR assessments showed that while the ABR did not markedly change for total (5.15 versus 7.3) and traumatic bleeds (3.52 versus 4.0), the spontaneous ABR did approximately halve (1.63 versus 3.3) and 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). It was suggested that this subject was conceded an outlier impacting mean ABR calculations.

Table 6: Descriptive Statistics of ABR During Routine Prophylaxis Treatment in Study 310						
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	8	97%*	Mean±SD	1.5±2.20	0.6±1.31	0.9±1.30
			Median (Min-Max)	0.6 (0.0-6.2)	0.0 (0.0-3.7)	0.0 (0.0-3.2)
≥12 years (outlier removed)	93	92%	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 years (outlier included)	94	88%	Mean±SD	4.0±6.64	2.0±4.25	2.0±4.10
			Median (Min-Max)	1.9 (0.0-44.2)	0.0 (0.0-32.1)	0.0 (0.0-23.3).
12 to <17 years (outlier removed)	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)
12 to <17 years (outlier included)	18	84%	Mean±SD	7.3±11.37	3.3±7.73	4.0±5.94
			Median (Min-Max)	3.0 (0.0-44.2)	0.0 (0.0-32.1)	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)
ABR = annualized bleeding rate; SD = standard deviation, Min=minimum, Max=maximum.						

* In the OD cohort the ABR for 8 subjects was 52.9 and 47 for 9 subjects (8 subjects treated for both the OD and RP regimen).
"Source: BLA 125264/1670.15, Module 1.14.1.3, Draft Labeling Text"

7.1.11 Efficacy Conclusions

Collectively the data show that ABRs are 89% lower in pediatric and adult subjects on routine prophylaxis with Xyntha compared to on-demand treatment periods. The results of Studies 313 and 310 were comparable in the percent of subjects with zero bleeds, with 45.1% of subjects having no bleeds in all age

groups. When excluding the outlier subject, 42 of 93 (45.2%) subjects reported no bleeding while on routine prophylaxis.

10. CONCLUSIONS

10.1 Statistical Issues and Collective Evidence

Study 313 (subjects <16 years of age) was complete on April 18, 2018. The mean ABR (±SE) for the 8 subjects in the OD cohort during the RP regimen (Regimen B [25 IU/kg EOD]) was 1.5 ± 2.2 (median = 0.6, range = 0, 6.2), and 47.0 ± 32.2 (median = 34.0, range = 0, 92.4) during the OD therapy. This is a 97% reduction in ABR. The model estimate of the ABR was 1.76 ± 0.798, significantly lower (p=0.004) than the ABR estimate for OD therapy which was 47.02 ± 10.75.

When excluding the outlier subject, the mean ABR (±SE) for the 93 subjects in age group ≥12 years (Study 310) was 3.6±5.18 (median 1.9 (0.0-23.3)) on RP, This is a 89% reduction in ABR from OD. Also, 42 of 93 (45.2%) subjects reported no bleeding while on RP. In subjects of all ages studied, the ABR was much lower (89%) for routine prophylaxis compared with the ABR for on-demand treatment alone. The results of Studies 313 and 310 were comparable in the percent of subjects with zero bleeds, with 45.1% of subjects having no bleeds in all age groups. For a given type of therapy, the mixed model estimates and descriptive statistics of the ABR are very close. There were no statistical issues in this submission.

10.2 Conclusions and Recommendations

Currently, the US prescribing information for Xyntha does not include an indication for routine prophylaxis. This submission supports the modification of the indication for Xyntha to include routine prophylaxis at a dosing regimen of 25 IU/kg every other day in children (<12 years), and 30 IU/kg 3 times weekly for both adolescents (12- <17 years) and adults (≥17 years) with hemophilia A (congenital factor VIII deficiency) to prevent or reduce the frequency of bleeding episodes.