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Human Medicines Evaluation Division

Assessment report for paediatric studies submitted according to Article 46 of the Regulation (EC) No 1901/2006

ReFacto AF

moroctocog alfa

Procedure no: EMEA/H/C/000232/P46/146

Note

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

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1. Introduction

The MAH has submitted a completed paediatric study; 3082B2-313-WW (B1831001); an open label study to evaluate prophylaxis treatment, and to characterise the efficacy, safety and pharmacokinetics of B-domain deleted recombinant factor VIII albumin free in children with hemophilia A.

This study is being submitted in accordance with Article 46 of the Paediatric Regulation (European Commission [EC]) No 1901/2006. The MAH plans to submit a type II variation Q1 2019 to update the ReFacto AF SmPC to include the safety data from this study once this Article 46 assessment has completed. The MAH will submit an RMP update as part of this type II variation, which will reflect the completion of studies 3082B2-313-WW (B1831001) and B1831007. This submission also fulfils MEA 116.

A short critical expert overview has also been provided.

Refacto (Moroctocog alfa) received its first regulatory approval on 13 April 1999 in the EU for the treatment and prophylaxis of bleeding in patients with haemophilia A (congenital factor VIII [FVIII] deficiency). Moroctocog alfa (AF-CC) is appropriate for use in adults and children of all ages, including newborns. Moroctocog alfa (AF-CC) does not contain von Willebrand factor, and hence, is not indicated for the treatment of von Willebrand's disease. Refacto AF (Moroctocog alfa (AF-CC)) was developed as a successor to Refacto (moroctocog alfa) in an effort to eliminate animal/human proteins from the manufacturing process of moroctocog alfa by making the product albumin free. Refacto (Moroctocog alfa) is approved globally, but is no longer manufactured.

Study B1831001 was undertaken to fulfil a FDA commitment with the primary objective to compare annualised bleeding rate during on demand versus routine prophylaxis and the secondary objective to compare 2 regimens of prophylaxis with Xyntha, the US approved product. The difference between ReFacto AF and Xyntha is the analytical method used to calibrate the working potency standard that is used in the potency assay. The standard for Xyntha has been calibrated using a one-stage assay, and the standard for ReFacto AF has been calibrated using a chromogenic substrate assay. The 2 products are not interchangeable.

2. Scientific discussion

2.1. Information on the development program

The MAH stated that study B1831001; is a part of the development of the product, changes to the EU SmPC is expected to be introduced via a type II variation.

2.2. Information on the pharmaceutical formulation used in the study

Xyntha, Recombinant coagulation factor VIII, 500 IU powder for injection vial in 1 × pack, for IV infusion.

2.3. Clinical aspects

2.3.1. Introduction

The MAH submitted the final report for:

- Study B1831001 an open label study to evaluate prophylaxis treatment, and to characterise the efficacy, safety and pharmacokinetics of B-domain deleted recombinant factor VIII albumin free in children with hemophilia A.

For this study, 2 previous interim analysis clinical study reports, dated 07 November 2013 and 11 April 2016, presented snapshot 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, pharmacokinetics (PK), and safety data, collected for approximately 4 years after initiation of study enrollment. The analyses for these summaries were based on descriptive statistics, using a data cut-off date of 31 December 2012. Moroctocog alfa (AF-CC), the study drug, was reported as efficacious in the treatment of hemophilia A when used for the OD treatment of bleeding episodes in children under 6 years of age. The majority of the bleeding episodes (93.7%) were resolved with 1 or 2 infusions. A total 468 of 493 bleeding episodes (94.9%) treated with study drug were rated "Excellent" or "Good" in their response to initial treatment and 22 (4.5%) were rated as "Moderate". No new safety signal was observed. PK data were reported for 5 children aged 3.7 to 5.8 years.

The second interim analysis CSR included data on safety, efficacy, and OD therapy compared to RP, collected for approximately 7 years after initiation of study enrollment up to a data cut-off date of 26 June 2015. An analysis was performed for the primary efficacy endpoint, comparing the mean number of bleeds per year (annualized bleeding rates [ABRs]) while on OD therapy versus RP on the intent to treat (ITT) population. Routine prophylaxis with moroctocog alfa (AF-CC) was reported to be efficacious for pediatric-aged subjects <6 years with moderately severe to severe hemophilia A, reducing significantly the ABR compared to OD therapy in addition to demonstrating efficacy when used as an OD treatment. No new safety findings were reported in this pediatric hemophilia A population.

2.3.2. Clinical study B1831001

Study B1831001 was an open label, multicentre study of Xyntha conducted at 42 sites in 17 countries worldwide between 11 December 2007 and 18 April 2018 in paediatric patients with moderately severe to severe haemophilia A.

The primary objective was to compare clinical outcomes during periods of study drug prophylaxis treatment versus periods of On-demand (OD) therapy in paediatric subjects to demonstrate that moroctocog alfa (AF-CC) prophylaxis reduces annualized bleeding rate (ABR) relative to OD therapy in infants to children aged <16 years with haemophilia A.

The secondary objectives included the comparison of the clinical outcomes of a high- (ie, 25 international unit(s) [IU]/kg every other day [EOD]) versus low-frequency dosing (ie, 45 IU/kg twice a week [BIW]) schedule on the efficacy of study drug prophylaxis. In addition, the study also evaluated the efficacy and safety of the drug in paediatric patients, including the characterisation of the incidence of less than expected therapeutic effect (LETE) and characterisation of the PK of FVIII following moroctocog alfa (AF-CC) administration to patients aged 6 months to <16 years with haemophilia A.

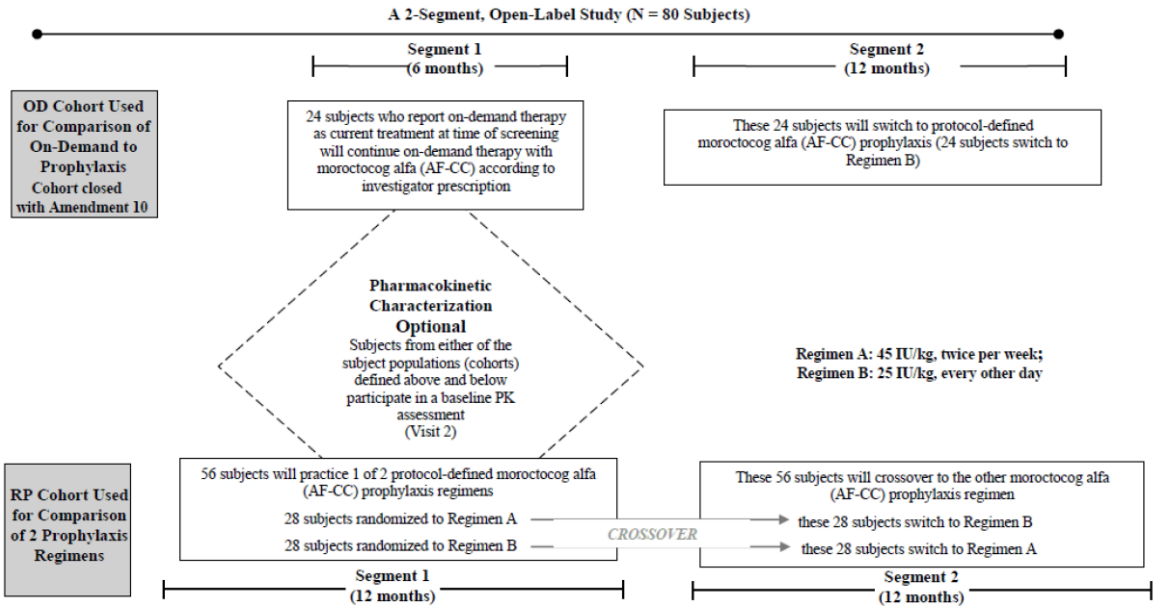
Overall study design

This was an open label, multicentre study of Xyntha that originally planned to recruit a total of approximately 72 paediatric subjects <6 years of age (<16 years after Amendment 10) with moderately severe to severe haemophilia A (confirmed Factor VIII activity in plasma [FVIII:C] ≤2% by both the local laboratory and the central laboratory at screening) at approximately 40 sites.

The study was conducted in two 6-to-12 month segments (Segment 1 and Segment 2); 2 cohorts were enrolled: the OD cohort included subjects who practised OD therapy for Segment 1 followed by RP for

Segment 2, and the RP cohort included subjects who practised RP for both segments. Segment 1 for the OD cohort was 12 months for subjects enrolled prior to Amendment 7 (dated 31 August 2011), and 6 months in duration for subjects enrolled after this. When a bleed occurred for a subject in the OD cohort during Segment 1, study drug was to be administered at a dose and frequency prescribed by the investigator as per local standard of care, based on the recommendation for OD treatment with the licensed product Xyntha.

Figure 1. Study Overview



For the OD cohort, study drug in Segment 2 was administered at the doses and frequencies defined by Regimen B only (25 ± 5 IU/kg EOD). For the RP subjects, each segment was 12 months in duration. Subjects in the RP cohort were randomised to receive low frequency Regimen A (45 ± 5 IU/kg BIW) followed by high frequency Regimen B (25 ± 5 IU/kg EOD) (prophylaxis sequence received during Segments 1 and 2: the low- followed by the high frequency dosing sequence [AB]), or vice versa (Regimen B followed by Regimen A; prophylaxis sequence received during Segments 1 and 2: the high- followed by the low frequency dosing sequence [BA]). Randomisation to prophylaxis treatment was stratified by haemophilia A severity: FVIII:C <1% or 1% to 2% (according to central laboratory screening result). There was no active control group in this study.

A subset of severe (FVIII:C ≤1% confirmed by the central laboratory screening test) haemophilia A subjects could participate in assessments to characterise the PK of FVIII:C after administration of study drug. Subjects who were eligible and opted to participate underwent a PK assessment, after receiving a single open-label dose (50 ± 5 IU/kg rounded to the nearest complete vial) over 2 minutes, with blood sampled for FVIII:C measurements before and at 0.5 hour, 8, 24, 28 (optional), and 32 hours after the start of the infusion.

Selection of Study Population

The subjects were considered eligible for enrolment into the study only when they met all the inclusion criteria outlined in the protocol.

The eligible subjects for screening included previously treated male subjects (≥20 exposure days [EDs] to any FVIII replacement product) aged 6 months to <16 years at the time of Screening Visit with moderately severe to severe haemophilia A (FVIII:C ≤2%) by both the local laboratory and the central

laboratory. The subjects were to have a medical history negative for past FVIII inhibitor. In addition, subjects had to have a FVIII:C of ≤1% confirmed by the central laboratory screening test to be eligible for PK assessments.

Statistical Considerations for the Determination of Sample Size

Approximately 72 subjects were originally planned to be enrolled in this study at approximately 40 sites. Subjects withdrawn from the study were not replaced, regardless of the reason for withdrawal. Twenty four (24) subjects in the OD cohort were planned to contribute to the comparison of ABR in the OD versus RP treatment settings; 48 subjects in the RP cohort were planned for the comparison of ABR in the 2 prophylaxis regimens (A and B). After the sample size re-estimation described in Amendment 10, planned enrolment for the RP cohort was revised to 56 subjects (6 months to <16 years), considering the subjects from Site 010 who were excluded from the analyses (allowing for an attrition rate of 30% [38 subjects)]. From the planned total of 72 subjects, a subset of approximately 23 PK subjects (meeting specific criteria) was planned for PK assessments for the objective of PK characterisation of FVIII:C.

Due to serious breaches of Good Clinical Practice compliance pertaining to data integrity at Site 010, data for 15 subjects at this site were presented separately to those of subjects from other study sites. Data from this site were excluded from safety, efficacy and baseline summary data (but included for protocol deviations and recovery/PK data and inhibitor incidence.

Subject Disposition and Demography

A total of 71 subjects were screened, and 51 subjects (excluding Site 010 in Poland) were enrolled into this study and included in the intent to treat (ITT) population. A total of 50 subjects were included in the modified intent to treat (mITT) population; 1 subject enrolled in the OD cohort did not receive any study drug. A total of 41 (80.4%) subjects completed the study, and 10 (19.6%) subjects discontinued the study early; the most common reason for discontinuation was adverse event (AE) (9.8%). The complete details about the disposition of the enrolled subjects are present in CSR B1831001.

Demographic and other baseline characteristics for all subjects dosed in the study are presented in Table 1. All subjects were male. The mean ± standard deviation (SD) age (range) was 4.65 ± 1.99 years (1.1 12.7 years). The majority of subjects (84.3%) were aged between 2 and 6 years, were white (78.4%) and of non Hispanic and non Latino ethnicity (86.3%). The mean ± SD height was 107.45 ± 13.31 cm, and 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 7 subjects with PK data available, and included in the PK analysis, were younger than 6 years of age (including 1 subject from Site 010).

Table 1. Demographic Characteristics at Baseline (ITT Population)

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

Table 1. Demographic Characteristics at Baseline (ITT Population)

Characteristic	AB (N = 18)	BA (N = 24)	OD (N = 9)	Total (N = 51)
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)
Height (cm)				
N	18	24	9	51
Mean (SD)	106.73 (15.42)	108.36 (13.77)	106.44 (7.16)	107.45 (13.31)
Min, Max	78.0, 149.5	83.0, 133.5	94.0, 118.0	78.0, 149.5
Median	107.50	111.00	107.00	108.00
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
BMI (kg/m^2)				
N	18	24	9	51
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: CSR B1831001 Table 8.
All Site 010 subjects were excluded from the analysis.
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; BMI = body mass index; CSR = clinical study report; ITT = intent to treat; min = minimum; max = maximum; n = number of observations; N = number of subjects in group; OD = on-demand; SD = standard deviation.

Medical History (ITT Population)

While enrollment eligibility allowed for subjects with based FVIII activity of <2%, all subjects enrolled were classified as having severe hemophilia, ie, with <1% FVIII activity level at screening. Most subjects had a life time exposure to FVIII of >50 days; 5 subjects had between 20 and 50 prior exposure dates. The mean (±SD) total number of bleeds in the last 12 months was 9.1±14.3. A total of 20 (39.2%) subjects had a target joint involvement bleed. The most commonly (>20%) reported medical history by System Organ Class (SOC) was Musculoskeletal and connective tissue disorders (11 [21.6%] subjects) (Table 14.1.4). Other SOCs reported for >10% of subjects were Gastrointestinal disorders, Injury, poisoning and procedural complications, and Vascular disorders (each reported for 6 [11.8%] subjects).

Efficacy, Safety Including Immunogenicity and Pharmacokinetic Evaluations

The measures of PK and safety in this study were standard measurements, widely used and generally recognised as reliable, accurate, and relevant. The safety measurements recorded in this clinical study were those employed in most clinical studies, including the recording of AEs coded in accordance with the Medical Dictionary for Regulatory Activities.

Inhibitor development was monitored as part of ongoing safety surveillance by the sponsor to ensure that subjects treated with study drug had an acceptable rate of inhibitor development. The study had testing for inhibitor development at a frequency consistent with commonly accepted standard of care practice in the usual clinical setting.

RESULTS

Pharmacokinetic Evaluations

The optional PK assessment occurred at the beginning of the study (Visit 2), before subjects initiated moroctocog alfa (AF-CC) treatment. Blood samples were collected at time 0 (prior to the dose) and then 0.5 hour, 8, 24, 28 (optional time point) and 32 hours after the start of the infusion. Plasma samples were analysed for FVIII activity and FVIII inhibitor at Covance Laboratories Inc (Chantilly, Virginia, USA) using validated, sensitive and specific analytical one-stage coagulation assays.

Immunogenicity – FVIII Inhibitors

Incidence of FVIII inhibitors was monitored throughout the duration of this study. Due to technical issues with the inhibitor assay at the Covance Central Laboratory Services in Chantilly, VA, testing of FVIII inhibitors needed to be transferred to a new laboratory, Esoterix/Labcorp Inc (Denver, CO). In addition, serum samples were collected and tested for anti-FVIII antibodies, antibodies to Chinese hamster ovary, and antibodies to the affinity ligand used in the study drug purification process (TN8.2) using validated enzyme-linked immunosorbent assay (ELISA) methods. The samples were analysed by Covance (Chantilly, VA).

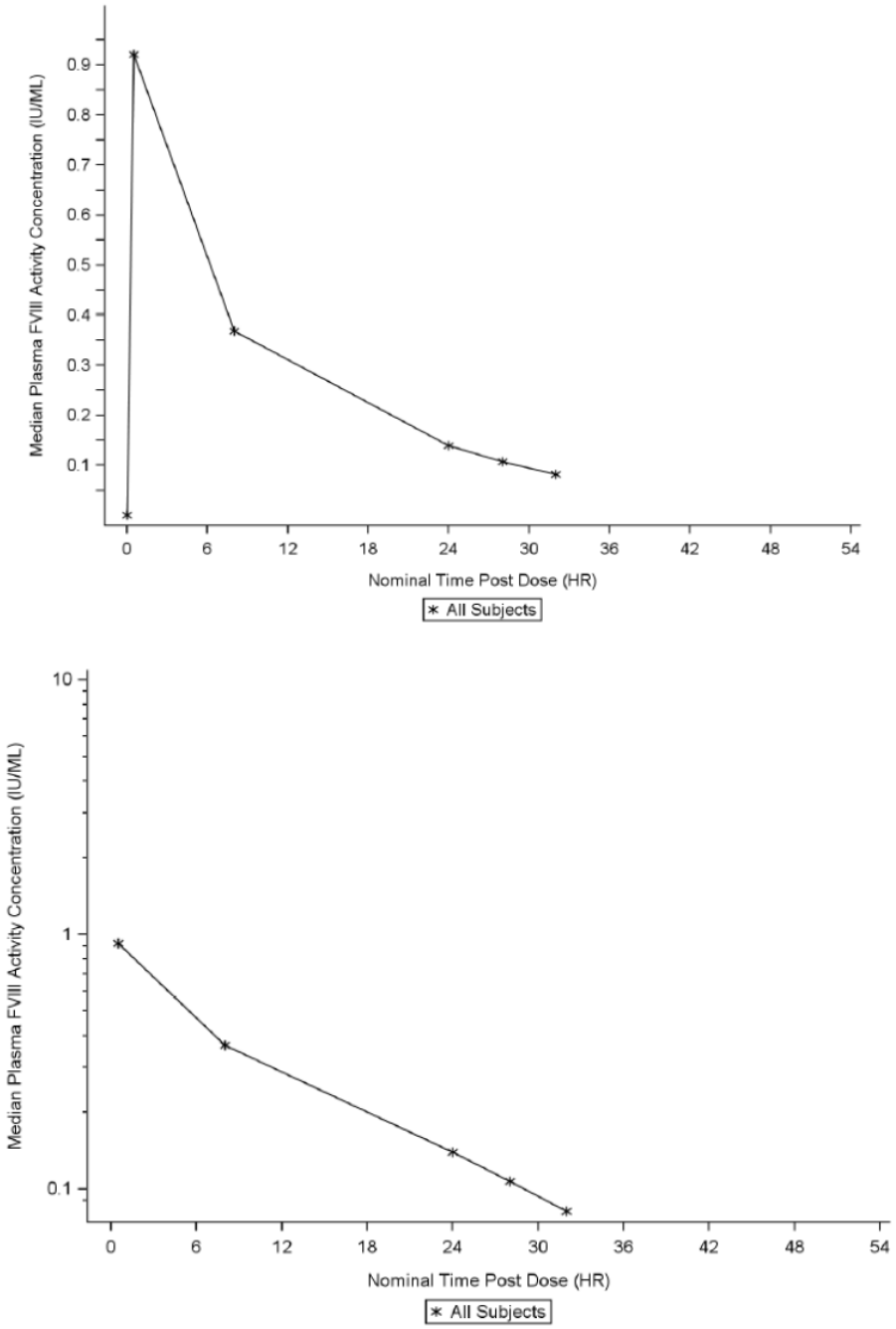
Overview of Clinical Pharmacology

The PK parameters for FVIII activity were calculated for each subject using noncompartmental analysis of plasma concentration-time for FVIII activity data.

Pharmacokinetics Results

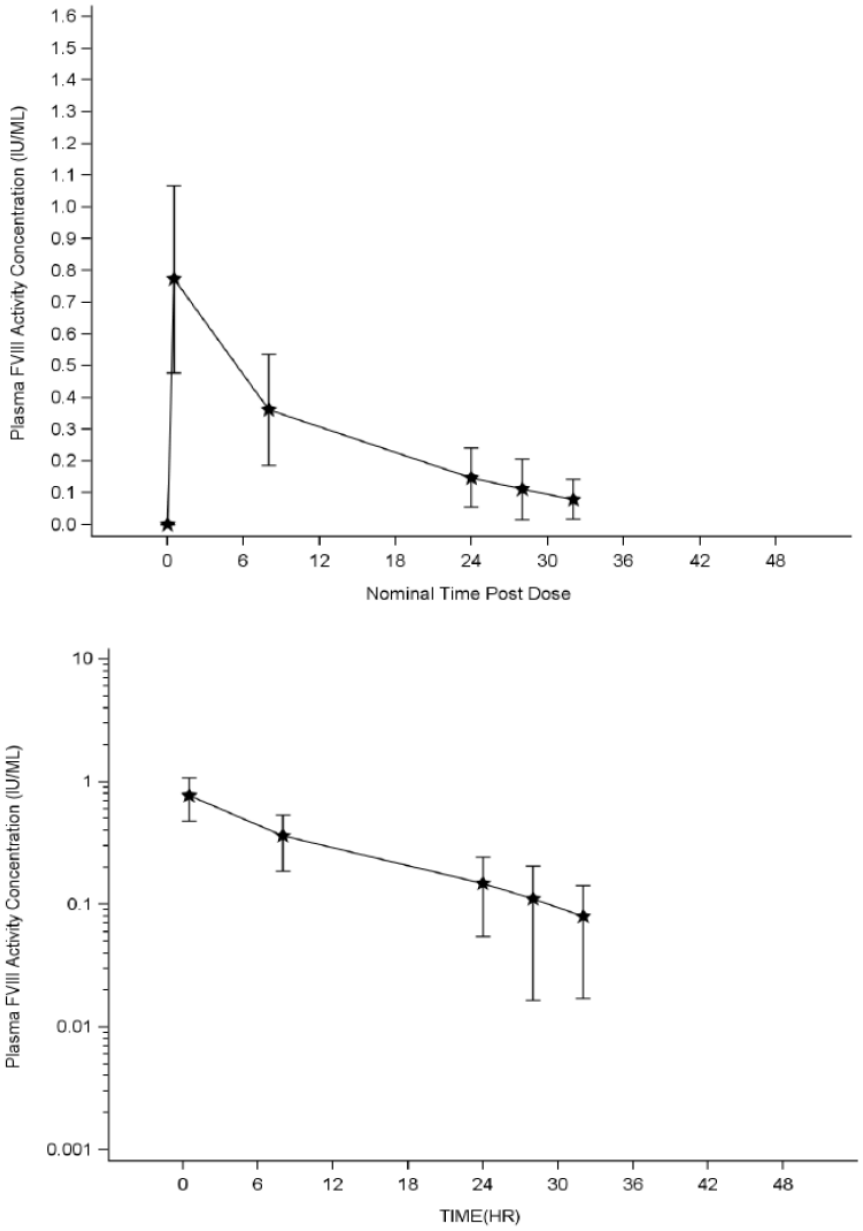
Median and mean plasma concentration-time profiles for FVIII activity following a single dose of 50 IU/kg of Xyntha are presented in figure 2 and 3. PK parameters are summarised descriptively in Table 19.

Figure 2. Median Plasma FVIII Activity Concentration-Time Profiles After 50 IU/kg



Source: Figures 14.5.1.1 and 14.5.1.2.
Abbreviations: HR=hour; FVIII=Factor VIII; IU=international unit (s)
All sites including Site 010 subjects are included in the analysis.

Figure 3. Mean Plasma FVIII Activity Concentration-Time Profiles after 50 IU/kg



Source: Figures 14.5.1.3 and 14.5.1.4.
Abbreviations: HR=hour; FVIII=Factor VIII; IU=international unit (s), SD=standard deviation.
All sites including Site 010 subjects are included in the analysis.

Table 19. Descriptive Summary of Plasma FVIII Activity Pharmacokinetic Parameter Values After 50 IU/kg, Study B1831001

Parameter, Units	Parameter Summary Statistics[a] Xyntha 50 IU/kg
N	7
AUC_{inf}, IU•h/mL	9.022 (50)
AUC_{last}, IU•h/mL	8.044 (46)
C_{max}, IU/mL	0.7005 (60)
T_{max}, hours	0.517 (0.500 – 7.17)
k_{el}, $hours^{-1}$	0.08103 (30)
$t_{½}$, hours	8.859 ± 2.35

Table 19. Descriptive Summary of Plasma FVIII Activity Pharmacokinetic Parameter Values After 50 IU/kg, Study B1831001

MRT, hours	13.46 (33)
CL, mL/h/kg	5.822 (59)
V_{ss}, mL/kg	78.38 (50)
Incremental recovery,[b] (IU/dL)/(IU/kg)	1.248 (43)

Source: CSR B1831001 Table 19.
All sites, including Site 10 subjects, were included in this analysis.
Parameters are defined in CSR B1831001 Table 5. Summary statistics are not presented if fewer than 3 subjects had reportable parameter values.
%CV = coefficient of variation; AUC_{inf} = area under the FVIII:C-versus-time curve from time 0 extrapolated to infinite time; AUC_{last} = area under the FVIII:C-versus-time curve from time zero to the time for last quantifiable concentration; C_{max} = maximum FVIII:C plasma concentration; CL = clearance; CSR = clinical study report; FVIII = Factor VIII; incremental recovery = the increase in FVIII:C reported as IU/dL per IU/kg of FVIII replacement product administered; IU = international units; k_{el} = terminal phase rate constant; MRT = mean residence time; N = number of subjects contributing to the summary statistics; SD = standard deviation; $t_{½}$ = terminal phase half-life; T_{max} = time for C_{max}; V_{ss} = volume of distribution at steady state.
a. Geometric mean (geometric %CV) for all, except: median (range) for T_{max}; arithmetic mean ± SD for $t_{½}$.
b. Baseline (Day 1) incremental recovery is presented. N = 6 for incremental recovery.

Pharmacokinetic Conclusions

The PK analysis of FVIII activity data for 5 of the 7 subjects included in this study was reported to the FDA in a previously completed interim analysis and is included in the US Package Insert. The data from the full study were re-analysed using current Pfizer processes and standards and results obtained were similar. PK analyses demonstrated that geometric mean clearance and volume of distribution at steady state (V_{ss}) were 5.822 mL/h/kg and 78.38 mL/kg, respectively. Mean $t_{½}$ was about 8.9 hours. Geometric mean incremental recovery was 1.248 IU/dL/IU/kg.

Efficacy Evaluation

Primary Efficacy Endpoints

Annualised Bleed Rate (On-Demand Cohort)

The estimate of the ABR (± standard error [SE]) for the OD cohort (ITT population) during the RP regimen (Regimen B [25 IU/kg EOD]) was 1.76 ± 0.798 and was significantly lower (p = 0.0040) than the estimate for the ABR (± SE) for OD therapy of 47.02 ± 10.749 using a linear mixed-effects model (Table 3). A supportive analysis was performed, using the paired t-test (p = 0.0020), based on the within-subject change in ABR for the 8 subjects who were evaluated with both OD and RP dosing during the study. The difference between the 2 treatment regimens, though not tested, was similar to that observed for the PP population, with or without washout data.

In addition, a 1-sided 95% confidence interval (CI) for the ratio of the arithmetic means for ABR during the RP regimen over the ABR during OD therapy in the ITT population was calculated. The 1-sided 95% upper confidence bound was 0.08, which is <0.5 indicating that the ABR during the RP regimen was at least 50% lower than that observed during OD therapy. The ratio and corresponding 1-sided 95% CI are presented in Table 3.

Table 2. Annualised Bleed Rate for On-Demand Cohort (On-Demand Regimen and Prophylaxis 25 IU/kg EOD Regimen) (ITT Population)

	Annualised 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	

Table 2. Annualised Bleed Rate for On-Demand Cohort (On-Demand Regimen and Prophylaxis 25 IU/kg EOD Regimen) (ITT Population)

	Annualised Bleed Rate[a]			
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)

Source: CSR B1831001 Table 10.
All Site 010 subjects are excluded from the analysis.
Subjects in the OD cohort followed an OD regimen in Segment 1 and RP25 in Segment 2.
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.
ABR = annualised bleeding rate; CI = confidence interval; CSR = clinical study report; 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; 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. Haemophilia Severity was not included in the model as planned because all enrolled subjects were severe.
d. Only the 8 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.

Annualised Bleed Rate by Type and Location of Bleed (On-Demand Cohort)

The majority of bleeding episodes for the OD cohort (ITT population) during OD therapy were traumatic events (mean [± SD] ABR was 37.9 ± 31.6 [median: 31.8] compared with 9.1 ± 9.2 [median: 7.6] for spontaneous bleeds.

Table 11. Annualized Bleed Rate by Bleed Type for On-Demand Cohort (On-Demand Regimen and Prophylaxis 25 IU/kg EOD Regimen) (ITT Population)

	Type of Bleed	
Characteristic	**Spontaneous**	**Traumatic**
Regimen: OD		
ITT Population		
N (Number of Subjects)	9	9
Mean (SD)	9.1 (9.2)	37.9 (31.6)
Min, Max	0.0, 28.7	0.0, 90.2
Median	7.6	31.8
Interquartile Range	2.2, 13.4	12.4, 64.7
Regimen: RP-B		
ITT Population		
N (Number of Subjects)	8	8
Mean (SD)	0.6 (1.3)	0.8 (1.3)
Min, Max	0.0, 3.7	0.0, 3.2
Median	0.0	0.0
Interquartile Range	0.0, 0.6	0.0, 1.8

Source: Table 14.2.4.4.
All Site 010 subjects are excluded from the analysis.
Abbreviations: ABR=annualized bleed rate; 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; RP-B=routine prophylaxis 25 IU/kg EOD; SD=standard deviation.

Of the 3 categories of bleeding location (joint, soft tissue/muscle, other), bleeding episodes occurred slightly more frequently in soft tissue/muscle during the RP regimen and occurred most frequently in joints during OD therapy. The RP-B regimen resulted in a mean (± SD) ABR for joint bleeding episodes of 0.5 ± 1.3 (median: 0.0), OD therapy resulted in a mean (± SD) ABR for joint bleeding episodes of 26.2±21.1 (median: 17.5). The mean (±SD) ABR for soft tissue/muscle bleeds was 0.7±1.1 (median: 0.0) during the RP-B regimen and 21.2±15.3 (median: 16.5) during OD therapy. A similar outcome was also observed for the PP population, with or without washout data.

Table 12. Annualized Bleed Rate by Bleed Location for On-Demand Cohort (On-Demand Regimen and Prophylaxis 25 IU/kg EOD Regimen) (ITT Population)

Characteristic	Location of Bleed		
	Joint	Soft Tissue/Muscle	Other
Regimen: OD			
ITT Population			
N (Number of Subjects)	9	9	9
Mean (SD)	26.2 (21.1)	21.2 (15.3)	2.2 (2.4)
Min, Max	0.0, 60.9	0.0, 40.6	0.0, 5.4
Median	17.5	16.5	1.1
Interquartile Range	13.4, 41.7	7.6, 36.1	0.0, 4.4
Regimen: RP-B			
ITT Population			
N (Number of Subjects)	8	8	8
Mean (SD)	0.5 (1.3)	0.7 (1.1)	0.3 (0.5)
Min, Max	0.0, 3.7	0.0, 2.5	0.0, 1.1
Median	0.0	0.0	0.0
Interquartile Range	0.0, 0.0	0.0, 1.6	0.0, 0.5

Source: Table 14.2.4.6.
All Site 010 subjects are excluded from the analysis.
Abbreviations: ABR=annualized bleed rate; 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; RP-B=routine prophylaxis 25 IU/kg EOD; SD=standard deviation.

Secondary Efficacy Endpoints

Annualised Bleed Rate of High- Versus Low-Frequency Prophylaxis (RP Cohort)

Table 4 presents the summary statistics for the analysis of ABR for the RP cohort (ITT population). The 90% 2-sided CI for the mean difference in ABRs for the 2 prophylactic regimens demonstrated equivalence for subjects in the ITT population, that is, the limits of the 90% CI were wholly within the prospectively defined equivalence limit of (−3, 3) bleeds per year. Sensitivity analyses that estimated the treatment effect and its 95% 2-sided CI obtained from a mixed-effect model were supportive of the results of the equivalence CI results.

Table 3. Annualized Bleed Rate: Summary Statistics for the RP Cohort (Regimen A [45 IU/kg BIW] and Regimen B [25 IU/kg EOD]) (ITT Population)

Statistics	Annualized Bleed Rate[a] Regimen A (RP45) (Number of Bleeds = 106)	Regimen B (RP25) (Number of Bleeds = 75)	Difference[b]
Descriptive Statistics			
N	38	38	35
Mean (SD)	3.3 (5.3)	2.2 (4.1)	1.1 (3.8)
Min, Max	0.0, 24.6	0.0, 18.4	-10.8, 12.8
Median	1.1	1.0	0.0
Interquartile range	0.0, 4.4	0.0, 2.1	0.0, 2.2
90% CI[c]			0.03, 2.22

Source: CSR B1831001 Table 13.
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.
ABR = annualised bleeding rate; BIW = twice a week; CI = confidence interval; CSR = clinical study report; EOD = every other day; ITT = intent to treat; IU = international units; min = minimum; max = maximum; N = number of subjects with ABR data included for each regimen; OD = on-demand; RP = routine prophylaxis; RP25 = routine prophylaxis 25 IU/kg EOD; RP45 = routine prophylaxis 45 IU/kg BIW; SD = standard deviation.
a. ABR = number of bleeds/(days on regimen/365.25).
b. Difference = prophylaxis RP45 ABR minus prophylaxis RP25 ABR.
c. The 90% 2-sided CI for the mean difference in ABRs for the 2 prophylactic regimens for ITT subjects was constructed using the t distribution with n-1 degrees of freedom (n = number of subjects) to assess the equivalence of these 2 regimens. The CI was based on the paired t-test. The subjects must have had ABR data for both regimens to be included in the analyses.

Other Efficacy Endpoints

Number of Infusions Used to Treat Each Bleeding Episode (ITT Population)

A total of 838 OD infusions were administered to treat the 562 bleeding episodes with a unique start date and time. The majority of bleeding episodes (76.5%) resolved with 1 infusion.

Table 14. The Number of Infusions Needed to Treat Each Bleed (ITT Population)

Number of Infusions	Number (%) of Bleeds N=38 n (%)
1	430 (76.5)
2	88 (15.7)
3	20 (3.6)
4	7 (1.2)
>4	17 (3.0)
Total	562

Source: Table 14.2.3.3.
Note: Any infusions with study drug or non-study FVIII are included.
Abbreviations: FVIII=factor VIII; ITT=intent to treat; N=number of subjects experiencing bleeds.
All Site 010 subjects were excluded from the analysis.

Response to On-Demand Treatment for All Bleeding Episodes (ITT Population)

Of the 559 first infusions in 38 subjects for bleeding episodes that were treated initially with a FVIII OD infusion, 555 had responses recorded according to the 4-point OD Haemostasis Efficacy Rating Scale. Most bleeds treated (>90%) had "excellent" or "good" responses to the first infusion. The majority (>60%) of the 279 follow-up infusions (in 31 subjects) had "excellent" or "good" responses. Of 279 follow-up infusions, 20 had no response data recorded. All 20 of these were in 2 subjects and were infusions of non-study FVIII and therefore were not required to record a response.

Table 15. Response Assessment of On-Demand Treatment of Bleeds (ITT Population)

Response to Infusion, n (%)	First Infusion (N=38)	Follow-Up Infusions (N=31)	All Infusions (N=38)
Excellent	376 (67.3)	89 (31.9)	465 (55.5)
Good	150 (26.8)	106 (38.0)	256 (30.5)
Moderate	27 (4.8)	63 (22.6)	90 (10.7)
No Response	2 (0.4)	1 (0.4)	3 (0.4)
Data Not Recorded	4 (0.7)	20 (7.2)	24 (2.9)
Total (Any)	559	279	838

Source: Table 14.2.3.5.
All Site 010 subjects are excluded from the analysis.
Note: Any infusions with study drug or non-study FVIII were included.
Note: The total number of first infusions may not match total number of bleeds if a bleed was missing start date or dose information, or was treated initially with non-study FVIII.
Abbreviations: FVIII=factor VIII; ITT=intent to treat; n=number of bleeds; N=number of subjects receiving actual dose per infusion.

Incidence of Less Than Expected Therapeutic Effect (ITT Population)

There were no occurrences of LETE in the OD or recovery setting. In the prophylaxis setting, 7 subjects were identified as having spontaneous bleeding episodes within 48 hours after a regularly scheduled prophylaxis dose of study drug with no confounding factors (the criteria for LETE); 5 (9.8%) subjects had a bleeding episode during Regimen B, and 3 (7.1%) subjects had a bleeding episode during Regimen A (1 subject had a bleeding episode in both Regimen A and Regimen B).

Out of 561 bleeding episodes with a unique start date and time that were treated with study drug, no bleeds met LETE criteria in the OD setting since there were no bleeds that failed to have a response to 2 successive OD infusions; the observed incidence rate of LETE was 0.0%. Out of a total of 10,927 RP infusions, 18 bleeding episodes met the criteria for LETE in the prophylaxis setting, and the observed incidence rate of LETE was 0.16%. No occurrences of LETE low recovery were reported following infusion of study drug, and a similar outcome was observed for the EE population.

Table 16. Number of Subjects Reporting Less Than Expected Therapeutic Effect (ITT Population)

Population	On-Demand	Regimen B 25 IU/kg EOD	Regimen A 45 IU/kg BIW	Total
ITT Population, N	9	51	42	51
	n (%)	n (%)	n (%)	n (%)
LETE in Prophylaxis setting[a]	N/A	5 (9.8)	3 (7.1)	7 (13.7)
LETE in On-Demand setting[b]	0	0	0	0
Low Recovery	0	0	0	0

Source: Table 14.2.6.6.
All Site 010 subjects are excluded from the analysis.
Abbreviations: BIW=twice weekly; EOD=every other day; ITT=intent to treat; LETE=less than expected therapeutic effect; N= number of subjects; N/A=not applicable.
[a] Prophylaxis setting LETEs with no confounding factors.
[b] On-demand setting LETEs with no confounding factors.

Consumption of Moroctocog Alfa (AF-CC) (ITT Population)

The cumulative total number of RP infusions was 10,899 including 3533 during Regimen A and 7366 during Regimen B.

Number of Spontaneous Bleeds and Time to Spontaneous Bleeds During the Prophylaxis Period (ITT Population)

During Regimen A (45 IU/kg BIW), 4 subjects experienced a mean (± SD) of 1.3 ± 0.50 spontaneous bleeding episodes within 48 hours of a previous RP infusion. During Regimen B (25 IU/kg EOD), 6 subjects experienced a mean (± SD) of 1.3 ± 0.52 spontaneous bleeding episodes within 48 hours of a previous RP infusion. A similar outcome was also observed for the EE population.

Compliance to Prophylaxis Regimen

Most subjects received a total actual number of infusions within ± 20% of the expected number of infusions (98.0%) and had an actual mean exposure within ± 20% of the expected mean exposure (84.0%). Eight (8) subjects had an actual mean exposure that was not within ± 20% of the expected mean exposure (2 in the OD cohort and 6 in the RP cohort). In the OD cohort during RP regimen B (25 IU/kg EOD), 2 subjects received total doses which were outside their expected doses: 1 subject received a total dose of 3141.9 IU/kg which was below the expected dose of 4062.5 IU/kg and 1 subject (001504) received a total dose of 5243.6 IU/kg which was above the expected dose of 4287.5 IU/kg.

The number (%) of subjects requiring prophylaxis regimen escalation during protocol-defined prophylaxis is provided for the ITT and EE populations. In the ITT population, a total of 3 subjects (2 during Regimen A and 1 during Regimen B) required intensification of their protocol-defined prophylaxis regimen. Results were similar in the EE population.

Efficacy Conclusions

The estimate of the ABR for the OD cohort (ITT population) during the RP regimen (25 IU/kg EOD) was significantly lower than the estimate for the ABR for OD therapy using a linear mixed-effects model (mean ABRs [± SE] were 1.76 ± 0.798 and 47.02 ± 10.749, respectively; p = 0.0040). This result was supported by a paired t-test based on the within-subject change in ABR for the 8 subjects who were evaluated with both OD and RP dosing during the study (p = 0.0020) and a 1-sided 95% upper confidence bound of 0.08 for the ratio of the arithmetic means for ABR during the RP regimen over the ABR during OD therapy (a ratio of <0.5 indicates the ABR during the RP regimen was at least 50% lower than that observed during OD therapy). These results are similar and support the same conclusions for prophylaxis as in the second interim CSR.

For the OD cohort (ITT population), the majority of bleeding episodes during OD therapy were traumatic events. The mean (±SD) ABR for traumatic bleeds was lower during the RP-B (25 IU/kg EOD) regimen (0.8±1.3 [median: 0.0]) than for OD therapy (37.9±31.6 [median: 31.8]).

In the RP cohort, the 90% 2-sided CI for the mean difference in ABRs for the 2 prophylaxis regimens demonstrated equivalence for subjects in the ITT population (the limits of the 90% CI fell wholly within the prospectively defined equivalence limit of [-3, 3] bleeds per year).

Sensitivity analyses that estimated the treatment effect and its 95% 2-sided CI obtained from a mixed-effect model were supportive of the results of the equivalence CI results.

A total of 838 OD infusions were administered to treat the 562 bleeding episodes with a unique start date and time. The majority of bleeding episodes (76.5%) resolved with 1 infusion. Of the 559 first infusions in 38 subjects for bleeding episodes that were treated initially with a FVIII OD infusion, 555 had responses recorded according to the 4-point On-Demand Hemostasis Efficacy Rating Scale. Most bleeds treated with the first infusion (>90%) had "excellent" or "good" responses. The majority (>60%) of the 279 follow-up infusions (in 31 subjects) had "excellent" or "good" responses.

There were no occurrences of LETE in the OD or recovery setting. In the prophylaxis setting, 7 subjects were identified as having spontaneous bleeding episodes within 48 hours after a regularly scheduled prophylaxis dose of study drug with no confounding factors (the criteria for LETE); 5 (9.8%) subjects had a bleeding episode during Regimen B and 3 (7.1%) subjects had a bleeding episode during Regimen A (1 subject had a bleeding episode in both Regimen A and Regimen B). Eighteen (18) bleeding episodes met the criteria for LETE in the prophylaxis setting and the observed incidence rate of LETE was 0.16%.

The cumulative total number of RP infusions was 10899 including 3533 during Regimen A and 7366 during Regimen B (including both cohorts). Most subjects received a total actual number of infusions within ±20% of the expected number of infusions (98.0%) and had an actual mean exposure within ±20% of the expected mean exposure (84.0%).

SAFETY EVALUATION

All safety analyses were performed on the ITT analysis population; additionally AEs, laboratory data, and the incidence of inhibitor development were performed on the mITT population. Safety data were presented for all subjects (OD and RP) combined. Safety outcome measures included the incidence of serious adverse events (SAEs) and non-SAEs. Any subject who received at least 1 dose of moroctocog alfa (AF-CC) after the informed consent document/assent form had been signed was included in the evaluation for safety in the final CSR. Information was also collected on the development of FVIII inhibitors. Subject withdrawal for safety reasons was at the discretion of the investigator and treating physicians.

Extent of Exposure

Extent of study drug exposure for all subjects is presented below. Overall, the median number of infusions per subject was 262 and the median number of EDs per subject was 261.

Table 20. Moroctocog Alfa (AF-CC) Total Factor Consumption and Exposure Days (mITT Population)

Characteristic	RP		OD (N=9)	Total (N=51)
	AB (N=18)	BA (N=24)		
Number of Subjects (mITT)	18	24	8	50
Total units (IU/kg) per subject				
Cumulative total	2762708	4292109	1053093	8107910
Median	161701	193071	118413	155004
Mean (SD)	153484 (68554.5)	178838 (80197.2)	131637 (44809.2)	162158 (72472.5)
Min, Max	500, 310950	7917, 337808	98903, 239595	500, 337808
Range of Units (IU/kg), all doses				
Min, Max	253, 2020	151, 2100	253, 2004	151, 2100
Dose (IU/kg) per infusion[a]				
N (Number of Infusions)[b]	4174	5802	1846	11822
Median	27	29	25	27
Mean (SD)	33 (10.9)	34 (11.7)	26 (5.6)	32 (11.1)
Min, Max	14, 108	6, 92	11, 64	6, 108
Number of infusions per subject				
Cumulative total (Number of Infusions)[c]	4177	5830	1847	11854
Median	264	262	239	262
Mean (SD)	232 (83.1)	243 (69.9)	231 (32.0)	237 (69.8)
Min, Max	1, 303	21, 308	169, 269	1, 308
Exposure Days per subject				
Cumulative total (Number of Exposure Days)	4143	5786	1819	11748
Median	263	261	238	261
Mean (SD)	230 (82.8)	241 (69.5)	227 (35.1)	235 (69.7)
Min, Max	1, 301	19, 300	158, 263	1, 301
Interquartile Range	255, 269	254, 274	209, 253	238, 269

Source: [illegible]
All Site 010 subjects are excluded from the analysis.
[a]Dose (IU/kg) per infusion is not based on per subject but overall number of infusions and corresponding dose.
[b]Includes only the infusions for which the dose (IU/kg) value was not missing.
[c]Includes all infusions, including those for which the dose (IU/kg) value was missing.
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; BIW=twice weekly; EOD/QOD=every other day; Max=maximum; Min=minimum; mITT=modified intent to treat; N=number of subjects; OD=On-Demand followed by Regimen B; Regimen A=RP 45 IU/kg BIW; Regimen B=RP 25 IU/kg EOD; RP=routine prophylaxis; SD=standard deviation.

Brief Summary of Adverse Events

Table 21 presents an overview of TAEs during the study for the mITT population

Table 21. Overview of Adverse Events (mITT Population)

Category	Number of events [# AEs] and number of subjects experiencing events n (%) Total (N=50)
All treatment-emergent AEs	[578] 50 (100.0)
Treatment-emergent AEs excluding hemophilia events	[549] 49 (98.0)
Treatment-emergent AEs causing discontinuation excluding hemophilia events	[3] 3 (6.0)
Treatment-emergent hemophilia AEs	[29] 15 (30.0)
Treatment-emergent hemophilia AEs causing discontinuation	[1] 1 (2.0)
Serious AEs	[30] 15 (30.0)
Death	0

Source: Table 14.3.1.25a, Table 14.3.1.10, Table 14.3.1.16, Table 14.3.1.2, Table 14.3.1.8, Table 14.3.2.3, Table 14.3.2.1.
All Site 010 subjects are excluded from the analysis.
Abbreviations: AE=adverse event; mITT=modified intent to treat; N= number of subjects; n=number of events.

Treatment emergent events

A total of 49 (98.0%) subjects in the mITT population reported 549 non-haemophilia related TEAEs. The most commonly reported (≥50% of subjects) non-haemophilia related TEAEs by System Organ Class (SOC) were in the infections and infestations, general disorders and administration site conditions, injury, poisoning and procedural complications, and gastrointestinal disorders. The most commonly reported (>20%) preferred terms were pyrexia, upper respiratory tract infection, cough and nasopharyngitis.

A total of 15 (30.0%) subjects in the mITT population reported at least 1 TEAE related to haemophilia. The most commonly reported (>25% of subjects) haemophilia related TEAEs were in the Musculoskeletal and connective tissues disorders SOC and included the PTs of Pain in extremity and Haemarthrosis. Other treatment emergent haemophilia related events were each reported by ≤5% subjects. A total of 6 subjects experienced a drug related TEAE: 3 subjects had FVIII inhibition, 1 subject had aminotransferase increased, 1 subject had joint injury, and 1 subject had drug hypersensitivity and pyrexia.

The majority of TEAEs were of mild or moderate intensity and no life threatening TEAEs were reported. Mild and moderate TEAEs were most commonly reported in the Infections and infestations SOC. The most commonly reported (>20% of subjects) mild TEAEs were upper respiratory tract infection, pyrexia, and cough. The most commonly reported (>20% of subjects) moderate TEAE was pyrexia. Severe TEAEs were reported for 8 subjects and were distributed around SOCs; only 1 of the severe TEAEs was reported for >1 subject (FVIII inhibition, 2 subjects [4.0%]). The other severe TEAEs (PTs) were Varicella, Device related infection, Pyrexia, Catheter site rash, Post procedural haemorrhage, Haemarthrosis, Muscle spasms, Torticollis, Monoplegia, Seizure, Drug hypersensitivity and Haematoma.

Serious Adverse Events

A total of 15 (30.0%) subjects reported a total of 30 SAEs. With the exception of FVIII inhibition (4 [8.0%] subjects), each PT was experienced by ≤2 subjects. All 4 subjects (including the 1 subject with inhibitor detected pre-study treatment) with FVIII inhibition were discontinued from the study as PP. A further subject was discontinued due to drug hypersensitivity.

Table 4. Number (%) of Subjects Reporting Serious Adverse Events (Unrelated and Related to Haemophilia) (mITT Population)

System Organ Class[a] Preferred Term, [AEs] n (%)	Total (N = 50)
Any AEs	[30] 15 (30.0)
Musculoskeletal and connective tissue disorders	[7] 6 (12.0)
Haemarthrosis	[2] 2 (4.0)
Muscle haemorrhage	[2] 2 (4.0)
Arthralgia	[1] 1 (2.0)
Muscle spasms	[1] 1 (2.0)
Torticollis	[1] 1 (2.0)
Blood and lymphatic system disorders	[4] 4 (8.0)
Factor VIII inhibition	[4] 4 (8.0)
Infections and infestations	[7] 3 (6.0)
Device related infection	[6] 2 (4.0)
Tonsillitis	[1] 1 (2.0)
Injury, poisoning and procedural complications	[2] 2 (4.0)
Limb injury	[1] 1 (2.0)
Post procedural haemorrhage	[1] 1 (2.0)
Gastrointestinal disorders	[1] 1 (2.0)
Abdominal pain	[1] 1 (2.0)
General disorders and administration site conditions	[1] 1 (2.0)
Catheter site rash	[1] 1 (2.0)
Immune system disorders	[1] 1 (2.0)
Drug hypersensitivity	[1] 1 (2.0)
Nervous system disorders	[6] 1 (2.0)
Monoplegia	[1] 1 (2.0)
Seizure	[5] 1 (2.0)
Vascular disorders	[1] 1 (2.0)
Haematoma	[1] 1 (2.0)

Source: CSR B1831001 Table 25.
All Site 010 subjects are excluded from the analysis.
MedDRA version: 21.0.
AE = adverse event; CSR = clinical study report; MedDRA = Medical Dictionary for Regulatory Activities; mITT = modified intent to treat; n = number of subjects with AEs; N = number of subjects; SOC = System Organ Class.
a. SOC totals are not necessarily the sum of the individual AEs since a subject may have reported 2 or more different AEs in the same SOC. AEs are presented in descending order of the total population within SOC.

Factor VIII Inhibitor Development

Investigators reported all FVIII inhibitors in the same expedited manner as outlined for SAEs.

Subjects who developed a confirmed FVIII inhibitor on the study were to be withdrawn from the study after completion of the procedures described in the protocol. Of the 50 subjects exposed to moroctocog alfa (AF-CC), 4 subjects tested positive for FVIII inhibitors. All 4 subjects were withdrawn from the study and considered as SAEs. For 1 of the 4 subjects, the FVIII inhibitor event occurred prior to receiving his first dose of study drug and was assessed as unrelated to treatment. This subject had taken study drug for 19 EDs before the baseline results became available. He was excluded from the numerator and denominator for inhibitor development as the inhibitor was present prior to receiving study drug.

Of the 3 treatment-emergent, treatment-related FVIII inhibitor events (reported in subjects <6 years of age), based on the absence of any clinical signs or symptoms along with negative inhibitor testing at an additional laboratory, 2 were classified by the sponsor as false positive inhibitors. The third case reported a low titer, clinically silent FVIII inhibitor that resolved. Further details of the 3 reports of positive FVIII inhibitor results are described below:

- Subject wmale subject with severe haemophilia A (FVIII activity ≤1%) had previously received both OD FVIII therapy and a FVIII RP regimen for a total of 35 EDs prior to entering the study. This subject was assigned to the prophylaxis cohort and received moroctocog alfa (AF CC) 25 IU/kg EOD during the first 12 months, and then switched to 45 IU/kg BIW for the remainder of the study. Samples obtained during visit 3 (month 1) and visit 5 (month 3) reported positive values via central laboratory evaluation of 1.73 BU/mL and 0.89 BU/mL, respectively. Based on these results the patient was withdrawn from the study. A subsequent sample collected during the follow up visit and assayed at the central laboratory showed persistence of low titer FVIII inhibitors 1.58 BU/mL with subsequent sample collection reporting negative (<0.6 BU/mL) and resolution of event. There were no concomitant medications taken as a

consequence of the event and the subject did not experience any clinical manifestations associated with the FVIII inhibition. The investigator and the sponsor considered the event of FVIII inhibition to be related to moroctocog alfa (AF CC).

- Subject male subject with severe hemophilia A (FVIII activity ≤1%) had previously been treated with both OD FVIII therapy and a FVIII RP regimen for a total of 362 EDs prior to entering the study. This subject was assigned to 45 IU/kg BIW during the first 12 months, and then switched to 25 IU/kg EOD for the remainder of the study. A blood sample obtained during the visit 7 (month 6) reported positive (1.84 BU/mL). A subsequent blood sample collected during month 9 was reported as positive (3.20 BU/mL) through central laboratory evaluation, however, re-test of the sample reported negative (<0.6 BU/mL) for FVIII inhibitor. The negative result was similarly reported through sample analysis at a second laboratory. A further 4 samples collected over an approximately 4 month period were reported as negative (<0.6 BU/mL) through central laboratory evaluation. The subject did not experience any clinical manifestations of FVIII inhibitor. The prophylaxis dose was not increased, no LETE was identified and the recovery assessment was reported normal. In view of the totality of the data and clinical profile of the subject, the sponsor classified this as a "false positive" for FVIII inhibitor development.
- Subject male subject with severe haemophilia A (FVIII activity ≤1%) had previously been treated with a total of >50 EDs prior to receiving the first dose of moroctocog alfa (AF CC). This subject was assigned to the prophylaxis cohort and received moroctocog alfa (AF CC) 25 IU/kg EOD during the first 12 months, and then switched to 45 IU/kg BIW for the remainder of the study. A blood sample to test for FVIII inhibitors was obtained on Visit 5 (month 3) and reported as positive (1.61 BU/mL) and confirmed through sample re-test (2.11 BU/mL) via the central laboratory. The sample was re-analysed at a second laboratory and was reported negative (<0.6 BU/mL) as was the local laboratory result. Three (3) subsequent samples collected across a period of approximately 5 months reported negative through central and local laboratory testing. The investigator and the sponsor considered FVIII inhibition was related to moroctocog alfa (AF-CC). The subject did not experience any clinical manifestations of FVIII inhibitor. Indeed the prophylaxis dose was not increased, no LETE was identified, and the recovery assessment report was normal. In view of the totality of the data and clinical profile of the subject, the sponsor classified this event as a "false positive" for FVIII inhibitor development.

Vital Signs, Electrocardiogram, Physical Findings and Other Observations Related to Safety

No clinically significant findings were reported for any subject related to vital signs and based on physical examination at ED 1.

Safety Analyses Conclusions

Overall, the median number of infusions per subject was 262, and the median number of EDs per subject was 261.

No new safety signals were observed for moroctocog alfa (AF-CC) during the course of this study. The majority of TEAEs were of mild or moderate intensity, and no life threatening TEAEs were reported. Severe TEAEs were reported for 8 subjects. Serious TEAEs were reported for 15 (30.0%) subjects, of which 3 led to withdrawal due to FVIII inhibition and 1 subject withdrew due to a SAE of drug hypersensitivity. A further subject was withdrawn due to FVIII inhibitor that was detected pre-study treatment. No deaths were reported during the study.

Three (3) subjects had central laboratory confirmed inhibitor testing after beginning treatment with study drug. Based on an absence of any clinical signs and symptoms and negative results with repeat inhibitor assessment of the same samples in a different central laboratory, 2 of the 3 cases were classified by the sponsor as false positive inhibitors. The third case was a low titer, clinically silent FVIII inhibitor that resolved. A fourth subject had a positive result for low titer FVIII inhibitor prior to receiving study drug.

Overall, the safety profile exhibited in the study would support treatment with moroctocog alfa (AF-CC) in a haemophilia A paediatric population as being well tolerated with no new safety findings detected.

Discussion and overall conclusions by the MAH

The primary objective of this study was to demonstrate that moroctocog alfa (AF-CC) prophylaxis reduces the ABR relative to OD therapy in pediatric aged hemophilia A patients with baseline FVIII <2%. The secondary objectives were to assess the effect of a high (25 IU/kg EOD) versus low (45 IU/kg BIW)-frequency dosing schedule on the efficacy of moroctocog alfa (AF-CC) prophylaxis, to continue to characterize the PK of FVIII:C after administration of moroctocog alfa (AF-CC) in children □6 months to <16 years of age with hemophilia A, and to describe moroctocog alfa (AF-CC) efficacy and safety in children, including characterization of the incidence of LETE. From Protocol Amendment 10, enrollment into the PK assessment was optional and could also include children aged 6 to <16 years; before this date only children aged 6 months to <6 years were included in the study (for all assessments).

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. This result is consistent with prior studies with moroctocog alfa and moroctocog alfa (AF-CC) and shows for the first time this effect with moroctocog alfa (AF-CC) in a pediatric population. Additionally, 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. This is the first study to demonstrate that a longer interval between prophylactic infusions of moroctocog alfa (AF-CC) is as effective as more frequent dosing in a pediatric population. This offers patients with hemophilia A a treatment option requiring fewer infusions, thus reducing the disease burden, which could correlate to greater compliance and a better quality of life. This is especially beneficial for pediatric patients in whom IV access can be challenging. Response to OD infusions for the treatment of bleeding episodes was similar to that seen in prior studies with moroctocog alfa and moroctocog alfa (AF-CC) with the majority of bleeding episodes responding to 2 or fewer infusions. FVIII recovery was similar to that seen in prior studies with young pediatric patients treated with moroctocog alfa (AF-CC). Rates of LETE were similar to those seen in prior studies.

A PK analysis of FVIII activity data for 5 of the 7 subjects included in this study was reported in a previously completed interim analysis. However, the data were reanalyzed using current Pfizer processes and standards and the results were similar. Although Amendment 10 allowed children aged 6 to <16 years to be enrolled in the study, none participated in the PK assessment.

No new safety signals emerged from this study. TEAEs were representative for the pediatric population that was studied. One subject experienced drug hypersensitivity. The inhibitor rate was 6.12%; however, 2 of the 3 cases were deemed to be false positive. Overall, taking into consideration that 2 of the cases were assessed as false positive, the incidence and clinical significance of FVIII inhibition observed in this study is consistent with that seen in prior studies with PTPs with moroctocog alfa and moroctocog alfa (AF-CC).

Taken together, this study met its objectives and has shown that moroctocog alfa (AF-CC) is safe and efficacious in pediatric-aged subjects for both OD treatment and RP. Additionally, it has shown that RP

with moroctocog alfa (AF-CC) is statistically more efficacious than an OD treatment regimen. The study also has shown for the first time that BIW prophylaxis infusions with moroctocog alfa (AF-CC) are as efficacious as EOD prophylaxis infusions.

In conclusion the study demonstrated that moroctocog alfa (AF-CC) prophylaxis reduced ABRs relative to OD therapy, showed for the first time that BIW prophylaxis infusions with moroctocog alfa (AF-CC) were as efficacious as EOD prophylaxis infusions, and demonstrated the PK parameters observed in this study are similar to those observed in other studies of young patients (<6 years) with hemophilia A. The study showed that Moroctocog alfa (AF-CC) is safe and efficacious in pediatric patients for both OD therapy and RP.

3. Overall conclusion and recommendation by the Rapporteur

The MAH has submitted the final CSR for the completed paediatric study; 3082B2-313-WW (B1831001); an open label study to evaluate prophylaxis treatment, and to characterise the efficacy, safety and pharmacokinetics of B-domain deleted recombinant factor VIII albumin free in children with hemophilia A. The study was undertaken to fulfil a FDA commitment with the primary objective to compare annualised bleeding rate during on demand versus routine prophylaxis and the secondary objective to compare 2 regimens of prophylaxis with Xyntha, the US approved product. The difference between ReFacto AF and Xyntha is the analytical method used to calibrate the working potency standard that is used in the potency assay. The standard for Xyntha has been calibrated using a one-stage assay, and the standard for ReFacto AF has been calibrated using a chromogenic substrate assay. The two products are not interchangeable.

It may be agreed that the results data support its objectives and has shown that Xyntha is safe and efficacious in paediatric-aged subjects for both OD treatment and RP.

No new safety signals emerged from this study. TEAEs were representative for the paediatric population that was studied. The MAH plans to submit a type II variation Q1 2019 to update the ReFacto AF SmPC to include the safety data from this study once this Article 46 assessment has completed. The MAH will submit an RMP update as part of this type II variation, which will reflect the completion of studies 3082B2-313-WW (B1831001) and B1831007. This submission also fulfils MEA 116.

☒ **Fulfilled:**

Annex. Line listing of all the studies included in the development program

Clinical studies

Product Name: Xyntha Active substance: moroctocog alfa (AF-CC)

Study title	Study number	Date of completion	Date of submission of final study report
an open label study to evaluate prophylaxis treatment, and to characterise the efficacy,	3082B2-313-WW (B1831001);	18 April 2018	19 October 2018

safety and pharmacokinetics of B-domain deleted recombinant factor VIII albumin free in children with hemophilia A			