10 November 2016
EMA/800795/2016
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/P46/142

Note

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

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Introduction

On 18 August 2016, the MAH submitted a completed paediatric study B1831082 for Refacto AF, in accordance with Article 46 of Regulation (EC) No1901/2006, as amended.

A short critical expert overview has also been provided.

1. Scientific discussion

1.1. Information on the development program

The MAH stated that study B1831082; An Open-Label, Single Dose Pharmacokinetic Study of Xyntha Moroctocog alfa [AF-CC: Ibumin-Free Cell Culture], Recombinant Factor VIII) in Male Chinese Subjects with Hemophilia A is a stand-alone study.

This single-dose PK study in male Chinese subjects with haemophilia A has been conducted as a post-marketing commitment to the China Food and Drug Administration for FVIII activity data post Xyntha administration in Chinese subjects.

1.2. Information on the pharmaceutical formulation used in the study

The formulation already approved for the US and Asian market was used in this study.

1.3. Clinical aspects

1.3.1. Introduction

The MAH submitted the final report for:

- B1831082; An Open-Label, Single Dose Pharmacokinetic Study of Xyntha Moroctocog alfa [AF-CC: albumin-Free Cell Culture], Recombinant Factor VIII) in Male Chinese Subjects with Hemophilia A.

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.

Moroctocog alfa (AF-CC) marketed in the United States (US) and in selected regions of the world is identified by the brand name Xyntha. Moroctocog alfa (AF-CC) marketed in the European Union and in selected regions of the world is identified by the brand name of ReFacto AF.

The difference between Xyntha and ReFacto AF 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 a chromogenic substrate assay is used for ReFacto AF. The two products are not interchangeable.

1.3.2. Clinical study

B1831082; An Open-Label, Single Dose Pharmacokinetic Study of Xyntha Moroctocog alfa [AF-CC: Ibumin-Free Cell Culture], Recombinant Factor VIII) in Male Chinese Subjects with Hemophilia A

Description

This was a multicenter, open-label, single-dose study of Xyntha in 13 male Chinese subjects with hemophilia A who were ≥6 years old with severe haemophilia A (FVIII activity <1%) and previously treated with >150 exposure days to any FVIII containing products. The objective of this study was to characterize the single-dose PK profile of FVIII activity after administration of Xyntha in male Chinese subjects with hemophilia A. The sample size was based on the CFDA requirement for a PK study in Chinese subjects and to support the continued registration of Xyntha in China. This study is the first PK study of FVIII activity after moroctocog alfa (AF-CC) administration in Chinese subjects.

Subjects underwent screening evaluation within 28 days of Day 1 dosing. Day 0 was defined as the day prior to first day of dosing (Day 1). Each subject participated for up to 33 days; 28 days between the start of Screening and Day -1, Day 0, and then 4 days after dosing on Day 1.

The dosage form administered was the commercial product approved in China, which was a vial in 1x pack containing 500 international units (IU) powder for injection.

Subjects did not receive any FVIII products, including Xyntha, for at least 3 days (at least 72 hours) before the administration of Xyntha on Day 1. The treatment was a single 50 IU/kg dose of Xyntha administered by intravenous infusion over 10 minutes (note: the start and stop time of the infusion were to be recorded in the case report form [CRF]) on Day 1.

The first subject's first study visit was on 27 July 2015 and the last subject's last visit occurred on 28 August 2015.

The PK and safety results in these subjects are reviewed below. There were no efficacy data collected in this study.

Demographics

Demographic characteristics by age group are summarized in

Table 1. Of the 13 subjects enrolled, 3 subjects were in the study-defined age range of ≥6 and <12 years (thereafter referred to as "younger subjects") and 10 subjects were age ≥12 years (thereafter referred to as "older subjects"). However, it is important to note that 5 of the older subjects were in age categories ranging ≥12 years to 17 years old, yielding a total of 8 subjects under 18 years of age. All subjects were Chinese males. Subjects ranged in age from 6 to 60 years, and had a mean (standard deviation [SD]) body mass index (BMI) of 20.5 (4.6) kg/m^2 with a range of 15.0 to 26.5 kg/m^2. Mean weight was 54.1 (19.2) kg with a range of 23.5 to 84.0 kg. Mean height was 159.7 (19.6) cm with a range of 125 to 178 cm.

Table 1. Demographic Characteristics

Demographic Characteristics	All Subjects Male (N = 13)
Age (years)	
6-11	3
12-17	5
18-44	2
45-64	3
Mean (SD)	24.4 (19.6)
Range	6-60
Race (n)	
Asian	13
Weight (kg)	
Mean (SD)	54.1 (19.2)
Range	23.5-84.0
Body mass index (kg/m^2)[a]	
Mean (SD)	20.5 (4.6)
Range	15.0-26.5
Height (cm)	
Mean (SD)	159.7 (19.6)
Range	125-178

Source: Table 14.1.2 of Clinical Study Report.
Abbreviations: N/n = number of subjects, SD = standard deviation.
a. Body mass index was defined as weight (kg)/(height [cm] × $0.01)^2$.

Biopharmaceutics

Human citrated plasma samples (collected on Screening [Day -28 to Day -1], Day 0 through Day 4) were analyzed for FVIII activity and FVIII inhibitor (Screening, Day 0, and Day 4 only) using validated, sensitive, and specific analytical one-stage coagulation assays. There were no issues related to bioavailability identified that would impact efficacy and/or safety of Xyntha.

Clinical Pharmacology

FVIII PK parameters following 50 IU/kg doses were assessed in the 13 Chinese male subjects with haemophilia A, 3 of whom were younger subjects (≥6 and <12 years of age), and 10 older subjects (≥12 years of age). The PK results of both younger subjects and older subjects are presented.

Pharmacokinetic Analysis Methodology

On Day 1, subjects received the dose of Xyntha by intravenous infusion over 10 minutes. Blood samples were collected pre-dose (within 2 hours before administration) and at 0.25, 0.5, 1, 3, 6, 9, 24, 28, 32, 48 and 72 hours after the start of the infusion. Each sample volume was 2.7 mL and the total volume of blood collection for PK was about 32.4 mL.

The PK parameters, listed in Table 2, for FVIII activity, were calculated for each subject using non-compartmental analysis of plasma concentration-time data. Samples below the lower limit of quantification were set to 0 for analysis. Actual sample collection times were used for the PK analysis. The PK parameters were summarized descriptively by age group (≥6 to <12 years and ≥12 years).

Table 2. Pharmacokinetic Parameters Determined

Parameter	Definition	Method of Determination
AUC_{last}	Area under the plasma FVIII activity-time profile from time 0 to the time of the last quantifiable concentration (C_{last})	Linear/Log trapezoidal method
AUC_{inf}[a]	Area under the plasma FVIII activity-time profile from time 0 extrapolated to infinite time	AUC_{last} + (C_{last}*/k_{el}), where C_{last}* was the predicted plasma FVIII activity at the last quantifiable time point estimated from the log-linear regression analysis.
C_{max}	Maximum plasma FVIII activity	Observed directly from data
T_{max}	Time for C_{max}	Observed directly from data as time of first occurrence
k_{el}[a]	Terminal phase rate constant	Linear regression of the log-linear FVIII activity -time curve. Only those data points judged to describe the terminal log-linear decline were used in the regression.
t½[a]	Terminal elimination half-life	$Log_e(2)/k_{el}$
Incremental recovery	Increase in circulating FVIII activity for every IU of Xyntha administered per kg of body weight.	(C_{max} – C_0) / Dose, where C_0 was the baseline (pre-dose) circulating FVIII activity in IU/dL and dose in IU/kg body weight.
CL[a]	Clearance	Dose/AUC_{inf}
MRT[a]	Mean residence time	$AUMC_{inf}$/AUC_{inf}, where $AUMC_{inf}$ is the area under the first moment curve from time 0 extrapolated to infinite time, calculated using the linear/log trapezoidal method.
V_{ss}[a]	Steady state volume of distribution	CL × MRT

Source: Section 16.1.1 of Clinical Study Report.
Pharmacokinetic parameters were calculated using an internally validated software system, electronic non-compartmental analysis (eNCA, version 2.2.4).
Abbreviations: eNCA = electronic non-compartmental analysis, IU = International Unit, FVIII = factor VIII.
a. If data permitted (only where a well-characterized terminal phase was observed). A well-characterized terminal phase was defined as one with at least 3 data points, $r^2 \geq 0.9$, and the percent of area under the plasma FVIII activity-time profile from time 0 extrapolated to infinite time (AUC_{inf}), obtained by forward extrapolation (AUC_{extrap}%) ≤20% (See Section 9.5.4.3 of Clinical Study Report).

Safety Evaluations:

Safety evaluations were assessed by AE and SAE monitoring, clinical safety laboratory assessments, vital signs (blood pressure [BP], pulse rate, temperature), 12-lead electrocardiogram (ECG) monitoring, physical examination and monitoring of bleeding episodes and medically important events (inhibitor development and thrombogenicity).

Statistical Methods:

Pharmacokinetics: The PK concentration analysis population was defined as all subjects enrolled and treated who had at least 1 reported FVIII activity measure.

The PK parameter analysis population was defined as all subjects enrolled and treated who had at least 1 of the PK parameters of primary interest reported.

The PK parameters: maximum observed FVIII activity (Cmax), time for Cmax (Tmax), area under the plasma FVIII activity-time profile from time 0 to the time of the last quantifiable concentration (AUClast), area under the plasma FVIII activity-time profile from time 0 extrapolated to infinite time (AUCinf), steady-state volume of distribution (Vss), terminal phase rate constant (kel), terminal elimination half-life ($t_{½}$), mean residence time (MRT), system clearance (CL), and incremental recovery were summarized descriptively by age group. FVIII activity results were listed and summarized descriptively by PK sampling time.

Samples collected more than 20% earlier or later in time than the nominal time were not included in the summary. Individual subject, mean (± standard deviation [SD]) and median profiles of the FVIII activity-time data by age group were plotted in both linear and semi-log scales. For summary statistics and summary (mean and median) plots by sampling time, the nominal PK sampling time was used. For individual subject plots by time, the actual sampling time was used.

The PK parameters were summarized descriptively for all subjects and by age group (6 - <12 years and ≥12 years).

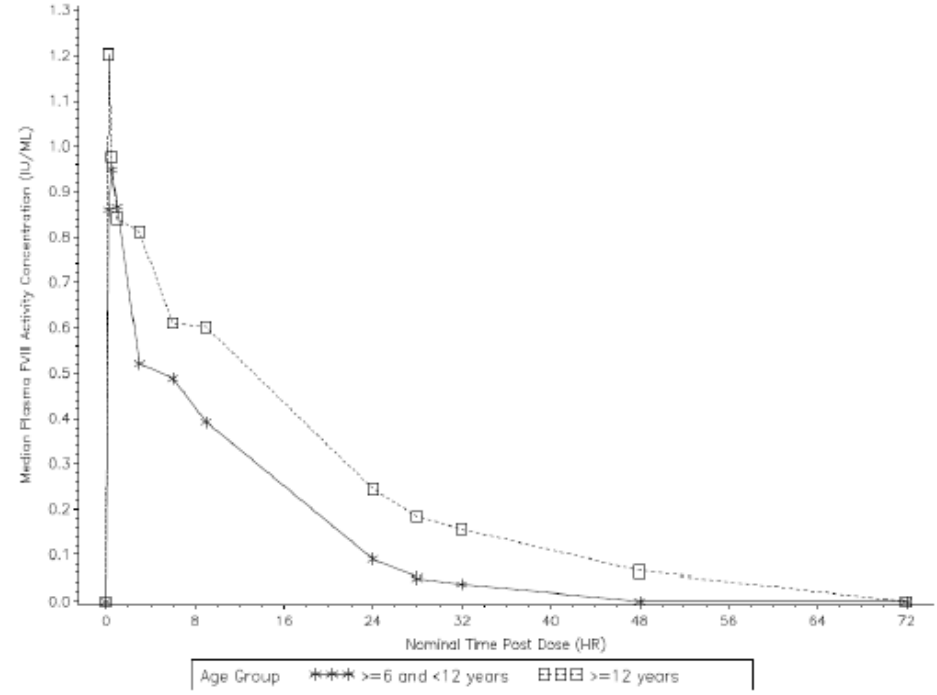
Safety: All subjects who received at least 1 dose of study medication were included in the safety analyses and listings. Safety evaluations were summarized descriptively in accordance with Pfizer's safety reporting standards.

RESULTS

Pharmacokinetic Results

Median and mean plasma concentration-time profiles for FVIII activity following a single dose of Xyntha 50 IU/kg are presented in Figure 1 and Figure 2.

Figure 1. Median Plasma FVIII Activity Concentration-Time Profiles by Age



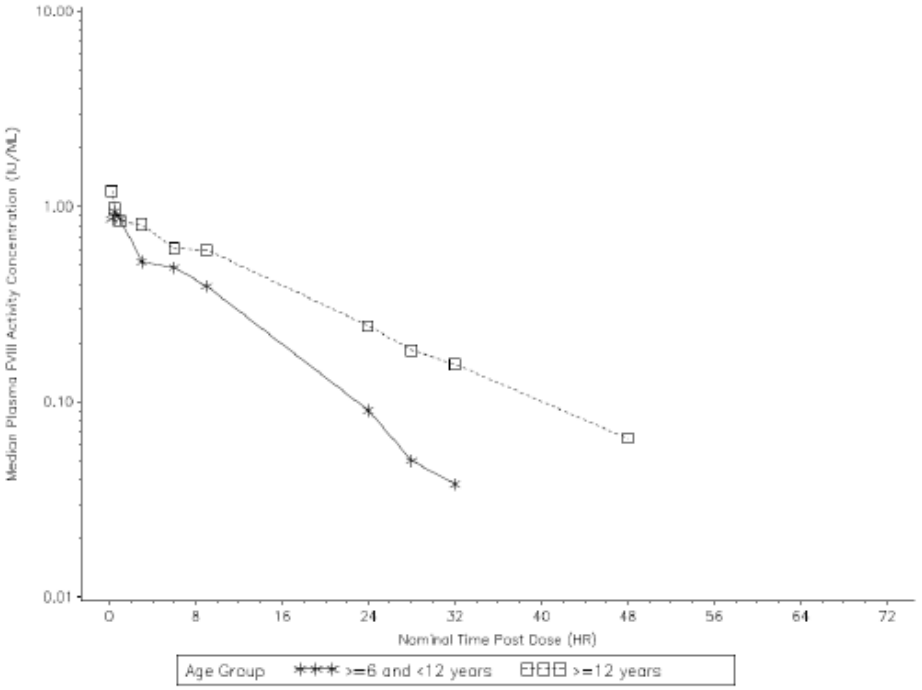
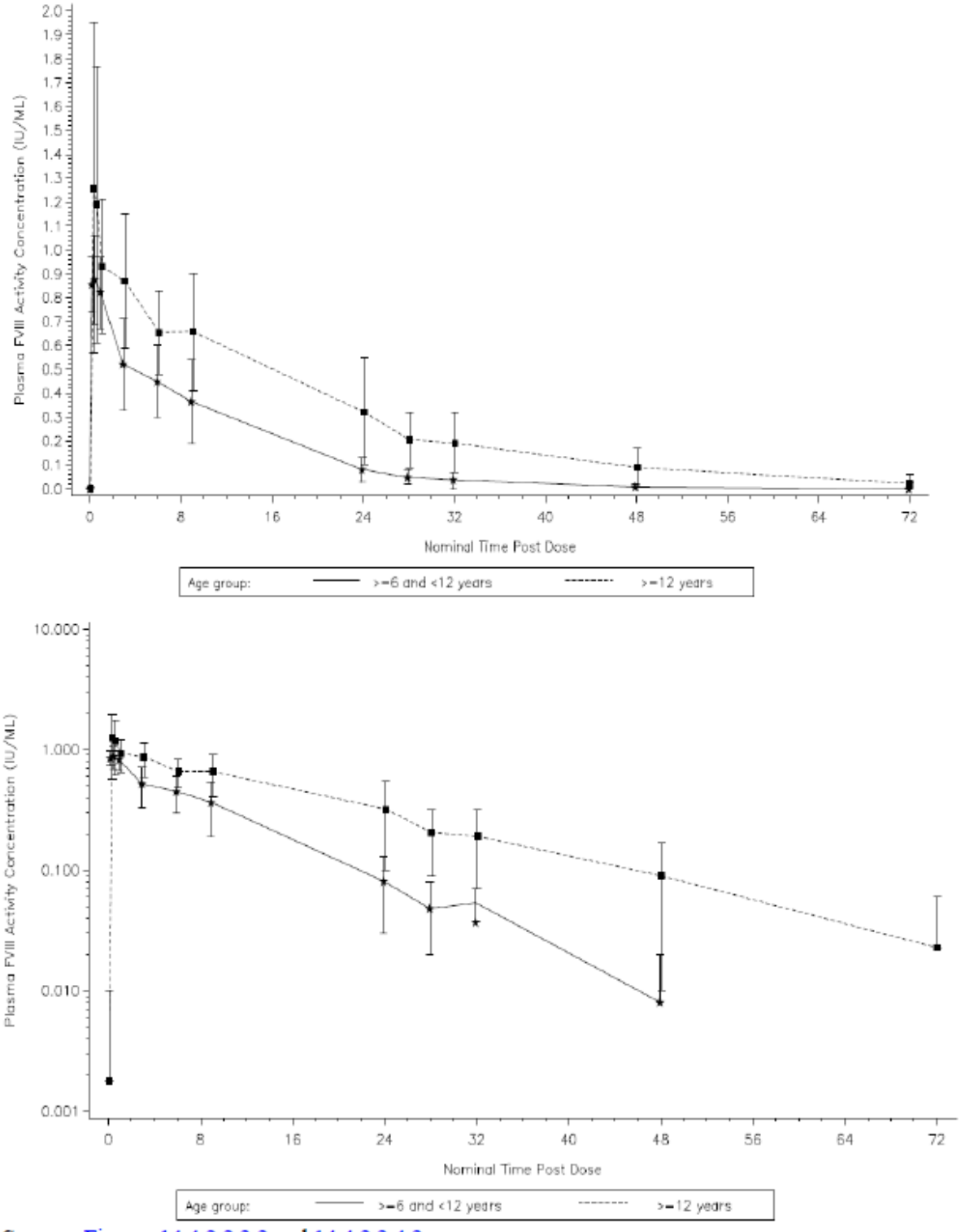


Figure 2. Mean Plasma FVIII Activity Concentration-Time Profiles by Age



Source: Figures 14.4.2.2.3.2 and 14.4.2.2.4.2

The PK parameter results are summarized descriptively in Table 3. Geometric mean AUC_{inf} was about 57% lower in the younger subjects (≥6 and <12 years) relative to the older subjects (≥12 years), while geometric mean C_{max} was 28% lower. Consistent with the lower exposures, CL was higher and t½ was shorter in younger subjects than those in older subjects. V_{ss} was higher in younger subjects compared to that in older subjects. Incremental recovery was lower in younger subjects compared to that in older subjects, with geometric mean values of 1.695 (IU/dL)/(IU/kg) and 2.498 (IU/dL)/(IU/kg) in younger subjects and older subjects, respectively.

Table 3. Descriptive Summary of Plasma FVIII Activity Pharmacokinetic Parameter Values

Parameters, units	Parameter Summary Statistics[a] by Age Group Xyntha 50 IU/kg		
	≥6 and <12 years	≥12 years	All Subjects
N	3	10	13
AUC_{inf}, IU•hr/mL	7.931 (50)	18.48 (41)	15.21 (58)
AUC_{last}, IU•hr/mL	7.702 (51)	17.51 (40)	14.49 (57)
C_{max}, IU/mL	0.8952 (18)	1.235 (47)	1.147 (44)
T_{max}, hr	0.250 (0.250 – 0.500)	0.500 (0.250 – 3.00)	0.500 (0.250 – 3.00)
k_{el}, 1/hr	0.09844 (24)	0.05215 (28)	0.06039 (39)
t½, hr	7.173 ± 1.77	13.76 ± 3.77	12.24 ± 4.42
MRT, hr	10.09 (27)	18.92 (26)	16.37 (38)
CL, mL/hr/kg	6.653 (30)	2.669 (38)	3.295 (56)
V_{ss}, mL/kg	67.18 (10)	50.53 (30)	53.96 (29)
Incremental recovery, (IU/dL)/(IU/kg)	1.695 (5)	2.498 (47)	2.284 (44)

Source: Tables 14.4.3.1.1 and 14.4.3.1.2 of Clinical Study Report.
Pharmacokinetic parameters are defined in Table 2.
Abbreviations: %CV = percent coefficient of variation, FVIII = Factor VIII, hr = hour(s), IU = International Unit, N = number of subjects contributing to the summary statistics, SD = standard deviation.
a. Geometric mean (%CV) for all except median (range) for T_{max} and arithmetic mean ±SD for $t_{½}$.

Efficacy

There were no efficacy evaluations performed in this study.

Safety

Safety was assessed on all subjects who received at least 1 dose of Xyntha 50 IU/kg during the study through last subject visit and included adverse events (AEs), serious adverse events (SAEs), laboratory evaluations, physical examinations, and vital signs. Any clinical laboratory, electrocardiogram (ECG), blood pressure, and pulse rate abnormalities of potential clinical concern were to be described.

Safety Methodology

The investigator obtained and recorded on the CRF all observed or volunteered AEs, the severity (mild, moderate, or severe) of the events, and the investigator's opinion of the relationship to the study treatment. Adverse events included adverse drug reactions, illnesses with onset during the study, and exacerbation of previous illnesses. Additionally, the investigator recorded as AEs any clinically significant changes in physical examination findings and abnormal objective test findings (eg, ECG, laboratory).

For all AEs, the investigator pursued and obtained information adequate both to determine the outcome of the AE and to assess whether it met the criteria for classification as an SAE.

Safety Results

A summary of all-causality treatment emergent adverse events (TEAE) and treatment-related AEs is provided in Table 4. All 13 treated subjects were evaluated for AEs. Overall, 4 of the 13 subjects experienced 4 TEAEs after a single dose of Xyntha 50 IU/kg administration (2 subjects [≥18 years of age] and 2 subjects [<18 years of age]). All TEAEs were treatment-related. There were no deaths, severe AEs, or permanent discontinuations due to TEAEs reported in this study. Two subjects (6 and 15 years old) reported SAEs (FVIII inhibition).

Table 4. Treatment-Emergent Adverse Events: All Causalities (Treatment-Related)

	Xyntha 50 IU/kg
	Number of Subjects All Causality (Treatment-Related)
Subjects evaluable for AEs	13
Number of AEs	4 (4)
Subjects with AEs	4 (4)
Subjects with SAEs	2 (2)
Subjects with severe AEs	0 (0)
Subjects discontinued due to AEs	0 (0)
Subjects with dose reduced or temporary discontinuation due to AEs	0 (0)

Source: Tables 14.3.1.2.1 and 14.3.1.3.1 of the Clinical Study Report.
Included all data collected since the first dose of study drug.
Except for the number of AEs, subjects were counted only once per treatment in each row.
SAEs were classified according to the investigator's assessment.
Severity counts were based on the maximum severity or grade of events.
MedDRA (Version 18.1) coding dictionary applied.
Abbreviations: AE = adverse event, IU = International Unit, MedDRA = Medical Dictionary for Regulatory Activities, SAE = serious adverse event.

A summary of all causalities and treatment-related TEAEs listed by System Organ Class and Medical Dictionary for Regulatory Activities (MedDRA) preferred term is listed in Table 5. These 4 TEAEs (2 events of FVIII inhibitions, 1 event of abdominal pain, and 1 event of headache) were reported as treatment-related and all were assessed by the investigator as being mild in severity.

Table 5. Incidence of Treatment-Emergent Adverse Events: All Causality (Treatment-Related)

Number of Subjects with AEs by: System Organ Class and MedDRA (version 18.1) Preferred Term	Xyntha 50 IU/kg (n = 13)
Blood and lymphatic system disorders	2 (2)
Factor VIII inhibition	2 (2)
Gastrointestinal disorders	1 (1)
Abdominal pain	1 (1)
Nervous system disorders	1 (1)
Headache	1 (1)
Total preferred term events	4 (4)

Source: Tables 14.3.1.2.2 and 14.3.1.3.2 of the Clinical Study Report.
Included all data collected since the first dose of study drug.
MedDRA (version 18.1) coding dictionary applied.
Abbreviations: AE = adverse event, IU = International Unit, MedDRA = Medical Dictionary for Regulatory Activities, n = number of subjects evaluable for adverse events.

Two subjects (6 and 15 years old) presented with FVIII inhibition and, as FVIII inhibition is medically important, these were reported as SAEs. For these two subjects, Day 4/last visit FVIII inhibitor was reported as positive by the central laboratory (0.7044 and 0.9840 Bethesda Unit (BU)/mL, respectively [negative <0.6 BU/mL]). As part of the routine follow-up, further FVIII inhibitor testing was carried out and results were negative for both subjects. These events were assessed by the investigator as being mild in severity. Both subjects did not experience any clinical manifestation of FVIII inhibitors and did not receive specific treatment for these events of transient, low-titre FVIII inhibitor.

Benefits and Risks Conclusions

Subjects aged 6 to <12 years have a lower exposure (AUC_{inf}, AUC_{last} and C_{max}), larger volumes of distribution, lower recovery, higher CL, and shorter $t_{½}$ compared with older subjects. Low titer, transient, positive FVIII inhibitor results occurred once in 2 subjects; these were considered as SAEs but neither was associated with clinical signs or symptoms.

Administration of a single dose of Xyntha 50 IU/kg by intravenous infusion is considered safe and well tolerated in this study.

Based on the PK and safety results for younger and older subjects in this study, the overall benefit-risk profile of Xyntha 50 IU/kg remains favourable for younger and older subjects. The PK parameters observed in this study of Chinese subjects are similar to those observed in other studies.

Conclusions:

The overall conclusion of the MAH is endorsed.

The MAH has submitted the final report for study B1831082; An Open-Label, Single Dose Pharmacokinetic Study of Xyntha Moroctocog alfa [AF-CC: albumin-Free Cell Culture], Recombinant Factor VIII) in Male Chinese Subjects with Hemophilia A. This is a study using the Xyntha product, a moroctocog alfa (AF-CC) product marketed in the United States (US) and in selected regions of the world. Moroctocog alfa (AF-CC) marketed in the European Union and in selected regions of the world is identified by the brand name of ReFacto AF.

The difference between Xyntha and ReFacto AF 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 a chromogenic substrate assay is used for ReFacto AF. The two products are not interchangeable.

The PK parameters observed in this study of Chinese subjects are similar to those observed in other studies. The study of Chinese subjects, showed a geometric mean of AUCinf, AUClast and Cmax 7.931 IU·hr/mL, 7.702 IU·hr/mL and 0.8952 IU/mL, respectively in the subjects ≥6 and <12 years. Geometric mean of Vss was 67.18 mL/kg, incremental recovery was 1.695 (IU/dL)/(IU/kg), and CL was 6.653 mL/hr/kg. Mean $t_{½}$ was 7.173 hours. In subjects aged ≥12 years, geometric mean of AUCinf, AUClast and Cmax were 18.48 IU·hr/mL, 17.51 IU·hr/mL and 1.235 IU/mL, respectively. Geometric mean of Vss was 50.53 mL/kg, incremental recovery was 2.498 (IU/dL)/(IU/kg), and CL was 2.669 mL/hr/kg. Mean $t_{½}$ was 13.76 hours. Children aged 6 to <12 years have lower exposure (AUCinf, AUClast and Cmax), larger volumes of distribution, lower recovery, higher CL, and shorter $t_{½}$ compared with older children and adults.

The administration of a single dose of Xyntha 50 IU/kg by intravenous infusion was considered to be safe and well tolerated in this study. Low titer, transient, positive FVIII inhibitor results occurred once

in 2 subjects; these were considered as SAEs. Neither of these was associated with clinical signs or symptoms.

The submission of this study do not have any impact on the overall benefit risk of Refacto AF, nor any impact on the already approved SmPC for Refacto AF.

2. Rapporteur's overall conclusion and recommendation

☒ **Fulfilled:**

No regulatory action required.

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

The studies should be listed by chronological date of completion:

Clinical studies

Product Name: Active substance:

Study title	Study number	Date of completion	Date of submission of final study report
An Open-Label, Single Dose Pharmacokinetic Study of Xyntha (Moroctocog alfa (AF-CC), Recombinant Factor VIII) in Male Chinese Subjects With Hemophilia A.	B1831082	28 August 2015	18 August 2016