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ReFacto AF

(Moroctocog Alfa)

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

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

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## Introduction

The MAH has in accordance with article 46 of the paediatric regulation 1901/2006 submitted the study "An evaluation of the Safety and Efficacy of On-demand Treatment with Xyntha (B-Domain Deleted Recombinant Factor VIII, Albumin Free) in Chinese Subjects with Hemophilia A (Study 3082B2-3316)"

## Summary of Study and Results

This open-label trial included assessments of safety, clinical efficacy and Factor VIII (FVIII) recovery in Chinese subjects with hemophilia A.

#### Methods

Subjects received on-demand treatments with Xyntha over a 6-month period. The subjects' response to treatment of bleeding episodes with Xyntha was evaluated by the Investigator using a 4-point rating scale (Excellent=1, Good=2, Moderate=3 and No response=4). The number of infusions required to resolve bleeding episodes were also collected. FVIII recovery was assessed by determining the FVIII concentration (FVIII: C) levels in individual subjects. Safety was assessed by the incidence of adverse events (AEs) and the incidence of FVIII inhibitors. Subjects who discontinued Xyntha therapy for clinical reasons during the active phase of the study were followed for safety for the duration of their planned participation in the study (i.e. until the Follow-up call or visit, which occurred 30 days after the completion of the 6 months on-demand period).

Subjects aged 6 years or older, with 1 or more prior exposure days (ED) to FVIII replacement products, who met all the inclusion and none of the exclusion criteria and were not currently utilizing FVIII prophylaxis were eligible to participate in the trial. A post-hoc analysis of the data from the paediatric subjects enrolled in the study was performed. (i.e. 16 out of 51)

Main inclusion criteria

1. Subjects  $\geq$ 6 years of age with mild, moderate or severe hemophilia A (FVIII activity: >5%, 1-5%, or <1%, respectively)

2. Subjects with previous exposure to FVIII replacement therapy

3. If HIV positive, documented CD4 count >200/ $\mu$ L within 6 months (calendar day) of study entry

Main exclusion criterias

1. Diagnosed with any bleeding disorder in addition to hemophilia A

2. Current FVIII inhibitor or history of FVIII inhibitor (defined as positive result of the reporting laboratory)

3. Subject has no history of exposure to FVIII products (previously untreated patient [PUP])

4. Subject is currently utilizing primary FVIII prophylaxis

5. Subjects anticipating elective surgery that may be planned to occur in the 6 months following study entry

6. Treated with immunomodulatory therapy within 30 days prior to study entry or planned use for the duration of their study participation

7. Participated in another investigational drug or device study within 30 days prior to study entry or planned participation for the duration of their study participation

8. Subjects with a known hypersensitivity to hamster protein

9. Significant hepatic or renal impairment (ALT and AST >5 x ULN, bilirubin >2 mg/dL or serum creatinine >1.25 x ULN)

- 10. Prothrombin Time >1.5 x ULN
- 11. Platelet count <80,000 / μL
- 12. Pregnant or breastfeeding women

The primary objective of this study was to describe the safety and clinical efficacy of Xyntha in previously treated Chinese subjects with haemophilia A. The secondary objective of this study was to describe FVIII recovery after exposure to Xyntha in previously treated Chinese subjects with haemophilia A.

Blood samples were collected from each subject (approximately 60 ml) at scheduled visits. The precise number of visits required varied from subject to subject and was determined by the frequency of bleeds requiring on-demand treatment.

Overall 55 subjects were screened, 53 of these subjects were enrolled in the study and 49 subjects completed the final evaluation.

The primary efficacy endpoint was the Investigator Haemostatic Efficacy assessment in subjects who received at least one dose of Xyntha. All efficacy results were analyzed using both the full analysis set (FAS N=51) and per protocol set (PPS N=47) populations.

#### Results

A post-hoc analysis of the data from the paediatric subjects enrolled in the study was performed which is presented below. The paediatric population of the study was comprised of 18 subjects at the screening phase, out of which 16 subjects reached the on-demand/active phase and 14 subjects completed the final recovery phase. The prior FVIII product ED history was identified for subjects as either > 100 EDs or  $\leq$  100 EDs with the majority of subjects having < 100 EDs, 12 and 10 respectively for subjects reaching the on-demand/active and final recovery phases.

The mean score of Haemostatic Efficacy assessment for pediatric population in FAS was  $1.80\pm0.65$  at 8 hours and  $1.74\pm0.59$  at 24 hours post-infusion. In the PPS population the mean score of Haemostatic Efficacy assessment for paediatric population was  $1.72\pm0.60$  at 8 hours and  $1.69\pm0.58$  at 24 hours post-infusion. All assessments of Haemostatic Efficacy in the FAS and PPS populations at 8 and 24 hours post-infusion were rated as good or excellent by the investigator.

A comparison of the Haemostatic Efficacy assessment of all subjects and paediatric subjects is shown in Table 1. No difference was noted between the results of the Haemostatic Efficacy assessment in the paediatric study population subset and the combined adult and paediatric study population.

	All Subjects				Pediatric Subjects only			
	8 hours post-		24 hours post-		8 hours post-		24 hours post-	
	infusion		infusion		infusion		infusion	
Score of Hemostatic Efficacy	FAS (n=51)	PPS (n=47)	FAS (n=51)	PPS (n=47)	FAS (n=16)	PPS (n=14)	FAS (n=16)	PPS (n=14)
Mean ±SD	1.86±0.	1.80±0.	1.74±0.	1.70±0.5	1.80±0.	1.72±0.	1.74±0.	1.69±0.
	65	62	61	9	65	60	59	58

 Table 1.
 Description of Investigator Haemostatic Efficacy Assessment

Excellent = 1, Good = 2, Moderate = 3, No response = 4

For the secondary endpoint "Mean frequency and dose of Xyntha infusions per haemorrhage" the mean frequency and dose (IU) of Xyntha infusions per hemorrhagic incidence was 1.16 infusions (1018.94

IU) and 1.16 infusions (1064.22 IU) for FAS and PPS paediatric populations respectively (see Table 2 for mean frequency in all subjects compared with paediatric population). No difference was noted between the results for the above mentioned parameters in the paediatric study population subset and the combined adult and paediatric study population.

	All Subjects		Pediatric Subjects only			
	Mean ±SD		Mean ±SD			
	FAS	PPS	FAS	PPS		
	(n=51)	(n=47)	(n=16)	(n=14)		
Infusion/bleed	$1.16 \pm 0.72$	1.13 ±0.56	1.16 ±0.69	1.16 ±0.73		
Dose/bleed (IU)	1226.28 ±1208.49	1188.66 ±944.58	1018.94 ±1160.61	1064.22 ±1230.33		
Exposure days/bleed	1.14 ±0.68	1.12 ±0.54	1.15 ±0.68	1.16 ±0.71		

#### Table 2.Description of treatment frequency and dose

For the secondary endpoint FVIII incremental recovery no analysis in the paediatric subset has been presented. For the full population the following results are presented:

FVIII recovery was assessed by evaluating FVIII:C after initial exposure and again following 6 months of repeated exposures to Xyntha. Incremental FVIII recovery values were calculated from the change before (pre) infusion at time 0 and at 30 min (5 minutes) after the start of infusion, and were analyzed by paired t-test.

In the FAS population, the average (  $\pm$ SD) recovery of FVIII activity at visits 2 and 4 are 1.77 $\pm$ 0.50 IU/dL per IU/kg and 1.67 $\pm$ 0.45 IU/dL per IU/kg, respectively. There was no significant difference between the 2 visits for the change of recovery (p>0.05). (Table 3)

In the PPS population, the average ( $\pm$  SD recovery of FVIII activity at visits 2 and 4 are 1.79 $\pm$ 0.50 IU/dL per IU/kg and 1.66 $\pm$ 0.45 IU/dL per IU/kg, respectively. There was no significant difference between the 2 visits for the change of recovery (p>0.05). (Table 3)

# Table 3 Description of FVIII incremental recovery (IU/dL per IU/kg) and change from baseline

		Median					
			$Mean\pmStd$	IU/dL per	Min, Max		
		N (missing)	IU/dL per IU/kg	IU/kg	IU/dL per IU/kg	р	t
FAS	Visit2	44 (7)	1.77±0.50	1.68	0.98,3.11		
	Visit4	43 (8)	1.67±0.45	1.61	0.81,2.96		

	Change	42 (9)	$-0.11 \pm 0.45$	-0.18	-1.12,0.74	0.120	-1.589
PPS	Visit2	41 (6)	1.79±0.50	1.70	0.98,3.11		
	Visit4	42 (5)	$1.66 {\pm} 0.45$	1.60	0.81,2.96		
	Change	41 (6)	-0.12±0.45	-0.19	-1.12,0.74	0.084	-1.771

Note: [1]Recovery= (FVIII activity after treatment - FVIII activity before treatment) / ( dose / weight )

[2]Subjects (IDs: 001, 010, 030, 069, 081, 086, 107) with positive inhibitor were not included into the

incremental recovery analysis

The safety variables included adverse events (AEs) occurring from the time informed consent was obtained until 30 days after the completion of 6 months on-demand period. Overall, during this study, there were 19 subjects with 31 treatment-emergent adverse events (TEAEs); 10 of these TEAEs occurred in 8 subjects and were considered related to the study drug by the Principal Investigator. Nine (9) subjects reported 11 serious adverse events (SAEs); 8 of these SAEs occurred in 7 subjects and were considered related to the Principal Investigator.

In the paediatric subset there were 14 AEs and 1 SAE reported. The SAE was a FVIII inhibitor that occurred during the screening period of the study. This subject did not receive Xyntha was and thus the SAE was considered unrelated to study drug by the investigator and he was excluded from study participation. Two (2) out of the 14 AEs, 2 occurrences of hypersensitivity in the same subject, were considered related to the study drug by the investigator. These events were considered mild by the investigator and required no treatment. Eight (8) of the AEs in the paediatric subjects were mild, 4 were moderate and 2 were considered severe. Both severe AEs, injury and FVIII inhibitor (during screening and described above) were considered unrelated by the investigator.

The incidence of FVIII inhibitor, was defined as any result determined as positive at a local laboratory (if done), and confirmed by testing of a concurrent aliquot at a central laboratory. There were no treatment-emergent events of FVIII inhibitor development in the paediatric population of this study. One subject had a positive FVIII inhibitor result that was detected during the screening period. This subject did not receive Xyntha and was excluded from participation in the study. No events of thrombosis or Less than Expected Therapeutic Effect (LETE) were reported.

Overall, the results of the safety data from the paediatric subset in study 3082B2-3316 were consistent with the known safety profile for Xyntha.

### **Conclusions of the MAH**

This study showed that the safety and efficacy of Xyntha in the paediatric population was acceptable and similar to the results of the overall study analysis and consistent with the information in the product labeling for Xyntha. There were no reports of LETE in paediatric subjects in this study. There were no treatment emergent FVIII inhibitors reported. No new safety findings were observed in this study.

## **Conclusion of the Rapporteur**

The MAH has submitted the results from an open label study in Chinese subjects > 6 years of age assessing safety, clinical efficacy, and FVIII recovery in Chinese subjects with haemophilia A. Subjects received on-demand treatments with Refacto Xyntha (i.e. the Refacto version approved also in US) over a 6-month period. The post hoc analysis performed in the paediatric part of the included subjects (16 out of 51) showed that the results seen in this Asian population is in line with what has formed the basis of the approval of Refacto AF in EU; study 310, which did not include Asian subjects.

The current approved SmPC in EU already reflects the data seen from the 310 study. The overall conclusion of the MAH is endorsed. None of the data submitted have implications for the overall benefit risk of the product.