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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

Moroctocog alfa (AF-CC), marketed under the trade names Xyntha in the United States and ReFacto AF in Europe, is a recombinant factor VIII (FVIII) product for use in the treatment of subjects with hemophilia A (congenital FVIII deficiency). It is produced using a modification of the previous process used for manufacture of its predecessor product (ReFacto) that eliminates the addition of all human- and animal-derived proteins.

The MAH has in accordance with article 46 of the paediatric regulation 1901/2006 submitted the study 3082B2-4418 (B1831003).

For the purpose of post-authorization safety surveillance, this study monitored development of clinically relevant and laboratory-confirmed inhibitors in a population of subjects with hemophilia A, who after consultation with their physician, chose to be treated with Xyntha independent of this study. The study was discontinued because the Sponsor has ongoing studies collecting similar safety data.

Study 3082B2-4418 (B1831003)

This was a nonrandomized, single treatment and prospective open-label study to evaluate the overall safety of Xyntha in subjects transitioning from ReFacto or other FVIII replacement products to Xyntha in usual care settings. Although the original protocol was designed to include only subjects transitioning from ReFacto or other FVIII, Amendment 3 allowed enrollment of subjects who had more than 5 EDs to Xyntha prior to enrollment. The study was conducted at 1 center in New Zealand and 4 centers in the United States.

The study had both observational and active safety surveillance components for assessment. During the active safety surveillance phase, FVIII inhibitor and FVIII recovery studies were performed at each visit. For the observational safety surveillance phase, subjects were treated under standard care with Xyntha at a dose and frequency prescribed by the treating physician, for up to 2 years. No efficacy data was collected.

Only previously treated male subjects, 12 years of age and older, with >150 EDs to any recombinant or plasma-derived FVIII products were eligible to enroll, as per the recommendations from regulatory authorities and scientific advisory committees for the evaluation of FVIII inhibitor development.

The primary objective of this study was to evaluate FVIII inhibitor development, defined as an inhibitor titer of ≥0.6 Bethesda Unit (BU) using the Nijmegen modification of the Bethesda assay and confirmed by the central laboratory, in subjects treated with Xyntha in usual use.

The secondary objective of this study was to evaluate the overall safety of Xyntha in this subject population.

Safety was assessed through the collection of nonserious adverse events (AEs) and serious adverse events (SAEs) as well as the incidence of less-than-expected therapeutic effect (LETE). Events of special circumstances (eg, inhibitor development and LETE) were reported in the same time frame as SAEs.

Overview of Safety results

Twelve (12) of the 14 subjects who signed informed consent were enrolled and treated with Xyntha. All subjects were male. Ages ranged from 13 to 56 years; 3 subjects were aged less than 18 years (ie, 13, 14, and 15 years). Three (25%) subjects (1 pediatric) completed the study before the study was discontinued by the Sponsor; 8 (67%) subjects did not complete because of the study closure and 1 subject (aged 14 years) withdrew at his own request.

Table S2. Summary of Subject Disposition

Subject Disposition	Number of Subjects (n, %)
Signed informed consent	14
Enrolled	12
Screening failure	2
Treated	12 (100%)
Ongoing	0 (0.0)
Study completed	3 (25.0)
Discontinued	9 (75.0)

n = Number of subjects
Source: Table 14.1.1.1

For the 12 subjects included in this report, the treatment regimen was on demand for 6 subjects (including 1 pediatric subject), primary prophylaxis for 3 subjects (including 2 pediatric subjects), secondary prophylaxis for 2 subjects, and preventive regimen for 1 subject. The cumulative total exposure for the 12 subjects was 1097 EDs (mean 91, median 71, range 16 to 342 days). Exposure for pediatric subjects was 18, 48, and 342 EDs.

Overall, 9 (75.0%) subjects had at least 1 treatment-emergent adverse event (TEAE) during the study. The system organ classes with the most frequently reported TEAEs were gastrointestinal disorders (58.3% subjects); injury, poisoning and procedural complications (50.0% subjects); infections and infestations (33.3% subjects); musculoskeletal and connective tissue disorders (33.3% subjects); and general disorders and administration site (25.0% subjects).

Table S7. Summary of Treatment Emergent Adverse Events by System Organ Class

System Organ Class	Number (%) of Subjects[a]	Number of Events
Any adverse events	9 (75.0)	53
Cardiac disorders	1 (8.3)	2
Congenital, familial and genetic disorders	1 (8.3)	1
Ear and labyrinth disorders	1 (8.3)	1
Gastrointestinal disorders	7 (58.3)	11
General disorders and administration site conditions	3 (25.0)	3
Hepatobiliary disorders	1 (8.3)	1
Infections and infestations	4 (33.3)	6
Injury, poisoning and procedural complications	6 (50.0)	7
Investigations	1 (8.3)	1
Musculoskeletal and connective tissue disorders	4 (33.3)	12
Renal and urinary disorders	2 (16.7)	2
Reproductive system and breast disorders	1 (8.3)	3
Skin and subcutaneous tissue disorders	2 (16.7)	2
Vascular disorders	1 (8.3)	1

[a] Number of subjects who reported at least 1 treatment-emergent adverse event.
Source: Table 14.3.1.3.1

The most frequently reported TEAEs were arthralgia and nausea (each in 3 [25.0%] subjects); and vomiting (2 [16.7%] subjects). The majority of TEAEs were mild or moderate in severity. TEAEs considered to be severe were reported for 4 subjects. None of the AEs led to a subject's withdrawal from the study.

Two (2) subjects each had an SAE: one case of therapeutic response decreased (LETE) was moderate in severity and was the only TEAE in the study that was considered to be treatment related; a case of tooth impacted was considered to be severe. Both SAEs resolved and no action was taken with the study drug due to the events.

Table 15. Summary of Serious Adverse Events by System Organ Class and Preferred Term

System Organ Class Preferred Term	Number (%) of Subjects* (N=12)	Number of Events
Any adverse events	2 (16.7)	2
Gastrointestinal disorders	1 (8.3)	1
Tooth impacted	1 (8.3)	1
General disorders and administration site conditions	1 (8.3)	1
Therapeutic response decreased	1 (8.3)	1

* Number of subjects who reported at least 1 serious adverse event.
N = Total number of subjects.
Source: Table 14.3.1.7.1

No local laboratory results ≥0.6 BU were reported; therefore, no positive cases from the central laboratory of FVIII inhibitor development were analyzed or reported.

Of the 3 paediatric subjects, diarrhea, vomiting, and arthralgia were reported for 1 subject; sinusitis, head injury, and nausea for a second subject; and no TEAEs were reported for the third subject. All of these TEAEs were mild and resolved. None were SAEs.

Conclusions of the MAH

No occurrences of FVIII inhibitor development were observed during this study, and no new safety risks or concerns were identified. Xyntha was safe and well tolerated during the study as assessed through the collection of nonserious AEs and SAEs as well as the incidence of LETE. The study was discontinued because the Sponsor has ongoing studies collecting similar safety data

Conclusion of the Rapporteur

The MAH has submitted the results from an open label study evaluating the overall safety of Xyntha in subjects transitioning from ReFacto or other FVIII replacement products to Xyntha in usual care setting. Twelve male subjects, ages ranging from 13 to 56 years with 3 subjects aged less than 18 years (i.e., 13, 14, and 15) received the Refacto AF version approved in US and the study took place outside Europe.

The collected safety data did not reveal any new adverse events and no reports of inhibitors were obtained. As the study also is terminated by the sponsor no more data is expected.

Being a small study with limited information it is somewhat difficult to make any definitive conclusions but based on the information and reports provided it is considered that the study results do not affect the currently approved SmPC for Refacto AF in the EU nor does it change the overall benefit/risk.