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Committee for Medicinal Products for Human Use (CHMP)

Assessment report for paediatric studies submitted in accordance with article 46 of regulation (EC) No 1901/2006, as amended

Elocta

International non-proprietary name: efmoroctocog alfa

Procedure no.: EMA/H/C/003964/P46/0008

Note

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

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Table of contents

1. Introduction

On 25 August 2021, the MAH submitted a completed paediatric study for Elocta (eCTD 0100), in accordance with Article 46 of Regulation (EC) No1901/2006, as amended.

A short critical expert overview has also been provided.

2. Scientific discussion

2.1. Information on the development program

The MAH stated that LPS16473/997HA402 (verITI-8) is a stand-alone study.

2.2. Information on the pharmaceutical formulation used in the study

Treatment administered was Eloctate as iv liquid formulation.

2.3. Clinical aspects

2.3.1. Introduction

This Article 46 procedure reflects a non-controlled, open-label study of rFVIIIFc for immune tolerance induction (ITI) in 16 severe hemophilia A subjects with inhibitors undergoing their first ITI treatment.

2.3.2. Clinical study

Clinical study number and title

Study No. LPS16473/997HA402/verITI-8
Title: A non-controlled, open-label, multicenter study of efficacy of rFVIIIFc for immune tolerance induction (ITI) in severe hemophilia A subjects with inhibitors undergoing the first ITI treatment.

Objective(s)

Primary objective: To describe the time to tolerization (ITI success, i.e. inhibitor titer <0.6 Bethesda Units (BU)/mL, rFVIIIFc incremental recovery [IR] ≥66% within a maximum of 12 months (48 weeks) of ITI treatment with rFVIIIFc.

Study design

This was a prospective, global, open-label, single-arm study of up to 17 patients. The maximum individual study duration was expected to be up to 12 months of ITI with a total study duration of approximately 2 years. Males of all ages with severe hemophilia A and high-titer inhibitors (historical

peak ≥5 BU/mL) received recombinant coagulation factor VIII Fc fusion protein (rFVIIIFc) for first-time ITI therapy, in order to eradicate anti-coagulation factor VIII inhibitors.

The study consisted of 4 periods:
1) a 4-week Screening Period
2) a maximum of a 48-week ITI Period
3) a minimum of a 16-week Tapering Period for patients that achieved ITI success
4) a 32-week Follow-Up Period

During the Tapering Period, the patient's dose was adjusted with the aim of tapering the dose to reach a dosing regimen suitable for effective prophylaxis. Length and dosing schedules were left to the discretion of the treating physician.

Patients not achieving ITI success did not enter the Tapering or Follow-up Periods and were to proceed to the End of Treatment (EOT) Visit.

Throughout the study, patients could receive bypassing agents (BPA) as needed for control of active bleeding. All treatments were to be collected in a study-specific electronic patient diary.

Study population /Sample size

Enrolled, treated and evaluated: 16 patients

Treatments

Investigational medicinal product: rFVIIIFc (Eloctate)

Formulation: Liquid

Route of administration: Intravenously

Dose regimen: During the ITI Period, the rFVIIIFc dose administered was 200 IU/kg/day (± 8 hours), which could be given as a once-daily dose or divided into several doses per day at the discretion of the Investigator.

Lot numbers: List of patients receiving specific lots of study drug has been provided.

Outcomes/endpoints

Efficacy:
Primary endpoint: Time to tolerization with a maximum of 12 months (48 weeks) of ITI treatment; tolerization defined as inhibitor titer <0.6 BU/mL, rFVIIIFc incremental recovery ≥66% of expected, and half-life of ≥7 hours).
Secondary endpoints: Percentage of patients achieving ITI success, occurrence of relapse during the Tapering or Follow-Up Periods, number of bleeding episodes during the ITI Period and during the Tapering and Follow-up Periods after successful ITI, number of days away from work or school, number of hospitalization days, adherence (defined as percentage of administered doses versus planned doses), and consumption of rFVIIIFc (measured in total rFVIIIFc use).

Safety:
Main Safety criteria (descriptive statistics): duration of exposure; rate, type, severity, and causality of treatment-emergent adverse events (TEAEs)
Medically important events: Inhibitor development, serious allergic reactions including anaphylaxis, and vascular thrombotic events.

Statistical Methods

Primary endpoint: Number of observations, mean, standard deviation (SD), median, 25th and 75th quartiles, minimum, and maximum (descriptive statistics); Kaplan-Meier estimates for median, 25th and 75th quartiles; Kaplan-Meier plot showing the percentage of patients who were tolerized against time from the first ITI infusion.
Patients not achieving ITI success during the ITI Period of 48 weeks were censored at the latest date with a positive inhibitor titer data.
ITI Full Analysis Set was used for these analyses.
Secondary endpoints: Descriptive statistics.

[An interim analysis was originally planned when at least 10 patients had completed at least 24 weeks (6 months) of ITI treatment. Interim data were analyzed (data cut off 23 Jan 2019) and published for presentation at the 27th Congress of the International Society on Thrombosis and Haemostasis 6–10 July 2019.
The same statistical analyses were used for the interim and final analyses, with the final data presented in this study report. Additions to the final analyses are a summary table of protocol deviations, 2 listings (ITI treatment outcomes, time to tolerization, and Periods) and 1 figure (Kaplan-Meier plot of time to tolerization).]

Results

Recruitment/ Number analysed

Population characteristics:

16 Patients were enrolled into the study, all of whom completed the trial. No patients were permanently discontinued from treatment and/or the study due to a TEAE.

The majority of patients (75.0%) were White with a non-Hispanic/non-Latino ethnicity (87.5%). Patients had been previously treated with FVIII products and had a historical peak FVIII inhibitor titer ≥5 BU/mL. The mean (SD) historical inhibitor titer at study entry was 67.1 (Min 6.2, Max 256) BU/mL.

Baseline data

Mean (SD) age at the time of study entry was 3.8 (4.06) years, with a range of 0.8 to 16 years. Mean inhibitor titer at rFVIIIFc initiation was 24.0 (Min 0.7, Max 144) BU/mL. Number of exposure days at first confirmed inhibitor development was <25 ED for 8 subjects, 25-50 ED for 5 subjects, 51-100 ED for 2 subjects and >100 ED for 1 subject.

Efficacy results

Primary endpoint**:**

10 patients (62.5%) met all 3 prespecified criteria and achieved ITI success/tolerization. Of the 10 patients who reached tolerization, the median time to tolerization was 11.7 weeks with a range of 8.1 to 49.8 weeks. There were no early withdrawals from ITI during the ITI Period.

Secondary endpoints:

Of the patients not having achieved ITI success, 1 patient (6.3%) achieved only partial success and 5 patients (31.3%) were considered treatment failures. Of the 10 patients achieving ITI success, all

entered and completed the Tapering and Follow-up Periods per the protocol. None relapsed to a positive inhibitor titer for FVIII during the Tapering and Follow-up Periods. The duration of follow-up for relapse was a minimum of 4 months for the Tapering Period with a subsequent 8-month Follow-Up Period.

The overall median ABR in 10 successfully tolerized patients was highest during the ITI Period (3.8, range 0;31.6). In comparison, the overall median ABR was lower in the Tapering Period (0, range 0;2.7). The overall median ABR remained low in the Follow-up Period (0; 0;9.3).

ITI success was accompanied by an increased percentage of patients without reported bleeding episodes. The percentage of patients without reported bleeding episodes was lowest during the ITI Period: 7 patients (43.8%). There were 6 patients (60%) without bleeding episodes during the Tapering Period and 7 patients (70.0%) without bleeding episodes during the Follow-up Period.

Median annualized consumption of rFVIIIFc during the ITI-period was 70677 (range 37179;75527), in the tapering period 22342 (range 15651;40465), and in the fup-period 9210 (range 6311;32572).

Safety results

Overall (all 3 study periods combined), 220 TEAEs were reported in 16 patients (100%). Of these, 28 TESAEs were reported in 9 patients (56.3%). Most TEAEs were reported during the ITI Period: 165 TEAEs were reported in 14 patients (87.5). During the ITI Period, most TESAEs were reported in only 1 patient by PT; the most frequently reported events by PT were vascular device infection, contusion, and hemarthrosis, reported in 2 patients (12.5%) each. The types and incidence of TESAEs observed in this study were consistent with what is expected for the severe hemophilia A population and none were considered to be related to study drug. Of note, there were no TESAEs associated with a bleeding episode.

No thrombotic events were reported over the duration of the trial. No Grade 2 or greater allergic reactions in association with administration of rFVIIIFc were reported. No relapses to a positive inhibitor titer were reported in patients who had achieved ITI success. There were no deaths reported during the study. No patients were permanently discontinued from treatment and/or the study due to a TEAE or TESAE.

2.3.3. Discussion on clinical aspects

Results of the presented ITI-study in 16 severe haemophilia patients regard an ITI-success-rate of 10 out of 16 patients, and an uneventful safety-profile in the expected frame.

Although this overall result seems to be highly encouraging, the following points should be taken into account:

Screening-data of the included patients reflect an overall patient-collective of good prognosis. Only 5 of 16 patients were of high risk (historical inhibitor titers of >100 BU/ml). Of note, all of them failed ITI or reached only partial success. On the other hand, 6 subjects show baseline-inhibitor-titers <5 BU/ml (low risk). Out of these, 4 subjects had titers of ≤3 BU/ml, and even 2 subjects had titers of <1 BU/ml. The outcome of all of these was successful.

Of note, there is still ongoing discussion regarding spontaneous disappearance of inhibitors in low-risk patients and the need of any tolerization-therapy at all[1]. Further, for low-risk patients the adequate dosage of factor-concentrates for tolerization is still subject to debate[2] – taking into account the high burden of twice daily infusion of – in this study chosen - very-high doses (200 IU/kg/d). Even the widely accepted gap between inhibitor detection and therapy for awaiting dropping titers is not generally agreed any more. Finally, upcoming non-factor-therapies have reached established places in treating inhibitor-patients[3] [4].

Regarding study design, the following issues are challenging with respect to the outcome of the study: Elocta is described as an "extended half-life" FVIII-product, with a half-life of 20.9 hours (chromogenic assay) according to the SmPC. Definition of "ITI-success" for the primary endpoint is a half-life of 7 hours. This value reflects 33% of 20.9 h - being far away from a "normal" – in the sense of a recovered - PK-behaviour. The uncontrolled study-design hampers the overall validity of the results, in addition.

Regarding safety, the overall safety-profile is considered to be in-line with similar products and therapy.
Of note, presentation of safety might be much more valuable if focused on the presentation of individual subjects and on the respective medicinal entity of safety concern – as the population covers 16 subjects overall, only. Reflection of fragmented AEs shows an artificially "diluting" effect and does not help to understand the overall medicinal context. For example, for device- or access-related complications diverse codes are reflected (1 administration site extravasation, 1 catheter site extravasation, 1 catheter site hematoma, 1 catheter site swelling, 1 complication associated with device, 1 injection site hematoma, 1 injection site pain, 1 vascular access site infection, 4 vascular device infections, 1 device breakage, 1 device occlusion), likely to distract from the risks evolving from difficult venous access in the respective small-age patient-population in correlation to the used therapeutic regimen. At least 6 patients are affected by namely severe and threatening events e.g. infections (Serratia marcescens, Staph. Epid.) certainly not related with Elocta itself but eased by the regimen.

However, no clear guidance on factor-tolerization-regimens is available with respect to certain risk-factors or including non-factor-therapies, yet – precluding comparison of outcome-data.

3. Rapporteur's overall conclusion and recommendation

☒ **Fulfilled** (No further action required)

[1] Caram C,de Souza RG, de Sousa JC; Araújo Pereira T, do Amaral Cerqueira AM, van Der Bom JG, Rezende SM: The long-term course of factor VIII inhibitors in patients with congenital haemophilia A without immune tolerance induction. Thromb Haemost 2011; 105: 59–65
[2] Santagostino E, Young G, Escuriola Ettingshausen C, Jimenez-Yuste V, Carcao M: Inhibitors: A Need for Eradication? Acta Haematol 2019;141:151–155
[3] Carcao M , Escuriola-Ettingshausen C , Santagostino E , et al. The changing face of immune tolerance induction in haemophilia A with the advent of emicizumab . *Haemophilia* . 2019 ; 25 (4): 676 - 684 .
[4] Batsuli, GM, Zimowski, KL, Tickle K, Meeks SL, Sidonio RF: The Atlanta Protocol: Immune Tolerance Induction in Pediatric Patients with Hemophilia a and Inhibitors on Emicizumab, Blood (2018) 132 (Suppl_ 1) : 634