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Committee for Medicinal Products for Human Use (CHMP)

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

BeneFIX

nonacog alfa

Procedure no: EMEA/H/C/000139/P46/147

Note

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

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1. Introduction

On 16 March 2021, the MAH submitted a completed study for BeneFIX, in accordance with Article 46 of Regulation (EC) No1901/2006, as amended.

A short clinical overview has also been provided.

2. Scientific discussion

2.1. Information on the development program

According to the MAH, Study B1821059 entitled "A Single Country, Multicenter, Open-label and Non-Randomized Clinical Trial with Nonacog Alfa Prophylaxis and Treatment of Bleeding Episodes in Previously Treated Patients with Moderately-Severe to Severe Haemophilia B for a Duration of 8 Weeks." is a stand-alone study.

2.2. Information on the pharmaceutical formulation used in the study

BeneFIX (nonacog alfa) is a recombinant DNA-based protein therapeutic, which has structural and functional characteristics comparable to endogenous factor IX. Nonacog alfa is a freeze-dried lyophilized powder for reconstitution in a single-use vial. Each vial contains nominally 250, 500, 1000, 2000, or 3000 international units (IU).

Nonacog alfa received first regulatory approval on 11 February 1997 in the United States (US). It was reformulated to decrease the occurrence of red blood cell agglutination in the syringe or tubing. The reformulation involved no changes to the active ingredient (recombinant FIX protein), but included a change in the diluent (from sterile water to 0.234% NaCl). Reformulated nonacog alfa was approved for use in the European Union and the US in 2007 and since January 2009, only the reformulated version of nonacog alfa is being distributed worldwide. Presently, BeneFIX is approved in 85 countries and marketed in 66 countries. In India, BeneFIX achieved regulatory approval on 26 September 2019 and is indicated for the treatment and prophylaxis of bleeding in patients with haemophilia B (congenital factor IX deficiency).

2.3. Clinical aspects

2.3.1. Introduction

On 16 March 2021, the MAH submitted the final report of Study B1821059, in accordance with Article 46 of Regulation (EC) No 1901/2006, as amended. In addition, a short clinical overview has been provided.

As stated by the applicant in the cover letter (dated 16 March 2021), this submission does not have any impact on the overall benefit-risk profile of BeneFIX, nor any impact on the already approved EU SmPC.

2.3.2. Clinical study

Clinical study number and title

Study B1821059: A Single Country, Multicenter, Open-label and Non-Randomized Clinical Trial with Nonacog Alfa Prophylaxis and Treatment of Bleeding Episodes in Previously Treated Patients with Moderately-Severe to Severe Haemophilia B for a Duration of 8 Weeks.

Description

Study B1821059 was a single-country, multicenter, open-label, single arm, interventional study conducted in India. This study evaluated BeneFIX (nonacog alfa, recombinant Factor IX) and was conducted as a post-approval commitment to fulfill the Central Drugs Standard Control Organization (CDSCO) written request for supplementary information relating to the use of nonacog alfa in Indian participants with haemophilia B. The study evaluated the safety and efficacy of nonacog alfa prophylaxis in a total of 25 Indian participants with congenital moderately-severe to severe haemophilia B (factor IX [FIX] activity ≤2%) including 3 adolescents. The overall treatment duration for each subject was up to 8 weeks, with up to a 4-week screening period and a subsequent 28-day safety observation period. The FSFV was on 10 February 2020 and the LSLV occurred on 24 September 2020.

Methods

Objective(s)

Primary Objective

To study the safety of nonacog alfa when administered for prophylaxis with respect to incidence of FIX inhibitor development.

Secondary Objectives

- To evaluate the incidence of serious adverse events (SAEs), in particular, medically important events (thrombotic events and hypersensitivity reactions), in subjects receiving a nonacog alfa prophylaxis.
- To evaluate the incidence of adverse events (AEs) in subjects receiving a nonacog alfa prophylaxis.
- To evaluate the efficacy of nonacog alfa during a prophylaxis regimen.

- To evaluate the total annualized consumption of nonacog alfa by subjects following a prophylaxis regimen.
- To evaluate the efficacy of nonacog alfa for the treatment of breakthrough bleeding episodes (on-demand treatment) while following a prophylaxis regimen

Study design

Study B1821059 was a single-country, multicenter, open-label, single arm, interventional study conducted in India. Subjects were monitored according to local standard of care, which should be in accordance with the local product document (LPD).

At least 25 male subjects aged ≥12 years to ≤65 years with congenital moderately-severe to severe hemophilia B (FIX activity ≤2%) who have had at least 50 exposure days (EDs) to FIX-containing products were planned to be enrolled.

The overall treatment duration for each subject was up to 8 weeks (or at least 16 EDs), with up to a 4-week screening period and a subsequent 28 day safety observation period. Subjects were treated with a dose and regimen of nonacog alfa prophylaxis in accordance with the LPD.

Study population /Sample size

Study B1821059 was open to male Indian participants aged ≥12 years to ≤65 years with congenital moderately-severe to severe haemophilia B (factor IX [FIX] activity ≤2%) who have had at least 50 EDs to FIX-containing products.

Treatments

Prophylaxis:

The mean prophylactic dose of nonacog alfa per the LPD was 40 IU/kg with a range 13 to 78 IU/kg at intervals of 3 to 4 days.

On-Demand Treatment:

The amount to be administered and the frequency of administration was tailored to the clinical effectiveness in individual participants.

Nonacog alfa was administered by the investigator or a delegate at Visits 2 and 3. For administration between study visits, the product was administered in accordance with procedures provided by their physicians. Subjects or caregivers/parents of subjects were trained on how to administer nonacog alfa, away from the study site, as applicable.

Outcomes/endpoints

Primary Endpoint

The proportion of subjects who develop FIX inhibitor (≥0.6 BU/mL), as confirmed by central laboratory testing, during the course of the study

Secondary Endpoints

- Incidence of SAEs (including medically important events, thrombotic events, and hypersensitivity reactions).
- Incidence of AEs.

- Annualized bleeding rate (ABR) during prophylaxis.
- Annualized total factor consumption (TFC) in international units (IU) and annualized TFC by weight (IU/kg) of nonacog alfa measured during the up to 8 weeks of treatment, by reason for infusion and total units consumed (across all reasons).
- Number of nonacog alfa infusions used to treat each bleed.

Statistical Methods

No formal statistical sample size computation was performed for this study. The sample size rationale was based on the written request of the CDSCO. Results of this study were presented using descriptive statistics.

Results

Recruitment/ Number analysed

Thirty participants were screened for the study and 25 (83.3%) participants were enrolled and completed the study. Five (16.7%) participants discontinued during the screening period and of those 3 discontinued during screening (were screen failures) due to a recruitment pause caused by the COVID-19 pandemic. All enrolled participants (25 [100.0%]) were male Indian Subcontinent Asian. The majority of participants (22 [88.0%]) were 18-65 years of age and 3 were <18 years old

Baseline data

Twelve (48.0%) participants had a family history of haemophilia (of which 1 was a pediatric subject). Factor IX mutation was not classified in any participants. Twenty-four (96.0%) participants had no family history of inhibitors to FIX products, and no participants had a history of allergy to FIX products. All participants (25 [100.0%]) were classified as having severe disease (determined based on investigator's assessment of clinical bleeding symptoms), and had at least 50 EDs to FIX-containing products. The mean number of prior FIX exposure days was 112.6 ± 108.94 days (median: 77.0; min-max: 50–500 days) Twenty-four (96.0%) participants had identified target joints at screening.

Efficacy results

Efficacy parameters included evaluation of ABR during prophylaxis (based on all bleeds requiring on-demand treatment with nonacog alfa during the treatment interval duration [up to 8 weeks of treatment, or sooner, once 16 EDs were achieved]), annualized TFC of nonacog alfa, and the number of nonacog alfa infusions used to treat each bleed.

There were no bleeding events during the treatment phase of the study that required on-demand infusion of nonacog alfa. There were 17 bleeding episodes (16 spontaneous (1 paediatric subject) and 1 traumatic) among 10 participants that were not treated with nonacog alfa infusions. Sixteen of these bleeding episodes occurred post-treatment while one bleeding episode occurred during the treatment phase. Fifteen of these bleeding episodes were treated with other FIX products, and 2 were minor bleeding events that resolved without treatment.

The mean annualized TFC per participant was 224,582.44 ± 75,526.750 IU (median: 205,052.63; min-max: 99050.9–431,114.8 IU). The mean annualized TFC by weight per participant was 3639.27 ± 572.778 IU/kg (median: 3749.24; min-max: 1792.5-4222.1 IU/kg) for infusions administered during the study. All study intervention infusions were administered as prophylaxis.

Safety results

Safety assessments throughout the study included collection of AEs, laboratory safety testing, vital signs, and physical examination. FIX inhibitor development, thrombotic events, and hypersensitivity reactions were considered medically important events.

Each participant in the study received a total of 16 prophylactic infusions of nonacog alfa; mean treatment interval duration was 61.80 ± 14.416 days (median: 59.00; min-max: 55.0–130.0 days).

Three out of the 25 (12.0%) participants had a total of 3 AEs (2 mild [pyrexia and cough] and 1 moderate [dental caries]), which were treatment-emergent. None of the 3 AEs occurred in a paediatric participant. None of the AEs were considered related to the study intervention or to be haemophilia or device-related and no severe AEs were reported. No participant discontinued the study or study intervention due to AEs and there were no dose reductions or temporary discontinuations due to AEs. There were no deaths or other SAEs among participants in the study.

2.3.3. Discussion on clinical aspects

As part of this Article 46 procedure, the MAH submitted the final study report of Study B1821059 together with a clinical overview. Study B1821059 was a post-approval commitment to fulfil the Central Drugs Standard Control Organization (CDSCO) written request for supplementary information relating to the use of nonacog alfa in Indian participants with haemophilia B.

In Study B1821059, safety and efficacy data were collected from a total of 25 previously treated Indian patients (>50 EDs) with moderately-severe to severe haemophilia B (FIX activity ≤2%). The study population included three paediatric subjects, i.e. three adolescents of 12, 15 and 17 years of age. Standard measurements (i.e. incidences of AE, SAEs, inhibitor development, ABR, no. of on-demand infusions, annualized factor consumption) were used to evaluate safety and efficacy of nonacog alfa based on an 8-week period of prophylactic treatment and a subsequent 28-day safety follow-up. Dosing recommendations were generally in line with the posology of BeneFIX as reflected in its EU SmPC (i.e. 40 IU/kg [range 13 to 78 IU/kg] at intervals of 3 to 4 days). The study was conducted during the COVID-19 pandemic. However, the impact of COVID-19-related restrictions remained minor, and the study achieved its objectives and could be completed despite the pandemic.

The clinical overview covers the whole study population. A separate evaluation of the paediatric data has not been provided. However, review of the clinical study report did not reveal any meaningful differences between adolescents and adults, neither with regard to the age-independent baseline characteristics nor to the clinical outcomes obtained in these two age groups. As regards efficacy, results of Study B1821059 generally support the notion of prophylaxis efficacy of nonacog alfa, with no reported bleeding events requiring treatment during prophylaxis compared to a total of fifteen bleeding events (in 8 subjects) requiring treatment that occurred in the subsequent 28-day safety follow up (i.e. after termination of nonacog alfa treatment). Both, average doses of nonacog alfa administered per prophylactic infusion as well as total FIX consumption were generally in line with the EU SmPC. As regards safety, treatment with nanocog alfa was well tolerated and none of the reported AEs were assessed as related to its administration. None of the participants developed a FIX inhibitor and there were no reports of thrombotic events or hypersensitivity reactions. Overall, safety data obtained in Study B1821059 were generally consistent with the known safety profile of BeneFIX.

However, according to the current EMA clinical guideline for factor IX products (EMA/CHMP/BPWP/144552/2009 rev. 2 Corr. 1), the number of patients typically needed in a post-marketing study to cover especially immunogenicity aspects (besides general efficacy and safety) is 50, followed up to 100 EDs. Hence, considering the small sample size of only 25 subjects and the extremely short treatment

period of only 8 weeks (or 16 EDs), the informative value of the data obtained in Study B1821059 remains limited.

3. Rapporteur's overall conclusion and recommendation

In summary, data obtained in the three paediatric subjects included in Study B1821059 do not change the favourable benefit risk profile of BeneFIX (Nonacog alfa) in children. The presented data do not warrant any update of the Product information. No additional clarifications requested.

☒ **Fulfilled:**

No regulatory action required.

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

According to the MAH, Study B1821059 is a stand-alone study. No line listing of concerned studies has been provided.