18 May 2017
EMA/333151/2017
Human Medicines Evaluation Division

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/P46/146

Note

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

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1. Introduction

On 21th February 2017, the MAH submitted the report of a completed BeneFIX (Nonacog Alfa, Recombinant Factor IX) clinical study (B1821052) including data from paediatric subjects, in accordance with Article 46 of Regulation (EC) No. 1901/2006, as amended. A clinical overview has been provided. The post-authorisation clinical trial assessed safety and efficacy of BeneFIX in subjects with hemophilia B in usual care settings and was conducted in China as a commitment to the China Food and Drug Administration (CFDA). The clinical study report (CSR) has been prepared in English using the required CFDA template which differs from ICH E3 in the organisation of the appendices which was considered acceptable by the EMA on 23 September 2016.

2. Scientific discussion

2.1. Information on the development program

The MAH stated that study B1821052 is a stand-alone study. BeneFIX is indicated in China for the control and prevention of bleeding episodes in adult and paediatric subjects with hemophilia B (congenital FIX deficiency or Christmas disease), and is indicated for peri-operative management in adult and paediatric subjects with hemophilia B. This study is a postmarketing commitment in China and was conducted to provide supplementary information relating to the use of BeneFIX in a real world clinical setting in Chinese subjects with hemophilia B.

2.2. Information on the pharmaceutical formulation used in the study

BeneFIX® (nonacog alfa) is a recombinant, single chain glycoprotein therapeutic that has structural and functional characteristics comparable to endogenous coagulation factor IX (FIX). BeneFIX is supplied as a powder for reconstitution and intravenous injection. Each single-use vial contains nominally 250, 500, 1000, 2000, or 3000 international units (IU).

BeneFIX first received regulatory approval on 11 February 1997 in the United States (US). Later, it was reformulated to decrease the occurrence of red blood cell agglutination in the syringe or tubing. Reformulated nonacog alfa was approved for use in the European Union (EU) and US in 2007 and since January 2009 only the reformulated version of nonacog alfa is being distributed worldwide. BeneFIX is now approved in 66 countries and marketed in 46 countries. For supporting licensure in China, the registration trial was conducted in 2008. BeneFIX received regulatory approval on 10 July 2012 in China.

2.3. Clinical aspects

2.3.1. Introduction

The MAH submitted a final report and clinical overview including data of pediatric subjects with hemophilia B from a trial assessing safety and efficacy of BeneFIX in usual care settings in China (study B1821052). The trial was a post-authorisation pragmatic study conducted in 17 investigational sites and enrolled 70 patients. 61 pediatric subjects (≤12 years of age) with hemophilia B were included, 11 of these were previously untreated patients. Haemophilia B is a X-linked recessive bleeding disorder caused by mutations of the *F9* gene leading to a partial or total deficiency of functionally active coagulation factor IX. The disease affects approximately 1 in 30,000 males

worldwide. Women, who carry a single mutated gene, are generally asymptomatic. The disease phenotype correlates with the residual activity of FIX and is characterised by bleeding into joints, soft tissues, muscles or internal organs, either after accidental or surgery trauma or spontaneously. The treatment of choice for hemophilia B is FIX replacement therapy.

2.3.2. Clinical study

Study B1821052 - An Open-Label, Single-Arm, Post-Authorization Pragmatic Clinical Trial on the Safety and Efficacy of BeneFIX (Nonacog Alfa, Recombinant Factor IX) in Subjects with Hemophilia B in Usual Care Settings in China.

Description

Objective(s)

The primary objective of the study was to evaluate the occurrence and severity of product medically important events (i.e. FIX inhibitor development, allergic reactions, and thrombotic events) of BeneFIX in subjects with hemophilia B in usual care settings in China.

Secondary objectives of the study were to evaluate the overall safety of BeneFIX, including the occurrence of adverse events (AEs) and serious adverse events (SAEs), and to evaluate the efficacy of BeneFIX in subjects with hemophilia B in usual care settings in China.

The exploratory objective of the study was to evaluate patient reported outcome in pediatric subjects.

Study design

This was an open-label, single-arm, multi-center, prospective post-authorization pragmatic study conducted in 17 (1 site did not enrol any subjects) hemophilia treatment centers in China, as requested by the CFDA. The study objective was to evaluate the efficacy and safety of BeneFIX in subjects <6 years of age, ≥6 to ≤12 years of age, previously untreated patients (PUPs), severe hemophilia patients (FIX activity <1%), and patients receiving prophylaxis treatment after enrollment in the study. A target of 30 subjects for each of these subgroups was to be enrolled to fulfil the China Center of Drug Evaluation (CDE) requirements. Subjects were treated by the investigator according to usual care in China and in accordance with the China BeneFIX Package Insert. The treatment duration was approximately 6 months or 50 exposure days (EDs). The study is completed and the last subject's last visit for this study was on 22 August 2016.

Study population /Sample size

Male and/or female subjects with hemophilia B, who or whose parents/legal representatives were able to comply with study procedures were eligible to participate in the study.

Subjects with presence of any of the following were ineligible to participate in this study: other bleeding disorder(s) in addition to hemophilia B, a past history of, or current FIX inhibitor, a known hypersensitivity to the active substance or to any of the excipients of BeneFIX, and/or a known hypersensitivity to Chinese Hamster Ovary cell proteins.

According to the requirements of the CDE, 30 subjects of each of the aforementioned subgroups (see study design) were planned to enrol resulting in a total of 60 planned subjects due to overlap among the subgroups. Finally, 70 subjects were enrolled and treated with intravenous infusions of BeneFIX.

Treatments

The treatment modality was decided by the investigators according to the China BeneFIX package insert and doses were adjusted solely according to medical and therapeutic necessity. Patients were treated for approximately 6 months (±7 days) or 50 ± 5 EDs (whichever occurred first).

According to the clinical overview provided in section 2.5 of the eCTD, the mean (±SD) average infusion doses by weight were 23.5 (±8.7), 24.5 (±8.9), and 39.1 (±12.2) IU/kg in the on-demand, prophylaxis, and the preventative and recovery settings, respectively. Subjects had a mean number of 35.6 (prophylaxis), 11.1 (on-demand), and 1.6 (preventative and recovery) exposure days with similar numbers of infusions per subject.

Outcomes/endpoints

Safety Endpoints:

The primary safety endpoints to be reported were development of FIX inhibitor, allergic reactions and thrombotic events. Secondary safety outcomes included the frequency of AEs and SAEs. All the primary safety endpoints were considered medically important events and reported as SAEs.

Efficacy Endpoints:

All efficacy endpoints were secondary endpoints in this study, which included:

Prophylaxis treatment:

- Annualized bleeding rates (ABRs) in subjects who received prophylaxis treatment with BeneFIX during their prophylaxis period;
- Number of spontaneous/non-traumatic breakthrough bleeds within 48 hours of a prophylaxis dose of BeneFIX;

On-demand treatment:

- ABRs in subjects who received on-demand treatment with BeneFIX during their on-demand period;
- The response to on-demand treatment with BeneFIX for all bleeds (4-point scale of assessment, one per infusion);
- Number of BeneFIX infusions to treat each new bleed;

Prophylaxis treatment, on-demand treatment, and recovery settings:

- The average infusion dose and total FIX consumption;
- The incidence of less than expected therapeutic effect (LETE) in the on-demand, prophylaxis, and low recovery (when available) settings.

Statistical Methods

The study was an open-label, single-arm post-authorization pragmatic study, with no statistical hypotheses to be tested. The results of the study were presented using descriptive statistics.

Results

Recruitment/ Number analysed

A total of 70 subjects were enrolled to study B1821052 and received at least 1 dose of BeneFIX. All these subjects were included in the full analysis set and in the safety analysis set (n=70 for both). Finally, a total of 57 patients received prophylaxis treatment and 18 subjects on-demand treatment. However, for calculation of FIX consumption, a total of 46 subjects were included in the on-demand analysis set with an overlap with the prophylaxis analysis set. Laboratory data were analysed from 68 patients.

Baseline data

From 70 enrolled and treated patients (all Asian and male), 66 patients completed the clinical trial. 4 subjects discontinued early. Of these, 1 subject withdrew due to lost to follow-up, 1 subject withdrew due to no longer willing to participate in the study, 1 subject withdrew due to protocol violation, and 1 subject withdrew due to other reasons (quit for family reasons).

For secondary endpoints, data of the 5 subgroups (see study design) are reported. However, the MAH stated that due to the challenges in recruiting PUP subjects, a total of 11 PUP subjects were enrolled and this subgroup did not reach the planned sample size (i.e. a total of 30 PUPs according to the requirements of the CDE). Thus, for FIX inhibitor analysis (the primary endpoint), data of "PUP+minimally treated patient (MTP, defined as subjects with previous EDs ≥1 and ≤50)" was additionally reported to complement the PUP subgroup. In summary, the following numbers of subjects were allocated to the respective subgroup: <6 years (n=30), ≥6 to ≤12 years (n=31), PUPs (n=11), MTP (n=27), PUP + MTP (n=38), subjects with severe hemophilia B (n=36), prophylaxis subjects (n=57). The mean body mass index of the study population was 17.3 kg/m^2 with a range of 12.4-27.7.

Efficacy results

In prophylaxis regimen, the 57 subjects treated with BeneFIX had a mean ABR of 6.5 (median: 2.0, range 0.0-34.8). There were no relevant variations between the 5 subgroups, however, PUPs in the prophylactic treatment regimen (n=7) had a mean ABR of 0.3 (range of 0.0-1.9). The number of spontaneous/non-traumatic breakthrough bleeds within 48 hours of a prophylaxis dose of BeneFIX was 23 per total of 2032 prophylactic infusions occurring in 11 subjects. No variations between the subgroups have been observed. A total of 2 LETEs (i.e. spontaneous bleed within 48 hours after a regularly scheduled prophylactic dose) were observed in 2 pediatric patients in the prophylaxis setting (incidence of 0.1%).

In the on-demand setting, a total of 18 subjects had a mean ABR of 26.3 (median: 15.9, range 0.0-73.8). Average ABRs were highest for pediatric subgroup ≥6 to ≤12 years (n=6, mean ABR: 28.2) and subjects with severe hemophilia (n=10, mean ABR: 29.3) and lowest for PUPs (n=4, mean ABR: 6.2). Bleeding events occurred in 65% of all subjects (i.e. 46/70). The mean number of BeneFIX infusions to treat each new bleed was 1.5 and most bleeds resolved with 1 infusion. The majority of responses to on-demand infusions were rated excellent or good in all subgroups (overall 88% for all infusions). No LETEs were confirmed in the on-demand setting (i.e. if 2 successive "No Response" ratings were recorded after 2 successive infusions, respectively).

The mean average infusion doses by weight were 23.5 (±8.7), 24.5 (±8.9), and 39.1 (±12.2) IU/kg in the on-demand, prophylaxis, and the preventative and recovery settings, respectively. The total mean FIX consumption per subject was 19224.1 (±15424.7), 9826.1 (±14816.3), and 1419.8 (±1192.6) IU

in the prophylaxis, on-demand, and the preventative and recovery settings, respectively. The mean numbers of exposure days (EDs) and number of infusions per subject were 35.6 and 35.6 for subjects in the prophylaxis setting and 11.1 and 11.3 for subjects in on-demand setting.

Safety results

Of 202 reported treatment emergent adverse events (TEAE), 3 TEAEs in 2 subjects were considered as treatment related (1xSAE and 2xAEs). One subject out of 70 subjects included in the safety analysis set experienced cough and rash, both events resolved and were rated mild in severity. The other patient developed a FIX inhibitor without clinical manifestation, i.e. a transient low-titer inhibitor (0.71 BU/mL) after discontinuation of prophylactic treatment (due to unwillingness to continue). The patient had received BeneFIX for a total of 25 EDs. On retesting one month after inhibitor detection, a negative result was obtained and the SAE was considered resolved. Thus, the overall observed inhibitor rate was 1.4%. No high-titer inhibitors, allergic reactions or thrombotic events occurred during the study. No deaths occurred during the study and no clinically important findings for laboratory safety or vital signs have been identified.

2.3.3. Discussion on clinical aspects

In accordance with Article 46 of Regulation (EC) No. 1901/2006, the MAH submitted the final report of a phase IV pragmatic trial designed to evaluate safety and efficacy of BeneFIX in Chinese subjects with hemophilia B in real-life routine practice setting. Of 70 enrolled and treated subjects, 61 were pediatric including 11 previously untreated and 27 minimally treated patients. The study results demonstrated that BeneFIX was efficacious in the treatment of hemophilia B in the Chinese population when used for prophylaxis as well as for on-demand treatment of bleeding episodes. With regard to age-staggered pediatric subgroups and FIX dosing, average infusion doses were slightly higher in the younger population (27.9 IU/kg in on-demand setting and 26.7 IU/kg in prophylaxis regimen) as compared to the older pediatric subjects (i.e. 22.4 and 20.6 IU/kg, respectively), however, total FIX consumption was higher in the older population (i.e. 6550 and 22102 IU in the on-demand and prophylaxis regimen, respectively) when compared to pediatric subjects <6 years of age (i.e. 4277 and 14709 IU, respectively). No specific data outlining dosing intervals in the prophylaxis setting have been provided. However, based on the mean numbers of EDs for the prophylaxis setting of 35.6 within a period of 6 month, dose intervals of approximately 5 days can be assumed. This is less frequently when compared to the approved EU summary of product characteristics (SmPC), where for routine secondary prophylaxis an average dose for previously treated patients of 40 IU/kg (range 13 to 78 IU/kg) at intervals of 3 to 4 days was outlined. In the Chinese trial subjects, ABRs did not show relevant differences with regard to age-graded pediatric subgroups. PUPs (n=7) had lower mean ABRs, i.e. 0.3 versus 6.7 for all pediatric subjects (n=55) in the prophylaxis setting, and lower FIX consumption. However, average infusion doses by weight were similar (i.e. 22.0 IU/kg for PUPs in the prophylaxis setting compared to 23.6 IU/kg for all pediatric patients). Taking differences in the treatment modality of Chinese subjects and subgroup sizes into account, provided data on FIX dosage are considered to be largely consistent with recommendations made in the EU SmPC and no regulatory consequences have been identified.

Regarding safety aspects of BeneFIX, three treatment emergent adverse events were reported including one case of transient low-titer FIX inhibitor and one patient who experienced mild cough and mild rash. All of these events resolved. No thrombotic or allergic events occurred during the study. Thus, no safety concerns arise and provided safety data do not have an impact on the EU SmPC.

Overall, safety and efficacy data of subjects from the phase IV trial do not change the favourable benefit risk profile of BeneFIX for use in pediatric patients. Provided data are not considered to have any impact on the BeneFIX EU SmPC.

3. apporteur's overall conclusion and recommendation

In summary, data reported from study B1821052 confirm efficacy and safety of prophylactic and on-demand use of BeneFIX in Asian pediatric patients with hemophilia B. The benefit risk profile remains favourable and study data do not have any impact on the current EU SmPC of BeneFIX. No regulatory action required. No additional clarification requested.

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☒ **Fulfilled**

4. Additional clarification requested

N/A

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

N/A