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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/P46/145

Note

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

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1. Introduction

On 13 July 2016, the MAH submitted a full clinical study report for study B1821048 in accordance with Article 46 of regulation (EC) No 1901/2006, as amended. A respective clinical overview has been provided.

2. Scientific discussion

2.1. Information on the development program

The submitted study **B1821048** is:

An Open-Label, Single Dose Pharmacokinetic Study of BeneFIX (Nonacog Alfa, Recombinant Factor IX) in Male Chinese Subjects with Hemophilia B

The purpose for conducting this single dose PK study of FIX activity after BeneFIX administration in male Chinese subjects (6 years or older) with hemophilia B is to support the China Food and Drug Administration (CFDA) regulatory requirement to fulfill a post marketing commitment for BeneFIX.

2.2. Information on the pharmaceutical formulation used in the study

BeneFIX (nonacog alfa) is a recombinant DNA-based protein therapeutic that has structural and functional characteristics comparable to endogenous coagulation factor IX (FIX). BeneFIX is indicated for the treatment and prophylaxis of bleeding in patients with haemophilia B (congenital factor IX deficiency). BeneFIX is supplied as a powder for reconstitution and intravenous (IV) injection.

2.3. Clinical aspects

2.3.1. Introduction

Data of 4 paediatric subjects included in the above mentioned BeneFIX study B1821048 (in total 12 patients) have been discussed.

2.3.2. Clinical study

Study design and Study description

Study B1821048 was a multiple center, open-label, single-dose BeneFIX study in 12 male Chinese subjects with haemophilia B who were age 6 years or older with moderately severe to severe haemophilia B (FIX activity ≤2%).

4 of these 12 patients were in the age range ≥6 and <12 years (paediatric subjects). The remaining 8 patients were ≥ 18 years old (older subjects).

The dosage form administered was the commercial product approved in China, which was a vial in 1x pack containing 250 IU powder for injection. This is the same as the EU commercial product.

Subjects underwent screening evaluation within 28 days of dosing. Day 0 was defined as the day prior to day of dosing (Day 1). On Day 1, subjects received a single dose of BeneFIX 50 IU/kg administered by IV infusion within 10 minutes. The dose was calculated based on the subject's actual body weight on Day 1 before dosing. The start and stop times of the infusion were recorded in the Case Report

Form (CRF). Blood samples (2.7 mL) were collected pre-dose (within 2 hours before administration) and at 0.25, 0.5, 1, 3, 6, 9, 24, 50, 72, and 96 hours post dose.

All subjects treated with BeneFIX were analyzed for PK and safety parameters up to Day 5 (96 hours post dose). Tolerability and safety were assessed during the study by monitoring adverse events (AEs) and serious AEs (SAEs).

The first subject's first study visit was on 02 March 2015 and the last subject's last visit occurred on 08 April 2015.

Study population

Of the 12 subjects enrolled, 4 subjects were in the age range of ≥6 and <12 years and 8 subjects age ≥12 years (all subjects enrolled in this older age group were ≥18 years of age). All subjects were Chinese males from two centers in China, all completed the study treatment. The weight of paediatric subjects ranged from 28 kg to 42 kg with a mean (±standard deviation [SD]) weight of 33.8 ±6.2 kg, and the height ranged from 137 cm to 149 cm with a mean height of 142.3 ±5.1 cm. The body mass index (BMI) ranged from 14.9 to 18.9 kg/m2 with a mean BMI of 16.6 ±1.8 kg/m2.

Samples

Plasma samples were analyzed for FIX activity using one-stage coagulation assay. Plasma samples (collected on Day 0 and Day 5) were analyzed for FIX inhibitor using one-stage coagulation assay. Both assays are the same as those that have been used in other clinical studies performed by the MAH. There were no issues related to bioavailability identified that would impact efficacy and/or safety of BeneFIX.

Pharmacology

Methods

FIX pharmacokinetic parameters following 50 IU/kg doses were assessed in 12 Chinese patients, 4 of whom were paediatric subjects, with haemophilia B.

Blood samples for PK analysis were collected at pre-dose and at 0.25, 0.5, 1, 3, 6, 9, 24, 50, 72, and 96 hours post dose. The PK parameters (maximum observed plasma concentration [Cmax], time for Cmax [Tmax], area under the plasma concentration-time profile from time 0 to the time of the last quantifiable concentration [AUClast], area under the plasma concentration-time profile from time 0 extrapolated to infinite time [AUCinf], steady state volume of distribution [Vss], terminal phase rate constant [kel], terminal half-life [t½], mean residence time [MRT], clearance [CL], and incremental recovery for FIX activity were calculated for each subject using noncompartmental analysis of plasma concentration (FIX activity)-time data. Samples below the lower limit of quantification (LLOQ) were set to 0 for the purpose of analysis. Actual sample collection times were used for the PK analysis. The PK parameters were summarized descriptively by age group (≥6 to <12 years and ≥12 years). Concentrations were listed and summarized descriptively by PK sampling time. For summary statistics and summary (mean and median) plots by sampling time, the nominal PK sampling time were used. For individual subject plots by time, the actual PK sampling times were used.

Results

Median plasma concentration-time profiles for FIX activity following a single dose of BeneFIX 50 IU/kg are presented in the submitted CSR. Median concentrations in the paediatric subjects were consistently lower than those in the older subjects. The PK parameters results are summarized descriptively in Table 2 of the clinical overview. Geometric mean AUCinf was about 33% lower in paediatric subjects relative to older subjects, while geometric mean Cmax was only slightly (8%) lower. Consistent with the lower exposures, systemic CL was higher and t½ was shorter in paediatric subjects than in older subjects. Steady-state volume of distribution (Vss) was similar in both age groups. Incremental

recovery was also similar in both age groups, with geometric mean values of 0.78 and 0.82 IU/dL/IU/kg in paediatric subjects and those in the older subjects, respectively.

In this study, with PK sampling to 96 hours post dose, terminal t½ for plasma FIX activity averaged 28 hours in the paediatric subjects and 40 hours in the older subjects. Estimates for t1/2 using truncated data at 72 hours were shorter, averaging 24 and 30 hours for paediatric and older subjects, respectively. With data truncated at 50 hours, the estimates for t1/2 were lower at 18 and 27 hours for paediatric and older subjects, respectively.

Efficacy

There were no efficacy evaluations done in this study.

Safety

Safety was assessed on all subjects who received at least one dose of BeneFIX during the study through last subject visit and included adverse events (AEs) and serious adverse events (SAEs), vital signs, physical examination, and laboratory evaluations. Any clinical laboratory, electrocardiogram (ECG), blood pressure (BP), and pulse rate abnormalities of potential clinical concern were to be described.

Methods

The investigator was to obtain and record on the CRF/DCT (data collection tool) all observed or volunteered AEs, the severity (mild, moderate, or severe) of the events, and the investigator's opinion of the relatedness to the study treatment. Adverse events were to include adverse drug reactions, illnesses with onset during the study, and exacerbation of previous illnesses. Additionally, the investigator was to record as AEs any clinically significant changes in physical examination findings and abnormal objective test findings (eg, ECG, laboratory).

For all AEs, the investigator was to pursue and obtain information adequate to determine both the outcome of the AE and whether it met the criteria for classification as an SAE.

Results

There were no AEs or study discontinuations reported in this study. Inhibitor against FIX has not been reported, no thrombogenicity or allergic reactions were reported during the study. There were no clinically meaningful median changes from baseline to last observation for laboratory parameters. Mean changes for supine systolic BP, diastolic BP, and supine pulse rate were small and not considered clinically relevant. One subject (10 years old) had a ≥20 mm Hg decrease from baseline in supine diastolic BP that met the categorical summarization criteria. The subject's supine diastolic BP at baseline was 70 mm Hg and at 96 hours post dose was 50 mm Hg with the reported decrease of ≥20 mm Hg not considered clinically significant by the Investigator. There were no abnormal vital sign values reported as AEs.

2.3.3. Discussion on clinical aspects

Continuing the duration of sample collection after administration of BeneFIX 50 IU/mL to 96 hours resulted in estimates of $t_{1/2}$ at 27.9 ±4.5 hours in paediatric subjects and 39.6 ±7.4 hours in older subjects.

Paediatric subjects had higher CL and shorter t½ compared with older subjects in this study.

Single doses of BeneFIX 50 IU/kg were safe and well tolerated in male Chinese subjects aged ≥6 years old with haemophilia B.

Based on the pharmacokinetic and safety results for the paediatric subjects in this study, the overall benefit-risk profile of BeneFIX remains favorable for paediatric subjects.

3. Rapporteur's overall conclusion and recommendation

As requested by Article 46 of the Pediatric Regulation (EC) No 1901/2006 the MAH provided the results of the use of BeneFIX in the pediatric study population of Clinical Study B1821048. Four out of 12 enrolled subjects were pediatric patients (≥6 to < 12 years). From the presented data, no issues have been identified for changing the product information concerning use of BeneFIX in pediatric patients.

☒ Fulfilled:

No regulatory action required.