Pharmacokinetics, Efficacy, and Safety of Nonacog Alfa in Previously Treated Patients with Moderately Severe to Severe Hemophilia B

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ABSTRACT

Purpose: Nonacog alfa, a recombinant factor IX (FIX) product, is used for FIX replacement in the treatment and prevention of bleeding events in patients with hemophilia B. This study aimed to provide supplemental pharmacokinetic (PK), efficacy, and safety data for nonacog alfa when administered as part of usual hemophilia care, including on-demand treatment, routine prophylaxis, and surgical prophylaxis.

Methods: Men with previously treated severe or moderately severe hemophilia B (FIX activity ≤2%) were enrolled in this prospective, open-label, nonrandomized, multicenter study. An initial 72-hour PK assessment was performed wherein patients received a single dose of nonacog alfa (75 IU/kg) as an infusion over 10 minutes. A final 72-hour PK assessment was performed at the patient's last visit, after a minimum washout period of 4 days. Correlations between C_{max} after the first dose and body weight and body mass index (BMI) were assessed post hoc using Spearman test after evaluating normality.

Findings: In total, 23 patients (age, 12–59 years; weight, 44–173 kg; and BMI, 16.3–45.1) with previous exposure to FIX products (median, 460 days; range, 150–2400 days) were enrolled; 21 were evaluable for efficacy. The median number of exposure days per efficacy-evaluable patient in this study was 48 (range, 31–103). The FIX activity profiles showed multiphasic disposition characteristics, with initial mean (SD) PK profiles as follows: C_{max}, 61.4 (12.5) IU/dL; AUC_{∞}, 1055 (227) IU·h/dL; $t_{½}$, 23.7 (5.6) hours; and recovery, 0.818 (0.167) IU/dL. Mean plasma FIX activity versus time profiles were essentially identical upon initial exposure and after repeated use (n = 17), and bioequivalence was confirmed. No apparent relationship was observed between C_{max} and either body weight ($P > 0.1732$) or BMI ($P > 0.1235$).

Implications: The FIX activity profile after administration of nonacog alfa is predictable and is not altered after repeated exposure during usual hemophilia care. PK parameters are consistent with nonacog alfa use for FIX replacement in on-demand treatment, routine prophylaxis, and surgical prophylaxis in patients with hemophilia B. (*Clin Ther.* 2016;38:936–944)

Key words: BeneFIX, factor IX, hemophilia B, nonacog alfa, pharmacokinetics.

INTRODUCTION

Hemophilia B is a rare, X-linked coagulation disorder caused by a deficiency of functionally active coagulation factor IX (FIX) clotting activity. Much less common than hemophilia A, hemophilia B occurs in 1 in 25,000 male births and affects approximately 3300 people in the United States.[1,2] Hemophilia B is characterized by spontaneous or trauma-induced bleeding in joints and soft tissues.[3,4] Repeated bleeding events can lead to crippling chronic joint disease, pain, and reduced quality of life, and some severe bleeding events (eg, intracranial or gastrointestinal bleeding) may be life-threatening.[3–6] Approximately 60% to 70% of patients with hemophilia B have a moderate or severe form of the disease.[7]

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Usual care of patients with hemophilia B is based on replacement of missing or defective FIX with recombinant FIX products or plasma-derived FIX concentrates and, more recently with a long-acting FIX product.[3,4,6,8] Patients may receive FIX replacement as on-demand treatment for acute bleeding events or as prophylaxis, with scheduled dosing to maintain adequate FIX levels and reduce the risk of bleeding.[3] In clinical practice, pharmacokinetic (PK) parameters of FIX products are increasingly important for selecting optimal management strategies for individuals with hemophilia B.[9,10]

Nonacog alfa (BeneFIX; Pfizer, Philadelphia, Pennsylvania), a recombinant FIX product, was licensed in the United States in 1997 and in Europe in 1998 for the control and prevention of bleeding events and for perioperative prophylaxis in adult and pediatric patients with hemophilia B.[11,12] Clinical data have established the benefits and favorable safety profile of nonacog alfa for FIX replacement in previously treated and treatment-naive patients with severe or moderately severe hemophilia B.[13–19] Whereas PK characterization has been challenging due to the limited number of patients with hemophilia B available for participation in clinical studies involving collection of full PK data sets, a handful of small trials have reported estimates of PK parameters.[16,20–23] After a short intravenous infusion, C_{max} is observed and FIX activity decreases rapidly at first, followed by a slower elimination phase, usually characterized using a 2-compartment model. After administration 75 IU/kg nonacog alfa, the following mean (SD) parameters were reported in 24 patients aged 12 to 61 years: C_{max}, 54.5 (15.0) IU/dL; AUC_{∞}, 940 (237) IU · h/dL; $t_{½}$, 22.4 (5.3) hours; and recovery, 0.726 (0.200) IU/dL/IU/kg.[21] Another study reported the following mean (SD) values for 28 patients aged 15 to 40 years: $t_{½}$, 19.4 (5.5) hours; and recovery, 0.77 (0.20) IU/dL/IU/kg.[13]

Herein, we report supplemental PK data from a prospective, open-label, multicenter study of nonacog alfa in previously treated patients with moderately severe to severe hemophilia B. The objectives were to better characterize PK parameters, both initially and after repeated nonacog alfa exposure with usual hemophilia B care (including on-demand treatment, routine prophylaxis, and surgical prophylaxis), collect additional efficacy and safety data, and examine the relationship between patient body weight and body mass index (BMI) and C_{max} of FIX activity.

PATIENTS AND METHODS

Study Design

The study protocol and amendments were approved by the institutional review board or ethics committee at each participating site, and the study was conducted in accordance with the ethical principles of the Declaration of Helsinki and the International Conference on Harmonisation Guidelines for Good Clinical Practice. This open-label, nonrandomized, multinational, multicenter study involved FIX activity PK assessments (at the start and end of the study after repeated exposure) after nonacog alfa administration, as well as efficacy and safety evaluations during usual hemophilia B care. For PK assessments, nonacog alfa (75 IU/kg) was administered as an infusion over 10 minutes. After the initial PK assessment, patients received nonacog alfa per their standard-of-care treatment regimen (eg, on-demand, prophylactic, and/or for surgery if needed during the study) for at least 6 months and up to 12 months, until a minimum of 30 exposure days was reached. The dose and frequency of infusions administered for on-demand treatment and as prophylaxis regimens were determined individually for each patient and clinical situation, and were at the investigator's discretion. Doses were adjusted to the patient's clinical response and, when indicated, FIX activity levels. Routine clinical and laboratory evaluations were performed every 3 months during the course of the study.

Patients

Eligible participants were aged at least 12 years, had moderately severe to severe hemophilia B (FIX activity [FIX:C] $\leq$2%), had previous treatment of at least 150 exposure days with any FIX replacement product(s), and had no history or current evidence of an FIX inhibitor. Patients had adequate hepatic, renal, and immune functions (alanine and aspartate aminotransferases or total bilirubin $\leq$2.5 times the upper limit of normal [ULN], serum creatinine $\leq$1.25 times ULN, or absolute CD4 count $>$400/μL, respectively) and had prothrombin times $\leq$1.25 times ULN and platelet count $\geq$100,000/μL. All patients (or parent/legal representative) provided written informed