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PROPRIETARY DRUG NAME® / GENERIC DRUG NAME: BeneFIX® / Nonacog Alfa / Recombinant Factor IX

PROTOCOL NO.: 3090X1-4405 (B1821006)

PROTOCOL TITLE: Reformulated BeneFIX Efficacy and Safety After Conversion From a Plasma-Derived Factor IX (pdFIX)

Study Center: The study was conducted at 1 site in France.

Study Initiation and Final Completion Dates: 20 May 2008 to 20 January 2009

The study was terminated because of slow enrollment.

Phase of Development: Phase 4

Study Objectives: The purpose of this study was to collect data around the period of the conversion from pdFIX to BeneFIX in subjects for whom a conversion to BeneFIX has already been decided by the Investigator.

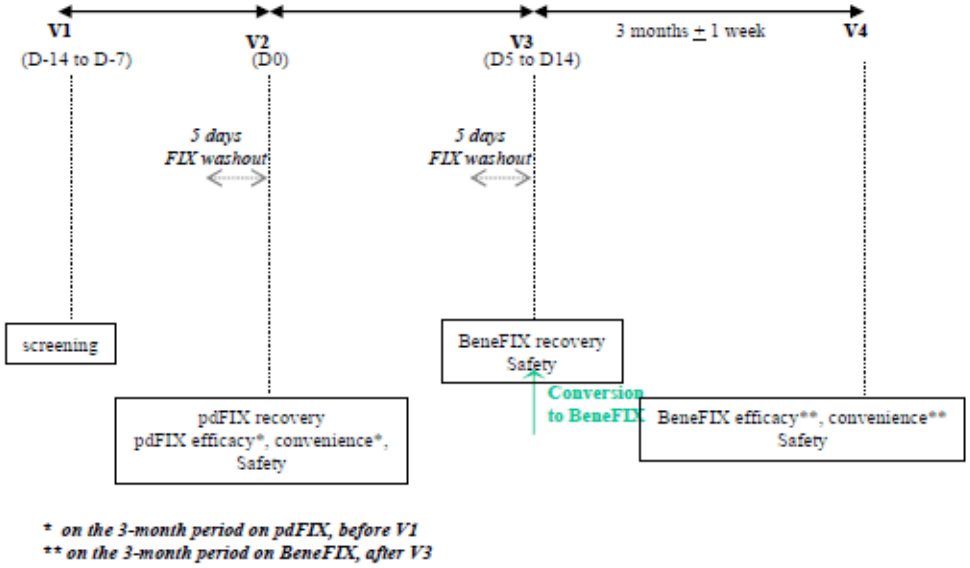
The main following parameters were collected:

- A retrospective history of the bleedings in the 3-month period before the conversion
- The recovery with the pdFIX (just before the conversion)
- The recovery with BeneFIX (just after the conversion)
- A prospective history of the bleedings in the 3-month period following the conversion
- BeneFIX safety data after the conversion
- Convenience evaluation with pdFIX (retrospective) and BeneFIX (prospective)

METHODS

Study Design: This was a prospective, interventional, open-label, non-randomized, multicenter study to compare efficacy, convenience, and safety of the conversion to BeneFIX (ie, a recombinant Factor IX recovery after a pdFIX recovery) in subjects with moderate to severe hemophilia B on previous treatment with pdFIX (Figure 1).

Figure 1 Overview of Study Design



The study duration was planned to be approximately 16 months: 12 months for enrollment and 3.5 to 4 months for subject participation.

The study flowchart is presented in Table 1.

Table 1. Study Flowchart

Study Procedures	**Days -14 to -7**	**Day 0**	**Day 5[a]**	**M3[b]**
Study Interval	**Screening**	**Inclusion and pdFIX Recovery**	**BeneFIX Recovery**	**Study End**
Visit Identification	**1**	**2**	**3**	**4**
Informed consent	X			
Demographics	X			
Medical history	X			
Physical examination	X			X
Vital signs		X	X	
Height		X		
Weight		X	X	X
Laboratory evaluation	X	X	X	X
pdFIX administration (recovery)		X		
Conversion to BeneFIX:				
BeneFIX administration (recovery)			X	
Recovery blood sample collection		X	X	
Efficacy evaluation		X		X
Safety evaluation	X	X	X	X
Convenience evaluation		X		X
Concomitant medications	X	X	X	X

pdFIX = plasma-derived Factor IX.
a. No later than 2 weeks after Visit 2.
b. Three months after Visit 3 (window ±1 week).

Number of Subjects (Planned and Analyzed): The study was planned to enroll 20 subjects. Only 1 subject was enrolled at 1 center in France.

Diagnosis and Main Criteria for Inclusion: The study included male subjects, ≥ 12 years of age, with moderately to severe hemophilia B (Factor IX activity ≤2%) for whom the switch from pdFIX to BeneFIX has already been decided by the Investigator and subjects previously treated with ≥150 exposure days to any Factor IX (FIX) product. The subject should have absolute cluster of differentiation 4 count ≥300/μL and normal platelet count (≥100'000/μL). Subject was in a non-bleeding state and has not received any coagulation FIX within 5 days of recovery.

Study Treatment: The study treatments BeneFIX 50±5 IU/kg and pdFIX 50±5 IU/kg (powder and diluent) were administered intravenously. For FIX recovery, subjects were to receive a single dose of 50±5 IU/kg of pdFIX at Visit 2 and a single dose of 50±5 IU/kg of BeneFIX at Visit 3 (Figure 1). During the 3-month observational follow-up period (Visit 3 to Visit 4), the BeneFIX dose and frequency of administration were to be adapted to the clinical response of the individual subject.

The total length of time a subject participating in the study was estimated between 3.5 to 4 months, including the screening period between Visit 1 and Visit 2, the 5 to 14-day FIX washout between Visit 2 and Visit 3, and the 3-month ±1 week follow-up period between Visit 3 and Visit 4.

Efficacy Endpoints:

- Number/location of bleeding episodes
- Number of injections per bleeding episode
- Factor IX consumption
- Global assessment of efficacy by the Investigator and the subject

Assessment Scale for Efficacy: The global assessment (ie, subjective evaluation by Investigator and subject) of efficacy was based on the following 4-point scale: Very good / Good / Moderate / Poor. Subjects completed the efficacy evaluation without the help of the Investigator.

Convenience: Convenience evaluations were performed at Visit 2 (retrospectively on the last 3-month period with pdIX) and at Visit 4 (on the 3-month period with BeneFIX). It was performed by the subject, according to the following 4-point scale: Very good/Good/Moderate/Poor. The subject completed the convenience evaluation without the help of the Investigator.

Safety Evaluations: All serious adverse events (SAEs) that occur from time of consent and events of special interest (development of FIX inhibitor, lack of effect/low recovery, thrombogenicity, FIX hypersensitivity reaction, red blood cell agglutination) would be

collected and reported within 24 hours to Sponsor by the Investigator. Other adverse events (AEs) were collected in the case report form.

Statistical Methods: Since only one subject was included in the study, no electronic database was set up and no statistical analysis was performed. Only descriptive results were presented.

RESULTS

Subject Disposition and Demography: Only 1 male subject, a 27 years old severe hemophilia B subject (FIX activity <1%), was enrolled in the study on 20 May 2008. This subject completed the study on 20 January 2009.

Efficacy Results: The subject did not attend the Visit 4 at the scheduled time: the time between Visit 3 and Visit 4 was 32 weeks (around 8 months) instead of 3 months (window ±1 weeks). The interval between the other visits was respected.

The incremental recovery and the in vivo recovery were higher with pdFIX (1.415 IU/dL per IU/kg injected and 68.49 %) than with BeneFIX (1.159 IU/dL per IU/kg injected and 54.14 %) (Table 2).

Table 2. FIX Activity and Recovery

Visit	Total Dose Administered (IU)	Dose Administered (IU/kg)	FIX activity					FIX recovery	
			t0 (IU/dL)	t15 (IU/dL)	t30 (IU/dL)	t60 (IU/dL)	C_{max} (IU/dl)	Incremental Recovery (IU/dL per IU/kg)	In Vivo Recovery (%)
Visit 2	4240	53.0	0	70	73	75	75	1.415	68.49
Visit 3	4020	50.9	0	59	56	48	59	1.159	54.14

C_{max} = the maximum activity values; FIX = Factor IX; t = time point.

The subject was treated on-demand with plasma-derived Factor IX (BetaFact) during the 3-month period before Visit 1 and with non-investigational BeneFIX during the 3-month period after Visit 3. During these periods, the subject experienced 5 spontaneous bleeding episodes with pdFIX and 5 spontaneous bleeding episodes with BeneFIX (Table 3).

Table 3. Bleeding Episodes

	Number of Episodes	Number of Injections Per Bleeding Episode	Factor IX Consumption for all Bleeding Episodes	Factor IX Consumption for Surgery
3 months before Visit 1	5 (spontaneous)	1	16 000 IU	No surgery
3 months after Visit 3	5 (spontaneous)	1 for 4 episodes 2 for 1 episode	18 000 IU	No surgery

During the period between the end of the 3-month period after Visit 3, and Visit 4, the subject received non-investigational BeneFIX for 4 spontaneous bleeding and 1 lumbar puncture.

Subjective evaluation of efficacy with pdFIX during the 3-month period before Visit 1 was evaluated by both the subject and the Investigator as "good". Subjective evaluation of efficacy with BeneFIX during the 3-month period after Visit 3 was evaluated by both the subject and the Investigator as "very good" (Table 4).

Table 4. Subjective Evaluation of Efficacy

	Investigation	Subject
3 months before Visit 1 (pdFIX)	Good	Good
3 months after Visit 3 (BeneFIX)	Very Good	Very Good

pdFIX = plasma-derived Factor IX.

The convenience with plasma-derived Factor IX during the 3-month period before Visit 1 was evaluated by the subject and the Investigator as "good". The convenience with BeneFIX during the 3-month period after Visit 3 was evaluated by the subject and the Investigator as "very good" (Table 5).

Table 5. Convenience Evaluation

	Overall Convenience	Ease of Reconstitution	Rapidity of Dissolution	Ease of Injection
3 months before Visit 1	Good	Good	Moderate	Moderate
3 months after Visit 3	Very Good	Very Good	Very Good	Very Good

Safety Results: The subject reported 4 AEs (allergic rhinitis, diarrhea, acute renal failure, lower back pain) and 1 SAE (Herpes simplex virus-2 [HSV-2] meningitis) during the study. None was considered related to the study drug by the Investigator.

The subject's concurrent illness included selective IgA immunodeficiency with a past history of HSV-2 meningitis and hepatitis C. The subject was hospitalized and diagnosed with meningitis due to HSV-2 (meningitis herpes) considered a Mollaret meningitis as it was a recurrent HSV2 meningitis on 19 November 2008. The subject was treated with Aciclovir which leads to acute renal failure and it disappeared after discontinuation of Aciclovir. The subject was recovered on 01 December 2008. The Investigator considered meningitis due to HSV-2 not related to the study treatment.

CONCLUSION: Only 1 subject was enrolled in this prematurely closed study (due to difficulties of recruitment) and thus there is no conclusion to be drawn regarding the initial objectives.