Long-term safety and efficacy of recombinant fusion protein linking coagulation factor IX with albumin (rIX-FP) in previously treated patients with hemophilia B

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Introduction

- A fusion protein genetically linking recombinant human coagulation FIX with recombinant human albumin (rIX-FP; Figure 1) has been developed with an improved PK profile, improving hemophilia B treatment by allowing less frequent dosing than required with standard plasma-derived (pd) and recombinant (r) FIX products
- The PROLONG-9FP clinical program has evaluated the use of rIX-FP for prophylaxis and on-demand treatment of bleeding in patients with severe hemophilia B. The clinical program is comprised of five clinical studies, including four completed studies (a Phase I pharmacokinetic [PK] study, a Phase II study, and two Phase III studies in adults and children), and an ongoing extension study, which includes previously untreated patients. Over 100 subjects from 42 hemophilia treatment centers in 12 countries have participated in the PROLONG-9FP clinical program (Figure 2)
- Here, we report on the long-term safety and efficacy of rIX-FP in 15 subjects who have continuously participated in three clinical studies (Phase II, Phase III and the ongoing Phase III extension studies) over a period of 4 years

Figure 1. Structure of rIX-FP

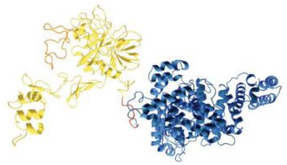
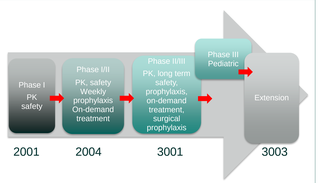


Figure 2. Overview of PROLONG-9FP Program



Objective and Methods

Objective
- To evaluate the safety, efficacy and PK of rIX-FP, during weekly (7-day) and 14-day prophylaxis in three studies; Phase II, Phase III and Phase IIIb

Methods
- Prospective, multicenter, open-label studies in subjects (12–65 years) to evaluate the safety, PK and efficacy of rIX-FP
- Previously treated patients (PTPs) with severe or moderately severe hemophilia B (FIX ≤2%) and no history of inhibitors
- Phase II 2004 study: subjects began either weekly prophylaxis treatment (PT) or on-demand treatment (ODT) with rIX-FP and continued that treatment regimen in the Phase III 3001 study
- Phase III 3001 study: ODT subjects received only ODT for 6 months and then switched to 7-day PT; PT subjects received 7-day PT for 6 months, and eligible subjects switched to 10- or 14-day PT interval
- Phase IIIb 3003 study: subjects received PT of 7-, 10-, 14- or 21-days

Results

Demographics
- 15 males (15–46 years) with hemophilia B (FIX ≤2%) (Table 1)

Safety and exposure
- No inhibitors to FIX or antibodies to rIX-FP
- Median number of exposure days (EDs) was 220 (range 151–249) for patients on prophylaxis and 138 EDs (range 121–145) for those initiating ODT (Table 2)
- Overall patients had a median (range) of 4.6 (3.2–4.7) years on rIX-FP

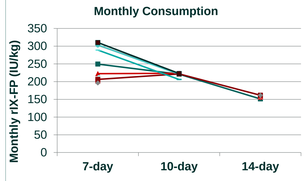
Table 1. Demographics and Baseline Characteristics

	Prophylaxis Treatment N=11	On-demand Treatment N=4	Total N=15
Age, y, mean (range)	24.5 (15–42)	35.8 (27–46)	27.5 (15–46)
<18 years, n (%)	2 (18.2)	0	2 (13.3)
Race			
White	11 (100.0)	4 (100.0)	15 (100.0)
Total ABR prior to study entry, mean (SD)	10.5 (15.63)	27.0 (3.37)	14.9 (15.28)
AsBR prior to study entry, mean (SD)	6.0 (10.99)	27.0 (3.37)	11.6 (13.46)
Prior treatment			
Prophylaxis, n (%)	9 (81.8)	0	9 (60.0)
On-demand, n (%)	2 (18.2)	4 (100.0)	6 (40.0)
HIV, n (%)	0	0	0
HBV, n (%)	0	1 (25.0)	1 (5.9)
HCV, n (%)	3 (27.3)	2 (50.0)	5 (33.3)
Hemophilic arthropathy, n (%)	5 (38.5)	4 (100.0)	9 (52.9)

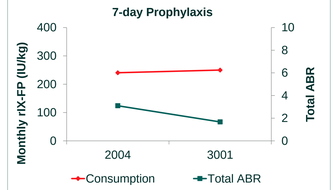
Demographics and baseline characteristics at the time of entry into the PROLONG-9FP program in study 2004

Efficacy
- Monthly consumption decreased with longer prophylaxis intervals
- Total annualized bleeding rate (ABR) decreased over time on rIX-FP, while maintaining constant monthly consumption

Monthly Consumption of rIX-FP Across Regimens



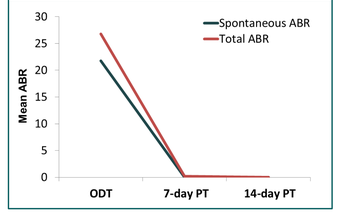
Total ABR and Monthly Consumption of rIX-FP in 7-day Prophylaxis



Results (cont.)

Efficacy
- Reduction of ABR with prophylaxis treatment in ODT patients
- Total ABR and annualized spontaneous bleeding rate (AsBR) decreased with increasing time on rIX-FP, even while lengthening the prophylaxis treatment interval

Reduction of Total ABR and AsBR with ODT to PT



Reduction of AsBR with Prophylaxis Treatment

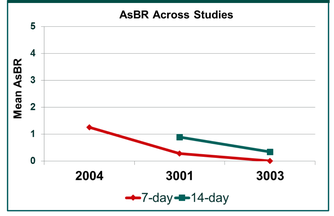


Table 2. Exposure to rIX-FP and Time on Study

	Prophylaxis N=11	On-demand* N=4	Total N=15
EDs, median (range)	220 (151–249)	138 (121–145)	182 (121–249)
Months on rIX-FP, median (range)	56.6 (53.5–57.3)	50.3 (39.1–52.6)	56.4 (39.1–57.3)
Years on rIX-FP, median (range)	4.6 (4.4–4.7)	4.1 (3.2–4.3)	4.6 (3.2–4.7)

*Patients started with on-demand treatment then switched to prophylaxis treatment during the 3001 study

Discussion and Conclusion

Long-term use of rIX-FP is safe and well-tolerated. No subjects developed inhibitors to FIX or antibodies to rIX-FP during the 4-year treatment period, with a mean of 180 EDs for PT subjects and 125 EDs for ODT subjects. ABR decreased over time with rIX-FP prophylaxis, and longer treatment intervals were possible with no increase in consumption.

Disclosures

ES received honoraria for speaking and/or for consulting from CSL Behring, Bayer, Baxter/Baxalta, Pfizer, Novo Nordisk, Roche, Sobi/Biogen Idec, Biotest, Kedrion, Octapharma and Grifols and received unrestricted research grants from NovoNordisk and Pfizer; IJ, CV and DW are employed at CSL Behring

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