Effect of once-weekly prophylaxis treatment with a recombinant fusion protein linking coagulation factor IX with albumin (rIX-FP) on target joints in patients with hemophilia B during the PROLONG-9FP clinical trial program

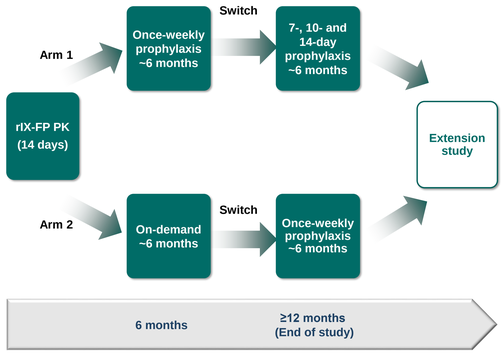
Hanabusa H[1], Négrier C[2], Laws H-J[3], Lissitchkov T[4], Castaman G[5], Tagliaferri A[6], Fukutake K[7], López Fernández MF[8], Voigt C[9], Wolko D[9], Jacobs I[9], Santagostino E[10]

[1]Department of Hematology, Ogikubo Hospital, Tokyo, Japan; [2]Centre Régional de Traitement de l'Hémophilie, Hôpital Edouard Herriot, University Claude Bernard, Lyon, France; [3]Department of Pediatric Oncology, Hematology and Clinical Immunology, University, Düsseldorf, Germany; [4]Department of Coagulation Disorders and Anemia, SHAT Joan Pavel, Sofia, Bulgaria; [5]Haemophilia and Thrombosis Centre, Department of Haematology, San Bortolo Hospital, Vicenza, Italy, and Center for Bleeding Disorders, Careggi University Hospital, Florence, Italy; [6]Regional Reference Centre for Inherited Bleeding Disorders, University Hospital, Parma, Italy; [7]Department of Clinical Laboratory Medicine, Tokyo Medical University, Tokyo, Japan; [8]Complejo Hospitalario Universitario A Coruña, Spain; [9]CSL Behring, CRD, King of Prussia, PA, USA; [10]Angelo Bianchi Bonomi Hemophilia and Thrombosis Center, IRCCS Ca' Granda Foundation, Maggiore Hospital Policlinico, Milan, Italy

Introduction

- rIX-FP is a fusion protein genetically linking rFIX with recombinant human albumin via a cleavable linker
- Joint bleeds are the most common complication in patients with severe hemophilia B and can cause debilitating arthropathy
- The safety and efficacy of rIX-FP as prophylactic and on-demand therapy has been evaluated in the PROLONG-9FP clinical program
- Adult and adolescent patients recruited into the Phase II/III trial (study 3001) received either once-weekly prophylaxis for 6 months before switching to 7-, 10- or 14-day prophylaxis (prophylaxis arm), or on-demand treatment for 6 months followed by once-weekly prophylaxis (on-demand arm) for a further 6–12 months (Figure 1)
- Pediatric patients participating in a Phase III study (study 3002) received once-weekly prophylaxis for approximately 12 months

Figure 1. Study design for the Phase II/III clinical trial (Study 3001)



Objective

- To determine the efficacy of rIX-FP on target joint bleeds in adult, adolescent and pediatric patients

Methods

Patients

- Previously treated patients, 12–65 years (study 3001) or <12 years (study 3002) with hemophilia B (FIX ≤2%)
- Key inclusion criteria:
  - 6–65 years: ≥150 exposure days (EDs) to FIX replacement therapy
  - <6 years: ≥50 EDs
  - No history, or family history, of FIX inhibitor, and no detectable inhibitors at screening
- For on-demand patients (study 3001):
  - A minimum average of two treated non-trauma-induced bleeding episodes per month in the 3–6 months prior to screening
  - Willingness to switch to a prophylaxis regimen
- Patients with target joints (joint with ≥3 bleeds in 6 months) were identified and the annualized joint bleeding rate compared prior to prophylaxis or prior to study entry

Results

Study 3001

- Prior to entry, target joints were reported in 52.5% (21/40) of patients receiving routine prophylaxis and 60.9% (14/23) of those treated on-demand (**Table 1**).
- Of the 19 on-demand patients who switched to weekly prophylaxis with rIX-FP after 6 months (on-demand arm), 10 (52.6%) had target joints at the start of the study.

Table 1. Baseline patient characteristics

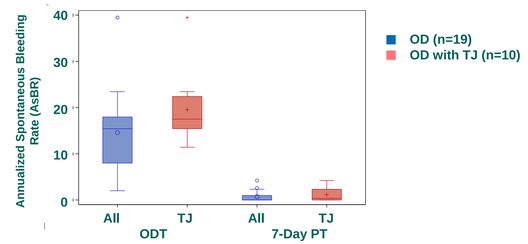
	Study 3001			Study 3002		
	Prophylaxis (n=40)	On-demand (n=23)	Total (n=63)	0–5 years (n=12)	6–11 years (n=15)	Total (n=27)
Age (years), mean (SD)	31.6 (15)	35.3 (11)	33.0 (14)	3.2 (1–5)	8.1 (6–10)	5.9 (1–10)
White, n (%)	33 (83)	19 (83)	52 (83)	11 (92)	15 (100)	26 (96)
European, n (%)	21 (53)	15 (65)	36 (57)	8 (67)	10 (67)	18 (67)
Previous regimen, n (%)						
On-demand		23 (100)		1 (9)	2 (7)	3 (7)
Prophylaxis	40 (100)			10 (91)	10 (83)	20 (83)
Chronic hemarthrosis/target joint, n (%)	21 (53)	14 (61)		1 (6.7)	2 (16.7)	3 (11)
ABR prior, median (range)	2.0 (0–14)	23.5 (10–50)		2.0 (0–42)	3.0 (1–34)	3.0 (0–42)

- Following 6 months of on-demand treatment with rIX-FP, 47.3% (9/19) patients had confirmed target joints. 100% of these resolved after patients switched to once-weekly prophylaxis
- Median annualized joint bleeding rate (joint ABR) fell from 15.3 with on-demand therapy (n=23) to 1.19 with weekly prophylaxis (n=19)
- Median joint ABR was 0.00 with all prophylaxis regimens

Results (cont.)

- Similarly, median and mean AsBR decreased markedly when patients switched from on-demand treatment to weekly prophylaxis (Figure 2)

Figure 2. AsBR in patients with and without target joints, comparing on-demand with prophylaxis treatment



OD, on-demand; ODT, on-demand treatment; PT, prophylaxis treatment; TJ, target joints
bar within box = median; o/+ within box = mean; box = IQR; whiskers = min, max

Study 3002

- In the pediatric study, target joints were reported in three patients on prophylaxis prior to study entry
- All target joints resolved with once-weekly rIX-FP prophylaxis treatment.
- Median joint ABR was 0.5 and 1.13 in patients aged 1–5 years (n=12) and 6–11 years (n=15), respectively, and 0.99 overall (n=27)

Conclusions

- Results from the rIX-FP clinical program have demonstrated that weekly prophylaxis resolved all target joints in both adult and pediatric patients
- rIX-FP is effective, not only for the prevention of bleeding episodes, but for resolving target joints in previously on-demand or under-treated prophylaxis patients

Disclosures

CN: grant/research support from Alnylam, Baxter, Bayer, Biogen Idec/Sobi, CSL Behring, Inspiration, Novo Nordisk, Octapharma and Pfizer, honoraria from Biogen Idec, Baxter, Bayer, CSL Behring, LFB, Novo Nordisk and Pfizer, travel support from Baxter, CSL Behring, Novo Nordisk and Octapharma; MLF: grant/research support from Baxalta, conference fees from Baxalta, Bayer, Amgen and Sobi; HH, H-JL, TL, GC, AT, KF: none declared; CV, DW and IJ are employees of CSL Behring; ES: grant/research support received from Pfizer, consultant for Bayer, Baxalta, CSL Behring, Novo Nordisk, Sobi/Biogen Idec, Pfizer, Roche, Grifols and Octapharma