Efficacy and safety of long-acting recombinant fusion protein linking factor IX with albumin (rIX-FP) in hemophilia B patients undergoing surgery

Négrier C[1], Karim FA[2], Lepatan LM[3], Lienhart A[1], López Fernández MF[4], Mahlangu J[5], Pabinger I[6], Li Y[7], Wolko D[7], Voigt C[7], Jacobs I[7], Santagostino E[8]

[1]Centre Régional de Traitement de l'Hémophilie (CRTH)/Unite d'Hemostase Clinique, Hôpital Cardiologique Louis Pradel, University Lyon I, France; [2]National Blood Centre, Kuala Lumpur; [3]Perpetual Succour Hospital, Cebu City, Philippines; [4]Complexo Hospitalario Universitario A Coruña, A Coruña, Spain; [5]Haemophilia Clinic, Comprehensive Care Centre Charlotte Maxeke Johannesburg Academic Hospital and Faculty of Health Sciences, University of the Witwatersrand and NHLS South Africa; [6]Clinical Division of Haematology and Haemostaseology, Medical Clinic I, Medical University Vienna, Vienna, Austria; [7]Clinical Research and Development, CSL Behring, King of Prussia, PA, USA; [8]Angelo Bianchi Bonomi Hemophilia and Thrombosis Center, IRCCS Ca' Granda Foundation, Maggiore Hospital Policlinico, Milan, Italy

Introduction

- A recombinant fusion protein linking recombinant coagulation factor IX (FIX) with recombinant human albumin (rIX-FP) has been developed to extend the plasma half-life of FIX[1,2]
- A surgical substudy was included in the Phase III studies as part of the global PROLONG-9FP clinical program to evaluate safety and efficacy in the perioperative setting

Objectives

- To evaluate the safety and efficacy of rIX-FP in the prevention and control of bleeding in patients with severe hemophilia B (FIX ≤2%) undergoing surgery

Methods

- Adult and pediatric moderately severe to severe hemophilia B patients (FIX ≤2%) participating in three Phase III clinical trials and undergoing a minor or major surgical procedure were included as part of the substudy
- All subjects continued on rIX-FP prophylaxis post-surgery
- Preoperatively the subject received a bolus dose of rIX-FP to increase the FIX level to 80% or higher
- FIX activity level was maintained at 60–80% during surgery according to WFH guidelines.
- Postoperatively the subject was to receive dosing up to 14 days (or longer if needed) depending on the FIX levels, type of surgery and WFH guidelines
- Efficacy was evaluated by:
  - Investigator assessment (4-point scale)*
  - Predicted and estimated actual blood loss by surgeon/investigator
  - Consumption of rIX-FP during the 14-day perioperative period
- Safety was assessed by inhibitors to FIX and adverse events (AEs)

*Investigator's Evaluation of Efficacy of Surgical Treatment: **Excellent**: hemostasis clinically not significantly different from normal in the absence of other hemostatic intervention or estimated actual blood loss during surgery is not more than 20% higher than the estimated predicted blood loss for intended surgery. **Good**: Normal or mildly abnormal hemostasis in terms of quantity and/or quality or estimated actual blood loss is greater than 20% but ≤30% higher than estimated predicted blood loss. **Moderate**: Moderately abnormal hemostasis in terms of quantity and/or quality with estimated blood loss greater than what is defined as good. **Poor/No Response**: Severely abnormal hemostasis in terms of quantity and/or quality and/or additional hemostatic intervention required with another Factor IX product for complete resolution.

Disclosures

CN: grant/research support from Alnylam, CSL Behring, Novo Nordisk and Pfizer, consultancy fees from Baxter, CSL Behring, LFB, Novo Nordisk and Octapharma; FK, LML, AL, MLF: none declared; JM: grant/research support from Baxalta, Bayer, Biogen, CSL Behring, NovoNordisk and Roche and consultancy for Amgen, Biotest, Baxalta, Bayer, Novo Nordisk and Roche; IP: grant/research support received from CSL Behring, consultancy from CSL Behring, Pfizer, Bayer and Novo Nordisk, speaker's fees from CSL Behring, Bayer, Pfizer and Biotest; YL, DW, CV and IJ are all 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

Results

Table 1. Hemostatic response to rIX-FP administered for major orthopedic surgeries

Surgical procedures	Age at screening	Assessment of hemostasis response*	Total no. of inj	Total rIX-FP consumption (IU/kg)†	Estimated blood loss (mL)‡		Unplanned transfusions
					Predicted	Actual	
Right ankle arthroplasty	50	Excellent	6	340	250–300	250	None
Total knee replacement	51	Good	6	375	200	200	None
Total knee replacement	49	Excellent	7	295	30–100	50	None
Total knee replacement (L)	43	Excellent	7§	380	1500–2000	500	None
Total knee replacement (R)	43	Excellent	7§	340	1500–2000	450	None
Total knee replacement	48	Good	9	458	300–400	500	None
Total knee replacement	37	Excellent	8	506	150–200	50	RBC
Total knee replacement	21	Excellent	7	430	150–200	55	RBC
Total knee replacement	57	Excellent	12	356	790–2000	600	None

RBC, red blood cells; rIX-FP, recombinant factor IX fusion protein
*Where multiple assessments were done over the postoperative period, the lowest rating was used, regardless of time point
†During the 14-day perioperative period, including preoperative dose and doses up through and including day 14
‡Based on the preoperative predicted surgical blood loss for a subject without hemophilia undergoing the same type and extent of surgical procedure
§The 14-day surgical period included both total knee replacements

Table 2. Hemostatic response to rIX-FP administered for non-orthopedic, major and minor surgeries

Surgical procedures	Age at screening	Assessment of hemostasis response*
Double mastectomy	43	Excellent
Endoscopic mucosal resection	56	Excellent
Excision of pigmental nevus	5	Excellent
Hemorrhoidal ligation and rectopexy	39	Excellent
Rhinoplasty; submucosal resection and inferior turbinectomy	19	Excellent
Tooth extraction	42	Excellent
Tooth extraction	14	Good
Teeth extraction (2)‡	9	Excellent
Teeth extraction (4)‡	8	Good
Dental root canal	31	Excellent
Circumcision	13	Excellent
Circumcision	24	Excellent

rIX-FP, recombinant factor IX fusion protein
*Where multiple assessments were done over the postoperative period, the lowest rating was used regardless of time point
‡Number of teeth extracted in brackets

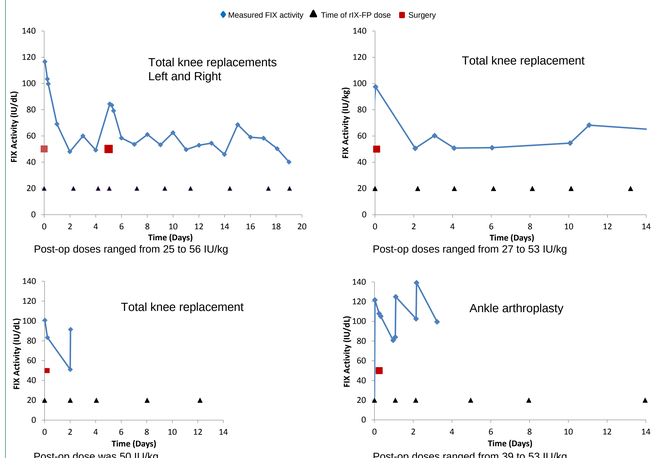
- A single preoperative dose maintained intraoperative hemostasis in 20 of 21 surgeries, and in 8 of 9 orthopedic surgeries. Overall perioperative consumption of rIX-FP was low at 375.3 IU/kg (295.5–506.7). The median consumption of rIX-FP for orthopedic surgeries was 87 IU/kg preoperatively and 375 IU/kg overall

References

1. Santagostino E, Negrier C, Klamroth R, *et al. Blood* 2012;120:2405–2411
2. Martinowitz U, Lissitchkov T, Lubetsky A, *et al. Haemophilia* 2015;21:784–90
3. Powell J, Apte S, Chambost H, *et al. British Journal of Haematology* 2015;168:124–34
4. Windyga J, Lissitchkov T, Stasyshyn O, *et al. Haemophilia* 2014;20:651–8

Results (cont.)

Figure 1. Measured factor IX activity and time of rIX-FP injections for orthopedic surgeries



Incremental recovery ranged from 1.0 to 1.2 IU/dL*IU/kg
Peak FIX activity levels not calculated

Conclusions

- rIX-FP will improve hemophilia B treatment by allowing less frequent dosing during surgery and the postoperative period compared with standard FIX products
- Over the 14-day postoperative period, use of rIX-FP results in less overall consumption and fewer injections than currently marketed FIX replacement products[3,4]
- A single preoperative dose maintained intraoperative hemostasis in 20 of 21 surgeries and in 8 of the 9 orthopedic surgeries
- Median number of rIX-FP injections over 14 days was 7 (range 6–7)
- Efficacy was evaluated by Investigator assessment (4-point scale) as excellent or good for all (100%) surgeries
- Overall, median consumption of rIX-FP from Day 0 to 14 was low at 375.3 IU/kg. The median consumption for orthopedic surgeries was 375 IU/kg
- No inhibitors to FIX or antibodies to rIX-FP were detected; no AEs were assessed by the Investigator as related to rIX-FP
- rIX-FP is safe and effective for use in all minor and major surgeries

Biotherapies for Life™ CSL Behring