Thrombosis Research 141S3 (2016) S5–S8

Contents lists available at ScienceDirect

Thrombosis Research

journal homepage: www.elsevier.com/locate/thromres

Review

Transforming the treatment for hemophilia B patients: update on the clinical development of recombinant fusion protein linking recombinant coagulation factor IX with recombinant albumin (rIX-FP)

Elena Santagostino*

Angelo Bianchi Bonomi Hemophilia and Thrombosis Center, IRCCS Cà Granda Foundation, Maggiore Hospital Policlinico and University of Milan, Milan, Italy

KEYWORDS

Hemophilia B
PROLONG-9FP
rIX-FP
Recombinant factor IX
On-demand
Prophylaxis

ABSTRACT

Recombinant fusion protein linking recombinant coagulation factor IX with recombinant albumin (rIX-FP; Idelvion®†) is an innovative new treatment designed to extend the half-life of factor IX (FIX) and ease the burden of care for hemophilia B patients. The rIX-FP clinical development program – PROLONG-9FP – is in its advanced phases, with pivotal studies in previously treated adults, adolescents, and pediatrics now completed. Across all age groups studied, rIX-FP has demonstrated a markedly improved pharmacokinetic profile compared with plasma-derived and recombinant FIX treatments, with a 30–40% higher incremental recovery, an approximately 5-fold longer half-life, a lower clearance, and a greater area under the curve. rIX-FP has been very well tolerated with an excellent safety profile. In the pivotal studies, there have been no reports of FIX inhibitors or antidrug antibodies, and few treatment-related adverse events have been observed. Prophylactic regimens of rIX-FP administered once weekly to once every 14 days have been highly effective. When used for surgical prophylaxis, a single infusion of rIX-FP has been sufficient to maintain hemostasis, even during major orthopedic surgery. An ongoing study is now enrolling previously untreated patients and evaluating the possibility of extending the dosing interval to every 21 days. There is little doubt that rIX-FP will transform the treatment of hemophilia B.

Introduction

Recombinant fusion protein linking recombinant coagulation factor IX with recombinant albumin (rIX-FP; Idelvion®†) is an innovative new treatment that was developed to extend the half-life of factor IX (FIX) and improve the lives of people with hemophilia B. The molecule was designed with a cleavable linker between the recombinant factor IX (rFIX) and the recombinant albumin moieties, allowing the fusion protein to benefit optimally from albumin's long half-life, while preserving the function of the wild-type coagulation factor [1,2]. The clinical development program for rIX-FP – PROLONG-9FP – was initiated in 2010 and is now in its advanced phases, with pivotal phase III studies in previously treated adults, adolescents, and pediatrics completed (Figure 1). A long-term extension study is ongoing. This paper provides an update on the clinical development of rIX-FP for the treatment of patients with hemophilia B.

Phase I study of the safety and pharmacokinetics (PK) of rIX-FP in previously treated adults and adolescents with severe hemophilia B

This first-in-human study enrolled 25 previously treated adolescents and adults (mean age 35 years; range 15–58 years) with severe hemophilia B (FIX activity ≤2%) and evaluated the safety and PK of single intravenous (IV) doses of rIX-FP at 25, 50, and 75 IU/kg when administered to patients in a non-bleeding state [3]. Patients who participated in the rIX-FP 50 IU/kg cohort also received a single 50 IU/kg dose of their previous FIX treatment for PK assessments. The primary objective of the study was to assess the safety of rIX-FP based on the occurrence of adverse events (AEs), inhibitors against FIX, antibodies against rIX-FP, local tolerability, physical examinations and vital signs, urinalysis, and laboratory assessments.

The tolerability of rIX-FP was found to be excellent in this study. There were no hypersensitivity reactions and no patients developed inhibitors to FIX or antidrug antibodies [3]. Only four AEs were considered to be possibly related to rIX-FP (mild headache, feeling hot 50 minutes after the injection, mild constipation, and mild erythema at the injection site), all of which resolved on the same day without treatment.

This study was the first to demonstrate the remarkable PK profile of rIX-FP and generated considerable excitement amongst

† License approval received March 2016 in the USA

* Corresponding author at: Angelo Bianchi Bonomi Hemophilia and Thrombosis Center, IRCCS Cà Granda Foundation, Maggiore Hospital Policlinico, Via Pace 9, 20122 Milan, Italy. Tel.: +39 02 55035273; fax: +39 02 55032072.
E-mail address: elena.santagostino@policlinico.mi.it (E. Santagostino).

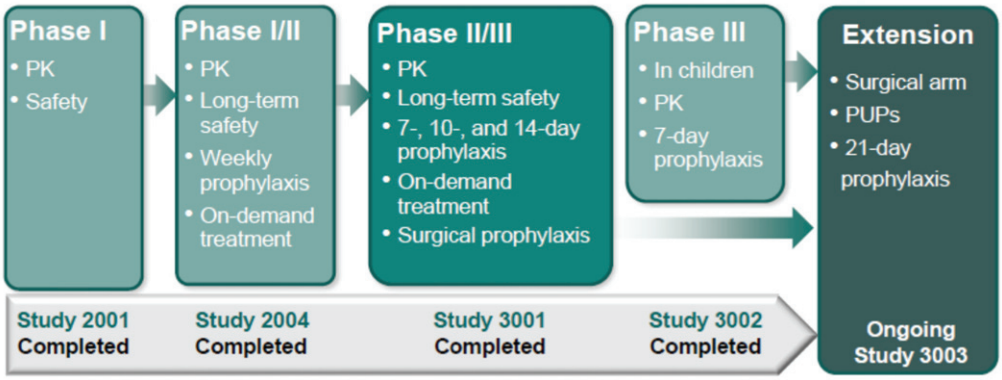

Fig. 1. PROLONG-9FP clinical program for evaluating the recombinant fusion protein linking recombinant coagulation factor IX with recombinant albumin (rIX-FP) in patients with severe hemophilia B. PK, pharmacokinetics; PUPs, previously untreated patients. Reproduced with permission from Schattauer GmbH: Swiss Medical Press GmbH. News from the XXV Congress of the International Society on Thrombosis and Haemostasis (ISTH) in Toronto, Canada. Pioneering therapeutic proteins in hemophilia care through innovative technologies. Thromb Haemost 2016;115:VI–X.

the hemophilia community. In the cohort of patients who received 50 IU/kg of rIX-FP and 50 IU/kg of either plasma-derived FIX (pdFIX) or rFIX (BeneFIX®), the mean half-life of rIX-FP was 92 hours, which was more than 5-fold longer than that of rFIX and more than 6-fold longer than that of pdFIX when used in the same patients. Importantly, mean FIX activity levels remained above 5% at the 2-week (36 hours) PK assessment – an unprecedented finding. Compared with the other FIX treatments assessed in this study, rFIX-FP was also associated with a substantially reduced clearance and greater area under the curve.

Phase I/II study of the safety, efficacy, and PK of rIX-FP in previously treated adults and adolescents with severe hemophilia B

This phase I/II, open-label study was conducted to evaluate the safety, PK, and efficacy of rIX-FP when used for weekly prophylaxis and on demand for the treatment of bleeding episodes [4]. The study enrolled 17 previously treated patients (mean age 26 years; range 13–46 years) with severe hemophilia B (FIX activity ≤2%). All patients entered a 10–14-day PK evaluation period, followed by an 11-month safety and efficacy evaluation period in which patients continued using rIX-FP either on demand (at a minimum dose of 25 IU/kg) or as prophylaxis. Thirteen patients received prophylaxis with rIX-FP throughout the study (range 37–48 weeks); of these 13 patients, three patients switched from an on-demand regimen with their previous FIX treatment to rIX-FP prophylaxis, and 10 patients continued prophylaxis but switched from their previous FIX product to rFIX-FP. Four patients switched from an on-demand regimen with their previous FIX treatment to rIX-FP on demand for the duration of the study (range 15–22 weeks).

The PK profile of the 25 IU/kg dose of rIX-FP was similar to that described in the phase I study. The mean incremental recovery of rIX-FP 25 IU/kg was 1.52 IU/dL per IU/kg, and the mean half-life was 94.8 hours [4]. The mean baseline-corrected FIX activity levels were 5.6% at Day 7 and 2.9% at Day 14 [4]. rIX-FP was well tolerated during a total exposure of over 700 days. None of the patients developed inhibitors to FIX or antibodies to rIX-FP. There were no hypersensitivity reactions and no significant treatment-emergent safety issues. None of the AEs reported were considered by the investigators to be related to rIX-FP, and no one withdrew from the study because of AEs.

The efficacy of rIX-FP was excellent when used as on-demand treatment and for prophylaxis [4]. A total of 85 bleeding episodes were treated with rIX-FP and all were treated successfully with one (95.3%) or two (4.7%) doses. Almost half (46%) of the patients receiving rIX-FP prophylaxis did not experience a single bleeding episode during this 11-month study [4].

Patients receiving rIX-FP prophylaxis experienced fewer spontaneous bleeding episodes than those receiving on-demand rIX-FP. A mean annualized spontaneous bleeding rate (AsBR) of 21.74 was reported for patients receiving rIX-FP on demand – a 20% reduction compared with their historical AsBR (Figure 2a). Patients receiving rIX-FP prophylaxis had a mean AsBR of 1.26 – a 50% reduction compared with their historical AsBR (Figure 2a). Most notably, however, patients switching from on-demand treatment with a previous FIX product to rIX-FP prophylaxis experienced a 95% reduction in AsBR (Figure 2a). Similar findings were observed for the total annualized bleeding rate (Figure 2b).

The results of this study confirmed that rIX-FP had an excellent safety and tolerability profile and that, as a result of its favorable PK profile, weekly prophylaxis was feasible and effective.

Phase II/III study of the efficacy and safety of rIX-FP in previously treated adults and adolescents with severe hemophilia B

The results of the pivotal phase II/III study of rIX-FP in previously treated adolescents and adults with severe hemophilia B (FIX activity ≤2%) [5] have recently been presented [6,7]. The study was designed to evaluate the long-term efficacy and safety of rIX-FP when used on demand and in prophylactic regimens of every 7, 10, and 14 days (Figure 3). All patients initially participated in a 14-day PK evaluation period and received a single dose of rIX-FP 50 IU/kg. Patients were subsequently allocated to one of two treatment groups: Group 1 received rIX-FP prophylaxis every 7 days for 6 months, then, where appropriate, the dosing interval could be extended to every 10 or 14 days. Patients in Group 2 received rIX-FP on demand for 6 months, and then switched to prophylaxis every 7 days. The primary efficacy endpoint was the change in AsBR between on-demand and once-weekly prophylaxis with rIX-FP, as assessed in study Group 2 [5].

A total of 63 patients took part in the study at centers in Europe, Japan, Israel, and the USA [7]. Nineteen patients switched from on-demand treatment with rIX-FP to weekly prophylaxis [7]. The median AsBR during rIX-FP on-demand treatment in this group of individuals was 15.43, which reduced to a median of 0.00 after switching to weekly rIX-FP prophylaxis – a highly statistically significant reduction of 100% ($p<0.0001$). Twenty-one patients extended their treatment interval to once every 14 days. The median AsBR amongst all prophylaxis patients on 7-, 10- and 14-day regimens (n=40) was 0.00; rIX-FP administered every 14 days was as effective as once-weekly prophylaxis. Moreover, patients receiving rIX-FP prophylaxis every 14 days were able to reduce the consumption of their previous FIX product by 50% [7].

rIX-FP was also effective at treating bleeds in this study [7]. Overall, 98.6% of bleeds were successfully treated with ≤2 injections

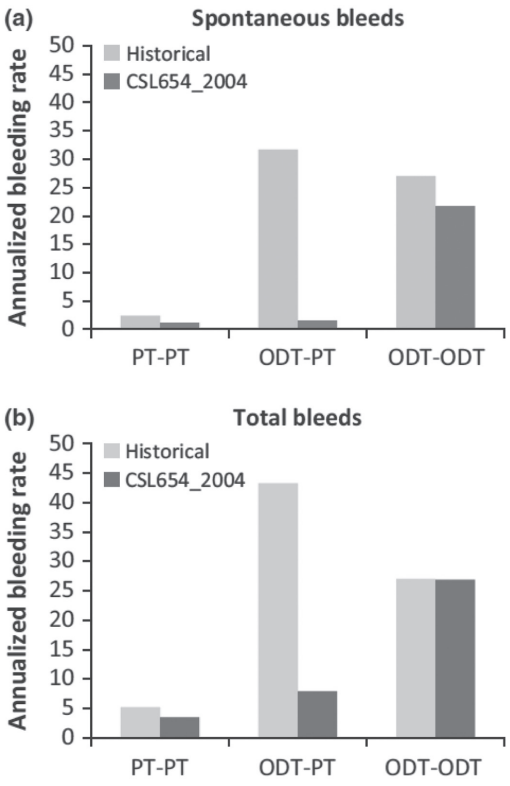

Fig. 2. Annualized bleeding rate for prophylaxis with coagulation factor IX (recombinant), albumin fusion protein compared to historical bleeding rate. The mean annualized bleeding rate for spontaneous bleeds are shown in (a) and for all bleeds are shown in (b) [4]. The annualized bleeding rate for each patient was calculated as the number of bleeds during the time in treatment period of the study in days, divided by 365.25. The historical bleeding rate for each patient was the number of bleeds in the 12 month period prior to study entry. PT, prophylaxis treatment; ODT, on-demand treatment. Reproduced from Martinowitz et al. Results of a phase I/II open-label, safety and efficacy trial of coagulation factor IX (recombinant), albumin fusion protein in haemophilia B patients. Haemophilia 2015; 21(6): 784–790. CC-BY-NC-ND © 2015 CSL Behring.

of rIX-FP. rIX-FP demonstrated a favorable long-term tolerability and safety profile: no patient developed inhibitors to FIX or antidrug antibodies; there were no serious AEs considered to be related to treatment with rIX-FP, and no safety concerns emerged during the study [7].

Phase III surgical substudy of the efficacy of rIX-FP prophylaxis in patients undergoing non-emergency surgery

A surgical sub-study [8] was performed during the phase III study, with 10 patients undergoing 12 major surgeries – five of which were orthopedic procedures [9]. The hemostatic response, as rated by the investigators on a four-point scale, was excellent or good for all surgeries.

For patients undergoing orthopedic surgery, the median rIX-FP consumption was 87 IU/kg preoperatively, 51 IU/kg during post-operative Days 1–2, and 340 IU/kg overall, which is low relative to other FIX replacement regimens used during surgery [9]. No inhibitors to FIX or antibodies to rIX-FP were detected and there were no AEs considered to be related to rIX-FP treatment.

Phase III study of the efficacy, PK, and safety of rIX-FP in previously treated pediatrics with severe hemophilia B

A phase III study evaluating the efficacy, PK, and safety of rIX-FP in 27 previously treated pediatrics (age <12 years) with severe hemophilia B (FIX activity ≤2%) has now been completed [10,11]. Following a 14-day PK analysis, patients received weekly prophylaxis with rIX-FP. The PK profile of rIX-FP was similar in the younger (aged 1–5 years) and older (aged 6–11 years) pediatrics [6]. Compared with their previous FIX treatment, rIX-FP 50 IU/kg was associated with a higher incremental recovery and more than a five-fold longer half-life, lower clearance, and greater area under the curve in this study. As expected, the incremental recovery of rIX-FP was slightly lower and clearance slightly higher in pediatrics compared with adults. After 14 days, plasma FIX activity levels remained at 3% in pediatrics, supporting a prolonged prophylaxis treatment interval [6].

Phase IIIb safety and efficacy extension study

This phase IIIb safety and efficacy extension study [12], which is currently ongoing, was designed for patients who had completed a previous study of rIX-FP in the treatment of hemophilia B and wished to continue treatment with rIX-FP. The study is also open to new previously treated patients scheduled to have non-emergency major surgery, and to previously untreated patients with documented severe hemophilia B. Additionally, a surgical prophylaxis substudy will examine the efficacy of rIX-FP in patients undergoing non-emergency major or minor surgery.

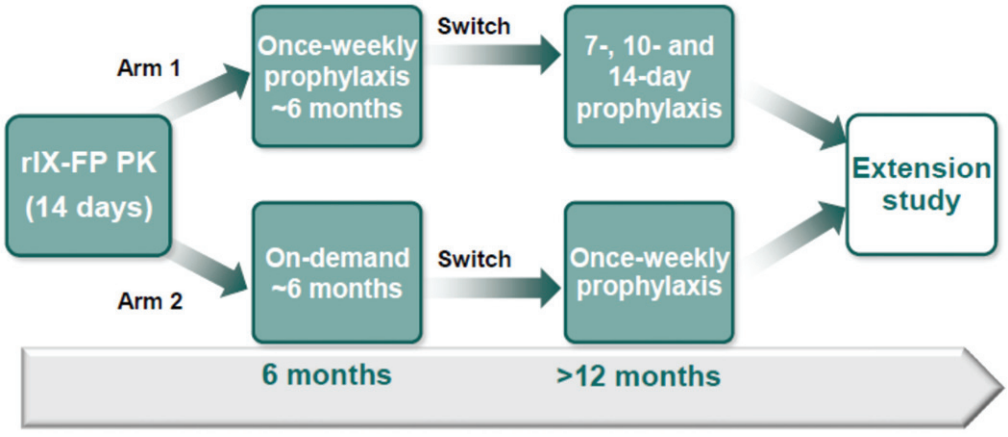

Fig. 3. Design schematic for the PROLONG-9FP phase II/III study of the recombinant fusion protein linking recombinant coagulation factor IX with recombinant albumin (rIX-FP) in previously treated adults and pediatrics with severe hemophilia B. PK, pharmacokinetics.

Conclusions

rIX-FP represents a significant advance in the management of hemophilia B that will ease the burden of treatment for patients of all ages. In prophylaxis, the opportunity to extend the dosing interval from every 3–4 days with currently available rFIX to up to every 14 days, or perhaps even longer, with rIX-FP, while, at the same time, reducing the number of spontaneous bleeds and improving joint health, is compelling. rIX-FP has also demonstrated excellent efficacy for the treatment of bleeding episodes and for surgical prophylaxis. Across all studies completed to date in all age groups, rIX-FP has been very well tolerated with a good safety profile. Based on its extended half-life and impressive clinical profile, there seems to be little doubt that rIX-FP will transform the treatment for many hemophilia B patients.

Abbreviations

AEs, adverse events; AsBR, annualized spontaneous bleeding rate; FIX, factor IX; IV, intravenous; pdFIX, plasma-derived factor IX; PK, pharmacokinetics; rFIX, recombinant factor IX; rIX-FP, recombinant fusion protein linking recombinant coagulation factor IX with recombinant albumin.

Conflict of interest

The author has received fees as a speaker in meetings organized by Kedrion, acted as a paid consultant to Bayer, Pfizer, CSL Behring, Novo Nordisk, Grifols, Baxter, Biogen/Idec, Sobi, Octapharma, and Roche, and received an unrestricted research grant from Pfizer.

References

[1] Metzner HJ, Weimer T, Kronthaler U, Lang W, Schulte S. Genetic fusion to albumin improves the pharmacokinetic properties of factor IX. Thromb Haemost 2009; 102: 634–644.

[2] Schulte S. Half-life extension through albumin fusion technologies. Thromb Res 2009; 124 (Suppl 2): S6–S9.

[3] Santagostino E, Negrier C, Klamroth R, Tiede A, Pabinger-Fasching I, Voigt C, et al. Safety and pharmacokinetics of a novel recombinant fusion protein linking coagulation factor IX with albumin (rIX-FP) in hemophilia B patients. Blood 2012; 120: 2405–2411.

[4] Martinowitz U, Lissitchkov T, Lubetsky A, Jotov G, Barazani-Brutman T, Voigt C, et al. Results of a phase I/II open-label, safety and efficacy trial of coagulation factor IX (recombinant), albumin fusion protein in haemophilia B patients. Haemophilia 2015; 21(6): 784–790.

[5] ClinicalTrials.gov. A safety and efficacy study of a recombinant fusion protein linking coagulation factor IX with albumin (rIX-FP) in patients with hemophilia B. https://clinicaltrials.gov/ct2/show/NCT01496274. Accessed 14 January 2016.

[6] Santagostino E, Jacobs I, Voigt C, Feussner A, Limsakun T. Pharmacokinetic results of two phase III clinical studies of coagulation factor IX (recombinant) albumin fusion protein (rIX-FP) in previously treated patients with hemophilia B (PROLONG-9FP). Blood 2014; 124: 1491 (Abstract).

[7] Santagostino E, Martinowitz U, Lissitchkov T, Pan-Petesch B, Hanabusa H, Oldenburg J, et al. Efficacy and safety results of a phase 3 pivotal clinical study of recombinant fusion protein linking coagulation factor IX with albumin (rIX-FP) in previously treated patients with hemophilia B. J Thromb Haemost 2015; 13 (Suppl 2): 228 (Abstract OR347).

[8] ClinicalTrials.gov. A safety and efficacy extension study of a recombinant fusion protein linking coagulation factor IX with albumin (rIX-FP) in patients with hemophilia B. https://clinicaltrials.gov/ct2/show/NCT02053792?term=NCT02053792&rank=1. Accessed 14 January 2016.

[9] Négrier C, Lepatan LM, Lubetsky A, Karim FA, Pan-Petesch B, Tagliaferri A, et al. Efficacy and safety of recombinant fusion protein linking coagulation factor IX with albumin (rIX-FP) in previously treated patients with hemophilia B undergoing a surgical procedure. J Thromb Haemost 2015; 13 (Suppl 2): 843 (Abstract PO253-WED).

[10] ClinicalTrials.gov. A safety, efficacy and pharmacokinetics study of a recombinant fusion protein linking coagulation factor IX with albumin (rIX-FP) in children with hemophilia B. https://clinicaltrials.gov/ct2/show/NCT01662531?term=NCT01662531&rank=1. Accessed 14 January 2016.

[11] Kenet G, Chambost H, Male C, Lambert T, Álvarez-Román M, Halimeh S, et al. Efficacy, pharmacokinetics (PK) and safety results of a phase 3 clinical study of recombinant fusion protein linking coagulation factor IX with albumin (RIX-FP) in previously treated children with hemophilia B. J Thromb Haemost 2015; 13 (Suppl 2): 227 (Abstract OR346).

[12] ClinicalTrials.gov. A pharmacokinetic, efficacy, and safety study of recombinant factor VIII single chain (rVIII-SingleChain) in children with severe hemophilia A. Available at: https://www.clinicaltrials.gov/ct2/show/NCT02093897?term=NCT02093897&rank=1. Accessed 14 January 2016.