

Updates in clinical trial data of extended half-life recombinant factor IX products for the treatment of haemophilia B

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Abstract: Whilst the global prevalence of haemophilia B is less than that of haemophilia A, rapid and remarkable innovations have been made in the development of haemophilia B therapies in the last decade. The most recent developments are the evolution of extended half-life haemophilia B replacement therapies which are designed to reduce the treatment burden associated with prophylactic infusion of factor IX (FIX) to prevent bleeding in haemophilia B participants. Clinical development programmes have culminated in the completion of three phase III studies on extended half-life (EHL) recombinant FIX (rFIX) products and subsequent approval and registration of these in many countries around the world. Current data from the three EHL rFIX clinical studies indicate that these products have acceptable safety profiles with no allergic reactions, thromboembolic phenomena or neutralizing antibodies when given to previously treated adolescent and adults for the prevention of bleeds, for the treatment of bleeds and in the perisurgical haemostasis use. Studies in previously untreated paediatric participants are currently ongoing. The EHL rFIX products have the potential impact to reduce the treatment burden associated with prophylactic infusion of replacement FIX, to treat and prevent bleeds in participants with haemophilia B and to improve the participant's health-related quality of life. The impact of EHL rFIX is likely to be modified by current development of other haemophilia B therapy such as antitissue factor pathway inhibitors and haemophilia B gene therapy. In this review, we aim to provide an update on the safety and efficacy data from the three EHL rFIX clinical studies and to consider their roles in the face of novel haemophilia B therapy currently evolving.

Keywords: efficacy, extended half-life, haemophilia B, pharmacokinetics, recombinant FIX, safety

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Introduction

Prophylaxis is increasingly adopted by the global haemophilia community as the optimum standard of care in haemophilia management.¹⁻⁷ However, despite its many benefits,⁸⁻¹⁰ prophylaxis using standard half-life (SHL) clotting factor concentrates (CFCs) is associated with a high treatment burden due to the frequency of intravenous injections (two to four injections a week) required to achieve protective plasma clotting factor trough levels which are adequate for bleed prevention and bleed treatment.¹¹⁻¹⁴ CFCs with improved pharmacokinetic (PK) profiles were developed specifically to address this unmet need.

To date, three recombinant factor IX (rFIX) products with extended half-life (EHL) have been designed and all have completed phase III clinical development programmes. The half-life extension of these rFIXs has been achieved through the application of now-well-established fusion and glycoPEGylated technologies, specifically formulated to confer a longer half-life of the rFIX protein relative to the unmodified FIX protein. In the fusion approach, either the human immunoglobulin constant region (fragment crystallizable, Fc) or recombinant albumin are covalently linked to the human rFIX molecule to produce a haemostatically active EHL rFIX.¹⁵⁻¹⁷

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Table 1. Summary of pharmacokinetic and pharmacodynamic properties of extended half-life recombinant factor IX products.

	rFIXFc	rFIX-FP	N9-GP	SHL-FIX
Dose used, IU/kg	50	50	40	50
AUC, IU.h/dl	3664	7176	14130	548
Clearance, ml/kg	0.74	0.77	0.42	8.62
Incremental recovery, IU/dl or IU/kg	0.92	1.27	2.00	0.084
Half-life for EHL product, mean	82.1	102.0	96.2	
Half-life extension relative to SHL product	2.4-fold	4.2-fold	4.8-fold	

AUC, area under the curve; EHL rFIX, extended half-life recombinant factor IX; N9-GP, nonacog beta pegol; rFIXFc, fragment crystallizable recombinant factor IX; rFIX-FP, recombinant factor IX albumin fusion protein; SHL, standard half-life.

The two fusion EHL rFIX products which have completed phase III clinical studies to date are the rFIXFc (INN eftrenonacog alfa, Alprolix, Biogen, Cambridge, MA, USA) and recombinant factor IX albumin fusion protein (rFIX-FP; INN albutrepenonacog alfa, Idelvion, CSL Behring, King of Prussia, PA, USA).^{17–23} The mechanism of half-life extension of these fusion EHL rFIX products involves the natural recycling of the Fc or albumin moiety which is bound to rFIX through the neonatal Fc receptor.^{24,25}

In the glycoPEGylated half-life extension approach, a single 40 kDa polyethylene glycol (PEG) moiety is attached to the N-glycan within the activation peptide of rFIX to produce N9-GP (INN nonacog beta pegol, Novo Nordisk A/S, Bagsværd, Denmark).^{26–29} The half-life extension in this case is achieved through the increased density conferred by the PEG moiety with consequent reduction in renal excretion of the PEG conjugated rFIX.^{24,30}

The BLONG clinical study evaluated safety, efficacy and PK profile of rFIXFc in previously treated adolescents and adults and the Kids BLONG enrolled previously treated paediatric participants younger than 12 years of age. Both BLONG and Kids BLONG were followed by enrolment of participants in the BYOND extension study which evaluated the long-term safety and efficacy of rFIXFc. The PROLONG-9FP clinical development programme was designed to assess the safety and efficacy of rFIX-FP in previously treated children, adolescents and adults. The safety and efficacy of N9-GP was evaluated in the PARADIGM clinical development programme conducted in previously treated adults,

adolescents and paediatric participants. All three development programmes are currently ongoing in the respective extension phases.

The PK and pharmacodynamic properties of the three EHL rFIXs were well characterized in the phase I and phase III studies^{21,22,31–34} and are summarized in Table 1. The three EHL rFIX products showed a 2.4, 4.2 and 4.8-fold increase in half-life of rFIXFc, rFIX-FP and N9-GP, respectively, when compared with SHL products.³⁵ The half-life extension of rFIX through fusion and PEGylation was considered a significant improvement when compared with FVIII Fc fusion which only achieved a modest 1.4–1.6 half-life extension relative to the SHL products.^{36–42} Following a single intravenous dose of 50 IU/kg of rFIXFc, 50 IU/kg of rFIX-FP or 40 IU/kg of N9-GP, there was reduced clearance and increased incremental recovery relative to SHL rFIX. As expected, the clearance of EHL rFIX products was higher when used in the paediatric population studies.^{43,44}

Safety of these three EHL rFIX products was assessed in the respective clinical development programmes in previously treated adult, adolescent and paediatric participants with moderately severe or severe haemophilia B. The clinically relevant safety features of the three products are summarized in Table 2. Although binding antibodies developed in the rFIXFc and N9-GP studies, these lacked neutralizing activities and therefore were clinically insignificant. In the course of participant follow up with antidrug antibodies, none evolved to become neutralizing in nature. No participant developed thrombotic episodes and there were no

Table 2. Summary of safety profile of extended half-life recombinant factor IX products in the published pivotal studies.

	rFIXFc	rFIX-FP	N9-GP
Number of participants with inhibitors	0	0	0
Number of participants with non-inhibitor antibodies	3	0	3
Number of deaths or thromboembolisms	0	0	0
Number of drug-related serious adverse events	0	0	0
Number of drug-unrelated serious adverse events	11	3	4

N9-GP, nonacog beta pegol; rFIXFc, fragment crystallizable recombinant factor IX; rFIX-FP, recombinant factor IX albumin fusion protein.

Table 3. Summary of efficacy of extended half-life recombinant factor IX products in the treatment of bleeds.

	rFIXFc	rFIX-FP	N9-GP
Dose, IU/kg	50	50	40
Number of injections, <i>n</i>	1 or 2	1 or 2	1 or 2
Overall haemostatic efficacy, %	97.2	96.7	97.1

N9-GP, nonacog beta pegol; rFIXFc, fragment crystallizable recombinant factor IX; rFIX-FP, recombinant factor IX albumin fusion protein.

Table 4. Summary of efficacy of extended half-life recombinant factor IX products in the prevention of bleeds.

	rFIXFc		rFIX-FP		N9-GP	
Number of participants, <i>n</i>	61	26	40	21	30	29
Dose, IU/kg	50	100	40	75	10	40
Dose frequency, qx days	q7 days	q10 days	q7 days	q4 days	q7 days	q7 days
ABR, median (IQR)	3.0 (1.0–4.4)	1.4 (0.0–3.4)	0.0 (0.0–1.87)	1.08 (0.0–2.7)	2.93 (0.9–6.0)	1.0 (0.0–4.0)

ABR, annualized bleeding rate; IQR, interquartile range; N9-GP, nonacog beta pegol; rFIXFc, fragment crystallizable recombinant factor IX; rFIX-FP, recombinant factor IX albumin fusion protein; qx days, every x number of days.

serious adverse events directly attributable to the study drugs in all three clinical trial studies.

The efficacy of the three EHL rFIX products in the treatment of bleeds and prevention of bleeding are compared in Tables 3 and 4. Overall, all three products showed high haemostatic efficacies of over 96% when given as a single or two injections to treat bleeding episodes. Relative to episodic treatment, the EHL rFIX produced very

low annualized bleeding rates (ABRs) whose median was three bleeds per year. This low ABR was not achieved at the expense of increased clotting factor consumption and was associated with a reduction in the treatment burden as a result of fewer injections required to maintain high trough levels with the EHL rFIX products

Data on the perisurgical use of the EHL rFIX products is shown in Table 5. Both major orthopaedic

Table 5. Summary of efficacy of extended half-life recombinant factor IX products in the perisurgical use.

	rFIXFc	rFIX-FP	N9-GP
Number of surgeries, <i>n</i>	12	8	9
Number of intraoperative injections, <i>n</i>	0	0	0
Overall excellent and good outcomes, %	100	100	100

N9-GP, nonacog beta pegol; rFIXFc, fragment crystallizable recombinant factor IX; rFIX-FP, recombinant factor IX albumin fusion protein.

and minor surgical procedures were performed under cover of these products. Haemostatic efficacy was rated as excellent or good in 100% of the surgeries done with all three products.

To date, all three EHL rFIX clotting factors have now been reviewed and approved by the US Food and Drug Administration and the European Medicines Agency for marketing in the USA and Europe. Review and approval outside the USA and European Union are currently ongoing, with some of these drugs already approved in Canada, Australia and the United Kingdom.

The aim of this review is to give an update on the published efficacy and safety data of the three EHL rFIX products in haemophilia B.

Extended half-life of fragment crystallizable recombinant factor IX

Efficacy of fragment crystallizable recombinant factor IX in the prevention of bleeds

In the pivotal BLONG study, efficacy of rFIXFc in the prevention of bleeding episodes was assessed in 123 adolescent and adult study participants.³¹ The BLONG study included participants with severe haemophilia B (endogenous FIX \leq 2 IU/dl) who had at least 100 exposure days to FIX replacement therapy. In this setting, rFIXFc prophylaxis reduced the ABR by 83% in the haemophilia B subgroup receiving weekly PK-driven rFIXFc prophylaxis and 87% in the subgroup receiving rFIXFc every-10-day PK-driven prophylaxis when compared with those receiving FIX episodic treatment. In the planned subgroup analysis, the reduction in ABR was shown to be consistent across demographic and disease subgroups. The reduction in the ABR was observed even in the participants with the highest bleeding frequencies (including those with \geq 36 bleeding episodes per annum) before

study entry. This finding confirmed that impact of rFIXFc in the prevention of bleeds is real and not a chance finding.

When rFIXFc was infused prophylactically to previously treated study participants less than 12 years of age, similar results to those seen in adolescent and adults were observed.⁴³ At weekly prophylactic doses of 50–60 IU/kg, the median (interquartile range, IQR) ABR was 2.0 (0.0–0 3.0). The median (IQR) ABR for spontaneous joint bleeds, which are the hallmark of the haemophilia bleeding phenotype, was 0.0 (0.0–0.0). Essentially, the results of rFIXFc prophylaxis in paediatric patients were consistent with those seen in the adolescent and adult populations, indicating efficacy of rFIXFc prophylaxis across all age groups.

To evaluate efficacy of rFIXFc in the perisurgical prophylaxis setting, 12 participants in the BLONG study underwent 14 major surgeries.⁴⁵ Haemostatic control using rFIXFc was judged by the investigator or surgeon as excellent or good in 100% of these surgeries. The perioperative blood loss was similar to that seen in nonhaemophilia participants undergoing the same surgical procedures. None of the participants received an intraoperative rFIXFc dose and none required perioperative blood transfusion. There were no thromboembolic events or allergic reactions during the use of rFIXFc in the perisurgical settings.

The impact of rFIXFc in the prevention of bleeding episodes was further evaluated in the adult, adolescent and paediatric populations by calculating the proportion of participant with zero bleeds whilst receiving rFIXFc. Among the adolescent and adults in the BLONG study receiving fixed-dose and fixed-interval rFIXFc prophylaxis, 23% and 42%, respectively, had no bleeding episodes when they were receiving rFIXFc prophylaxis at steady state in the last 3 months of the BLONG study. In the Kids BLONG study, the proportion

of participants with zero bleeds was 33% overall and almost double at 63% in those with no clinically overt joint bleeds. Previous published studies on recombinant or plasma-derived FIX did not calculate the proportion of participants with zero bleeds, therefore it is not possible to make a comparison of zero bleeds between SHL and EHL rFIX products.

Efficacy of fragment crystallizable recombinant factor IX in the treatment of bleeds

To evaluate efficacy of rFIXFc in the treatment of bleeds, studies were conducted in previously treated adult, adolescent and paediatric populations. In the adolescent and adult BLONG study participants, 636 bleeding episodes that occurred whilst on study were treated with rFIXFc. The median dose required to treat a bleed was 46 IU/kg which was close to the 50 IU/kg dose usually given for the treatment of a bleed using a SHL rFIX product. In this setting, rFIXFc was highly efficacious with 90.4% resolved with a single rFIXFc injection and 97.3% resolved with one or two injections. In the Kids BLONG, 60 bleeding episodes were treated in 20 participants whilst on the study. A total of 71% bleeds were controlled with one rFIXFc injection and 91.7% with one or two injections. The median (IQR) dose per injection was 63.51 IU/kg (48.92–99.44).

The long-term efficacy of rFIXFc in the prevention and treatment of bleeds has recently been evaluated in the BYOND extension study.³ The BYOND study accrued 116 participants, 93 from BLONG and 23 from Kids BLONG studies. From the start of the BLONG and Kids BLONG to the BYOND interim analysis, the median follow up was 40 and 22 months for adolescents/adults and paediatrics, respectively. The ABR across the four prophylactic groups of the BYOND study was <3. In the BYOND study, 97% of adolescents/adults and 93% of children responded to one or two injections of rFIXFc. These efficacy results are consistent with those of the BLONG and Kids BLONG studies and confirm the long-term consistency of rFIXFc efficacy in the prevention and treatment of haemophilic bleeding episodes.

Safety of fragment crystallizable recombinant factor IX

In the pivotal and extension adult, adolescent and paediatric studies, rFIXFc demonstrated an

acceptable safety profile with no thromboembolic events, vascular events or allergic reactions reported. The infusion of rFIXFc did not elicit development of anti-rFIXFc-neutralizing antibodies in previously treated adults, adolescents and paediatric participants included in the BLONG, Kids BLONG and BYOND studies. The PUP study is currently ongoing and the immunogenicity results from this study are eagerly awaited. Following registration of rFIXFc, a number of real-life experience databases were setup and these results will give a clearer picture of the long-term and real-life safety profile of using rFIXFc across all ages.

Impact of fragment crystallizable recombinant factor IX on participant health-related quality of life

Health-related quality of life (HRQoL) was evaluated in the BLONG and the Kids BLONG studies using age-appropriate Haem-A-QoL for adults and Haemo-QoL for adolescents.^{43,46,47} Adults participating in arms 1 and 2 of the BLONG study completed the Haem-A-QoL instrument at baseline, 26 weeks and 52 weeks on study. A total of 58 subjects aged 18 or older completed the questionnaire at baseline, and week 26 or 52, or both. There were 38 from arm 1 and 20 from arm 2. The results showed small decreases in scores consistent with improved quality of life. Unfortunately, the number of participants who completed the QoL instrument in the paediatric population was too small for meaningful interpretation of the impact of rFIXFc in their quality of life.⁴³

Fragment crystallizable recombinant factor IX and immune tolerance induction

Whilst there has been much speculation on the role of Fc moiety of the rFIXFc-FP in modulating immune tolerance, to date, there are no data to demonstrate this benefit in humans. In the pre-clinical models, rFIXFc has been shown to have a possible interaction with a repertoire of Fc receptors (FcR) that can modulate immune responses.⁴⁸ There is only one report in humans in which rFIXFc has been used for immune tolerance induction in a severe Haemophilia B participant with an inhibitor and prior history of immune-tolerance-induction-related nephrotic syndrome.⁴⁹ This important possible role of Fc in immune tolerance remains a subject of interest currently explored in a number of real-life uses of the product.

Extended half-life recombinant factor IX albumin fusion protein

The PROLONG-9FP clinical development programme was setup to establish the PK, efficacy and safety properties of rFIX-FP in previously treated paediatric, adolescents and adults. The programme comprised several clinical trials including a phase I dose-finding study,⁵⁰ a phase I/II in adolescent and adults,⁵¹ two phase III studies^{22,52} and a currently ongoing phase IIIb extension study.

Efficacy of recombinant factor IX albumin fusion protein in the prevention of bleeds

A total of 63 adolescent and adults were accrued in the open-label multicentre phase III study.²² In the prophylaxis arms, participants received 40 IU/kg of rFIX-FP intravenously every 7 days or 75 IU/kg of rFIX-FP intravenously every 14 days. The prophylaxis results were compared with haemophilia B participants receiving episodic treatment. The median ABR for all prophylaxis regimens in this study was 0.00 compared with the ABR of 23 for episodic treatment. Switching from episodic to prophylactic infusion with rFIX-FP resulted in 100% reduction in spontaneous ABRs and 100% resolution of target joints.

The rFIX-FP paediatric study enrolled 27 children < 12 years of age with severe or moderately severe haemophilia B who were all on the weekly rFIX-FP prophylaxis regimen. During the on-study follow up of 77 weeks in the kids receiving prophylaxis, the median ABR (IQR) was 0.00 (0.00–0.91) for all children and there was no difference between those under 6 years and those 6–12 years of age. The weekly median prophylactic dose was 46 IU/kg which maintained a median trough level of 13.4 IU/dl FIX on a weekly prophylaxis regimen.

In the perisurgical setting, rFIX-FP was evaluated in paediatric, adolescent and adult participants undergoing major and minor surgical procedures. A total of 21 surgeries were performed in 19 participants; 8 participants underwent 9 orthopaedic surgeries and 12 participants had 12 nonorthopaedic surgeries; all participants were followed up for a minimum of 14 days post-surgery. The haemostatic response on a 4-point rating scale was good or excellent in all 21 surgeries. A single preoperative injection of rFIX-FP maintained intraoperative haemostasis in 20 of the 21 surgical procedures performed. The

median intraoperative consumption was 87 IU/kg preoperatively and 375 IU/kg overall. None of the participants developed anti-rFIX-FP antibodies in the perisurgical period.

Efficacy of recombinant factor IX albumin fusion protein in the treatment of bleeds

There were 358 bleeds in 53 participants, of which 220 were treated episodically and 138 were treated prophylactically with rFIX-FP infusion. Overall, 93.6% of bleeds responded to one rFIX-FP dose and 98.6% of bleeds responded to one or two doses of rFIX-FP infusion. The haemostatic clinical response, rated on a 4-point response scale, was evaluated as excellent or good in 94.2% of the bleeds treated with rFIX-FP infusion.

There were 106 bleeding episodes recorded in 23 participants enrolled in the rFIX-FP paediatric study requiring treatment. A total of 69% bleeds were non-traumatic, whilst 15% were traumatic. Overall, 88.7% of treated bleeds resolved with one injection and 97.2% resolved with one or two injections of rFIX-FP. The clinical haemostatic response was rated by the investigators as excellent or good in 96% of the rFIX-FP treated bleeds.

Overall, in previously treated paediatric, adolescent and adult participants, rFIX-FP is highly efficacious in the prevention of bleeds, in the treatment of spontaneous and episodic bleeds and in the maintenance of perisurgical haemostasis. In the rFIX-FP studies, the proportion of participants achieving zero bleeds were not published.

Safety of recombinant factor IX albumin fusion protein

Both the paediatric and adolescent/adult studies showed an acceptable safety profile of rFIX-FP when used in previously treated haemophilia B participants for the prevention and treatment of bleeds as well as the perisurgical haemostatic control. In these studies, infusion of rFIX-FP was not immunogenic with none of the study participants developing neutralizing antibodies against rFIX-FP. During the study conducted, none of the participants developed thrombosis, vascular events or allergic reaction to rFIX-FP. Studies in previously untreated paediatric populations are currently ongoing and would be of interest from the immunogenicity perspective.

Impact of recombinant factor IX albumin fusion protein on quality of life

QoL assessment data in the pivotal phase III rFIX-FP study have not yet been presented. Data from the paediatric study were recently presented.⁵³ In this analysis of 27 children, HRQoL was measured at baseline and at the end of the paediatric phase III study. Of the 19 children who completed the age-appropriate Haem-A-QoL, there was improvement in the QoL scores between baseline and end of study particularly in the age group 8–12 years of age. However, there was no improvement of QoL in parents who completed the QoL assessments in the same period as the children.

Extended half-life of nonacog beta pegol

Evaluation of PKs, efficacy and safety of nonacog beta pegol (N9-GP) was undertaken in the PARADIGM clinical development programme comprising several clinical trials conducted in adults, adolescents and the paediatric populations. The completed studies include a phase I study,³³ two phase III studies,^{32,44} and an extension study.⁵⁴ The N9-GP study in previously untreated participants is currently ongoing and results are awaited.

Efficacy of nonacog beta pegol in bleed prevention

The efficacy of N9-GP has now been evaluated in adolescents/adults haemophilia B participants, paediatric participants when used in the prevention of bleeds, treatment of bleeds, as well as perisurgical prophylaxis in four PARADIGM programmes. The completed studies included a phase III PARADIGM 2 which evaluated efficacy and safety of N9-GP in adolescents/adults; PARADIGM 3 evaluated efficacy and safety in the perisurgical use of N9-GP; PARADIGM 4 was an extension study for participants in PARADIGM 2 and 3; and PARADIGM 5 was the paediatric study.

PARADIGM 2 enrolled 74 severe or moderately severe previously treated haemophilia B participants who received either 10 IU/kg and 40 IU/kg of N9-GP for the prevention and treatment of bleeding episodes. The median ABR (IQR) using 10 IU/kg and 40 IU/kg N9-GP infusion once weekly was 2.94 and 1.04, respectively. This was markedly low when compared with the demand-treatment ABR of 15.58.

The perisurgical haemostatic use of N9-GP was explored in PARADIGM 3, which enrolled 13 participants undergoing major surgeries.⁵⁵ The surgeries included nine orthopaedic procedures, three dental procedures and one gastrointestinal procedure. All participants received a single pre-operative dose of 80 IU/kg of N9-GP and were followed up with subsequent doses based on the intraoperative or postoperative FIX trough level. The haemostatic efficacy was judged by the investigator as excellent or good in all 13 (100%) surgical procedures. None of the participants required an additional N9-GP dose intraoperatively or within 24 h postsurgery.

PARADIGM 4 accrued 66 participants from the PARADIGM 2 and 3 programmes. Of these participants, 20 were in the 10 IU/kg and 49 were in the 40 IU/kg weekly N9-GP prophylaxis dosing arms. The median (IQR) ABR was 1.36 (0.00–2.23) in the 10 IU/kg dose and 1.00 (0.00–2.03) in the 40 IU/kg dosing regimen. The PARADIGM 4 results confirmed the consistency of the 40 IU/kg dose for the prevention of bleeds; this was the dose chosen for registration filing of N9-GP.

Efficacy of nonacog beta pegol in bleed treatment

The use of N9-GP in the treatment of bleeds was evaluated in both the PARADIGM 2 and 4 programmes. In PARADIGM 2, 74 participants experienced 345 bleeds whilst on N9-GP prophylaxis. Haemostatic efficacy when these bleeds were treated with one dose of 40 IU/kg or 80 IU/kg for severe bleeds was overall 92.4%. Participants receiving the 10 IU/kg prophylaxis had a lower haemostatic efficacy of 86.9% when compared with the 97.1% for those receiving the 40 IU/kg prophylaxis dose. In PARADIGM 4, a total of 207 bleeds were treated in 71 participants. The results of the PARADIGM 4 study were similar to those seen in PARADIGM 2, with overall haemostatic efficacy of 94.6% when using N9-GP for bleed management.

The use of N9-GP in the prevention and treatment of bleeds in children was explored in PARADIGM 5⁴⁴ which enrolled 25 severe or moderately severe haemophilia B patients aged 12 years or younger. They received 40 IU/kg weekly N9-GP prophylaxis for 50 exposure days. The ABR was 1.00 for the total population, 0.00 for the 0–6-year-old group and 1.88 for the 7–12 year group. In the

22 participants who had data for intraparticipant comparison, the historical ABR was 2.52 in the prior prophylaxis regimen and 1.38 on N9-GP prophylaxis. During the PARADIGM 5 study, 42 bleeds were treated in 15 participants. Participants received a single 40 IU/kg dose for mild/moderate bleeds or 80 IU/kg for severe bleeds. The overall haemostatic efficacy was 92.9% and there was no difference in the treatment success rate between spontaneous and traumatic bleeds.

Safety of nonacog beta pegol

Safety of N9-GP has been evaluated in all five clinical studies in the PARADIGM clinical development programme (PARADIGM 1, 2, 3, 4 and 5). These studies included over 100 participants with more than 8000 exposure days. To date, no participant has developed anti-N9-GP neutralizing antibodies. None of the studies has reported development of thromboembolic events or allergic reactions.

Health-related quality-of-life impact of nonacog beta pegol

HRQoL during the use of N9-GP was evaluated in the PARADIGM 2, PARADIGM 4 and PARADIGM 5 clinical trials.⁵⁶ In the PARADIGM 2 and 4 studies baseline HRQoL were measured using the validated Haem-QoL III for adolescents 13–16 years of age, Haem-A-QoL for participants 17 years and older, as well as EQ-5D-3L for all study participants. The tools were administered at three time points, which were the beginning of the PARADIGM 2, end of PARADIGM 2 and end of PARADIGM 4 studies. The results showed significant improvement of the QoL in the overall score as well as the sports domain score.

In the PARADIGM 5 study, 12 of the 25 boys aged 8–12 years who completed the HRQoL questionnaires were evaluated.⁵⁷ Overall, the 12 boys and their parents reported reasonably consistent improvements in the domains most likely to be impacted by switching to an EHL factor (treatment and dealing) and little to no improvement in domains less likely to be impacted by switching to an EHL FIX. Whilst the reasons for improvement in the HRQoL remains to be explored further, it is speculated that these are most likely due to reduced burden of treatment associated with using an EHL product as well as high trough levels achieved during the use of N9-GP.

The role of extended half-life recombinant factor IX products in the era of nonreplacement therapies and gene therapy for haemophilia B

Haemophilia has seen an unprecedented evolution of therapies, many of which have emerged at the same time as the EHL rFIX products. These therapies have included the antitissue factor pathway inhibitors (anti-TFPIs) which can be used for the management of haemophilia A and B, antithrombin ribonucleic acid (RNA) interference, as well as haemophilia B gene therapy programmes. At least one anti-TFPI agent has completed human phase I study and is proceeding to the planned phase II/III study.⁵⁸ Preliminary results from this study suggest it is safe and has the added advantage of being given subcutaneously. The recent phase I/II results on the safety and efficacy of the antithrombin RNA interference are promising and this product is currently evaluated in the phase II/III programme.⁵⁹ The two haemophilia B gene therapy programmes using adeno-associated viral vectors have completed phase I/II and are proceeding to phase III studies^{60,61} Apart from transaminitis seen in a subset of participants included in these two studies, there are currently no clinically meaningful safety concerns. Preliminary efficacy results are encouraging, with all participants converted from severe to mild or moderate phenotypes.

How the nonreplacement haemophilia B treatments will impact the future use of EHL rFIX products remains to be seen. What is however clear is that whilst some haemophilia participants are embracing and switching over to the EHL rFIX products, it is the authors' impression that others are holding back and awaiting results of the new therapies. Having demonstrated efficacy in the treatment and prevention of bleeds, the role of EHL rFIX products is likely to be similar to that of the SHL rFIX and plasma-derived FIX products.

Potential challenges with extended half-life recombinant factor IX products

Head-to-head comparison among the EHL FIX has not yet been conducted. Whilst data from Tables 1–5 suggest they have favourable and acceptable efficacy and safety profiles in the clinical trial settings, the long-term safety of these products remains to be evaluated. In particular, the long-term effects of PEGylated rFIX products will need to be carefully monitored when these are used in a lifelong setting such as haemophilia.

It may not be possible to extrapolate data in non-haemophilia clinical use of PEGylated proteins to haemophilia use, in part due to dose and extended duration of exposure required in haemophilia

Laboratory measurement and monitoring is an important consideration with the use of some of the of EHL rFIX products. Measurement of rFIXFc and rFIX-FP using the one-stage clot assay does not require any standards or adjustments.^{20,62} However, measurement of N9-GP does require an adjustment, as the one-stage assay overestimates the FIX results.^{63–65} The implication would then be that each laboratory will have to set up its assay validated against the recommended FIX specific standard.

Concluding remarks

Current data on the three EHL rFIX products indicate that they represent an important advance in the management of haemophilia B. Their improved PK properties have a direct impact in reducing the treatment burden associated with prophylactic replacement therapies in haemophilia B. These products have comparable safety profiles with existing recombinant and plasma-derived FIX products in previously treated paediatric, adolescent and adult participants. Safety and immunogenicity in previously untreated participants remain the subject of ongoing clinical trial investigations. The EHL rFIX products show high efficacies both in the treatment of bleeds, as well as prevention of bleeding episodes in routine prophylaxis use and in perisurgical haemostasis.

How the EHL rFIX products will be positioned in relation to other evolving haemophilia B novel therapies remains to be established.

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Conflict of interest statement

The author declares that there is no conflict of interest.

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