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BRIEF REPORT

Extending recombinant factor IX Fc fusion protein dosing interval to 14 or more days in patients with hemophilia B

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Abstract

Background: In the phase 3 B-LONG study (NCT01027364), prophylaxis with recombinant factor IX Fc fusion protein (rFIXFc) every 7 to >14 days was associated with low annualized bleed rates (ABRs) in males aged ≥ 12 years with severe hemophilia B. The long-term safety and efficacy of rFIXFc prophylaxis was confirmed in the B-YOND study (NCT01425723), an extension of the B-LONG clinical trial.

Objective: The aim of this post-hoc analysis was to evaluate the efficacy of a ≥ 14 -day rFIXFc dosing interval in patients treated prophylactically during B-LONG or B-YOND.

Methods: The analysis included 22 patients aged ≥ 12 years who received prophylactic rFIXFc with a ≥ 14 -day dosing interval at any time during B-LONG or B-YOND up until the second interim analysis of B-YOND (September 2015).

Results: The median (interquartile range [IQR]) rFIXFc exposure on the ≥ 14 -day dosing interval was 3.4 (1.8-4) years. Patients treated with a ≥ 14 -day dosing interval were well controlled with a median (IQR) overall ABR of 1.6 (0.6-2.7) and a median (IQR) spontaneous ABR of 0.7 (0.3-1.1) in 18 evaluable patients. A rFIXFc dosing interval of ≥ 14 days was well tolerated, with no new safety concerns identified.

Conclusion: Most patients on rFIXFc prophylaxis, with a dosing interval of ≥ 14 days, remained well controlled; ABRs were consistent with those reported in the overall study population. A ≥ 14 -day dosing interval can be utilized in some well controlled individuals and reduces the burden imposed by frequent prophylactic injections while maintaining adequate bleed suppression.

KEYWORDS

clinical trial, factor IX, hemophilia B, prophylaxis, recombinant fusion proteins

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Essentials

- Prophylactic replacement of coagulation factor IX (FIX) is recommended in severe hemophilia B.
- Recombinant FIX Fc fusion protein (rFIXFc) is effective and well tolerated.
- Phase 3 post-hoc analysis shows that some patients are well controlled with rFIXFc every ≥ 14 days.
- A ≥ 14 -day rFIXFc dosing interval may help reduce treatment burden for well-controlled patients.

1 | INTRODUCTION

Compared with on-demand treatment, prophylactic factor replacement therapy improves clinical outcomes in people with hemophilia, reducing the frequency of bleeding episodes, and improving joint outcomes and quality of life.^{1,2} For prophylaxis in hemophilia B, the use of conventional half-life factor IX (FIX) products requires frequent injections to maintain protective FIX levels. The burden imposed by frequent injections is an important barrier to adherence in individuals with hemophilia treated prophylactically.³

Recombinant FIX Fc fusion protein (rFIXFc; eftrenonacog alfa) is one of the approved extended half-life products for hemophilia B. rFIXFc is a fusion protein comprising human coagulation FIX covalently bound without a linker to the Fc domain of human immunoglobulin G1 (IgG1) produced in a well-characterized human cell line.⁴ The Fc portion of rFIXFc binds to the endogenous neonatal Fc receptor and uses the IgG recycling pathway, delaying lysosomal degradation of Fc-containing proteins by recycling them back into the circulation, thereby resulting in prolonged half-life of rFIXFc.⁴ rFIXFc is approved for prophylaxis and treatment of bleeding in individuals of all age groups who have hemophilia B.⁵

The phase 3 B-LONG study demonstrated that prophylaxis with rFIXFc is associated with low annualized bleeding rates (ABRs) in male patients aged ≥ 12 years with severe hemophilia B.⁶ The extension study, B-YOND, has confirmed the long-term safety and efficacy of prophylaxis with rFIXFc⁷; key results upon completion of the B-YOND study are expected in 2018.

The approved indication for rFIXFc in the EU was updated in July 2017 to include a dosing interval of ≥ 14 days for use in patients with hemophilia B who are well controlled with rFIXFc administered every 10 days.⁵ The aim of the current post-hoc analysis was to characterize long-term experience with extended interval dosing using data up to the second data cut of B-YOND (September 2015).

2 | METHODS

B-LONG (NCT01027364) was a phase 3, non-randomized, open-label, multicenter study, with primary and secondary endpoints reported previously.⁶ The study enrolled 123 male patients aged ≥ 12 years with severe hemophilia B ($\leq 2\%$ of normal FIX levels) whose prior treatment regimen was either prophylaxis or on demand.

In B-LONG, patients were assigned to one of four treatment groups: Group 1 received prophylaxis with rFIXFc 50 IU/kg weekly, with the dose adjusted as needed ($n = 63$); Group 2 received prophylaxis with

rFIXFc 100 IU/kg at an interval of every 10 days, with the interval adjusted as needed based on pharmacokinetics (PK) and/or outcome ($n = 29$); Group 3 received on-demand treatment with rFIXFc 20-100 IU/kg for bleeding episodes, with the dose adjusted according to bleeding severity ($n = 27$); and Group 4 received treatment with rFIXFc as part of perioperative care ($n = 12$). The primary efficacy endpoint in B-LONG was the ABR, and primary safety endpoints were the development of inhibitors (neutralizing antibodies) and adverse events.

B-YOND (NCT01425723) was a non-randomized, open-label, extension study that enrolled patients who completed B-LONG⁶ or Kids B-LONG.⁸ Interim data from October 2014 have been reported previously.⁷ Of the 115 patients who completed B-LONG, 93 were enrolled in B-YOND. Data from patients enrolled in B-YOND from B-LONG are reported in this post-hoc analysis; patients enrolled in B-YOND from Kids B-LONG were not included as the Kids B-LONG study design did not allow dosing intervals longer than 1 week.

There were four treatment groups in B-YOND: Group 1 received prophylaxis with rFIXFc 20-100 IU/kg every 7 days (weekly prophylaxis); Group 2 received interval-adjusted prophylaxis with rFIXFc 100 IU/kg every 8-16 days with dosing based on the patient's clinical profile observed in the parent study and individual PK profile, trough, and/or peak (recovery) values; Group 3 received modified prophylaxis with the possibility to further personalize dosing by eg, changing dosing frequency, adding prevention doses before strenuous activities, or targeting a trough FIX level of >5 IU/dL if warranted by bleeding history and/or activity level to improve prophylaxis; and Group 4 received on-demand treatment. The primary endpoint in B-YOND was the development of inhibitors.

This post-hoc analysis included patients aged ≥ 12 years who received prophylactic rFIXFc with a dosing interval of ≥ 14 days at any time during B-LONG or B-YOND, up until the time of the second interim analysis (September 2015; see Figure 1). Descriptive statistics were used to summarize data.

3 | RESULTS AND DISCUSSION

Twenty-two patients received rFIXFc prophylaxis with a dosing interval of ≥ 14 days at any time during B-LONG or B-YOND, until the time of the second interim B-YOND analysis (September 2015). The median age at baseline was 34.5 years with the vast majority of patients having $<1\%$ endogenous FIX activity. The median terminal half-life ($t_{1/2}$) of rFIXFc was 99.8 hours (Table 1).

The majority of patients (18 of 22) whose dosing interval was extended to ≥ 14 days were on interval-adjusted prophylaxis

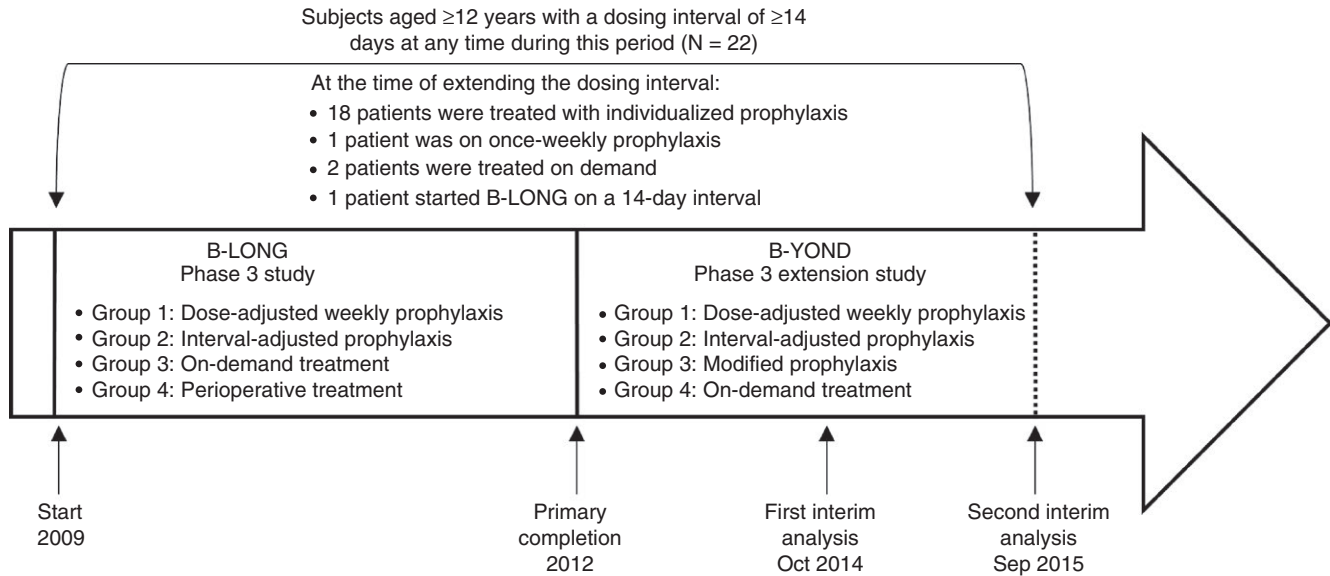


FIGURE 1 Study flow in B-LONG and the B-YOND extension study

TABLE 1 Baseline patient characteristics

Characteristic Median (IQR) or n (%)	Patients treated with ≥ 14 -day dosing interval, N = 22
Age, y	34.5 (23-48)
Race	
White	13 (59.1)
Black	2 (9.1)
Asian	7 (31.8)
Other	0
Severity	
<1% endogenous FIX activity	20 (90.9)
1%-2% endogenous FIX activity	2 (9.1)
Genotype	
Missense	16 (72.7)
Nonsense	1 (4.5)
Frameshift	1 (4.5)
Splice mutation	2 (9.1)
Partial gene deletion	1 (4.5)
Large deletions	0
Unknown	1 (4.5)
rFIXFc $t_{1/2}$, h	99.8 (86.3-105.9) ^a

Data represent values at baseline of B-LONG for patients treated with ≥ 14 -day dosing interval any time during B-LONG or B-YOND, until the time of the second interim B-YOND analysis.

FIX, factor IX; IQR, interquartile range; rFIXFc, recombinant factor IX Fc fusion protein; $t_{1/2}$, terminal half-life.

^aGeometric mean calculations (as reported in B-LONG⁶) are not presented because of differences in sampling profiles.

prior to the extension (Figure 1). The median (IQR) rFIXFc exposure duration before extending the dosing interval was 116 (61-205) days, the median (IQR) weekly consumption was 63

TABLE 2 Exposure to rFIXFc on a ≥ 14 -day dosing interval

Parameter Median (IQR)	N = 22
Exposure duration, days	1261 (648-1448)
Exposure days, days	91 (69-106)
Weekly consumption, IU/kg	50 (46-51)
Dose per injection, IU/kg	100 (92-102)
Dosing interval, days	14 (14-14)

IQR, interquartile range; rFIXFc, recombinant factor IX Fc fusion protein.

(59-72) IU/kg, and the median (IQR) dosing interval was 10 (10-12) days.

Patients had a median rFIXFc exposure on the ≥ 14 -day dosing interval of 3.4 years, with a median dose per injection of 100 IU/kg, and a median dosing interval of 14 days (Table 2). Six patients had dosing intervals that extended beyond 14 days: 1 on 15 days, 3 on 16 days, 1 on 17 days, and 1 on 21 days. The median (IQR) trough level while on ≥ 14 -day dosing was estimated to be 2.80 (2.3-3.8) IU/dL based on 149 measurements.

The majority of patients treated prophylactically appeared well controlled and experienced zero bleeds during the period before their dosing interval was extended to ≥ 14 days. However, 5 of 22 patients returned permanently to a dosing interval of <14 days due to a PK result (n = 1), patient request (n = 3: two of which were for personal reasons, the third due to bleeding), or repeated bleeding (elbow; n = 1). Among these five patients, one had previously been treated on-demand and three others had either a very short or no observation period on rFIXFc prior to extending the dosing interval and it is therefore uncertain if these patients truly were well controlled before extending their dosing interval to ≥ 14 days. The remaining 17 of the 22 patients (77.3%) continued on a dosing

TABLE 3 Annualized bleeding rate in patients treated prophylactically with a ≥ 14 -day dosing interval

Annualized bleeding rate Median (IQR)	Patients treated prophylactically with ≥ 14 -day dosing interval, N = 18 ^a
Overall	1.6 (0.6-2.7)
Joint	1.0 (0.3-1.6)
Spontaneous	0.7 (0.3-1.1)
Traumatic	0.5 (0.3-1)

IQR, interquartile range.

^aThis analysis included patients who were on prophylaxis before extending the dosing interval to ≥ 14 day (ie, the two patients receiving on-demand treatment were excluded), and who had been observed for ≥ 6 mo (thereby excluding an additional two patients).

interval of ≥ 14 days at the time of the second interim data cut, although three of these 17 patients had had a temporary reduction (50, 30, and 22 days) in the dosing interval to < 14 days at some point before the data cut because of bleeding (n = 1), repeated bleeding into the knee following arthroscopy (n = 1) and PK result (n = 1).

The ABR during the period with a ≥ 14 -day dosing interval was estimated for patients on prior prophylaxis who had an observation period of ≥ 6 months on the extended dosing regimen. These patients had a median (IQR) overall ABR of 1.6 (0.6-2.7) (Table 3), which is consistent with the ABR reported for the overall study population. In comparison, the median (IQR) overall ABR was 1.4 (0.0-3.4) with interval-adjusted prophylaxis in B-LONG,⁶ 2.25 (0.87-4.47) with interval-adjusted prophylaxis and 2.42 (1.26-5.40) with modified prophylaxis the interim analysis of B-YOND.⁷

The median (IQR) spontaneous ABR during the period with a ≥ 14 -day dosing interval was 0.7 (0.3-1.1) (Table 3). This compares with a median (IQR) spontaneous ABR of 0.9 (0.0-2.3) with interval-adjusted prophylaxis in B-LONG,⁶ 0.68 (0-2.58) with interval-adjusted prophylaxis and 0.41 (0-1.84) with modified prophylaxis in the interim analysis in B-YOND.⁷ These data provide further support that patients with hemophilia B can remain well controlled with an individualized 14-day dosing interval.

In total, four patients were excluded from the ABR calculation; two because they had an observation period that was too short (28 and 57 days) to obtain robust estimates of ABR and an additional two patients because they had received on-demand treatment before the dosing interval was changed to ≥ 14 days.

A total of 120 bleeding episodes in 22 patients occurred over 744 patient months of exposure while on a ≥ 14 -day dosing interval. Approximately 60% of the bleeds occurred during the first 10 days since previous dosing. The majority of bleeding episodes (114 [95%]) were controlled with either one or two injections. The median (IQR) total rFIXFc dose used to treat a bleed was 56.3 (37-99.1) IU/kg.

The adverse event profile was consistent with that expected in a hemophilia B population, and no new safety concerns were identified, compared with the overall populations in B-LONG⁶ or B-YOND.⁷

There were no reports of serious allergic reactions, anaphylaxis, vascular thrombotic events, or development of inhibitors.^{6,7}

In conclusion, these data confirm that patients who were well controlled on a 10-day dosing interval of rFIXFc prophylaxis remained well controlled with low ABRs when treated long-term on a ≥ 14 -day dosing interval, and the treatment was well tolerated. A rFIXFc dosing interval of ≥ 14 days allows for broader treatment flexibility and treatment individualization compared with conventional FIX products, and further reduces the burden for patients, potentially positively impacting adherence.

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RELATIONSHIP DISCLOSURES

A.D. Shapiro reports clinical research with Bioverativ, Octapharma, NovoNordisk and Shire, and advisory boards with NovoNordisk and Shire. K. Pasi reports research funding, fees for advisory boards and travel grants from Bioverativ, Sobi and Biomarin, fees for lectures and serving on advisory boards from Shire, research funding, fees for lectures, serving on advisory boards and travel grants from Octapharma, fees for lectures from NovoNordisk, research funding, fees for lectures and serving on advisory boards for Alnylam, fees for lectures from Pfizer, and fees for advisory board from Catalyst Bio. M.C. Ozelo reports research support from Sobi and Bioverativ, research support and participation on advisory boards and on a speakers bureau from NovoNordisk, Shire, Pfizer, participation on a speakers bureau and grant review panel for Grifols, participation on advisory boards for CSL Behring. R. Kulkarni reports clinical trial involvement with Bioverativ/Biogen, advisory boards for Bioverativ, BPL, NovoNordisk, Shire, Roche and Kendrion. C. Barnowski is an employee of Bioverativ, a Sanofi company. J. Szamosi is an employee of Sobi and holder of Sobi shares. B. Winding is an employee of Sobi. S. Lethagen is an employee of Sobi.

AUTHOR CONTRIBUTIONS

A.D. Shapiro: Investigator in the clinical trial and participated in drafting and revising the manuscript, and read and approved the final version as submitted. K.J. Pasi: Investigator in the clinical trial and participated in drafting and revising the manuscript, and read and approved the final version as submitted. M.C. Ozelo: Investigator in the clinical trial and participated in drafting and revising the manuscript, and read and approved the final version as submitted. R. Kulkarni: Investigator in the clinical trial and participated in drafting and revising the manuscript, and read and approved the final version

as submitted. C. Barnowski: Contributed to the design of the analysis and the interpretation of the data, and participated in drafting and revising of the manuscript and read and approved the final version as submitted. B. Winding: Substantially contributed to the design of the analyses and the interpretation of data. Participated in drafting and revising of the manuscript and read and approved the final version as submitted. J. Szamosi: Performed all analyses and participated in the interpretation of data. Participated in drafting and revising of the manuscript and read and approved the final version as submitted. S. Lethagen: Substantially contributed to the design of the analyses and the interpretation of data. Participated in drafting and revising of the manuscript and read and approved the final version as submitted.

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