Title Page

Long-term safety and efficacy of extended-interval prophylaxis with recombinant factor IX Fc fusion protein (rFIXFc) in subjects with haemophilia B

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Financial Support: This study was funded by Biogen and Sobi.

Target journal: *Thrombosis and Haemostasis*

Short title: *Long-term safety and efficacy of rFIXFc*

Body text: 3,780 / 5,000 word limit

Tables/Figures: No limit (Currently: 2 Tables / 5 Fig in main text; 6 Tables / 1 Fig in Suppl.)

References: 24 / 50 reference limit

Summary

The safety, efficacy, and prolonged half-life of recombinant factor IX Fc fusion protein (rFIXFc) were demonstrated in the Phase 3 B-LONG (adults/adolescents ≥12 years) and Kids B-LONG (children <12 years) studies of subjects with haemophilia B (≤2 IU/dl). Here, we report interim, long-term safety and efficacy data from B-YOND, the rFIXFc extension study. Eligible subjects who completed B-LONG or Kids B-LONG could enrol in B-YOND. There were four treatment groups: weekly prophylaxis (20–100 IU/kg every 7 days), individualised prophylaxis (100 IU/kg every 8–16 days), modified prophylaxis (further dosing personalisation to optimise prophylaxis), and episodic (on-demand) treatment. Subjects could change treatment groups at any point. Primary endpoint was inhibitor development. 116 subjects enrolled in B-YOND. From the start of the parent studies to the B-YOND interim data cut, median duration of rFIXFc treatment was 39.5 months and 21.9 months among adults/adolescents and children, respectively; 68/93 (73.1%) adults/adolescents and 9/23 (39.1%) children had ≥100 cumulative rFIXFc exposure days. No inhibitors were observed. Median annualised bleeding rates (ABRs) were low in all prophylaxis regimens: weekly (≥12 years: 2.3; <6 years: 0.0; 6 to <12 years: 2.7), individualised (≥12 years: 2.3; 6 to <12 years: 2.4), and modified (≥12 years: 2.4). One or two infusions were sufficient to control 97% (adults/adolescents) and 95% (children) of bleeding episodes. Interim data from B-YOND are consistent with data from B-LONG and Kids B-LONG, and confirm the long-term safety of rFIXFc, absence of inhibitors, and maintenance of low ABRs with prophylactic dosing every 1–2 weeks.

Keywords: Factor IX, haemophilia, prophylaxis, recombinant fusion proteins

Context Table

What is known on this topic?	• In people with haemophilia B, prophylactic treatment with two to three intravenous infusions per week is often necessary to prevent bleeding. • The frequency of administration can be a barrier to adherence to a prophylactic regimen.
What this paper adds	• No inhibitors were observed with rFIXFc treatment as of the B-YOND interim data cut date • Interim data from B-YOND confirm the long-term safety of rFIXFc and the maintenance of a low ABR with prophylactic dosing every 1–2 weeks.

Introduction

Severe haemophilia B is characterised by spontaneous and traumatic bleeding into joints and muscles that results in pain, decreased mobility, and disability (1, 2). Prophylactic treatment with replacement coagulation factor IX (FIX) has been shown to reduce the frequency of bleeding episodes while improving joint outcomes and quality of life, particularly when prophylaxis is initiated early in life (1, 3-5). However, conventional prophylaxis regimens with plasma-derived FIX or recombinant FIX products typically require two to three intravenous infusions per week to prevent bleeding (1, 6). The time commitment involved for prophylaxis, the interference of prophylactic infusions with daily activities, and difficulties with vascular access in young children are often cited as barriers to adherence to a prophylactic regimen (7-10). A FIX product that requires fewer infusions to maintain a threshold factor activity level that is protective against bleeding may alleviate some of the burden of treatment and improve adherence and clinical outcome (11).

Recombinant FIX Fc fusion protein (rFIXFc) was developed to prolong the half-life of FIX, in order to reduce prophylactic infusion frequency (12-14). The Fc portion of rFIXFc binds to the neonatal Fc receptor and utilises the endogenous IgG recycling pathway to delay lysosomal degradation of IgG and Fc fusion proteins, cycling them back into the circulation (12). The safety, efficacy, and prolonged half-life of rFIXFc were demonstrated in previously treated adults, adolescents, and children with haemophilia B in the Phase 3 B-LONG (15-17) and Kids B-LONG (18) studies. Here, we report on an interim data cut of the ongoing rFIXFc extension study, B-YOND (ClinicalTrials.gov Identifier: NCT01425723), which evaluates the long-term

safety of rFIXFc and its efficacy in the prevention and treatment of bleeding episodes in subjects with haemophilia B.

Materials and Methods

Study Design

B-YOND is an open-label, nonrandomised extension study. Previously treated male subjects with haemophilia B (≤2 IU/dl endogenous FIX activity) who completed the Phase 3 B-LONG (≥12 years of age) or Kids B-LONG (<12 years of age) studies were eligible for enrolment. Key eligibility criteria for the parent studies were as follows: B-LONG study subjects were ≥12 years of age, had no history of or currently detectable inhibitors, and prior to enrollment in B-LONG had been on a prophylactic treatment regimen or had a history of ≥8 bleeding episodes in the previous year and had ≥100 exposure days (EDs) to replacement FIX (see supplement of primary manuscript (15) for complete eligibility criteria). Kids B-LONG study subjects were <12 years of age, had no history of or currently detectable inhibitors, and prior to enrollment in Kids B-LONG had ≥50 EDs to replacement FIX (see Supplemental Material for additional eligibility criteria). For this interim analysis, the data cut date was 17 October 2014.

B-YOND had three prophylactic treatment groups: weekly prophylaxis, individualised prophylaxis, and modified prophylaxis. Subjects in the weekly prophylaxis group were treated with 20–100 IU/kg rFIXFc every seven days and subjects in the individualised prophylaxis group received 100 IU/kg rFIXFc every eight to 16 days, with dosing based on the subject's clinical profile observed in the parent study and individual pharmacokinetic (PK) profile, trough,

and/or peak (recovery) values. The third prophylaxis group, modified prophylaxis, allowed investigators to further personalise dosing to achieve optimal prophylaxis (see Supplemental Material for details). The study also had an episodic (on-demand) treatment group, in which dosing was based on the subject's clinical condition and the type and severity of bleeding. Subjects of any age could participate in any of the prophylaxis treatment groups; however, the episodic treatment group was available only to subjects aged ≥12 years. The protocol permitted subjects to change treatment groups at the time of enrolment into the extension study or at any time during the study. Detailed methods for perioperative management with rFIXFc have been published (16).

Outcome Measures

The primary endpoint of the study was development of inhibitors (neutralising antibodies). A positive inhibitor result was defined as a neutralising antibody value ≥0.6 BU/ml, measured by a Nijmegen-modified Bethesda assay at a central laboratory, and confirmed on retesting within two to four weeks per European Medicines Agency guidelines (19). Subjects were tested for inhibitor formation at each clinic visit (ie, approximately every six months). Additional visits could be conducted to perform inhibitor testing as needed during 10–15 EDs, 50–75 EDs, and after achieving 100 EDs.

Secondary endpoints included the annualised number of bleeding episodes (including spontaneous joint bleeding episodes) per subject, rFIXFc EDs per subject, rFIXFc consumption

(total IU/kg per subject per year), and the subject's assessment of response to treatment of a bleeding episode. Additional outcomes included the incidence of adverse events (AEs), the number of infusions and dose per infusion needed to control a bleeding episode, and the assessment of haemostatic response in subjects undergoing major surgery. FIX activity was measured using the one-stage aPTT clotting assay and performed at a central laboratory.

Statistical Analysis

Safety analyses were conducted on data from subjects who received at least one dose of rFIXFc. Efficacy analyses were performed on data from subjects who received at least one dose of rFIXFc during the efficacy period, which encompassed all intervals of time during which subjects were treated with rFIXFc according to the treatment regimens of the study, excluding major and minor surgical/rehabilitation periods.

Results were analysed by treatment group. Subjects who changed groups during the study were included in summary analyses of each treatment group for the time period they were in that treatment group from the beginning of the study to the interim data cut, and therefore may be represented in more than one treatment group for safety and efficacy analyses (see "Total in group [at any time]" populations in Figure 2). Efficacy analyses performed for subjects in each treatment group at the time of the B-YOND interim data cut are indicated as such (see "Treatment group at interim data cut" populations in Figure 2). All analyses of paediatric

subjects were performed according to age (<6 years of age and 6 to <12 years of age) at the time of entry into the parent study.

Results

Study Population and rFIXFc Exposure

At the time of the interim data cut, 116 male subjects were enrolled in B-YOND (Figure 1, Suppl. Table 1). Of the 123 adults and adolescents (≥12 years of age) who had enrolled in B-LONG, 115 completed B-LONG, and 93 of these subjects (81%) enrolled in B-YOND. The median (range) age of adult/adolescent subjects at enrolment into B-YOND was 29.0 (13–63) years (Suppl. Table 1). Seven adult/adolescent subjects prematurely discontinued B-YOND. The interim data cut for B-YOND occurred prior to the completion of the Kids B-LONG study; at this time, 23 of the 30 subjects enrolled in Kids B-LONG had completed the study and all (100%) enrolled in B-YOND (<6 years of age, n = 9; 6 to <12 years of age, n = 14). The median (range) ages of paediatric subjects in the <6 years and 6 to <12 years cohorts at enrolment into B-YOND were 4.0 (3–5) years and 9.5 (7–12) years, respectively. None of the paediatric subjects discontinued the extension study prematurely.

Among adult/adolescent subjects entering B-YOND from the B-LONG prophylactic (n = 71) and episodic (n = 19) treatment arms, 29 subjects (32%) changed treatment groups at the start of or during the extension study (Figure 2A). This included nine of the 19 subjects who were being treated episodically at the end of B-LONG and changed to a prophylaxis group during B-YOND; one of these subjects switched back to episodic treatment prior to the B-YOND interim data cut.

Of the 23 paediatric subjects entering B-YOND from Kids B-LONG, 18 subjects (78%) remained in the once-weekly prophylaxis treatment group; four subjects changed to the individualised prophylaxis treatment group, and one changed to the modified prophylaxis treatment group (Figure 2B).

From the start of B-LONG to the B-YOND interim data cut, adult/adolescent subjects had a median of 39.5 months of cumulative rFIXFc treatment, and a median of 162 cumulative rFIXFc EDs (Suppl. Table 2). From the start of Kids B-LONG to the B-YOND interim data cut, paediatric subjects had a median of 21.9 months of cumulative rFIXFc treatment, and a median of 94 cumulative rFIXFc EDs (Suppl. Table 2). Overall, 93.5% of adult/adolescent subjects and 100% of paediatric subjects had ≥50 cumulative rFIXFc EDs (Suppl. Figure 1).

Safety Overview

Among 116 subjects who completed the B-LONG or Kids B-LONG parent studies and enrolled in the extension study, all had at least one evaluable inhibitor test result during B-YOND, with no inhibitors observed; the estimated inhibitor incidence rate was 0.0% (95% confidence interval, 0.0%–3.1%). Overall, these results are consistent with the parent studies, wherein no inhibitors were observed in any subjects. As of the B-YOND interim data cut, there were no reports of serious allergic reactions or anaphylaxis associated with rFIXFc, no vascular thrombotic events, and no deaths. rFIXFc was well-tolerated, with a pattern of AEs typical of the

population studied (Table 1, Suppl. Table 3). None of the subjects discontinued rFIXFc treatment or withdrew from the study due to an AE.

A summary of AEs during B-YOND is provided in Table 1. During B-YOND, 75.9% of subjects reported at least one AE, not including AEs emergent during the perioperative management period. The most common AEs were headache in 14 subjects (12.1%) and nasopharyngitis in 13 subjects (11.2%). The majority of AEs were considered by the investigator to be unrelated to rFIXFc treatment. Three adult/adolescent subjects experienced one nonserious AE each (noncardiac chest pain, haematuria, obstructive uropathy) that were assessed by the investigator as related to rFIXFc treatment; all three of these AEs resolved, and none led to study discontinuation. One adult/adolescent subject had experienced a mild, nonserious AE of breath odour during B-LONG, and one paediatric subject had experienced a mild, nonserious AE of decreased appetite during Kids B-LONG; these AEs were considered by the investigator to be related to rFIXFc treatment, continued into B-YOND, and were unresolved at the time of the interim data cut. A total of 39 serious AEs (SAEs) were reported in 23 subjects (19.8%) treated with rFIXFc. All SAEs were assessed by the investigator as unrelated to rFIXFc, with the exception of one SAE of renal colic in one adult/adolescent subject with a medical history of previous clot colic; the event resolved and did not lead to study discontinuation.

Prophylactic Dosing With rFIXFc

The protocol for B-YOND allowed subjects to adjust both their dose and dosing interval to optimise prophylaxis. The median dosing interval and average weekly prophylactic dose during B-YOND for each treatment group is shown in Table 2.

Overall, the majority of subjects previously on a prophylactic regimen in the B-LONG and Kids B-LONG parent studies either maintained or lengthened their infusion interval during B-YOND. Fifty-nine of the 71 adult/adolescent subjects (83.1%) who were treated prophylactically during B-LONG maintained their prophylactic infusion interval during the extension study and four subjects (5.6%) lengthened their prophylactic infusion interval compared with their regimen in B-LONG (Figure 3A). Similarly, 18 of 23 paediatric subjects (78.3%) maintained their prophylactic infusion interval during B-YOND, while four subjects (17.4%) lengthened their prophylactic infusion interval compared to their regimen in Kids B-LONG. The remaining eight adult/adolescent subjects (11.3%) and one paediatric subject (4.3%) shortened their prophylactic infusion interval during B-YOND compared to their regimen during the parent study (Figure 3B). Regardless of age, the majority of subjects in B-YOND remained in the treatment group in which they had participated in the parent study. Among 46 adult/adolescent subjects participating in the weekly prophylaxis treatment group at the end of B-LONG, 37 subjects (80.4%) chose to remain in the weekly prophylaxis group at enrolment into B-YOND (Figure 2A); among 25 adult/adolescent subjects participating in the individualised prophylaxis treatment group at the end of B-LONG, 23 subjects (92.0%) chose to remain in this treatment group at enrolment into B-YOND (Figure 2A). Among the 23 paediatric subjects who enrolled in B-

YOND, 22 subjects (95.7%) were dosing once weekly and one subject (4.3%) was dosing every five days at the end of Kids B-LONG. Among these 23 paediatric subjects, 19 subjects (82.6%) remained in the weekly prophylaxis group at enrolment into B-YOND (Figure 2B). The remaining four subjects (17.4%) switched to the individualised prophylaxis group at enrolment in B-YOND and were dosing every 10 to 14 days at the interim data cut (Figures 2B and 3B).

As of the B-YOND interim data cut, a total of 26 subjects had a dosing interval longer than once weekly. The median dosing interval in the individualised prophylaxis group was 13.7 days for adult/adolescent subjects and 10.0 days for paediatric subjects aged 6 to <12 years (Table 2). Fifteen of 26 adult/adolescent subjects (57.7%) in the individualised prophylaxis treatment group at the time of the B-YOND interim data cut had a dosing interval of every 14 days or longer (Figure 3A). However, among paediatric subjects, only four subjects (17.4%) infused less frequently than once weekly; three subjects were infusing every 10 days and one subject was infusing every 14 days (Figure 3B). Considering rFIXFc dose, the median average weekly prophylactic dose was similar for subjects in the weekly and individualised prophylaxis groups (≥12 years cohort: 49.5 IU/kg and 50.2 IU/kg, respectively; 6 to <12 years cohort: 63.1 IU/kg and 66.6 IU/kg, respectively; <6 years cohort: 64.4 IU/kg for weekly prophylaxis; Table 2). Most adult/adolescent subjects maintained (66.2%) or reduced (11.3%) their weekly prophylactic dose during B-YOND; 22.5% increased their total weekly prophylactic dose (Figure 4). Most paediatric subjects maintained (47.8%) or reduced (21.7%) their weekly prophylactic dose during B-YOND; 30.4% increased their total weekly prophylactic dose (Figure 4). The median total annualised rFIXFc consumption during B-YOND in the weekly prophylaxis group was

2647.0 IU/kg for subjects aged ≥12 years and 3327.9 IU/kg and 3313.8 IU/kg for subjects aged <6 years and 6 to <12 years of age, respectively (Suppl. Table 4). The median total annualised rFIXFc consumption during B-YOND in the individualised prophylaxis group was 2781.5 IU/kg for adult/adolescent subjects and 3698.2 IU/kg for paediatric subjects.

Annualised bleeding rate during B-YOND

Among adult/adolescent subjects, the overall median annualised bleeding rate (ABR) during B-YOND was similar in the weekly (2.3; n = 50), individualised (2.3, n = 30), and modified (2.4; n = 13) prophylaxis groups (Figure 5, Suppl. Table 5). The median ABR in adult/adolescent subjects treated episodically with rFIXFc during B-YOND was 11.3 (n = 15); median spontaneous ABRs were also similar in the weekly, individualised, and modified prophylaxis groups (0.8, 0.7, and 0.4, respectively) and higher in subjects treated episodically (4.7). Among paediatric subjects aged <6 years (n = 9), the median ABR in the weekly prophylaxis group was 0.0. Among subjects aged 6 to <12 years, the median ABR was similar in the weekly (2.7; n = 10) and individualised (2.4; n=5) prophylaxis groups. The one subject from the 6 to <12 years cohort who participated in the modified prophylaxis group had an ABR of 3.1. The median ABR for spontaneous bleeding episodes was 0.0 for both paediatric age cohorts.

Treatment of Bleeding Episodes

During B-YOND, a total of 1013 bleeding episodes occurred in 92 adult/adolescent subjects, including 752 bleeding episodes located in joints that occurred in 73 adults/adolescents. Overall,

87.3% of bleeding episodes that occurred in adult/adolescent subjects were controlled with one infusion and 97.2% with one or two infusions; the median average rFIXFc dose per infusion required to treat a bleeding episode was 46.2 (interquartile range [IQR]: 33.3–60.0) IU/kg. A total of 60 bleeding episodes occurred in 17 paediatric subjects during B-YOND, including 41 bleeding episodes located in joints that occurred in 13 paediatric subjects. In paediatric subjects, 80% of bleeding episodes were controlled with one infusion and 95% with one or two infusions; the median average rFIXFc dose per infusion to treat a bleeding episode was 57.8 (IQR: 43.2–74.9) IU/kg. Details on dosing recommendations for the treatment of bleeding episodes can be found in the Supplemental Material.

Perioperative Management

During B-YOND, 14 major surgeries were performed in seven adult/adolescent subjects, and included transarterial chemoembolisation (n = 3), craniotomy (n = 2), hip replacement or repair (n = 2), arthroscopy (n = 1), installation/removal of external Ilizarov fixation (n = 1), liver transplant (n = 1), orchiectomy (n = 1), percutaneous-ablation of hepatic carcinoma (n = 1), spinal surgery (n = 1), and unilateral ankle fusion (n = 1). Additionally, four adult/adolescent subjects who underwent major surgery in the B-LONG parent study had their rehabilitation period during B-YOND. The one major surgery among paediatric subjects during B-YOND was a tonsillectomy. No unique safety concerns emerged during the perioperative period. Of the 15 major surgeries during B-YOND, 14 were assessed for haemostatic response; haemostasis was rated by the investigator/surgeon as excellent in 13 surgeries (including one liver transplant) and good in one surgery, meaning that intraoperative and postoperative blood loss were comparable

to what would be expected for a subject who did not have haemophilia. All 15 major surgeries were evaluated for rFIXFc dosing during the perioperative period. During surgery, the total rFIXFc dose (including any pre-surgery loading dose) ranged from 60.6 to 152.3 IU/kg for the 12 major surgeries for which a single infusion was required to maintain haemostasis; in addition to these 12 surgeries, 1 surgery did not require any rFIXFc infusion and 2 surgeries required 2 rFIXFc infusions (with average doses per infusion of 83.3 and 89.9 IU/kg). On the day of surgery (including any loading dose, infusion during surgery, and infusion later on the day of surgery [which was required for 8 surgeries]), the total rFIXFc dose ranged from 60.6 to 317.9 IU/kg. During post-surgery Days 1 to 3, the total rFIXFc dose ranged from 59.6 to 681.8 IU/kg; on post-surgery Days 4-14, the total rFIXFc dose ranged from 76.4 to 1265 IU/kg.

Discussion

The interim data from B-YOND presented here add to the findings from the Phase 3 B-LONG (15-17) and Kids B-LONG (18) parent studies, and confirm the long-term safety and efficacy of rFIXFc for the prevention and treatment of bleeding episodes in adults, adolescents, and children with haemophilia B. The B-YOND extension study represents the most extensive exposure to a long-acting replacement FIX product to date; from the start of the parent study to the B-YOND interim data cut, the median cumulative rFIXFc EDs was 162 in adult/adolescent subjects and 94 in paediatric subjects. The median cumulative duration of rFIXFc treatment was 39.5 months and 21.9 months from the start of B-LONG and Kids B-LONG, respectively, to the B-YOND interim data cut. No inhibitors were observed with rFIXFc treatment and the pattern of AEs was typical of the population studied. Efficacy data from both the parent studies and extension study

demonstrate consistently low bleeding rates with extended-interval rFIXFc prophylaxis. In particular, the median ABRs for spontaneous bleeding episodes were <1.0 in adult/adolescent subjects and 0 in paediatric subjects treated with rFIXFc prophylaxis—as good or better than what was observed in the parent studies (15, 18).

The flexibility of the B-YOND protocol allowed subjects to make dose and dosing-interval adjustments, according to clinical needs and personal preference, to achieve optimised rFIXFc prophylaxis for individual subjects and provide a near real-world experience. Regardless of age, the majority of subjects remained in the treatment group in which they had participated in the parent study. Notably, 47% of adult/adolescent subjects treated episodically during B-LONG moved to a prophylactic treatment group during B-YOND, highlighting the appeal of prophylactic dosing with rFIXFc. Overall, the infusion interval remained stable during B-YOND and 16 adult/adolescent subjects and one paediatric subject had a dosing interval of ≥14 days at the B-YOND interim data cut. The total weekly prophylactic dose also remained consistent during B-YOND with the majority of subjects maintaining or reducing their total weekly prophylactic dose relative to the end of the parent study. Regardless of whether subjects were on a once-weekly or an individualised dosing regimen, the median average weekly prophylactic dose of rFIXFc was similar across treatment groups (~50 IU/kg in adult/adolescent subjects and ~65 IU/kg in paediatric subjects aged 6 to <12 years).

Clinical trial design in haemophilia B is associated with several inherent challenges and limitations that result from the small number of individuals affected by the disease. Although the

flexibility of the B-YOND protocol was advantageous for the individualisation and optimisation of subjects' dosing regimens and provided a near real-world setting, the movement of subjects between treatment groups during the study does introduce a measure of selection bias and complicates comparisons between prestudy and on-study data at the individual subject level. Additional study limitations include the reliance on self-reported data (in the form of patient diaries) for treatment of bleeding information and the small number of paediatric subjects in the individualised and modified prophylaxis groups.

Previously untreated patients and patients with a history of inhibitor development were excluded from the parent studies and B-YOND extension study. Therefore, the safety and efficacy of rFIXFc among these high-risk patient populations warrants future investigation. Notably, the safety of rFIXFc in previously untreated patients is currently being studied in a separate clinical trial (NCT02234310). Future studies may also investigate the potential long-term effects of rFIXFc on factors beyond haemostasis, such as immunogenicity, the ability to induce tolerance, and joint health outcomes. Finally, although imaging confirmation of joint bleeding episodes is not standard of care, if imaging can be incorporated into future practice, this may improve the diagnosis and treatment of joint bleeds.

In conclusion, the interim data reported here from the B-YOND extension study confirm the long-term safety and efficacy of rFIXFc prophylaxis in adult, adolescent, and paediatric subjects with haemophilia B, and demonstrate low ABRs with extended prophylactic dosing intervals of every one to two weeks. These results build upon the B-LONG and Kids B-LONG parent studies

(15, 18), which previously established the prolonged half-life of rFIXFc compared with conventional factor replacement therapies (20, 21). Although additional work is needed to optimise treatment protocols with rFIXFc, the low bleeding rates reported in the B-LONG/Kids B-LONG parent studies and B-YOND extension study suggest that individuals with haemophilia B receiving rFIXFc prophylaxis may be able to achieve low ABRs with similar or reduced factor consumption compared with regimens utilising conventional FIX products. Additionally, these individuals may be able to successfully transition to rFIXFc on the basis of empiric dosing strategies rather than pharmacokinetic assessment. The extended dosing intervals observed in both the parent studies and in the B-YOND extension study suggest that prophylactic regimens with rFIXFc may confer improved treatment flexibility compared with conventional FIX therapies. Thus, rFIXFc, the first in a new class of extended half-life therapies (22-24), has the potential to reduce treatment burden and improve adherence to prophylactic regimens and long-term outcomes among people with haemophilia B.

Disclosures

KJP: grant/research support from Octapharma, Pfizer, Biogen, and Novo Nordisk; consultant for Bayer, BPL, Octapharma, Biogen, and Pfizer.

KF: grant/research support from Bayer, Wyeth/Pfizer, Baxter, and Novo Nordisk; consultant for Bayer, Baxter, Biogen, Freeline, Novo Nordisk, and Pfizer; received speaker's fees from Bayer, Baxter, CSL Behring, Biotest, Octapharma, Pfizer, and Novo Nordisk.

MR: grant/research support from Alnylam, Baxalta, Baxter Bioscience, Biogen, CSL Behring, Dimension Therapeutics, Genentech/Roche, Novo Nordisk, and SPARK; consultant for Alnylam, Baxalta, Biogen, Biomarin, Medscape, Shire, and Tacere Benitec.

BN: grant/research support from Biogen and Sobi.

DJP: advisory board for Novo Nordisk; consultant for Biogen and Novo Nordisk; honoraria from Biogen.

RK: grant/research support from Biogen, Novo Nordisk, and Baxalta; consultant for Bayer, Baxalta, Biogen, Kedrion, Pfizer, and BPL.

MO: speakers bureau for Novo Nordisk.

JM: advisory boards for Amgen, Bayer, Genentech, and Novo Nordisk; research funding from Biogen, Bayer, CSL Behring and Novo Nordisk.

ADS: consultant for Baxter, Novo Nordisk, and LFB Biotechnologies.

RIB: grant/research support from Boehringer Ingelheim, Bayer, Baxter, Pfizer, Daiichi Sankyo, Astellas, Novo Nordisk, and CSL Behring; consultant for Amgen, Biogen, Boehringer Ingelheim, Bayer, and Pfizer.

CMB: nothing to disclose.

CB: grant/research support from Bayer, Novo Nordisk, and Pfizer; advisory boards for Bayer, Baxter, and Novo Nordisk.

JO: grant/research support from, and consultant and speaker for, Baxter, Bayer, Biogen, Biotest, CSL Behring, Grifols, Novo Nordisk, Octapharma, Sobi, and Pfizer.

TM: honoraria from Baxter and Novo Nordisk.

HY, AR-S, BM: employees and shareholders of Biogen.

GA, GFP: shareholders and former employees of Biogen.

This study was funded by Biogen and Sobi.

Acknowledgements

This study was funded by Biogen and Sobi. The authors are grateful to all of the patients, families, and investigators who were involved in the B-YOND study. The authors also thank Elisa Tsao, PhD, from Biogen, for data analysis support and MaryEllen Carlile Klusacek, PhD, from Biogen, for providing writing support based on input from the authors. Additional editorial support was provided by Allison Michaelis, PhD, of MedErgy, and was funded by Biogen and Sobi.

Biogen and Sobi reviewed and provided feedback on the paper. The authors had full editorial control of the paper and provided their final approval of all content.

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Figure Legends

Figure 1. Subject disposition.

Subjects who completed the Phase 3 B-LONG and Kids B-LONG studies were eligible for enrolment in the B-YOND extension study. Of the subjects who had completed the Phase 3 studies by the time of the interim data cut, 93/115 B-LONG subjects (81%) and 23/23 (100%) Kids B-LONG subjects, respectively, enrolled in B-YOND.

rFIXFc, recombinant factor IX Fc fusion protein.

[a]Completed: ended participation in the study without premature discontinuation.

[b]At the time of the B-YOND interim data cut, four subjects were ongoing in Kids B-LONG; three subjects discontinued Kids B-LONG prematurely.

[c]Subject was on an episodic treatment regimen for 519 days during B-YOND. This subject believed that his bleeding was not being well controlled and asked to be withdrawn from the study. No inhibitors were detected.

[d]Subject was incarcerated and therefore ineligible to continue in the study.

Figure 2. Change in treatment group from end of parent study ([A], B-LONG; [B], Kids B-LONG) to the B-YOND interim data cut.

[a]One subject in the weekly prophylaxis group at the start of B-YOND switched to the individualised prophylaxis group, then back to the weekly prophylaxis group before the interim data cut (null net change in group).

[b]Two subjects began B-YOND in the individualised prophylaxis group, switched to weekly prophylaxis, then switched back to the individualised prophylaxis group before the interim data cut (null net change in group).

[c]One subject in the episodic treatment group at the start of B-YOND switched to the modified prophylaxis group, then returned to the episodic treatment group before the interim data cut (null net change in group).

[d]Protocol permitted subjects to change treatment regimens over the course of this extension study; therefore, subjects may be represented in more than one treatment regimen. "Total" indicates the number of subjects on the given regimen at any time from the beginning of the study to the interim data cut.

[e]One subject who initially received once-weekly prophylaxis at the beginning of Kids B-LONG was dosing once every five days at the end of Kids B-LONG.

Figure 3. Change in infusion frequency from end of parent study to B-YOND interim data cut.

Changes in prophylactic infusion frequency from the end of B-LONG [A] and Kids B-LONG [B] to the time of the B-YOND interim data cut are shown for individual subjects. The majority of these subjects had either no change to (white boxes) or lengthened (dark grey boxes) their infusion interval during B-YOND. The infusion frequency at the time of the B-YOND interim data cut is also shown for subjects previously in the episodic arm of B-LONG (n = 19).

[a]Excludes three subjects who were only in the surgery arm in B-LONG. The B-YOND interim data cut dosing interval in these three subjects was twice weekly, every four days, and every 13 days.

[b]Every 10 days, n = 3; every 14 days, n = 1.

Figure 4. Change in total weekly prophylactic dose during B-YOND among subjects treated prophylactically in B-LONG or Kids B-LONG.

Overall, 66.2% of subjects from B-LONG and 47.8% of subjects from Kids B-LONG had no change in their total weekly prophylactic dose during the extension study relative to their total weekly prophylactic dose at the end of the parent study. The median change in weekly prophylactic dose was 0.0 IU/kg/week for both sets of subjects.

[a]Two Kids B-LONG subjects with an increase in total weekly prophylactic dose (10–20 IU/kg) transitioned from a once-weekly regimen in Kids B-LONG (50–60 IU/kg once weekly) to individualised interval prophylaxis in B-YOND (100 IU/kg every 10 days).

Figure 5. Summary of median (IQR) ABRs during B-YOND.

Bleeding rates, including the rate of spontaneous and spontaneous joint bleeding episodes, were consistently low in all rFIXFc prophylaxis groups compared with episodic treatment.

ABR, annualised bleeding rate; IQR, interquartile range.

[a]One subject from B-LONG in the modified prophylaxis group did not meet the definition for having an efficacy period, and thus was not included in the ABR analysis.

Tables and Figures

Table 1. Summary of Adverse Events During B-YOND (≥5% in Either Study Population)[a]

	Parent study		
	B-LONG	**Kids B-LONG**	**Overall**
	N = 93	**N = 23**	**N = 116**
Subjects who experienced ≥1 AE, n (%)	**71 (76.3)[b]**	**17 (73.9)[c]**	**88 (75.9)**
Headache	13 (14.0)	1 (4.3)	14 (12.1)
Nasopharyngitis	9 (9.7)	4 (17.4)	13 (11.2)
Fall	4 (4.3)	5 (21.7)	9 (7.8)
Vomiting	7 (7.5)	2 (8.7)	9 (7.8)
Upper respiratory tract infection	6 (6.5)	1 (4.3)	7 (6.0)
Influenza	6 (6.5)	0	6 (5.2)
Arthralgia	4 (4.3)	2 (8.7)	6 (5.2)
Haematuria	5 (5.4)	0	5 (4.3)
Hypertension	5 (5.4)	0	5 (4.3)
Nausea	5 (5.4)	0	5 (4.3)
Epistaxis	3 (3.2)	2 (8.7)	5 (4.3)
Diarrhoea	2 (2.2)	2 (8.7)	4 (3.4)
Seasonal allergy	2 (2.2)	3 (13.0)	5 (4.3)

Subjects who experienced ≥1 SAE, n (%)	**21 (22.6)**	**2 (8.7)[d]**	**23 (19.8)**
Total number of SAEs, n	**36[e]**	**3**	**39**

AE, adverse event; SAE, serious adverse event; rFIXFc, recombinant factor IX Fc fusion protein.

[a]Percents are based on the number of subjects treated with rFIXFc and exclude AEs occurring during the perioperative management period; five AEs in three subjects emerged during the perioperative management period (all were mild to moderate, and were assessed as unrelated to rFIXFc).

[b]Three subjects from B-LONG experienced one nonserious AE each that was assessed by the investigator as related to rFIXFc (noncardiac chest pain, haematuria, obstructive uropathy); all resolved and none led to study discontinuation.

[c]During Kids B-LONG, one subject experienced a mild, nonserious AE of decreased appetite that was considered related to rFIXFc treatment; the AE continued into the extension study and was unresolved at the time of the interim data cut.

[d]Two subjects from Kids B-LONG experienced a total of three SAEs (tonsillitis, upper limb fracture, fall); all were assessed by the investigator as unrelated to rFIXFc.

[e]One subject from B-LONG with a medical history of previous clot colic experienced an SAE of renal colic that was assessed by the investigator as related to rFIXFc treatment; the event resolved and did not lead to study discontinuation. The remaining 35 SAEs were assessed by the investigator as unrelated to rFIXFc treatment

Table 2. rFIXFc Prophylactic Dose and Dosing Interval by Treatment Group

Parent study	B-YOND treatment group: Weekly prophylaxis	B-YOND treatment group: Individualised prophylaxis	B-YOND treatment group: Modified prophylaxis
B-LONG	**N = 50**	**N = 30**	**N = 13[a]**
Average dosing interval (days), median (IQR)	7.0 (7.0–7.0)	13.7 (10.1–14.0)	6.9 (4.9–7.0)
Average weekly prophylactic dose (IU/kg), median (IQR)[b]	49.5 (39.9–62.8)	50.2 (48.2–61.5)	61.7 (41.5–81.8)
Kids B-LONG			
<6 years of age cohort	**N = 9**	**–**	**–**
Average dosing interval (days), median (IQR)	7.0 (7.0–7.0)	**–**	**–**
Average weekly prophylactic dose (IU/kg), median (IQR)[b]	64.4 (52.3–66.5)	**–**	**–**

6 to <12 years of age cohort	**N = 10**	**N = 5**	**N = 1[c]**
Average dosing interval (days), median (IQR)	7.0 (7.0–7.0)	10.0 (10.0–10.8)	4.1
Average weekly prophylactic dose (IU/kg), median (IQR)[b]	63.1 (59.7–64.7)	66.6 (63.3–69.5)	157.9

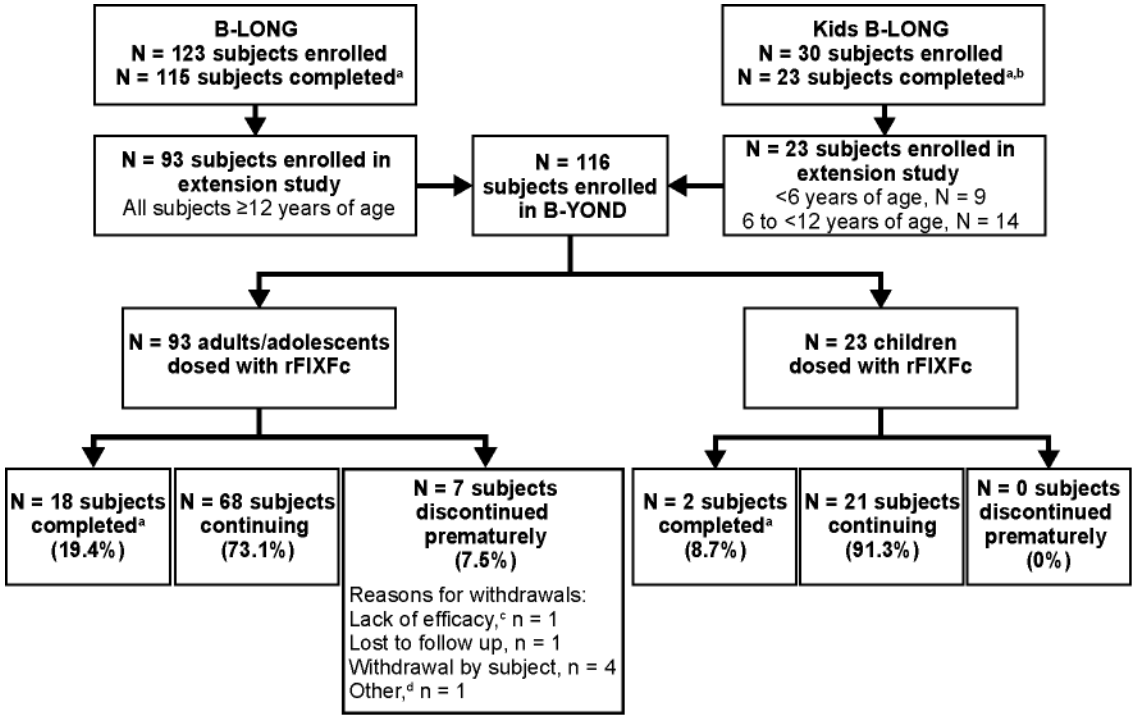
rFIXFc, recombinant factor IX Fc fusion protein; IQR, interquartile range.

[a]One subject in the modified prophylaxis group of B-LONG did not meet the definition for having an efficacy period, and thus was not included in the dosing analysis.

[b]The average prophylactic weekly dose is the total IU/kg of all eligible prophylactic doses extrapolated to a weekly amount; an eligible dose is the first of the two doses that defines the intervals not separated by a bleeding episode or surgery.

[c]During Kids B-LONG, subject was first treated with 60–100 IU/kg weekly, then 100 IU/kg every five days; subject enrolled in the individualised prophylaxis group of B-YOND (100 IU/kg every five days), then switched to the modified prophylaxis group (50 IU/kg every five days, then twice weekly with 50 IU/kg and 100 IU/kg).

Figure 1.



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rFIXFc, recombinant factor IX Fc fusion protein.

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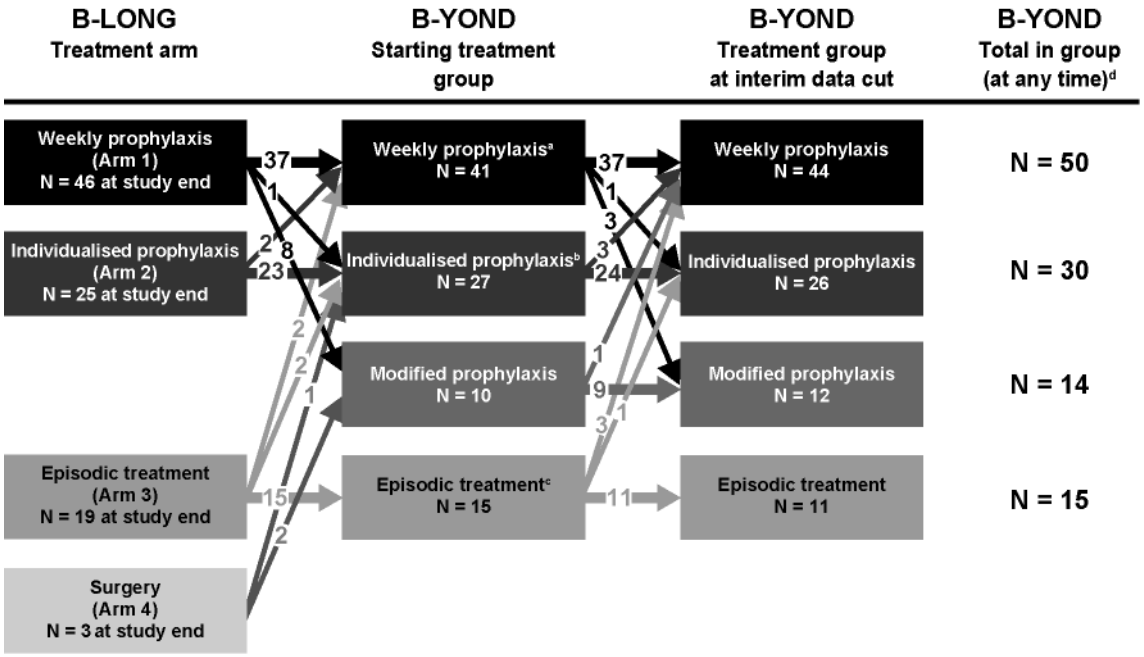
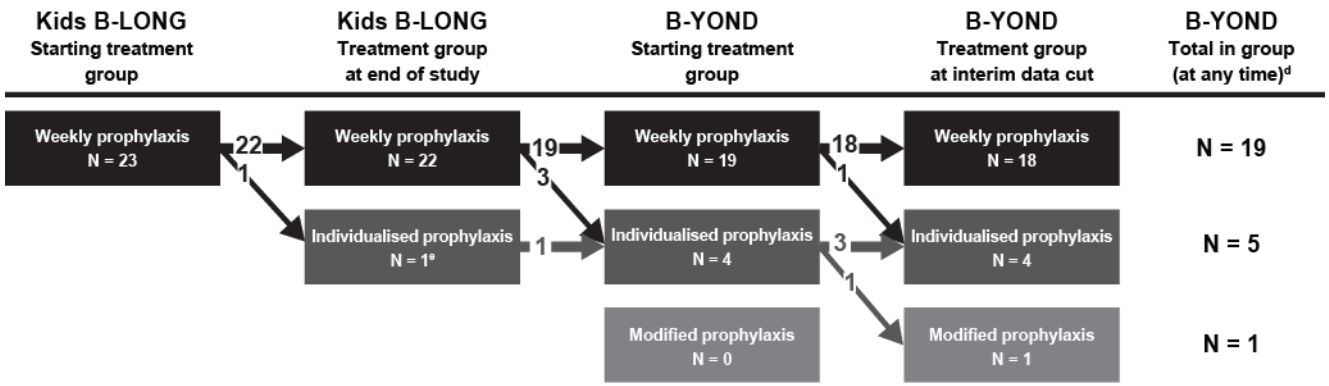
[d]Subject was incarcerated and therefore ineligible to continue in the study.

Figure 2.

A. Subjects entering B-YOND from B-LONG (n = 93)



B. Subjects entering B-YOND from Kids B-LONG (n = 23)



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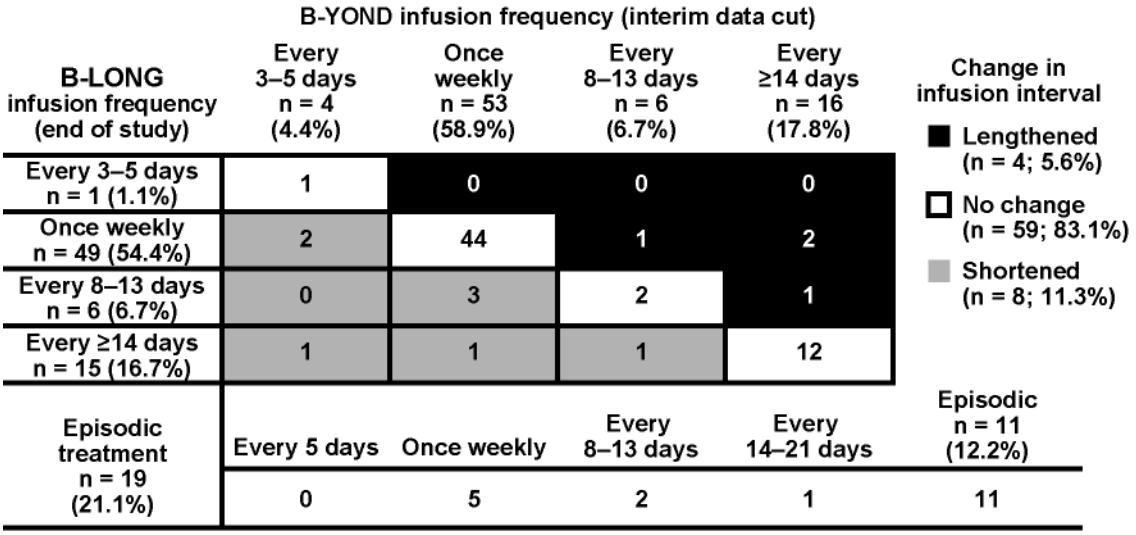
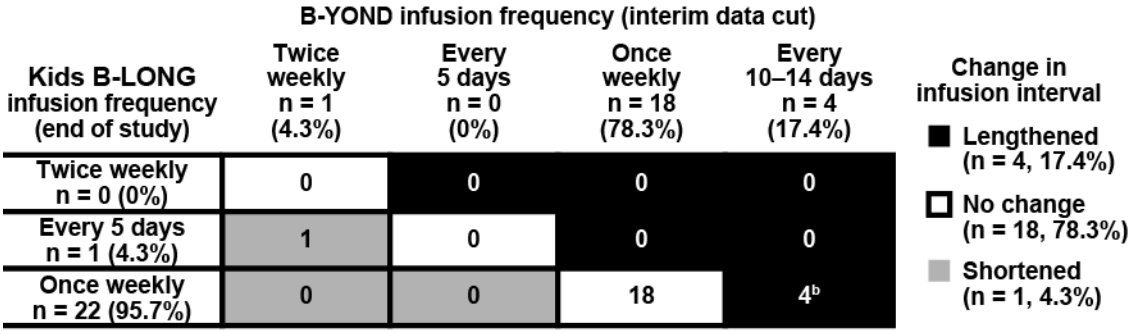
[e]One subject who initially received once-weekly prophylaxis at the beginning of Kids B-LONG was dosing once every five days at the end of Kids B-LONG.

Figure 3.

A. B-LONG subjects (N = 90)[a]



B. Kids B-LONG subjects (N = 23)



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[a]Excludes three subjects who were only in the surgery arm in B-LONG. The B-YOND interim data cut dosing interval in these three subjects was twice weekly, every four days, and every 13 days.

[b]Every 10 days, n = 3; every 14 days, n = 1.

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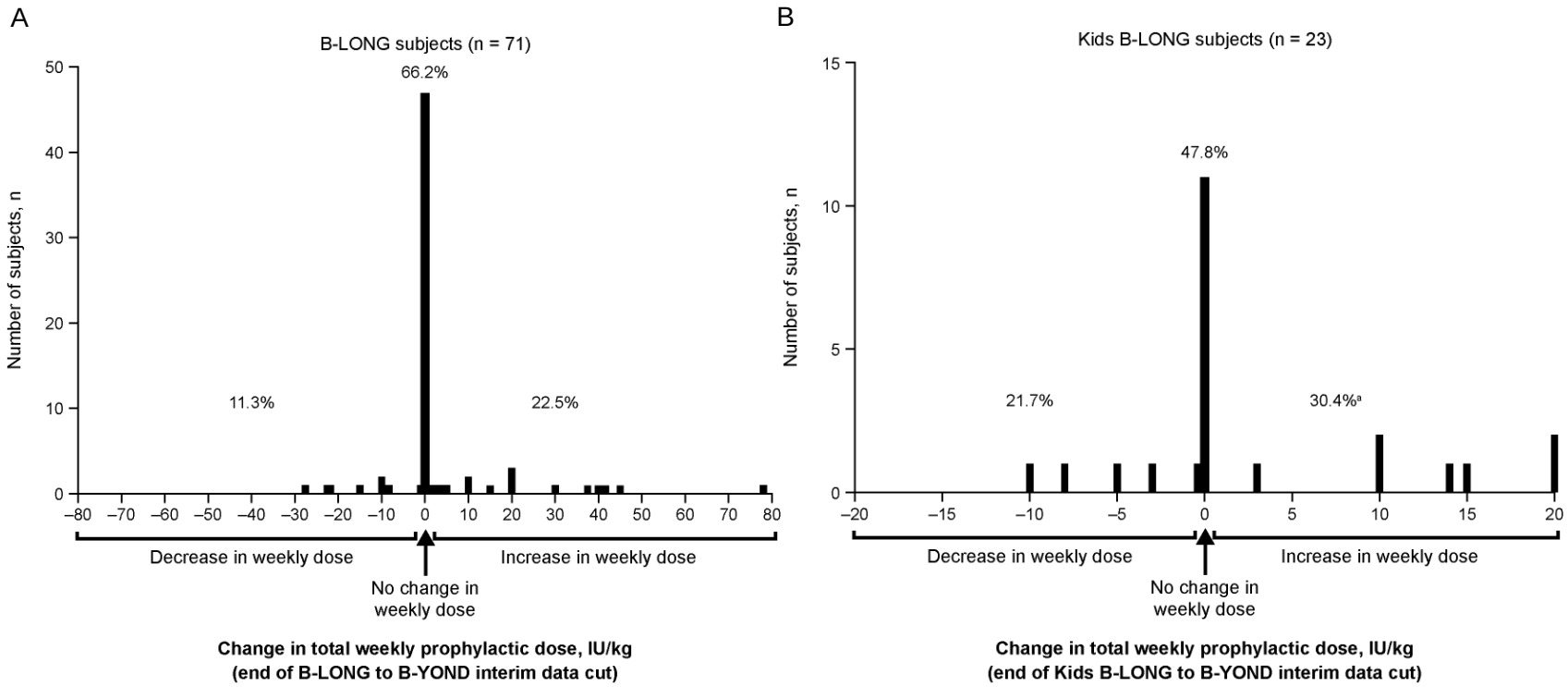

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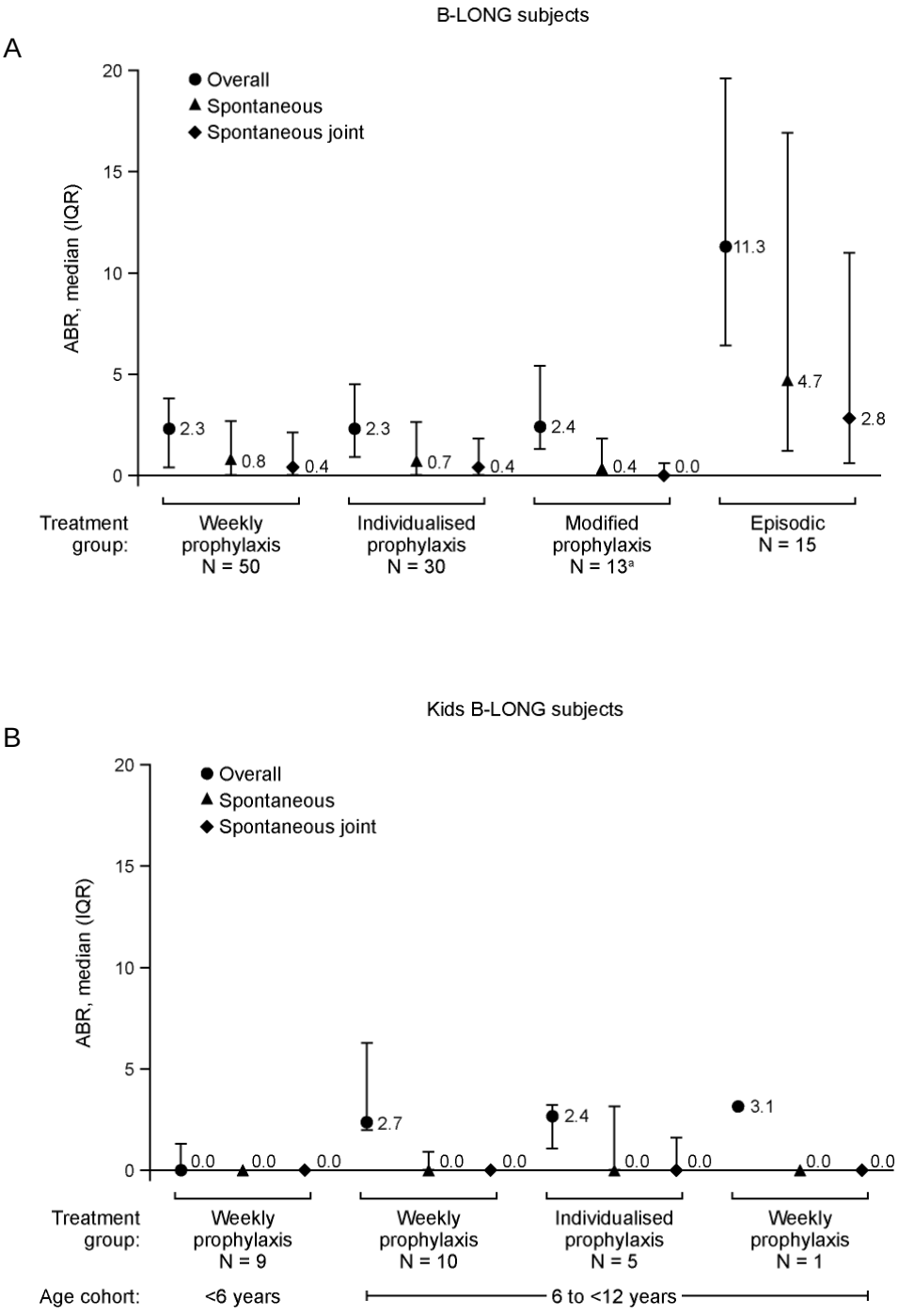
A
B-LONG subjects
Overall
Spontaneous
Spontaneous joint
ABR, median (IQR)
20
15
10
5
0
2.3
0.8
0.4
2.3
0.7
0.4
2.4
0.4
0.0
11.3
4.7
2.8
Treatment group:
Weekly prophylaxis N = 50
Individualised prophylaxis N = 30
Modified prophylaxis N = 13[a]
Episodic N = 15
B
Kids B-LONG subjects
Overall
Spontaneous
Spontaneous joint
ABR, median (IQR)
20
15
10
5
0
0.0
0.0
0.0
2.7
0.0
0.0
2.4
0.0
0.0
3.1
0.0
0.0
Treatment group:
Weekly prophylaxis N = 9
Weekly prophylaxis N = 10
Individualised prophylaxis N = 5
Weekly prophylaxis N = 1
Age cohort:
<6 years
6 to <12 years

Figure 5. Summary of median (IQR) ABRs during B-YOND.

Bleeding rates, including the rate of spontaneous and spontaneous joint bleeding episodes, were consistently low in all rFIXFc prophylaxis groups compared with episodic treatment.

ABR, annualised bleeding rate; IQR, interquartile range.

[a]One subject from B-LONG in the modified prophylaxis group did not meet the definition for having an efficacy period, and thus was not included in the ABR analysis.

Supplemental Material

This supplemental material has been provided by the authors to give readers additional information about their work.

Supplemental to: Pasi KJ, Fischer K, Ragni M, et al.

Short title: Long-term safety and efficacy of rFIXFc

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Supplemental Text

Study Inclusion/Exclusion Criteria

To be eligible to participate in B-YOND, subjects must have completed the B-LONG or Kids B-LONG study and must have the ability to provide signed and dated informed consent and authorisation to use protected health information, in accordance with national and local subject privacy regulations. Parental or guardian consent was required for subjects <18 years of age or who were unable to give consent, or as applicable per local laws. Subjects <18 years of age provided assent in addition to the parental/guardian consent, if appropriate. Written informed consent was provided before any screening tests or assessments are performed.

Subjects were excluded from study entry if they had a high-titre inhibitor (identified by Nijmegen-modified Bethesda assay performed at the central laboratory of ≥5.00 BU/ml, confirmed on two separate samples drawn approximately two to four weeks apart), were currently enrolled in any other clinical study, were unable to comply with study requirements, or for other unspecified reasons that, in the opinion of the investigator or sponsor, made the subject unsuitable for enrolment.

Prophylactic Treatment With rFIXFc

All subjects enrolled in B-YOND had the opportunity to continue in the study for up to four years or until rFIXFc became commercially available in the applicable participating country. Subjects first dosed with rFIXFc when <12 years of age were followed to at least 100 EDs, even if rFIXFc became commercially available.

Prophylactic treatment with rFIXFc was self-administered as follows:

Weekly prophylaxis: Doses of approximately 20 IU/kg to 100 IU/kg every seven days, based on the subject's clinical profile observed in the parent rFIXFc study and his individual PK profile, trough, and/or peak (recovery) values (note, trough levels were not routinely measured during B-YOND).

Individualised prophylaxis: Doses of approximately 100 IU/kg every eight to 16 days, based on the subject's clinical profile observed in the parent rFIXFc study and his individual PK, trough, and/or peak (recovery) values (note, trough levels were not routinely measured during B-YOND).

Modified prophylaxis: If necessary to optimise prophylaxis, the investigator could further personalise dosing to meet the needs of individual subjects. Personalisation could be accomplished by, but was not limited to, more frequent prophylactic dosing or the addition of prevention doses prior to strenuous activity, or by targeting a FIX trough level >5 IU/dl, if warranted by bleeding history and/or activity level. For subjects <12 years of age participating in the modified prophylaxis group, the dose could be adjusted to up to 100 IU/kg twice weekly.

Episodic (on-demand) treatment: The individual dose of rFIXFc to treat bleeding episodes was based on the subject's clinical condition, type and severity of the bleeding event, and FIX levels (if indicated). A subject's PK profile and dosing levels from the parent study could also be used to guide dosing decisions. Per the investigator's discretion, subjects >12 years of age are permitted to change from prophylaxis regimens to episodic treatment and from episodic treatment to prophylaxis during the study. Subjects <12 years of age are prescribed a prophylactic regimen and do not have the option to change to episodic treatment until they reach the age of 12 years during the study.

Treatment of Bleeding Episodes

Subjects were provided the following guidance for dosing with rFIXFc for bleeding episodes, and were instructed to consult with the investigator for an optimal rFIXFc level and dosing frequency.

Type of haemorrhage	**FIX level required (%)**
Minor	20–30
Moderate	25–50
Moderate haemarthroses, with limited motion	40–80
Major	50–100

Because of the long lasting effect of rFIXFc, it was recommended that the subject take the first follow-up dose no less than 48 hours after the initial dose. However, if the subject experienced

persistent pain or other signs of ongoing bleeding, the first follow-up dose could be administered before 48 hours. For major bleeding episodes, the subject was instructed to administer treatment and contact the study staff as soon as possible.

Additional Results

Suppl. Table 1: Subject Demographic and Clinical Characteristics

	Parent study		
	B-LONG	**Kids B-LONG**	
Age cohort at time of parent study enrolment:	**≥12 years N = 93**	**<6 years N = 9**	**6 to <12 years N = 14**
Age at enrolment to B-YOND, years, median (min, max)[a]	29.0 (13, 63)	4.0 (3, 5)	9.5 (7, 12)
Race, n (%)[b]			
White	47 (50.5)	6 (66.7)	9 (64.3)
Black	9 (9.7)	1 (11.1)	1 (7.1)
Asian	27 (29.0)	2 (22.2)	3 (21.4)
Other	10 (10.8)	0	1 (7.1)
Geographic region, n (%)[c]			
Europe	23 (24.7)	3 (33.3)	7 (50.0)

North America	23 (24.7)	6 (66.7)	4 (28.6)
Other	47 (50.5)	0	3 (21.4)

[a]Age at time of enrolment into B-YOND extension study.

[b]Data taken from parent studies.

[c]Europe includes Belgium, France, Germany, Ireland, Italy, The Netherlands, Poland, Sweden, and the United Kingdom. North America includes Canada and the United States. Other countries include Australia, Brazil, China, Hong Kong, India, Japan, and South Africa.

Suppl. Table 2: rFIXFc Exposure During B-YOND and From the Beginning of the Parent Study to the B-YOND Interim Data Cut

	Parent study			
	B-LONG	**Kids B-LONG**		
	N = 93	**<6 years** **N = 9**	**6 to <12 years** **N = 14**	**Overall** **N = 23**
Time on rFIXFc, months				
B-YOND; median (min, max)	27.6 (3.2, 32.7)	7.6 (2.7, 10.4)	11.4 (7.5, 13.9)	11.0 (2.7, 13.9)
Parent study + B-YOND; median (min, max)	39.5 (8.1, 52.7)	19.2 (14.4, 21.4)	22.9 (19.2, 25.4)	21.9 (14.4, 25.4)
rFIXFc EDs				
B-YOND; median (min, max)	111.0 (8.0, 264.0)	35.0 (11.0, 45.0)	50.5 (31.0, 94.0)	43.0 (11.0, 94.0)
Parent study + B-YOND; median (min, max)	162.0 (26.0, 351.0)	87.0 (64.0, 96.0)	102.5 (82.0, 164.0)	94.0 (64.0, 164.0)

rFIXFc, recombinant factor IX Fc fusion protein; ED, exposure day.

Suppl. Table 3: SAEs Occurring During B-YOND, by System Organ Class

	Parent study		
	B-LONG	**Kids B-LONG**	**Overall**
	N = 93	**N = 23**	**N = 116**
Subjects who experienced ≥1 SAE, n (%)[a,b]	**21 (22.6)**	**2 (8.7)**	**23 (19.8)**
Gastrointestinal disorders	2 (2.2)	0	2 (1.7)
Administration site condition (pain)	1 (1.1)	0	1 (0.9)
Infections and infestations	8 (8.6)	1 (4.3)	9 (7.8)
Injury, poisoning, and procedural complications	6 (6.5)	1 (4.3)	7 (6.0)
Musculoskeletal and connective tissue disorders	6 (6.5)	0	6 (5.2)
Renal and urinary disorders	6 (6.5)	0	6 (5.2)
Nervous system disorders	1 (1.1)	0	1 (0.9)
Respiratory, thoracic, and mediastinal disorders	1 (1.1)	0	1 (0.9)

SAE, serious adverse event; rFIXFc, recombinant factor IX Fc fusion protein.

[a]Percents are based on the number of subjects treated with rFIXFc and exclude SAEs occurring during the perioperative management period.

[b]One subject from B-LONG with a medical history of previous clot colic experienced an SAE of renal colic that was assessed by the investigator as related to rFIXFc treatment; the event

resolved and did not lead to study discontinuation. All of the remaining SAEs were assessed by the investigator as unrelated to rFIXFc treatment; none led to discontinuation from the study and none were associated with a fatal outcome.

Suppl. Table 4: Total Annualised rFIXFc Consumption During B-YOND

	B-YOND treatment group			
Annualised rFIXFc consumption,[a] IU/kg, median (IQR)	**Weekly prophylaxis**	**Individualised prophylaxis**	**Modified prophylaxis**	**Episodic**
B-LONG	N = 50	N = 30	N = 13	N = 15
	2647.0 (1903.4–3383.9)	2781.5 (2579.4–3397.3)	3504.6 (2408.9–4473.8)	587.7 (366.6–977.2)
Kids B-LONG				
<6 years of age cohort	N = 9	N = 0	N = 0	N.A.
	3327.9 (2724.1–3853.1)	–	–	
6 to <12 years of age cohort	N = 10	N = 5	N = 1	N.A.
	3313.8 (2913.0–3372.1)	3698.2 (3673.9–3845.1)	8987.3	

rFIXFc, recombinant factor IX Fc fusion protein; IQR, interquartile range; N.A., not applicable.

[a]Annualised consumption is the total rFIXFc (IU/kg) received during the efficacy period (prophylactic doses + dosing for treatment of a bleeding episode), extrapolated to a one-year interval of time.

Suppl. Table 5: Summary of Median (IQR) ABRs During B-YOND (by Parent Study and Treatment Group)

B-LONG	
Weekly prophylaxis, n	**50**
Overall ABR	2.28 (0.44–3.76)
Spontaneous ABR	0.82 (0.00–2.65)
Spontaneous joint ABR	0.40 (0.00–2.05)
Traumatic ABR	0.50 (0.00–1.74)
Individualised prophylaxis, n	**30**
Overall ABR	2.25 (0.87 – 4.47)
Spontaneous ABR	0.68 (0.00–2.58)
Spontaneous joint ABR	0.40 (0.00–1.75)
Traumatic ABR	0.89 (0.00–1.59)
Modified prophylaxis, n	**13[a]**
Overall ABR	2.42 (1.26–5.40)
Spontaneous ABR	0.41 (0.00–1.84)
Spontaneous joint ABR	0.00 (0.00–0.56)
Traumatic ABR	1.75 (0.56–2.76)
Episodic, n	**15**
Overall ABR	11.27 (6.41–19.62)
Spontaneous ABR	4.66 (1.17–16.87)

Spontaneous joint ABR	2.80 (0.58–11.00)	
Traumatic ABR	1.47 (0.00–5.25)	
Kids B-LONG	**<6 years cohort**	**6 to <12 years cohort**
Weekly prophylaxis, n	**9**	**10**
Overall ABR	0.00 (0.00–1.30)	2.65 (1.07–3.21)
Spontaneous ABR	0.00 (0.00–0.00)	0.00 (0.00–3.15)
Spontaneous joint ABR	0.00 (0.00–0.00)	0.00 (0.00–1.61)
Traumatic ABR	0.00 (0.00–0.00)	0.97 (0.00–2.14)
Individualised prophylaxis, n		**5**
Overall ABR		2.37 (1.99–6.28)
Spontaneous ABR		0.00 (0.00–0.90)
Spontaneous joint ABR		0.00 (0.00–0.00)
Traumatic ABR		1.18 (0.90–1.99)
Modified prophylaxis, n		**1**
Overall ABR		3.13
Spontaneous ABR		0.00
Spontaneous joint ABR		0.00
Traumatic ABR		3.13

IQR, interquartile range; ABR, annualised bleeding rate; rFIXFc, recombinant factor IX Fc fusion protein.

[a]One subject in the modified prophylaxis group of B-LONG did not meet the definition for having an efficacy period (ie, at least one infusion of rFIXFc for subjects treated episodically or at least two infusions of rFIXFc for subjects on a prophylactic regimen), and thus was not included in the ABR analysis.

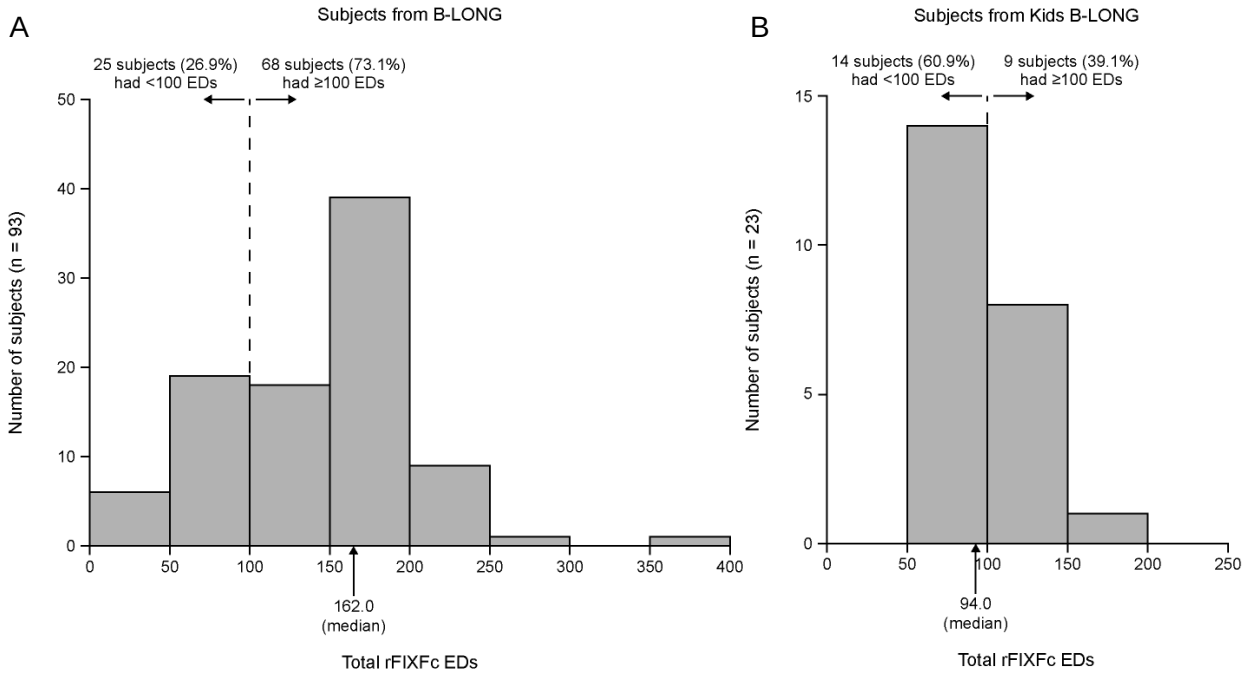
Suppl. Table 6: Major Surgeries Performed in B-YOND and Rating of Haemostatic Response

Surgical procedure	Haemostatic response
B-LONG subjects	
L5 + S1 laminectomy and discectomy	Excellent
Left orchidectomy	Excellent
Removal of external fixator	Excellent
Hepatic operation: percutaneous ablation by HIFU	Excellent
Transarterial chemoembolization	Excellent
Transarterial chemoembolization	Excellent
Transarterial chemoembolization	Excellent
Closed reduction and fixation-dynamic hip screw, screw fixation to right proximal femur	Excellent
Liver transplant	Excellent
Arthroscopy of right ankle	Excellent
Primary total hip replacement with cement	Good
Right (frontoparietal) FTP craniotomy	Excellent

Redo craniotomy, EVAC epidural haematoma	N.A.
Left ankle fusion	Excellent
Kids B-LONG subjects	
Tonsillectomy	Excellent

HIFU, high intensity focused ultrasound; EVAC, evacuation; N.A., not assessed for haemostatic response.

Suppl. Figure 1.



Suppl. Figure 1: Cumulative rFIXFc EDs Among B-LONG (n = 93) and Kids B-LONG (n = 23) Subjects Continuing Into B-YOND.[a]

[a]Chart depicts cumulative EDs from beginning of parent study (B-LONG or Kids B-LONG) to B-YOND interim data cut (17 October 2014).