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REGULAR ARTICLE

blood advances

Post hoc longitudinal assessment of the efficacy and safety of recombinant factor IX Fc fusion protein in hemophilia B

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Key Points

- Pooled longitudinal efficacy and safety data for rFIXFc demonstrates sustained benefits in hemophilia B.
- All evaluable target joints resolved during treatment, and no recurrence was reported in most (90%) baseline target joints during follow-up.

Long-term efficacy and safety of the extended half-life recombinant factor IX Fc fusion protein (rFIXFc) has been established among previously treated patients with severe hemophilia B in 2 phase 3 trials (B-LONG [#NCT01027364] and Kids B-LONG [#NCT01440946]) and a long-term extension study (B-YOND [#NCT01425723]). In this study, we report post hoc analyses of pooled longitudinal data for up to 6.5 years for rFIXFc prophylaxis. In the B-LONG study, subjects ≥12 years received weekly dose-adjusted prophylaxis (WP; starting dose, 50 IU/kg), individualized interval-adjusted prophylaxis (IP; initially, 100 IU/kg every 10 days), or on-demand dosing. In the Kids B-LONG study, subjects <12 years received 50 to 60 IU/kg every 7 days, adjusted as needed. In the B-YOND study, subjects received WP (20-100 IU/kg every 7 days), IP (100 IU/kg every 8-16 days), modified prophylaxis, or on-demand dosing; switching between treatment groups was permitted. A total of 123 subjects from B-LONG and 30 from Kids B-LONG study were included, of whom 93 and 27, respectively, enrolled in the B-YOND study. The median cumulative duration of treatment was 3.63 years (range, 0.003-6.48 years) in B-LONG/B-YOND and 2.88 years (range, 0.30-4.80 years) in Kids B-LONG/B-YOND group. Annualized bleed rates (ABRs) remained low, annualized factor consumption remained stable, and adherence remained high throughout treatment. Low ABRs were also maintained in subjects with dosing intervals ≥14 days or with target joints at baseline. Complete resolution of evaluable target joints and no recurrence in 90.2% of baseline target joints during follow-up were observed. rFIXFc prophylaxis was associated with sustained clinical benefits, including long-term bleed prevention and target joint resolution, for severe hemophilia B.

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Qualified researchers may request access to data and related documents (including, eg, the clinical study report, study protocol with any amendments, blank case report form, statistical analysis plan, and dataset specifications). Any patient-level data provided will be anonymized, and study documents will be redacted, including to protect the privacy of trial participants. Further details on Sanofi's data sharing criteria, eligible studies, and process for requesting access can be found at https://vivli.org/.

The full-text version of this article contains a data supplement.

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Introduction

Severe hemophilia B is characterized by recurrent, spontaneous bleeds into soft tissues and joints.[1,2] Recurrent joint bleeds result in hemophilic arthropathy, which affects overall joint health and is associated with chronic pain, impaired functionality, and reduced quality of life.[1,3,4]

Prophylactic replacement of coagulation factor IX (FIX) is the current standard of care for the long-term management of severe hemophilia B.[5] Individuals who are initiated on prophylaxis early in life experience the best long-term outcomes, though the most extensive evidence for this is derived from individuals with hemophilia A.[6] Nonetheless, the World Federation of Hemophilia and other national and international organizations support FIX prophylaxis as the standard of care for children with severe hemophilia B. Current clinical guidelines recommend that prophylaxis should be sustained throughout an individual's life and should be personalized to meet the needs of each patient, taking into consideration bleed phenotype, joint status, individual pharmacokinetic (PK) profile, and personal preference.[5]

The development and availability of extended half-life (EHL) FIX products represent a marked improvement in the treatment landscape for individuals with hemophilia B. These agents require less frequent infusions than standard half-life factor products and, with reduced treatment burden, offer the potential for improved adherence and long-term clinical outcomes.[7-9] The reduced frequency of infusions with EHL factors has also been shown to significantly reduce the emotional and practical burden on caregivers for those with severe hemophilia B.[10]

The long-term efficacy and safety of the EHL recombinant FIX Fc fusion protein (rFIXFc) has been established among previously treated adults, adolescents, and children with severe hemophilia B. Two phase 3 trials (B-LONG [#NCT01027364] and Kids B-LONG [#NCT01440946])[11,12] and a long-term extension study (B-YOND [#NCT01425723]) provide data for a cumulative treatment duration up to a maximum of 6.5 years.[13,14] In addition, numerous reports of real-world experience with rFIXFc support the clinical study results.[15-23] More recently, the efficacy and safety of rFIXFc has been evaluated among previously untreated individuals in the phase 3 PUPs B-LONG study (#NCT02234310).[24]

Here, we report a post hoc assessment of longitudinal efficacy and safety data for prophylactic rFIXFc regimens from the clinical trials in previously treated subjects, including those treated with dosing intervals ≥14 days and those with target joints at baseline.

Materials and methods

Study design

Complete details on the design of the B-LONG (#NCT01027364), Kids B-LONG (#NCT01440946), and B-YOND studies (#NCT01425723), and the treatments evaluated therein, have been published previously.[11-14]

In brief, B-LONG and Kids B-LONG were open-label, nonrandomized, multicenter studies evaluating the safety, efficacy, and PKs of rFIXFc in previously treated subjects with severe hemophilia B (≤2 IU/dL [≤2%]) and no history of inhibitors.[10,11] In the B-LONG study, eligible subjects were required to be ≥12 years of age and either receiving prophylaxis or having a history of ≥8 bleeding episodes in the year before enrollment.[12] Subjects in the B-LONG study were also required to have accrued ≥100 exposure days to replacement FIX therapy.[12]

Subjects in the B-LONG study were assigned to 1 of the following 4 treatment groups:[11]

1. Weekly prophylaxis (WP) with 50 IU/kg IV initially, with the dose adjusted as needed for a target trough from 1% to 3% above baseline or higher, as clinically indicated.
2. Interval-adjusted prophylaxis (IP) with 100 IU/kg IV at intervals of 10 days initally, for a target trough from 1% to 3% above baseline or higher, as clinically indicated.
3. On-demand treatment of 20-100 IU/kg IV for acute bleeds, dependent on bleed severity.
4. Treatment as part of perioperative care.

In the Kids B-LONG study, the subjects were aged <12 years and required to have ≥50 exposure days to FIX replacement therapy.[11] Subjects in the Kids B-LONG study initially received prophylactic rFIXFc once weekly, starting with 50-60 IU/kg; dose and frequency could be adjusted based on the subject's rFIXFc PK, FIX trough concentration, and bleed profile.[10]

B-YOND was a global long-term extension study for eligible subjects who completed either B-LONG or Kids B-LONG study.[13]

Subjects who were eligible to participate in the B-YOND study received 1 or more of the following 4 treatment regimens (supplemental Table 1):

1. WP consisting of 20-100 IU/kg IV given every 7 days.
2. Individualized interval prophylaxis consisting of 100 IU/kg IV given every 8 to 16 days or twice monthly.
3. Modified prophylaxis consisting of IV dosing tailored to meet the needs of those requiring more personalized dosing and not fulfilling the definitions of individualized, weekly, or on-demand regimens.
4. On-demand IV treatment, based on the type and severity of bleed episodes. On-demand treatment was offered only to subjects ≥12 years.

The treatment regimen selected for each subject was based on their individual clinical profile in the parent trial, PK profile, and individual trough and/or peak (recovery) levels and aimed to target a trough level between 1% and 3% above baseline. Switching of treatment regimens was permitted at any time during the B-YOND study, per the investigator's discretion.

The studies were conducted in accordance with the ethical principles of good clinical practice and the harmonized tripartite guideline of the International Conference on Harmonization. Ethics approval was obtained at each study site. The protocol was approved by all individual institutional review boards. All the subjects and their guardians provided written informed consent. Written subject assent was obtained from the subjects aged <16 years who were able to read and understand the assent form, a summary of the study process, its benefits, and the risks involved (per local institutional review board standards).

Outcome measures (post hoc analyses)

Outcome measures included the cumulative duration of rFIXFc, number of rFIXFc exposure days, longitudinal overall annualized bleed rate (ABR), annualized joint bleed rate (AjBR), annualized spontaneous bleed rate, annualized traumatic bleed rate, and the consumption of rFIXFc (total IU/kg per subject per year). Change in the dosing interval was also evaluated (if it was applicable).

Subanalysis populations

Post hoc analyses were performed among the 3 subanalysis populations described hereafter that are based on the patient/treatment characteristics during the overall follow-up. The outcome measures for each subanalysis are described:

Subanalysis 1. Subanalysis 1 was conducted for all the subjects who remained on WP or individualized prophylaxis until year 5 (year 4 for children) in the studies. In this cohort, the ABR and annualized consumption by year on study were evaluated. In addition, the infusion intervals (median and range) at the start of the parent study and the end of the B-YOND study were evaluated.

Subanalysis 2. Subanalysis 2 was conducted for the subjects who received rFIXFc prophylaxis at least once with a dosing interval ≥14 days. For this cohort, exposure to rFIXFc was determined for the period before and during the extended dosing interval. ABRs were evaluated for (1) the period before the first ≥14-day dosing interval and (2) the period during the ≥14-day dosing interval in those being observed for ≥6 months. In addition, data on bleeds and the treatment of bleeds occurring while on the extended dosing interval regimen were collated. The number of subjects who returned to a dosing interval regimen of <14 days was determined.

Subanalysis 3. Subanalysis 3 was conducted for subjects with target joints at the start point of the B-LONG or Kids B-LONG study who received prophylactic treatment. A target joint was defined as a major joint (ie, knee, ankle, elbow, hip, shoulder, and wrist) into which repeated bleeds occurred (a frequency ≥3 bleeding episodes into the same joint in a consecutive 3-month period). Among these subjects, ABR and AjBR were determined. Target joint resolution (≤2 bleeds in a consecutive 12-month period in the target joint) and recurrence (≥3 spontaneous bleeds in a single joint within a consecutive 6-month period after target joint resolution) were also evaluated for this group.

Statistical analyses

Descriptive statistics are presented for demographics, clinical characteristics, and prophylaxis adherence rates. Compliance was measured in terms of dose compliance and dose interval compliance. The dose compliance rate was equivalent to the number of doses taken within 80% and 125% of the prescribed dose ÷ (total number of doses × 100), and the nominal dose taken was determined from the nominal potency labeled on the vials used by the subject for each infusion of rFIXFc. The dose interval compliance rate equated to the number of doses taken within ±36 hours of the prescribed day or time per total number of intervals × 100.

A subject was considered as dose compliant or dosing interval compliant if their respective rate of each compliance measure was at least 80%. Efficacy and safety analyses included all subjects who received ≥1 dose of rFIXFc prophylaxis. Data from B-LONG, Kids B-LONG, and B-YOND studies were pooled, and longitudinal efficacy data were analyzed separately, based on the parent study. Subjects who switched from 1 regimen to another during the B-YOND study were included in the summary analysis of each treatment group for the specific period they were in that group; therefore, subjects may be included in >1 efficacy analysis. The start date of each treatment is used as time zero for the longitudinal analysis. Adverse events were classified using the Medical Dictionary for Regulatory Activities system organ classes and preferred terms.

Results

Overall study population

A total of 123 and 30 subjects were enrolled in B-LONG and Kids B-LONG studies, respectively.[11-13] Of these, 93 and 27, respectively, enrolled in the B-YOND study. Baseline demographics and clinical characteristics are summarized in Table 1; additional baseline data have been reported previously.[11-13]

Duration and exposure

In the B-LONG/B-YOND study's pooled analysis, the median duration of treatment and the number of exposure days from the beginning of the B-LONG study to the end of follow-up were 3.63 years (range, 0.003-6.48 years) and 165 days (range, 1-528 days), respectively. For the subjects who entered the Kids B-LONG trial, the median duration of treatment and the number of exposure days from the beginning of Kids B-LONG to the end of follow-up were 2.88 years (range, 0.30-4.80 years) and 166 days (range, 18-256 days), respectively. The minimum duration of treatment was short because not all subjects enrolled in the B-YOND study. No central venous access devices were placed during the studies.

Efficacy

The longitudinal analysis revealed that ABRs remained low across all the age groups in subjects receiving prophylactic rFIXFc treatment from 1 to 5 years (1-4 years for the subjects of Kids B-LONG study; supplemental Table 2). The efficacy remained consistent as shown by the ABRs for WP and individualized prophylactic rFIXFc treatment at the end of the B-LONG, Kids B-LONG, and B-YOND studies (supplemental Figure 1). ABRs for subjects on modified prophylaxis are not reported here because this treatment regimen was only available during the extension trial; B-YOND data stratified based on the treatment regimen were published recently.[13]

Factor consumption and adherence

Annualized factor consumption remained stable from years 1 to 5 (year 4 for the subjects of Kids B-LONG) for the subjects of all ages receiving individualized and WP during the parent and extension trials (supplemental Table 3). Pre–B-LONG and pre–Kids B-LONG annualized factor consumptions (prophylactic standard half-life) are included in supplemental Table 3 as a reference only; subjects in this column are not matched to subjects contributing to consumption values for years from 1 to 5.

Adherence to prophylactic regimens was high. Pooled B-LONG/Kids B-LONG and B-YOND dose adherence rates for subjects

Table 1. Baseline characteristics for the total population

	Phase 3 parent trial		B-YOND (extension trial)	
	B-LONG	Kids B-LONG	From B-LONG	From Kids B-LONG
Subjects enrolled, n	119*	30	93	27
Median (range) age at the enrollment into the parent or extension study, y	30 (12-71)	5 (1-11)	29 (13-63)	7 (3-12)
Race, n (%)				
White	70 (58.8)	22 (73.3)	47 (50.5)	19 (70.4)
Black	10 (8.4)	2 (6.7)	9 (9.7)	2 (7.4)
Asian	28 (23.5)	5 (16.7)	27 (29.0)	5 (18.5)
Other	11 (9.2)	1 (3.3)	10 (10.8)	1 (3.7)
Median (IQR) estimated ABR before the start of rFIXFc treatment (prestudy)†				
Prior prophylactic regimen	2 (1-6); n = 41	2.5 (0-5); n = 30		
Prior on-demand regimen	22 (12-33); n = 66	N/A		
rFIXFc regimen, n‡				
WP	63	30	51	23
Individualized IP	29	N/A	31	5
Modified prophylaxis	N/A	N/A	16	2
On-demand treatment	27	N/A	15	N/A

N/A, not applicable.
*Four of the 123 B-LONG subjects were enrolled in the surgery-only group and are not included here.
†In the B-LONG study, 10 subjects had either missing prestudy ABR data or missing prestudy regimen, and 2 subjects received a prestudy sports prophylaxis regimen. Their prestudy ABRs were not included in this analysis.
‡Subjects were permitted to switch treatment regimens on enrollment and at any time during the B-YOND study and may appear in ≥1 treatment regimen.

receiving individualized IPs or WPs were 99.3% (96.2% to 100.0%) in the group that started treatment in B-LONG and 99.1% (98.5% to 100.0%) in the group that started treatment in Kids B-LONG. Pooled B-LONG/Kids B-LONG and B-YOND interval adherence rates for subjects receiving individualized IPs or WPs were 97.7% (95.7% to 99.7%) in the group that started treatment in B-LONG and 97.4% (92.9% to 99.0%) in those who started treatment in Kids B-LONG.

Subgroup analyses

Subanalysis 1: long-term follow-up of same subjects for 4 or 5 years. The longitudinal analysis revealed that ABRs remained low across all age groups remaining on rFIXFc prophylaxis for 4 or 5 years (Table 2). During the follow-up, the factor consumption remained stable for this population (supplemental Table 4), and subjects remaining on individualized prophylaxis extended their dosing interval from a median of 10 days at the beginning of the B-LONG study to a median of 14 days at the end of the B-YOND study (Table 3).

Subanalysis 2: subjects with a dosing interval of at least 14 days or longer, at any time. A total of 23 subjects were treated with ≥14-day dosing interval at any time during the B-LONG/B-YOND study, most of whom (83% [n = 19]) were on individualized prophylaxis. Their baseline characteristics are summarized in supplemental Table 5. The minimum age was 15 years, and the majority (87%) of subjects had <1% endogenous FIX activity. This is in line with the overall B-LONG population of whom 82% had <1% endogenous FIX activity. The median terminal half-life of rFIXFc was 98.7 hours (range, 60.6-118.2 hours) for subjects with a ≥14-day dosing interval. By comparison, the median terminal half-life was 76.9 hours (range, 37.8-135.2 hours) for the subjects without a dosing interval of at least 14 days at any time.

The median dosing interval of those who had a dosing interval ≥14 days (n = 20) was 11.0 days (interquartile range [IQR], 10.0-12.0 days) before extending the dosing interval to a median of 14 days (IQR, 14.0-14.0 days; n = 23; Table 4). The median exposure period was 1565.2 days (IQR, 647.8-1766.7 days). Six subjects extended their dosing interval to ≥15 days at any time, with 1 subject who extended the dosing interval to ≥21 days (supplemental Table 6). Median ABR remained low after extending the dosing interval among the subjects (n = 19) who received prophylaxis before the dosing interval extension (median, 1.4; IQR, 0.6-2.1); all the individuals included in this analysis had a prior treatment period of ≥6 months (supplemental Table 7). For this population of 23 subjects, 142 bleeds occurred during the extended dosing interval, of which 95% were resolved successfully with ≤2 infusions. A median total dose of 53.6 IU/kg (IQR, 36.6-98.0 IU/kg) was required to resolve a bleeding episode.

Most subjects (70% [n = 16]) did not return to <14-day dosing intervals after they began their extended dosing regimens. Three (13%) subjects switched temporarily to a <14-day dosing interval, and 5 subjects returned to a dosing interval of <14 days at the study end (supplemental Table 8). Individual reasons for the change in the dosing interval are also presented in supplemental Table 8.

Table 2. Median (IQR) ABR for subjects who received prophylaxis for 4 or 5 years (subanalysis 1)

Treatment regimen	Type of ABR	Year 1	Year 2	Year 3	Year 4	Year 5
Subjects from B-LONG						
WP		n = 21	n = 21	n = 21	n = 21	n = 21
	Overall	1.0 (0.0-2.1)	1.0 (0.0-2.2)	1.0 (1.0-3.0)	2.0 (0.0-5.0)	1.0 (0.0-4.0)
	Spontaneous	1.0 (0.0-1.1)	0.0 (0.0-1.0)	1.0 (0.0-2.0)	1.0 (0.0-2.0)	0.0 (0.0-1.2)
	Traumatic	0.0 (0.0-1.0)	0.0 (0.0-1.0)	0.0 (0.0-1.0)	0.0 (0.0-1.0)	0.0 (0.0-2.0)
	Joint	1.0 (0.0-1.1)	0.0 (0.0-1.0)	1.0 (0.0-2.1)	0.0 (0.0-2.0)	0.0 (0.0-2.3)
	Joint spontaneous	0.0 (0.0-1.0)	0.0 (0.0-1.0)	0.0 (0.0-1.0)	0.0 (0.0-0.0)	0.0 (0.0-1.0)
	Joint traumatic	0.0 (0.0-0.0)	0.0 (0.0-1.0)	0.0 (0.0-1.0)	0.0 (0.0-1.0)	0.0 (0.0-0.0)
Individualized IP		n = 17	n = 17	n = 17	n = 17	n = 17
	Overall	1.0 (0.0-3.0)	1.0 (1.0-3.0)	2.0 (1.0-5.0)	1.0 (0.0-1.0)	1.0 (0.0-2.0)
	Spontaneous	1.0 (0.0-2.3)	1.0 (0.0-1.0)	0.0 (0.0-1.0)	0.0 (0.0-1.0)	0.0 (0.0-1.0)
	Traumatic	0.0 (0.0-0.0)	1.0 (0.0-1.0)	1.0 (1.0-2.0)	0.0 (0.0-0.0)	0.0 (0.0-1.0)
	Joint	0.0 (0.0-3.0)	0.0 (0.0-1.0)	1.0 (0.0-4.0)	0.0 (0.0-1.0)	1.0 (0.0-1.3)
	Joint spontaneous	0.0 (0.0-2.3)	0.0 (0.0-1.0)	0.0 (0.0-1.0)	0.0 (0.0-1.0)	0.0 (0.0-1.0)
	Joint traumatic	0.0 (0.0-0.0)	0.0 (0.0-1.0)	0.0 (0.0-1.0)	0.0 (0.0-0.0)	0.0 (0.0-1.0)
Subjects from Kids B-LONG						
WP		n = 10	n = 10	n = 10	n = 10	
	Overall	2.0 (1.0-3.0)	2.0 (1.0-3.2)	0.5 (0.0-5.1)	0.0 (0.0-2.2)	
	Spontaneous	0.0 (0.0-1.0)	0.0 (0.0-2.0)	0.0 (0.0-1.0)	0.0 (0.0-1.1)	
	Traumatic	1.0 (0.0-2.0)	1.0 (0.0-2.0)	0.0 (0.0-1.0)	0.0 (0.0-1.1)	
	Joint	0.5 (0.0-2.0)	1.0 (0.0-3.0)	0.0 (0.0-3.4)	0.0 (0.0-1.3)	
	Joint spontaneous	0.0 (0.0-0.0)	0.0 (0.0-1.0)	0.0 (0.0-0.0)	0.0 (0.0-1.0)	
	Joint traumatic	0.0 (0.0-1.0)	0.0 (0.0-1.0)	0.0 (0.0-1.0)	0.0 (0.0-0.0)	

The adverse event profile among subjects while on a ≥14-day dosing regimen was consistent with previously reported findings.

Subanalysis 3: subjects with target joints at entry into parent study. Among the 117 subjects who were enrolled in the B-LONG study with available on-study data, 60 (51%) had ≥1 target joint at baseline. with the knee being the most often affected (70% [n = 42]; supplemental Table 9). One subject who was enrolled in the Kids B-LONG study (in the age group from 6 to <12 years) had ≥1 target joint at baseline.[11,13]

Table 3. Median (IQR) infusion interval (days) during the first 5 years (subanalysis 1)

Treatment regimen	Start of the parent study	End of follow-up	Change (end to start)
Subjects from B-LONG			
WP	n = 21	n = 21	n = 21
	7.0 (7.0-7.0)	7.0 (7.0-7.0)	0.0 (0.0-0.0)
Individualized IP	n = 17	n = 17	n = 17
	10.0 (10.0-10.0)	14.0 (10.0-14.0)	4.0 (0.0-4.0)
Subjects from Kids B-LONG			
WP	n = 10	n = 10	n = 10
	7.0 (7.0-7.0)	7.0 (7.0-7.0)	0.0 (0.0-0.0)

Subjects with target joints received rFIXFc for a cumulative median duration of 3.6 years (IQR, 1.4-6.0 years). Weekly dosing and dosing intervals among this population are summarized based on the treatment regimen in Table 5. For subjects with target joints at entry into the B-LONG study, overall median ABRs were consistently low across all prophylaxis regimens (range, 2.3-3.9) and was 22.7 for on-demand treatment. Median ABRs for pre-existing target

Table 4. Median (IQR) exposure in subjects with extended dosing interval (14 or more days at any time) (subanalysis 2)

	Before the first ≥14-day dosing interval	During the ≥14-day dosing interval
Exposure period,* d	n = 22	n = 23
	122.1 (61.0-269.0)	1565.2 (647.8-1766.7)
Exposure d*	n = 22	n = 23
	12.5 (6.0-22.0)	113.0 (69.0-139.0)
Dosing interval,† d	n = 20	n = 23
	11.0 (10.0- 12.0)	14.0 (14.0-14.0)
Weekly dose,‡ IU/kg	n = 20	n = 23
	62.5 (59.0-71.3)	50.0 (45.6-51.0)

*Based on all prior dosing intervals.
†Based on the latest prior prescribed dosing interval, excluding subjects with an on-demand regimen directly before the ≥14-day dosing.
‡Based on the latest prior dosing interval, excluding subjects with an on-demand regimen directly before the ≥14-day dosing.

Table 5. Median (IQR) exposure in subjects with target joints at the start point of the B-LONG study (subanalysis 3)

Treatment group*	WP (n = 41)	Individualized IP (n = 13)	Modified prophylaxis (n = 13)
Average weekly dose, IU/kg	46.2 (37.8-55.6)	69.6 (46.7-73.2)	62.1 (41.7-115.1)
Dosing interval, d	7.0 (6.9-7.0)	10.1 (9.9-13.1)	6.4 (4.9-6.9)

*Subjects are included in each treatment regimen they participated in for the duration of time on that regimen and, as such, may appear in ≥1 treatment regimen.

joints were also low during the study for those receiving prophylactic rFIXFc (range, 0.0-2.3; Table 6).

Among the subjects who received the prophylactic treatment, 93 baseline target joints in 37 subjects were considered evaluable (ie, had ≥12 months of consecutive follow-up and no surgery on the target joint within the 12 months since the start of the follow-up) and were assessed for target joint resolution. Resolution of 100% of all evaluable target joints was observed among all subjects who received prophylaxis (Table 7), and a median spontaneous ABR per evaluable target joint after resolution was 0.0 (IQR, 0.0-0.4).

There was no recurrence in 90.2% of baseline target joints during follow-up (Table 7). A total of 9 target joint recurrences were reported among 6 subjects of the B-LONG study, all of which resolved by the end of the B-YOND study (supplemental Table 10). Five of these 6 subjects had prestudy bleed information available, 3 were receiving prophylaxis and 2 were receiving on-demand treatment. The median AjBR for this subset of 5 subjects at baseline was 6.0 (range, 5-80).

Discussion

To our knowledge, longitudinal data from the B-LONG, Kids B-LONG, and B-YOND studies represent the longest cumulative duration of exposure (up to 6.5 years) to EHL rFIXFc prophylaxis to date.[13] rFIXFc improved the prevention of bleeds, reduced the overall factor consumption and frequency of infusion, and was associated with high compliance.[13] Notably, the low-reported ABRs achieved at low target trough levels from 1 to 3 IU/dL above baseline were comparable with ABRs previously reported for other EHL rFIX products at higher trough levels.[7,25-29] Different technologies for half-life extension and large differences in the volume of distribution may contribute to differences in the relationship between plasma levels and clinical outcomes.[30]

There were no reports of inhibitor development to FIX, anaphylaxis or serious hypersensitivity, or vascular thrombotic events during long-term treatment with rFIXFc.[13] In the current longitudinal analysis, the long-term treatment profile of rFIXFc was characterized further by the exploration of annual outcomes across 5 years of treatment among subjects aged ≥12 years and across 4 years of treatment among those aged <12 years. These post hoc analyses show that during up to 5 years (4 years for children) of individualized and weekly prophylactic rFIXFc treatment, the ABR remained low, and annualized factor consumption remained stable across all age groups.

Subjects who remained on individualized prophylaxis extended their dosing interval from a median of 10 days at the beginning of the B-LONG study to a median of 14 days at the end of the B-YOND study. Among the subgroup of subjects who extended their dosing interval to ≥14 days, most were on individualized prophylaxis beforehand and collectively demonstrated a longer terminal half-life than those who did not prolong their dosing interval; the majority of those with ≥14-day intervals remained on their extended dosing interval. Among these subjects, the extended dosing interval continued to provide protection from bleeding events, as reflected by a low spontaneous ABR. Although the number of subjects was small, the AjBR was low during the period when the subjects received treatment with an extended dosing interval (median, 0.9; IQR, 0.2-1.6 among 19 subjects with prior prophylactic treatment). These data were consistent with previously reported interim findings amonf subjects with ≥14-day dosing intervals from the B-LONG/B-YOND study.[31] rFIXFc was well tolerated when administered at intervals ≥14 days, with no new safety signals or concerns emerging during the long-term follow-up, which is in alignment with additional reports of the use of rFIXFc.[15-23]

Table 6. Median (IQR) ABR among subjects with target joints at the start point of B-LONG (subanalysis 3)

	Prestudy treatment regimen					
	Prophylaxis*		On-demand			
	Treatment regimen in B-LONG or B-YOND†					
	WP (n = 13)	Modified prophylaxis (n = 6)	WP (n = 26)	Individualized IP (n = 11)	Modified prophylaxis (n = 5)	On-demand (n = 14)
Prestudy ABR	6.0 (2.0-15.0)‡	8.0 (5.0-20.0)	23.0 (12.0-36.0)§	25.0 (22.0-36.0)	23.0 (22.0-29.0)	24.0 (16.0-36.0)
On-study ABR, overall	3.4 (1.3-5.9)	3.9 (3.2-6.4)	3.1 (1.1-5.2)	3.7 (1.0-5.1)	2.3 (0.0-3.9)	22.7 (14.2-26.9)
On-study ABR, joint	2.2 (1.0-3.7)	1.5 (0.9-3.2)	1.1 (0.4-4.4)	3.4 (0.8-3.9)	0.6 (0.0-2.2)	15.7 (8.2-23.3)
On-study ABR, pre-existing target joint‖	1.1 (0.0-3.7)	1.5 (0.5-3.2)	0.5 (0.0-1.3)	2.3 (0.8-3.6)	0.0 (0.0-0.0)	15.1 (2.6-23.0)
On-study ABR, pre-existing target joint spontaneous bleed	0.4 (0.0-3.2)	0.3 (0.0-2.2)	0.3 (0.0-1.1)	0.9 (0.0-1.9)	0.0 (0.0-0.0)	7.9 (1.2-19.8)

All data are median (IQR).
*For subjects receiving prestudy prophylaxis and on-study individualized prophylaxis (n = 2), ABRs for prestudy, on-study overall, on-study joint, on-study pre-existing target joint, and on-study pre-existing target joint spontaneous bleed were 5.0 (n = 1), 5.7 and 8.6, 5.7 and 7.8, 4.6 and 7.0, and 4.6 and 5.4, respectively.
†Subjects are included in each treatment regimen they participated in for the duration of time on that regimen and, as such, may appear in ≥1 treatment regimen.
‡n = 11.
§n = 25.
‖A bleeding episode was considered to involve a target joint if any of the bleeding joints was a target joint identified at the entry into the parent study.

Table 7. Resolution of evaluable target joints in subjects receiving prophylaxis in B-LONG/B-YOND (subanalysis 3)

Target joints, n	93
Target joints resolved, n (%)	93 (100.0)
Resolved target joints with ≥6 mo follow-up postresolution, n (%)*	92 (98.9)
Evaluable target joints with recurrence postresolution, n (%)†,‡	9 (9.8)
Evaluable target joints without recurrence in the postresolution period, n (%)†,‡	83 (90.2)
Median (IQR) postresolution follow-up per target joint, mo	47.4 (19.8-60.6)

A target joint was considered resolved if there were ≤2 spontaneous bleeds in a consecutive 12-month period in the target joint. Target joints were considered evaluable if they had ≥12 months consecutive follow-up and there had been no surgery on the target joint within the 12 months since the start of follow-up.

*Percentage based on the number of resolved target joints.

†Percentage is based on the number of resolved target joints with ≥6 months' follow-up after resolution.

‡Recurrence is defined as ≥3 spontaneous bleeds in a single joint within any consecutive 6-month period after the target joint resolution.

In addition to confirming the sustained, long-term efficacy of rFIXFc prophylaxis for all types of bleeds in subjects of all age groups with severe hemophilia B, the results of the post hoc analyses presented in this study demonstrate that rFIXFc prophylaxis affects target joint status. Just over half of the subjects in this analysis had target joints at baseline (entry into the B-LONG study) and, thus, had experienced at least 3 bleeds in the same joint in a consecutive 3-month period before entering the parent study. rFIXFc WP was the most used regimen in subjects with target joints, although individualized prophylaxis (median interval of 10 days) and modified prophylaxis (median interval of 6 days) were also used. A personalized treatment approach is crucial to achieve the optimal outcome for subjects with target joints. All target joint recurrences resolved during the B-YOND study. Further supporting this is the recent publication by Astermark et al[32] that assessed pain and physical activity among those individuals in the B-LONG study receiving either WP or IP regimens; a greater proportion of individuals did not experience swollen or painful joints at the end of the B-LONG study compared with at baseline. Overall, prophylaxis with rFIXFc provided long-term and sustained improvement in joint outcomes among adults and adolescents with severe hemophilia B.

Limitations of this analysis include its post hoc nature. Furthermore, the subjects included may not be representative of a real-world cohort of individuals with severe hemophilia B. However, the findings of this study are consistent with several reports of real-world data using rFIXFc.[15-23] For example, a long-term (up to 5 years), real-world retrospective chart review among 64 subjects who switched to rFIXFc and extended their dosing interval supports clinical trial data.[15] Bleed control was improved, factor consumption was reduced by ~50%, and adherence levels were high.[15] This also aligns with data from a further real-world retrospective chart review in which 28 subjects switched to rFIXFc and were monitored for >2 years.[16] Improved ABRs and a 28% reduction in factor consumption were similarly observed, although adherence was not described.[16] The high adherence rates observed in this study, reflecting close subject monitoring, may not be typical of real-world cohorts, and further evaluation of adherence rates outside of a clinical trial setting is warranted. It is also notable that the protocol definition of baseline target joints in the parent studies was defined before the publication of the International Society on Thrombosis and Haemostasis (ISTH) definition and required ≥3 bleeds in 3 months, whereas the subsequent ISTH definition required ≥3 spontaneous bleeds in 6 months.[33] As a result of this discrepancy, although it was possible to report target joint recurrences using the ISTH definition, it was not possible to evaluate the incidence of new target joints because some may have been present before the study entry and not classified as such, owing to a shift in definitions. Finally, the number of subjects included in analyses for 4 and 5 year and 14-day dosing is relatively small, thus limiting the conclusions that can be drawn from the data at these extended time points.

A strength of the B-YOND study is that it provides insights into the possibility of individualized dosing regimens, the option to switch treatment regimens, and dosing flexibility across most treatment groups. The component of shared decision-making regarding dosing intervals of the study drug further contributed to personalization. These are important elements for the individualization of treatment in the real world.

Conclusions

This longitudinal post hoc analysis of B-YOND demonstrates that the benefits of rFIXFc prophylaxis are sustained year-by-year for at least 4 years in children and 5 years in adults and adolescents, adding further detail to the well-characterized long-term efficacy and safety profile of rFIXFc and being consistent with the provision of sustained long-term bleed prevention as well as target joint resolution. The EHL and associated reduction in treatment burden may allow increased use of prophylaxis, a currently underused option in hemophilia B. Overall, rFIXFc prophylaxis offers individuals with hemophilia B the opportunity for personalized single-agent protection with the flexibility to target desired trough levels to meet patient needs.

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