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ORIGINAL ARTICLE

Managing surgery in hemophilia with recombinant factor VIII Fc and factor IX Fc: Data on safety and effectiveness from phase 3 pivotal studies

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Abstract

Background: Surgical procedures impose hemostatic risk to people with hemophilia, which may be minimized by optimal factor (F) replacement therapy.

Methods: This analysis evaluates the efficacy and safety of extended half-life factor replacement recombinant FVIII and FIX Fc fusion proteins (rFVIIIFc and rFIXFc) during surgery in phase 3 pivotal (A-LONG/Kids A-LONG and B-LONG/Kids B-LONG) and extension (ASPIRE and B-YOND) studies. Dosing regimens were determined by investigators. Injection frequency, dosing, blood loss, transfusions, and hemostatic response were assessed.

Results: Forty-five major ($n = 31$ subjects) and 90 minor ($n = 70$ subjects) procedures were performed in hemophilia A; 35 major ($n = 22$) and 62 minor ($n = 37$) procedures

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were performed in hemophilia B. Unilateral knee arthroplasty was the most common major orthopedic procedure (hemophilia A: $n = 15/34$; hemophilia B: $n = 8/24$). On the day of surgery, median total dose in adults/adolescents was 81 IU/kg for rFVIIIFc and 144 IU/kg for rFIXFc; most major procedures required ≤2 injections (including loading dose). Through days 1–14, most major procedures had ≤1 injection/day. Hemostasis was rated excellent (rFVIIIFc: $n = 39/42$; rFIXFc: $n = 29/33$) or good ($n = 3/42$; $n = 4/33$) in evaluable major surgeries, with blood loss comparable with subjects without hemophilia. Most minor procedures in adults/adolescents required one injection on the day of surgery, including median loading dose of 51 IU/kg (rFVIIIFc) and 80 IU/kg (rFIXFc). No major treatment-related safety concerns were identified. No subjects developed inhibitors or serious vascular thromboembolic events.

Conclusions: rFVIIIFc and rFIXFc were efficacious and well tolerated for the management of perioperative hemostasis across a wide spectrum of major and minor surgeries in hemophilia.

KEYWORDS

factor IX fc fusion protein, factor VIII Fc fusion protein, hemophilia A, hemophilia B, recombinant fusion proteins, safety, surgical procedures

Essentials

- Clotting factor replacement in hemophilia reduces complications during and after surgery.
- Extended half-life (EHL) factor products used for surgery in phase 3 trials were evaluated.
- Most major surgeries had ≤2 injections on surgery day and similar blood loss to non-hemophilia.
- EHL factor replacement was well tolerated and effective across major and minor surgeries.

1 | INTRODUCTION

Surgical procedures are a significant hemostatic challenge in hemophilia, with patients at risk for serious intraoperative and postoperative complications, including bleeding and infection, if not properly managed.[1–3] Factor (F) replacement remains the standard of care for the perioperative management of patients without inhibitors to establish effective bleed resolution and hemostatic control.[4] Sufficient hemostatic coverage may also serve to facilitate healing and reduce infection risk.[2–4]

Because of their extended half-life (EHL), recombinant FVIII and FIX Fc fusion proteins (rFVIIIFc and rFIXFc) can maintain adequate, stable factor levels during surgical periods, supporting lower dosing frequency and more sustained protection compared with standard half-life (SHL) products.[5] EHL therapies also encourage greater long-term adherence to prophylaxis, which may facilitate continuation of physiotherapy following hospital discharge. Functional rehabilitation, facilitated by adequate hemostatic coverage, is key for restoring joint motion and maintaining the benefits of orthopedic surgery, such as total knee arthroplasty.[4,6,7] Such procedures are typically required for people with hemophilia to ameliorate musculoskeletal complications, including arthropathy.[1,4,8,9]

rFVIIIFc and rFIXFc are approved in the United States, Europe, and many other regions of the world for the treatment and prophylaxis of bleeding in people with hemophilia across all age groups.[10–19] The efficacy and safety of these products was evaluated in phase 3 pivotal and extension studies (A-LONG/Kids A-LONG [pivotal] and ASPIRE [extension] for rFVIIIFc; B-LONG/Kids B-LONG [pivotal] and B-YOND [extension] for rFIXFc) with up to 6.5 years of cumulative treatment duration.[20–25] Previous analyses of the surgical experience with rFVIIIFc and rFIXFc includes data from pivotal studies and interim data from ASPIRE. Data from 23 major and 52 minor surgeries in hemophilia A studies, and 14 major and 15 minor surgeries from subjects enrolled in pivotal hemophilia B studies have been reported previously.[26,27]

Here, we summarize the full collated surgical experience with rFVIIIFc and rFIXFc in adult, adolescent, and pediatric patients across all phase 3 pivotal and extension studies (A-LONG, Kids A-LONG, ASPIRE, B-LONG, Kids B-LONG, and B-YOND). This represents the first report on surgical outcomes using final collated data from these studies. Specifically, the analyses aim to evaluate the efficacy and safety of rFVIIIFc and rFIXFc during surgical interventions and describe dosing and management of surgical interventions with these products.

2 | METHODS

2.1 | Study design and participants

This study reports prospectively collected surgical data from subjects enrolled in open-label, phase 3 pivotal (A-LONG/Kids A-LONG or B-LONG/Kids B-LONG) and extension (ASPIRE or B-YOND) studies who underwent major or minor surgery. A-LONG and B-LONG enrolled previously treated male subjects ≥12 years of age with severe hemophilia A (<1 IU/dl [<1%] endogenous FVIII activity) or B (≤2 IU/dl [≤2%] endogenous FIX activity), respectively. Subjects aged <12 years were enrolled in the corresponding pediatric studies (Kids A-LONG and Kids B-LONG). Subjects completing these studies were eligible to enter ASPIRE and B-YOND. Detailed study design and methods are described elsewhere.[20,21,23,24,28,29]

Following trial enrollment, and before major surgery, A-LONG subjects were required to have ≥12 rFVIIIFc exposure days (EDs) with a negative inhibitor (<0.6 BU/ml) and B-LONG subjects were required to have a negative inhibitor test after ≥4 rFIXFc EDs. Before major or minor surgery, Kids A-LONG and Kids B-LONG subjects required ≥5 rFVIIIFc EDs and ≥3 rFIXFc EDs, respectively, without safety concerns.

Study protocols were approved by institutional review boards and/or ethics committees at participating institutions. Subjects, or their guardians, provided written informed consent before participation in the studies; if appropriate, adolescent/pediatric subjects also provided assent. All studies included in this analysis were conducted in accordance with the International Conference on Harmonization Guidelines for Good Clinical Practice[30] and ethical principles that comply with the Declaration of Helsinki,[31] and are registered with ClinicalTrials.gov (ClinicalTrials.gov identifiers: NCT01181128, NCT01458106, NCT01454739, NCT01027364, NCT01440946, NCT01425723).

2.2 | Surgical approach

A major surgery was defined as any surgical procedure, elective or emergent, that usually, but not always, involved general anesthesia and/or respiratory assistance in which a major body cavity was penetrated and exposed, or for which a substantial impairment of physical or physiological function was produced. Surgical procedures not meeting these criteria were classified as minor.

The surgical period began with the first preoperative rFVIIIFc or rFIXFc dose and ended immediately before the first regular prophylactic dose (or at midnight on the last day of the rehabilitation period for subjects receiving on-demand rFVIIIFc or rFIXFc). The surgical period consisted of intraoperative and postoperative care, and postoperative rehabilitation periods (up to 14 days).

During the surgical period, rFVIIIFc and rFIXFc were administered as bolus injections. Continuous infusion was not permitted. Individualized treatment regimens were determined by the investigator according to local standard of care based on the type of surgery, subject's pharmacokinetic profile and clinical status in consultation with the sponsor medical monitor as required.

2.3 | Outcome measures

Efficacy outcomes for surgeries included rFVIIIFc or rFIXFc dosing, number of injections to maintain hemostasis during the surgical period, total estimated blood loss for major surgeries, and number of surgeries requiring blood transfusion. These outcomes were evaluated on the day of surgery (day 0; including loading dose) and postoperative days 1–14. Loading dose was defined as the first dose administered on the day of surgery. If there was no dose administered on the day of surgery, loading dose was defined as the dose administered 1 day before surgery.

Investigators/surgeons who performed the surgical procedures used a 4-point scale to assess the subject's hemostatic response to treatment (i.e., excellent, good, fair, poor/none) in line with criteria defined by the Scientific and Standardization Committee of the International Society on Thrombosis and Hemostasis (see Supplementary Material for details).[32]

Safety endpoints were inhibitor development, measured in a central laboratory by Nijmegen-modified Bethesda assay (positive result defined as assay titer ≥0.6 BU/ml, confirmed on retesting within 2–4 weeks), and adverse events (AEs) for major surgeries reported during the surgical period.

2.4 | Statistical analysis

Efficacy outcomes were summarized using descriptive statistics (median and interquartile range). The investigator/surgeon assessment of hemostatic response was summarized as the number and proportion of surgeries achieving each rating on a 4-point scale.

3 | RESULTS

3.1 | Perioperative management with rFVIIIFc (A-LONG, Kids A-LONG, ASPIRE)

3.1.1 | Subjects

Demographics and baseline characteristics of subjects who underwent major or minor surgery in pivotal and extension studies were representative of a population with severe hemophilia A (Table 1). One subject (anterior transposition of the ulnar nerve) was treated with a non-study FVIII product instead of rFVIIIFc during the surgical period and was excluded from the analysis.

TABLE 1 Demographics and baseline characteristics of subjects who underwent major or minor surgery in phase 3 pivotal and extension studies

Characteristic at pivotal study baseline	Subjects with surgery in A-LONG, Kids A-LONG or ASPIRE		Subjects with surgery in B-LONG, Kids B-LONG or B-YOND	
	Major surgery[a] (*N* = 31)	Minor surgery (*N* = 70)	Major surgery[b] (*N* = 22)	Minor surgery (*N* = 37)
Age (years), median (range)	40 (3–62)	26 (1–65)	37 (9–62)	35 (2–71)
<12, *n* (%)	2 (6.5)	23 (32.9)	1 (4.5)	4 (10.8)
12–18, *n* (%)	0	4 (5.7)	3 (13.6)	3 (8.1)
>18–40, *n* (%)	14 (45.2)	25 (35.7)	8 (36.4)	16 (43.2)
>40, *n* (%)	15 (48.4)	18 (25.7)	10 (45.5)	14 (37.8)
Weight (kg), median (range)	75.5 (19–104)	63.5 (13–116.5)	67 (30.4–100.5)	70.2 (15.3–118)
Race, *n* (%)				
White	24 (77.4)	46 (65.7)	10 (45.5)	22 (59.5)
Black or African American	1 (3.2)	8 (11.4)	3 (13.6)	3 (8.1)
Asian	6 (19.4)	14 (20.0)	4 (18.2)	10 (27.0)
Other	0	2 (2.9)	5 (22.7)	2 (5.4)
Region, *n* (%)				
Europe	15 (48.4)	23 (32.9)	6 (27.3)	13 (35.1)
North America	6 (19.4)	15 (21.4)	4 (18.2)	11 (29.7)
Other	10 (32.3)	32 (45.7)	12 (54.5)	13 (35.1)
Family history of inhibitor, *n* (%)	1 (3.2)	4 (5.7)	1 (4.5)	2 (5.4)
≥1 target joints, *n* (%)	21 (67.7)	38 (54.3)	14 (63.6)	21 (56.8)

Note: *N* numbers indicate number of subjects. Subjects who underwent major and minor surgery were included in both cohorts.

[a]Includes two subjects from Kids A-LONG who had major surgery (arm K-wire replacement and dental extraction).

[b]Includes one subject from Kids B-LONG who had major surgery (tonsillectomy).

3.1.2 | Surgeries

Forty-five major (*n* = 31 subjects) and 90 minor (*n* = 70 subjects) surgeries were performed across hemophilia A studies. Nine major (all in A-LONG subjects) and 21 minor (14 A-LONG; 7 Kids A-LONG) surgeries occurred during pivotal studies; 36 major (34 in subjects from A-LONG; two in subjects from Kids A-LONG) and 69 minor (50 in subjects from A-LONG; 19 in subjects from Kids A-LONG) surgeries occurred during ASPIRE. The most common types of major surgery were joint replacement/revision (*n* = 22; Table 2), including 15 unilateral knee arthroplasties (Table S1). Refer to Table S2 for a full list of minor surgeries.

3.1.3 | rFVIIIFc dosing for major surgery

One major surgery (right shoulder replacement) of 45 did not have available data on factor consumption for the day of surgery. For the 44 remaining major surgeries with available data on rFVIIIFc administration on the day of surgery, most (86%, *n* = 38/44) reported one injection of rFVIIIFc to maintain hemostasis during surgery, defined as loading dose until the end of surgery (for one surgery, rFVIIIFc was administered on the day of surgery but time of rFVIIIFc injection in relation to surgery was not specified; Table S5). Forty-two major surgeries in A-LONG/ASPIRE subjects and two surgeries (arm K-wire replacement and dental extraction) in Kids A-LONG/ASPIRE subjects had administration data for the day of surgery (Table 3).

In orthopedic procedures (*n* = 33), median dose per injection on the day of surgery was 42 IU/kg (with a median of two injections) and between 26 and 30 IU/kg on postoperative days 1–14, for the procedures dosed on those days. In nonorthopedic (*n* = 11) procedures, median dose per injection on the day of surgery was 52 IU/kg (with a median of one injection), subsequently ranging between 26 and 50 IU/kg on days 1–14 (Table 4) Most surgeries required ≤1 injection/day between days 1 and 14 (Figure 1). A moderate correlation was noted between higher dose per injection and fewer injections after the first few days after surgery (data not shown).

TABLE 2 Types of major and minor surgeries performed

Surgeries in A-LONG, Kids A-LONG, or ASPIRE				Surgeries in B-LONG, Kids B-LONG, or B-YOND			
Major surgeries	***n***	**Minor surgeries**	***n***	**Major surgeries**	***n***	**Minor surgeries**	***n***
Joint replacement/ revision	22	Tooth extraction	31	Joint replacement/ revision	10	Tooth extraction	24
Abdominal	7	Port placement or removal	17	Abdominal	6	Eye surgery	5
Joint fusion	4	Other dental	10	Other orthopedic	5	Oral surgery	5
Arthroscopy	3	Other non-orthopedic	9	Fracture and fixation	3	Incision and drainage	5
Other orthopedic	2	Cystoscopy with/without Procedure	6	Arthroscopy	2	Vascular procedures	5
Spinal surgery	2	Minor skin procedures	6	Cranial/brain	2	Minor orthopedic	4
Chest	2	Endoscopy with/without Procedure	4	Joint fusion	2	Other non-orthopedic	4
Cranial/brain	1	Incision and drainage	2	Other nonorthopedic	2	Other dental	4
Dental[a]	1	Oral surgery	2	Spinal surgery	2	Port placement or removal	3
Fracture and fixation	1	Minor orthopedic	2	Dental[b]	1	Minor skin procedures	2
–	–	Vascular procedure	1	–	–	Endoscopy with/ without Procedure	1
Total	45	Total	90	Total	35	Total	62

Note: *n* numbers indicate number of surgeries.

[a]Oral surgery due to teeth abscess requiring hospitalization for extraction of four teeth (two incisors and two molars) performed in subject from Kids A-LONG.

[b]Surgical procedure under general anesthesia to incise and drain a dental abscess and remove two teeth.

3.1.4 | rFVIIIFc dosing for minor surgery

Of 84 procedures with available data on rFVIIIFc administration during surgery, 70 (83%) reported 1 injection to maintain hemostasis (Table S5). rFVIIIFc dosing regimen for the 84 minor surgeries with administration data on the day of surgery is shown in Table 3.

3.1.5 | Assessment of hemostatic response to treatment with rFVIIIFc

Of 42 major surgeries assessed for hemostatic response to rFVIIIFc, most (93%, *n* = 39/42) were rated as excellent, defined as intraoperative and postoperative blood loss comparable to a subject without hemophilia. The remaining three surgeries (7%) were rated as good.

All minor surgeries with a hemostatic assessment (*n* = 65/90) were rated as excellent (85%, *n* = 55) or good (15%, *n* = 10).

3.1.6 | Blood loss

Median (range) estimated blood loss during the total surgical period for major surgeries was 90 ml (0–1600). Overall, eight major surgeries reported a total blood loss ≥500 ml, including one bilateral knee arthroplasty (1600 ml), four unilateral knee arthroplasties (1260, 1000, 600 and 900 ml), one above-the-knee amputation (1200 ml), one unilateral ankle fusion (930 ml), and one unilateral hip arthroplasty (900 ml). Four of 45 (9%) major surgeries required transfusion of blood products (bilateral knee arthroplasty, above-the-knee amputation, unilateral knee arthroplasty, and unilateral hip arthroplasty), of which three reported a total blood loss ≥500 ml during surgery.

Potential correlations between individual half-life or incremental recovery obtained at pivotal study baseline and blood loss, as well as between dose regimen and blood loss, during the surgical period were assessed. However, no clear correlations were observed, potentially because of confounding factors such as type of surgeries, local practice for loading dose, and injection frequency (data not shown).

3.1.7 | Thromboprophylaxis

Thromboprophylaxis (low molecular weight heparin or heparin) was administered according to local practice (Table S6) during nine (20%) major surgeries [six knee replacements, one hip replacement, one ankle fusion, and one arm fracture and fixation] in eight adult subjects (median [range] age 47 (26–57) years at A-LONG baseline). Of these subjects, one had a previous deep vein thrombosis (DVT). Median (range) duration of thromboprophylaxis was 7.5 (1–29) days (longest duration in subject with previous DVT). In all nine surgeries, hemostatic response to rFVIIIFc was rated excellent.

3.1.8 | Hospitalization

Median (range) total duration of hospitalization for major surgeries in A-LONG/ASPIRE subjects was 5.0 (2–32) days for orthopedic

TABLE 3 Summary of rFVIIIFc regimen on the day of surgery[a]

	Major surgery (*N* = 44)	Minor surgery (*N* = 84)
Surgeries in A-LONG	42[b]	58[c,d]
Median (range) loading dose,[e] IU/kg	59 (35–111)	51 (25–100)
Median (range) injections, *n*	2 (1–3)	1 (1–2)
Median (range) consumption, IU/kg	81 (39–158)	52 (25–112)
Surgeries in Kids A-LONG	2[f]	26
Median (range) loading dose,[e] IU/kg	38, 66[f]	63 (30–108)
Median (range) injections, *n*	1, 1[f]	2 (1–3)
Median (range) consumption, IU/kg	38, 66[f]	88 (53–216)

Note: *N* numbers indicate number of surgeries.Abbreviation: rFVIIIFc, recombinant factor VIII Fc fusion protein.

[a]Data derived from surgeries performed during A-LONG, Kids A-LONG, and ASPIRE; includes all doses given on the day of surgery (including pre-, during, and postsurgery).

[b]One major surgery did not have information on rFVIIIFc dosing on the day of surgery and is therefore not included in this table.

[c]Six minor surgeries did not use rFVIIIFc on the day of surgery and are not included in this table.

[d]Four surgeries (two tooth extractions, one surgical removal of wisdom tooth, and one incision and drainage) had no reported rFVIIIFc injections or missing data during surgery, but reported rFVIIIFc administration on the day of surgery (included in table).

[e]Loading dose was defined as the first dose administered on the day of surgery. If there was no dose administered on the day of surgery, loading dose was defined as the dose administered 1 day before surgery.

[f]Individual values are listed.

surgeries and 5.5 (1–15) days for nonorthopedic surgeries. Median (range) time from day of surgery until hospital discharge (excluding hospitalization before surgery) was 5.0 (2–29) days for orthopedic surgeries and 4.5 (1–15) days for nonorthopedic surgeries. For both major surgeries in Kids A-LONG/ASPIRE subjects, total duration of hospitalization (and from day of surgery until discharge) was 2 days.

3.1.9 | Total knee replacement

The most common type of major surgery was unilateral knee arthroplasty ($n = 15$), performed in 14 subjects (age span 25–65 years at study baseline). Of the 15 unilateral knee arthroplasties, most ($n = 13/15$) required one injection (including loading dose) of rFVIIIFc during surgery, with median (range) loading dose of 59 IU/kg (48–79; for one surgery, time of injection on the day of surgery in relation to time of surgery was not specified). On the day of surgery, median (range) number of injections was 2 (1–2) and total factor consumption was 80 IU/kg (59–158). During the postoperative period (days 1–14), median (range) number of injections, and dose per injection were 15 (7–22) and 30 IU/kg (20–54), respectively.

Of 14 knee replacement surgeries assessed for hemostatic response to rFVIIIFc, 13 (93%) were rated as excellent and one (7%) as good. Median (range) estimated blood loss for intraoperative and postoperative periods was 50 ml (0–600; data not recorded for two surgeries) and 145 ml (0–1200; data not recorded for three surgeries), respectively, consistent with or lower than published reports of knee arthroplasties performed in subjects without hematologic disorders.[33,34]

Median (range) total duration of hospitalization for unilateral knee arthroplasty was 8 (2–32) days and from day of surgery until hospital discharge was 8 (2–29) days.

3.1.10 | Safety

No subjects developed inhibitors to rFVIIIFc or experienced anaphylaxis or serious vascular thromboembolic events resulting from treatment during the surgical period. One AE (postprocedural hemorrhage after knee arthroplasty resulting from dislocation) during the major surgical period was considered serious because of the requirement for hospitalization; the postoperative bleed was assessed as moderate in severity. Postoperative wound infections (nonserious) were reported for two major surgeries (one elbow replacement and one above-the-knee amputation). No AEs were deemed by investigators as related to treatment with rFVIIIFc and none resulted in any changes to study treatment.

3.2 | Perioperative management with rFIXFc (B-LONG, Kids B-LONG, B-YOND)

3.2.1 | Subjects

Demographics and baseline characteristics of subjects who underwent major or minor surgery in pivotal and extension studies were representative of a population with severe hemophilia B (Table 1).

3.2.2 | Surgeries

Overall, 35 major ($n = 22$ subjects) and 62 minor ($n = 37$ subjects) surgeries were performed in hemophilia B studies. Fourteen major (all in subjects from B-LONG) and 18 minor (15 B-LONG; three Kids B-LONG) surgeries occurred during pivotal studies, whereas 21 major (20 in subjects from B-LONG; one in a subject from Kids B-LONG) and 44 minor (42 in subjects from B-LONG; two in subjects from Kids B-LONG) surgeries occurred during B-YOND. Most major surgeries were orthopedic ($n = 24$; Table 2); unilateral knee arthroplasties were the most common procedure ($n = 8$; Table S3). Types of minor surgery are listed in Table 2 and Table S4.

TABLE 4 rFVIIIFc dosing on day of surgery and postoperative days 1–14 for orthopedic and nonorthopedic major surgeries

	Loading dose[b]	Day of surgery, including loading dose	Postoperative day							
			Day 1	Day 2	Day 3	Day 4	Day 5	Day 6	Day 7	Days 8–14
Orthopedic ($n = 33$)										
Number of procedures dosed with rFVIIIFc[a]	$n = 33$	$n = 33$	$n = 30$	$n = 29$	$n = 31$	$n = 29$	$n = 29$	$n = 25$	$n = 28$	$n = 28$
Dose per injection (IU/kg)										
Median	60	42	30	30	28	30	30	26	28	30[c]
IQR	55–69	39–59	23–42	24–43	22–41	23–38	20–41	22–37	22–38	22–36
Range	38–102	30–102	15–88	15–88	7–79	17–54	13–61	13–53	13–91	15–98
Total dose (IU/kg)										
Median	60	81	46	44	41	41	39	35	33	30[d]
IQR	55–69	73–87	34–57	36–52	28–51	25–51	22–51	22–51	24–46	22–38
Range	38–102	38–158	15–88	15–102	7–85	17–77	15–85	15–79	20–91	15–98
Nonorthopedic ($n = 11$)										
Number of procedures dosed with rFVIIIFc[a]	$n = 11$	$n = 11$	$n = 10$	$n = 8$	$n = 8$	$n = 7$	$n = 8$	$n = 6$	$n = 5$	$n = 5$
Dose per injection (IU/kg)										
Median	54	52	32	29	26	28	50	50	47	32[c]
IQR	41–66	34–66	26–52	26–44	24–42	23–52	24–53	25–56	32–52	26–52
Range	35–111	22–111	23–66	25–56	22–56	22–56	22–56	22–72	16–56	16–63
Total dose (IU/kg)										
Median	54	66	44	44	35	43	50	50	47	32[d]
IQR	41–66	60–105	26–65	29–55	25–54	25–52	34–53	43–56	32–52	26–52
Range	35–111	39–116	23–105	25–105	23–63	23–56	23–56	25–72	16–56	16–63

Abbreviations: IQR, interquartile range; rFVIIIFc, recombinant factor VIII Fc fusion protein.

[a]Dose shown only for surgical events where dosing of rFVIIIFc was given in conjunction with the surgical intervention for a specific day/period; one major surgery did not have information on rFVIIIFc dosing on the day of surgery and is not included in this table.

[b]Loading dose was defined as the first dose administered on the day of surgery. If there was no dose administered on the day of surgery, the loading dose was defined as the dose administered 1 day before surgery.

[c]Based on mean dose per injection per day in the period of days 8–14 (on day[s] of injection) per surgery with ≥1 injections during this period.

[d]Based on mean total daily dose per day in the period of days 8–14 (on day[s] of injection) per surgery with ≥1 injection during this period.

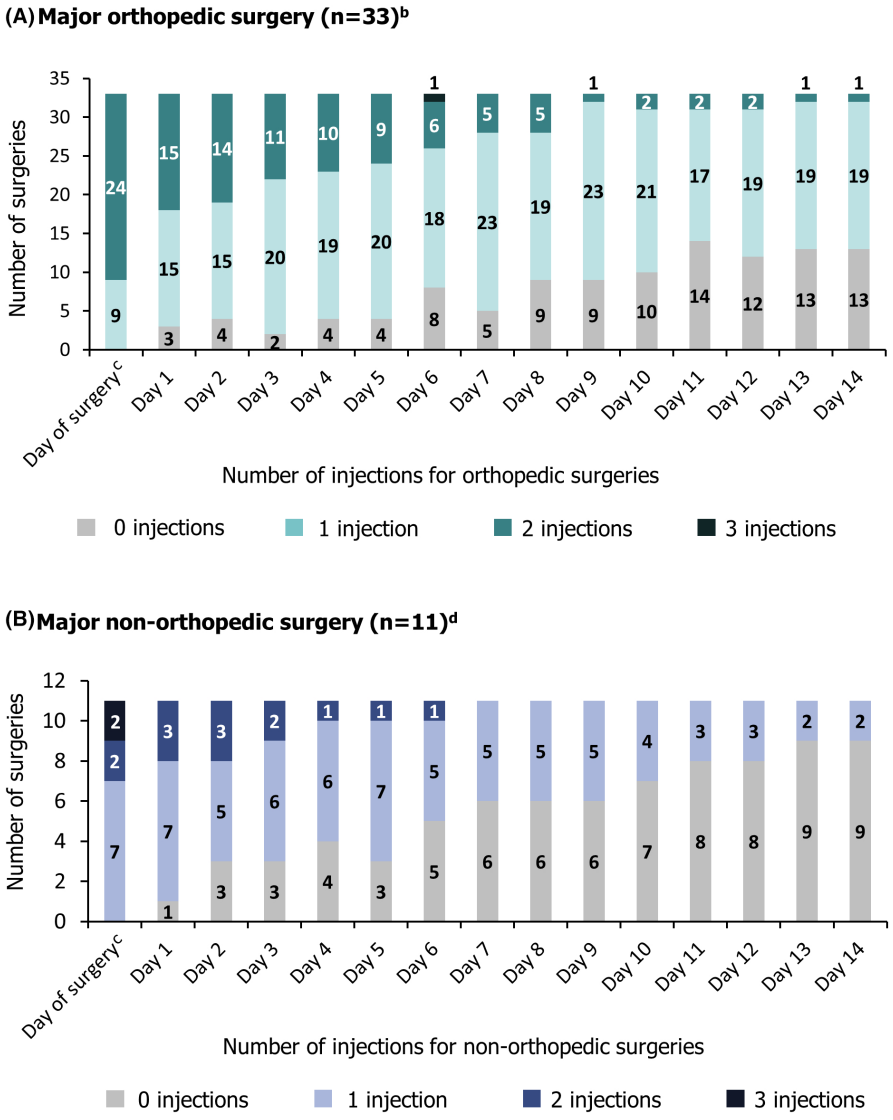

FIGURE 1 Number of injections of rFVIIIFc on day of surgery and postoperative days 1–14 in major orthopedic and nonorthopedic surgeries[a]. [a]Dose shown only for surgical events where dosing of rFVIIIFc was given in conjunction with the surgical intervention (and for a specific day/period); one major surgery did not have information on rFVIIIFc dosing on the day of surgery and is not included in this figure. [b]Includes one subject from Kids A-LONG (arm K-wire replacement). [c]Includes loading dose. Loading dose was defined as the first dose administered on the day of surgery. If there was no dose administered on the day of surgery, the loading dose was defined as the dose administered 1 day before surgery. [d]Includes one subject from Kids A-LONG (dental extraction). Abbreviations: rFVIIIFc, recombinant factor VIII Fc fusion protein

3.2.3 | rFIXFc dosing for major surgery

Most major surgeries (83%, *n* = 29/35) reported one injection of rFIXFc (including loading dose) to maintain hemostasis during surgery (Table S7). The 34 major surgeries in B-LONG/B-YOND subjects and one major pediatric surgery (tonsillectomy) all had administration data for the day of surgery (Table 5).

For the 24 orthopedic procedures, median dose per injection (for a median of two injections) was 96 IU/kg on the day of surgery and between 48 and 68 IU/kg on postoperative days 1–14; for nonorthopedic procedures (*n* = 11), median dose per injection (median of 1 injection) was 80 IU/kg and between 49–64 IU/kg (Table 6). Most surgeries required ≤1 injection/day from days 1 to 14 (Figure 2). Similar to hemophilia A, there was a moderate correlation between higher doses per injection and fewer injections after the first few days postsurgery (data not shown).

3.2.4 | rFIXFc dosing for minor surgery

Of 62 minor surgeries, 46 (74%) had one injection of rFIXFc (including loading dose) during surgery (Table S7). Fifty-five minor surgeries had rFIXFc administration on the day of surgery (Table 5).

3.2.5 | Assessment of hemostatic response to treatment with rFIXFc

Hemostatic response to rFIXFc was assessed in 33 of 35 major surgeries; all were rated as excellent (88%, *n* = 29/33) or good (12%, *n* = 4/33).

Most minor surgeries with a hemostatic assessment (*n* = 38/62) were rated as excellent (84%, *n* = 32/38) or good (11%, *n* = 4/38). Remaining assessed surgeries (5%, *n* = 2/38) were rated as fair (both were dental surgeries/extractions).

TABLE 5 Summary of rFIXFc regimen on the day of surgery[a]

	Major surgery (*N* = 35)	Minor surgery (*N* = 55)
Surgeries in B-LONG	34	50[b,c]
Median (range) loading dose,[d] IU/kg	100 (49–183)	80 (29–142)
Median (range) injections, *n*	2 (1–4)	1 (1–3)
Median (range) consumption, IU/kg	144 (51–421[e])	84 (29–293)
Surgeries in Kids B-LONG	1[f]	5
Median (range) loading dose,[d] IU/kg	99[f]	128 (67–153)
Median (range) injections, *n*	1[f]	2 (1–2)
Median (range) consumption, IU/kg	99[f]	202 (67–261)

Note: *N* numbers indicate number of surgeries.

Abbreviation: rFIXFc, recombinant factor IX Fc fusion protein.

[a]Data derived from surgeries performed during B-LONG, Kids B-LONG, and B-YOND; includes all doses given on the day of surgery (including pre-, during, and postsurgery).

[b]Seven of 57 minor surgeries in subjects from B-LONG did not use rFIXFc on the day of surgery and are therefore not included in this table.

[c]One surgery (evacuation of right breast hematoma and drain placement) had no reported rFIXFc injections during surgery, but rFIXFc was administered on the day of surgery (included in table).

[d]Loading dose was defined as the first dose administered on the day of surgery. If there was no dose administered on the day of surgery, loading dose was defined as the dose administered 1 day before surgery.

[e]The highest consumption was reported for a malignant hepatic neoplasm surgery, with hepatectomy and cholecystectomy on the same day.

[f]Individual values are listed.

3.2.6 | Blood loss

Median (range) estimated blood loss during the total surgical period for major surgery was 100 ml (0–5610). Seven major surgeries reported a total blood loss ≥500 ml; hemostatic response was rated as excellent ($n = 4$) or good ($n = 3$) in all cases. These included a liver transplant (5610 ml), total hip replacement with cement (1300 ml), posterior lumbar interbody fusion (910 ml), closure of rectal fistula (800 ml), knee replacement and femur implantation (600 ml), hepatic open-wedge resection cholecystectomy (568 ml), and a total knee replacement (500 ml). Three major surgeries required transfusion of blood products (liver transplant, closure of rectal fistula, and total knee arthroplasty), of which one (liver transplant) reported a blood loss of ≥500 ml during surgery. No blood transfusions were required for any minor surgery.

Potential correlations between individual half-life or incremental recovery obtained at pivotal study baseline and blood loss, and between dose regimen and blood loss, during the surgical period were assessed. Similar to hemophilia A studies, no clear correlations were observed (data not shown).

3.2.7 | Thromboprophylaxis

Thromboprophylaxis (low molecular weight heparin) was administered according to local practice (Table S8) during three (9%) major surgeries (two knee replacements and one spinal fusion surgery) in three adult subjects (aged between 30 and 65 years at B-LONG baseline). One subject had several risk factors for thromboembolic complications (including previous DVT and obesity). Duration of thromboprophylaxis was 54 days (subject with previous DVT), 15, and 6 days. The hemostatic response was rated as excellent in one surgery and good in two surgeries.

3.2.8 | Hospitalization

Median (range) total duration of hospitalization for major surgeries in subjects from B-LONG/B-YOND was 7.5 (1–21) days for orthopedic surgeries and 9.0 (2–41) days for nonorthopedic surgeries. Median (range) time from day of surgery until hospital discharge (i.e., excluding days of hospitalization before surgery) was 6.0 (1–20) days for orthopedic surgeries and 8.0 (2–32) days for nonorthopedic surgeries. For the one major surgery (tonsillectomy) in a subject from Kids B-LONG/B-YOND, total duration of hospitalization was 6 days (5 days from day of surgery until discharge).

3.2.9 | Total knee replacement

Of the eight unilateral knee arthroplasties (in eight subjects with an age span of 15 to 65 years at baseline), seven (88%) had one injection (including loading dose) of rFIXFc to maintain hemostasis during surgery; the remaining surgery required two injections. On the day of surgery, median (range) number of injections was two (one–two) and total factor consumption was 151 IU/kg (105–242). During the postoperative period (day 1–14), median (range) number of injections and dose per injection were nine (6–12) and 63 IU/kg (47–87), respectively.

Hemostatic response to rFIXFc was rated as excellent for six (75%) surgeries and good for the remaining 2 (25%) surgeries. Median (range) estimated blood loss ($n = 8$) was 125 ml (56–500) for the intraoperative period and 35 ml (0–300) for the postoperative period, which was comparable or lower than blood loss reported for the same type of surgery in subjects without bleeding disorders.[33,34]

Median (range) total duration of hospitalization for unilateral knee arthroplasty was nine (6–21) days and median (range) time from day of surgery until hospital discharge was nine (4–20) days.

3.2.10 | Safety

No subjects developed inhibitors to rFIXFc, anaphylaxis, or serious vascular thromboembolic events during these studies, including during the surgical periods. Five serious AEs occurred during the

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TABLE 6 rFIXFc dosing on day of surgery and postoperative days 1–14 for orthopedic and nonorthopedic major surgeries

	Loading dose[b]	Day of surgery, including loading dose	Postoperative day							
			Day 1	Day 2	Day 3	Day 4	Day 5	Day 6	Day 7	Days 8–14
Orthopedic ($n = 24$)										
Number of procedures dosed with rFIXFc[a]	$n = 24$	$n = 24$	$n = 23$	$n = 21$	$n = 20$	$n = 17$	$n = 16$	$n = 14$	$n = 18$	$n = 23$
Dose per injection (IU/kg)										
Median	101	96	58	68	68	50	61	48	50	49[c]
IQR	82–133	70–114	47–89	50–83	48–82	39–79	43–86	35–63	39–66	27–62
Range	49–152	55–150	13–101	33–101	21–93	21–101	21–102	21–101	21–91	12–95
Total dose (IU/kg)										
Median	101	145	67	68	68	50	61	48	50	49[d]
IQR	82–133	126–192	50–89	50–83	48–82	39–79	43–86	35–63	39–66	27–62
Range	49–152	56–318	13–101	33–101	21–93	21–101	21–102	21–101	21–91	12–95
Nonorthopedic ($n = 11$)										
Number of procedures dosed with rFIXFc[a]	$n = 11$	$n = 11$	$n = 8$	$n = 9$	$n = 8$	$n = 7$	$n = 4$	$n = 4$	$n = 5$	$n = 6$
Dose per injection (IU/kg)										
Median	83	80	64	60	58	57	58	50	52	49[c]
IQR	61–103	61–90	57–83	53–71	54–60	42–61	50–60	38–59	42–54	38–52
Range	51–183	51–105	40–96	25–91	27–61	27–76	42–61	33–61	28–61	28–103
Total dose (IU/kg)										
Median	85	99	83	60	59	60	72	76	54	57[d]
IQR	59–139	61–180	59–124	53–85	58–107	51–85	58–133	62–103	52–85	42–102
Range	51–183	51–421	40–288	25–212	27–182	27–182	57–182	57–121	28–121	28–121

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

[a]Dose shown only for surgical events where dosing of rFIXFc was given in conjunction with the surgical intervention for a specific day/period.

[b]Loading dose was defined as the first dose administered on the day of surgery. If there was no dose administered on the day of surgery, the loading dose was defined as the dose administered 1 day before surgery.

[c]Based on mean dose per injection per day in the period of days 8–14 (on day[s] of injection) per surgery with ≥1 injection during this period.

[d]Based on mean total daily dose per day in the period of days 8–14 (on day[s] of injection) per surgery with ≥1 injection during this period.

surgical period for major surgeries (bacterial sepsis [two events], tachycardia, anal sphincter atony, and epididymitis). No postoperative wound infections were reported after major surgeries. No AEs were deemed by investigators as related to treatment with rFIXFc and none resulted in any changes to study treatment.

4 | DISCUSSION

This analysis aimed to comprehensively assess the efficacy and safety of rFVIIIFc and rFIXFc during the surgical period in people with hemophilia using data from large, international phase 3 studies. To the best of our knowledge, this is the largest report of surgical procedures with EHL products to date.[35–40]

Findings were consistent with previous analyses and interim data cuts of pivotal and extension studies in rFVIIIFc and rFIXFc,[24,26,27] demonstrating that both EHL factor products were efficacious for the management of perioperative hemostasis across a wide spectrum of major and minor surgeries. Safety data also show that rFVIIIFc and rFIXFc were well tolerated for perioperative use; no major safety concerns related to study treatment were identified and no subjects developed inhibitors. Compared with previous analyses,[26,27] this analysis reports data from an additional 22 major and 38 minor surgeries for hemophilia A and 21 major and 47 minor surgeries for hemophilia B. Outcomes pertaining to hospitalization and summary-level data for the thromboprophylaxis subgroup have not been reported previously. Furthermore, this is the first time that extensive data for unilateral knee arthroplasty procedures have been reported. Dosing and injection frequency analyses in the postoperative period are also more extensive.

In this analysis, all patients were treated with bolus injections of rFVIIIFc and rFIXFc, which maintained protective hemostasis with a low injection frequency throughout the surgical period. The majority of major procedures required ≤2 injections on the day of surgery (including loading dose) and ≤1 injection per day through days 1–14. Hemostatic response was rated favorably by investigators or surgeons in all major surgeries assessed, with most responses rated as excellent, defined as blood loss similar to that expected for subjects without hemophilia. The efficacy of continuous infusion with SHL products has previously been demonstrated for the management of

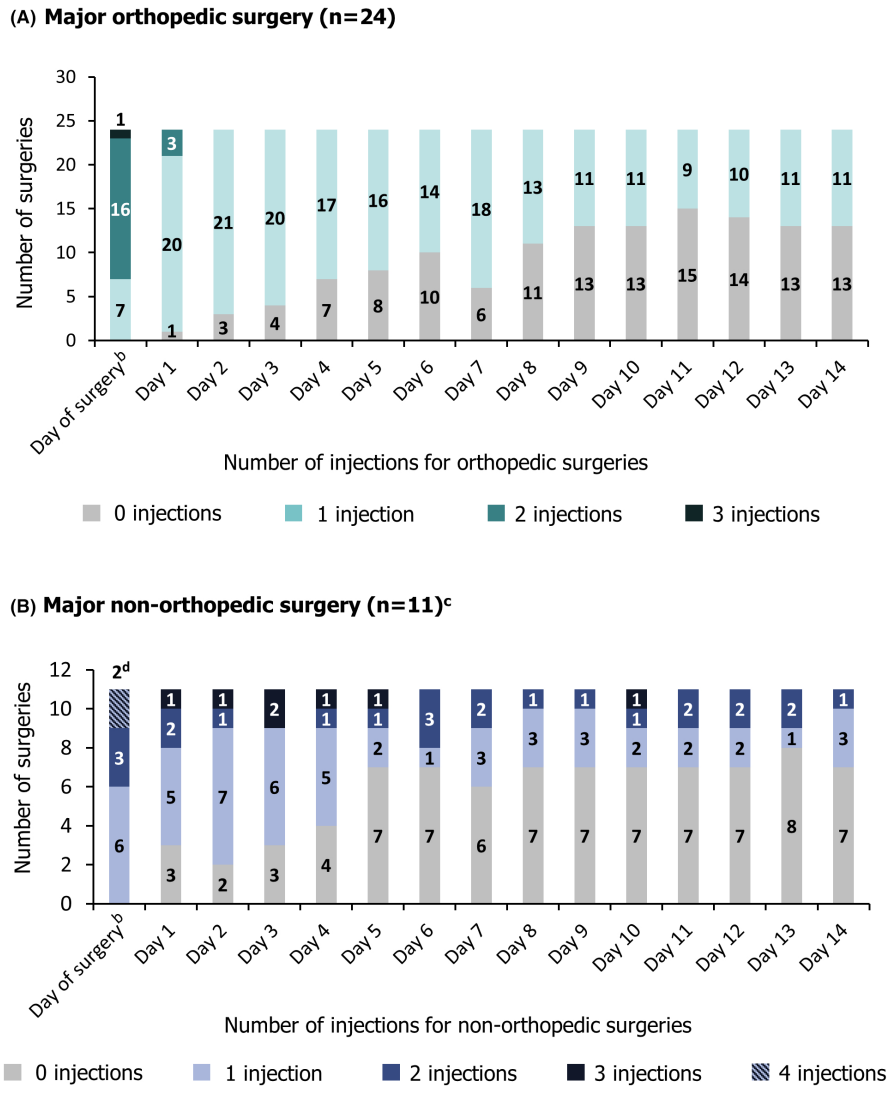

FIGURE 2 Number of injections of rFIXFc on day of surgery and postoperative days 1–14 in major orthopedic and non-orthopedic surgeries[a]. [a]Dose shown only for surgical events where dosing of rFIXFc was given in conjunction with the surgical intervention (and for a specific day/period). [b]Includes loading dose. Loading dose was defined as the first dose administered on the day of surgery. If there was no dose administered on the day of surgery, the loading dose was defined as the dose administered 1 day before surgery. [c]Includes one subject from Kids B-LONG (tonsillectomy). [d]One rectal fistula closure and one liver resection. Abbreviation: rFIXFc, recombinant factor IX Fc fusion protein

major orthopedic procedures.[41] However, the findings of this analysis suggest that continuous infusion is not necessary for the perioperative management of hemostasis with EHL rFVIIIFc and rFIXFc.

The majority of major surgeries were orthopedic. Of these, the most common procedures were unilateral knee replacement or revision. This is expected, given the knee joint is associated with the greatest disability and patient burden in hemophilia.[42] To our knowledge, this study is the most extensive report of surgical data for total knee arthroplasties, compared with other hemophilia studies in patients treated with factor replacement.[35,37,39,40,43–49] The requirement for blood transfusion was comparable to or lower than that previously reported for patients without hemophilia undergoing total arthroplasty.[34] Median duration of hospitalization for unilateral knee arthroplasties was generally within the expected range for people with hemophilia.[42,50,51] However, comparisons between studies are limited by factors such as allogenic blood transfusion, hospital policies, and rehabilitation practices.[42,52–54]

Studies comparing the efficacy and safety of EHL and SHL products are mostly limited to case reports (within patient comparisons) or comparative studies with historical controls. Differences in local practices, variability in study design, as well as types and severity of surgery, make it difficult to compare factor consumption with other studies. Therefore, comparisons should be interpreted with caution. However, in general, the average (mean/median) bolus dose required to maintain hemostasis throughout the surgical period with EHL rFVIIIFc and rFIXFc was similar to that previously reported for SHL products.[43,45,47,49,55,56] In addition, hemostatic response of rFVIIIFc and rFIXFc was consistent with SHL products.[44–49,56,57] Comparable hemostatic efficacy during the perioperative period has also been demonstrated for other EHL FVIII and FIX replacement therapies.[35–40]

Real-world surveillance data from more than 7 years post-marketing experience[10,11] confirms the risk–benefit profile of rFVIIIFc and rFIXFc established during clinical studies and further underlines the potential for their perioperative use.[7,58–64] An intraindividual comparison of FIX products for orthopedic surgery showed a reduction in number of injections and total factor consumption with rFIXFc versus plasma-derived FIX.[7] Similarly, an analysis of 21 subjects with hemophilia A who underwent major surgery with rFVIIIFc at a single center (provided through the WFH humanitarian aid program) demonstrated a lower median total factor consumption with rFVIIIFc during the surgical period than previously reported for SHL products.[46,49,60] However, differences in factor consumption because of potential variability in local standards of care and surgical experience with EHL products should be considered.

Factor replacement therapies are the cornerstone of bleed prevention during surgery in hemophilia; they may be required to achieve protective hemostatic levels even in the presence of non-factor replacement products, which cannot completely prevent perioperative bleeding alone.[5] Recommended pre- and postoperative plasma factor levels for major and minor surgeries are provided by the WFH and are generally well adopted in published studies.[4,5,8] Factor activity levels are generally accepted as a surrogate marker for clinical efficacy. However, for FIX products, there are differences between products regarding the relationship between measured plasma FIX activity and clinical hemostatic efficacy, probably because of differences in their extravascular distribution.[65,66]

Currently, optimal dosing of factor replacement products during surgery relies on the ability to accurately monitor plasma factor activity levels, ensuring patients remain protected against excessive blood loss.[5,67] Both rFVIIIFc and rFIXFc can be accurately monitored by either the one-stage clotting assay or chromogenic assay using commercial assay reagents readily available in laboratories.[68–70] This is important for securing both efficacy and safety, and serves to facilitate their implementation into real-world practice.[5,70] However, assay reagents that use kaolin as an activator may result in an underestimation of FIX levels for rFIXFc.[11]

Although individualized dosing regimens approximated real-world practice, treatment differences (from variation in practice between treating physicians, hospitals, or countries) may be considered a potential limitation of this analysis.

In summary, this analysis reports extensive data on the use of rFVIIIFc and rFIXFc in the perioperative setting, including a large subgroup of total knee arthroplasty procedures, and demonstrates the efficacy and safety of these products in a broad age range of patients undergoing a variety of major and minor procedures typical for a population with severe hemophilia.

AUTHOR CONTRIBUTIONS

Substantial contributions to study conception and design and/or to acquisition, analysis and interpretation of the data: P. Chowdary, M. Holmström, J.N. Mahlangu, M.C. Ozelo, I. Pabinger, K.J. Pasi, M.V. Ragni, A. Shapiro, C. Barnowski, S. Lethagen; drafting the article or revising it critically for important intellectual content: P. Chowdary, M. Holmström, J.N. Mahlangu, M.C. Ozelo, I. Pabinger, K.J. Pasi, M.V. Ragni, A. Shapiro, C. Barnowski, S. Lethagen; final approval of the version of the article to be published: P. Chowdary, M. Holmström, J.N. Mahlangu, M.C. Ozelo, I. Pabinger, K.J. Pasi, M.V. Ragni, A. Shapiro, C. Barnowski, S. Lethagen.

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RELATIONSHIP DISCLOSURE

P. Chowdary: served on advisory boards for Bayer, Boehringer Ingelheim, CSL Behring, Chugai, Freeline, Novo Nordisk, Pfizer, Roche, Sanofi, Spark, Sobi, and Takeda; and has received research funding from Bayer, CSL Behring, Freeline, Novo Nordisk, Pfizer, Sobi, and Takeda; M. Holmström: participated in clinical trials in collaboration with NovoNordisk, Roche, Sobi, and Takeda. J.N. Mahlangu: received consultancy from Alnylam, Amgen, Catalyst, Biosciences, Chugai, CSL Behring, Novo Nordisk, LFB, Roche, Shire, and Spark; and research

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DATA AVAILABILITY STATEMENT

Sobi is committed to responsible and ethical sharing of data on participant level and summary data for medicines and indications approved by the European Medicines Association Agency and/or Food and Drug Agency, while protecting individual participant integrity and compliance with applicable legislation. Data access will be granted in response to qualified research requests. All requests are evaluated by a cross-functional panel of experts within Sobi and a decision on sharing will be based on the scientific merit and feasibility of the research proposal, maintenance of personal integrity, and commitment to publication of the results. To request access to study data, a data sharing request form (available on www.sobi.com) should be sent to medical.info@sobi.com. Further information on Sobi's data sharing policy and process for requesting access can be found at: https://www.sobi.com/en/policies.

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REFERENCES

1. Rodríguez-Merchán EC. The role of orthopedic surgery in hemophilia: current rationale, indications and results. *EFORT Open Rev*. 2019;4(5):165-173.
2. Wong JM, Mann HA, Goddard NJ. Perioperative clotting factor replacement and infection in total knee arthroplasty. *Haemophilia*. 2012;18(4):607-612.
3. Tong KM, Wang JD, Chang ST, Cheng YY, Wang SS. Outcome of perioperative hemostatic management in patients with hemophilia without inhibitors undergoing 161 invasive or surgical procedures. *J Chin Med Assoc*. 2018;81(10):926-929.
4. Srivastava A, Santagostino E, Dougall A, et al. WFH guidelines for the management of hemophilia, 3rd edition. *Haemophilia*. 2020;26(Suppl 6):1-158.
5. Hermans C, Apte S, Santagostino E. Invasive procedures in patients with hemophilia: review of low-dose protocols and experience with extended half-life FVIII and FIX concentrates and non-replacement therapies. *Haemophilia*. 2020;27(Suppl 3):46-52.
6. Atilla B, Güney-Deniz H. Musculoskeletal treatment in hemophilia. *EFORT Open Rev*. 2019;4(6):230-239.
7. Valeri F, Agnelli Giacchello J, Dainese C, et al. Extended half-life rFIX in major surgery — how to improve clinical practice: an intraindividual comparison. *Clin Case Rep*. 2020;8(3):531-534.
8. Hermans C, Altisent C, Batorova A, et al. Replacement therapy for invasive procedures in patients with hemophilia: literature review, European ssurvey and recommendations. *Haemophilia*. 2009;15(3):639-658.
9. Coppola A, Windyga J, Tufano A, Yeung C, Di Minno MND. Treatment for preventing bleeding in people with hemophilia or other congenital bleeding disorders undergoing surgery. *Cochrane Database Syst Rev*. 2015;(2):CD009961. https://doi.org/10.1002/14651858.CD009961.pub2.
10. FDA. Eloctate® [Antihemophilic factor (recombinant), Fc fusion protein] Prescribing Information (last updated December 2020). Accessed September 15, 2021. http://products.sanofi.us/Eloctate/Eloctate.pdf
11. FDA. Alprolix® [Coagulation Factor IX (Recombinant), Fc Fusion Protein] Prescribing Information (last updated October 2020). Accessed September 15, 2021. http://products.sanofi.us/Alprolix/alprolix.pdf
12. EMA. Elocta® (Efmoroctocog alfa) Summary of Product Characteristics (last updated February 2021). Accessed September 15, 2021. https://www.ema.europa.eu/en/documents/product-information/elocta-epar-product-information_en.pdf
13. EMA. Alprolix® (Eftrenonacog alfa) Summary of Product Characteristics (last updated March 2021). Accessed September 15, 2021. https://www.ema.europa.eu/en/documents/product-information/alprolix-epar-product-information_en.pdf
14. Health Canada. Eloctate® [Antihemophilic Factor (Recombinant BDD), Fc Fusion Protein] Product Mongraph (last updated September 2020). Accessed September 15, 2021. https://pdf.hres.ca/dpd_pm/00058299.PDF
15. Health Canada. Alprolix® [Coagulation Factor IX (Recombinant), Fc Fusion Protein] Product Mongraph (last updated September 2020). Accessed September 15, 2021. http://products.sanofi.us/Alprolix/alprolix.pdf
16. TGA, Australia. Alprolix® (Eftrenonacog alfa) Product Information (last updated May 2020). Accessed September 15, 2021. https://www.ebs.tga.gov.au/ebs/picmi/picmirepository.nsf/pdf?OpenAgent&id=CP-2018-PI-01156-1&d=20210915172310101
17. TGA, Australia. Eloctate® (Efmoroctocog alfa) Product Information (last updated September 2020). Accessed September 15, 2021. https://www.ebs.tga.gov.au/ebs/picmi/picmirepository.nsf/pdf?OpenAgent&id=CP-2018-PI-01241-1
18. PMDA, Japan. Alprolix® (Intravenous 250, 500, 1000, 2000, 3000, 4000) Product Information (last updated May 2019). Accessed September 15, 2021. https://www.pmda.go.jp/PmdaSearch/iyakuDetail/ResultDataSetPDF/780069_6343441D1028_3_01
19. PMDA, Japan. Eloctate® (Intravenous 250, 500, 750, 1000, 1500, 2000, 3000, 4000) Product Information (last updated May 2019). Accessed September 15, 2021. https://www.pmda.go.jp/PmdaSearch/iyakuDetail/ResultDataSetPDF/780069_6343442D1022_3_02

20. Mahlangu J, Powell JS, Ragni MV, et al. Phase 3 study of recombinant factor VIII Fc fusion protein in severe hemophilia A. *Blood*. 2014;123(3):317-325.
21. Young G, Mahlangu J, Kulkarni R, et al. Recombinant factor VIII Fc fusion protein for the prevention and treatment of bleeding in children with severe hemophilia A. *J Thromb Hemost*. 2015;13(6):967-977.
22. Nolan B, Mahlangu J, Pabinger I, et al. Recombinant factor VIII Fc fusion protein for the treatment of severe hemophilia A: final results from the ASPIRE extension study. *Haemophilia*. 2020;26(3):494-502.
23. Powell JS, Pasi KJ, Ragni MV, et al. Phase 3 study of recombinant factor IX fc fusion protein in hemophilia B. *N Engl J Med*. 2013;369(24):2313-2323.
24. Fischer K, Kulkarni R, Nolan B, et al. Recombinant factor IX fc fusion protein in children with hemophilia B (kids B-LONG): results from a multicentre, non-randomised phase 3 study. *Lancet Haematol*. 2017;4(2):e75-e82.
25. Pasi KJ, Fischer K, Ragni M, et al. Long-term safety and sustained efficacy for up to 5 years of treatment with recombinant factor IX Fc fusion protein in subjects with hemophilia B: results from the B-YOND extension study. *Haemophilia*. 2020;26(6):e262-e271.
26. Mahlangu JN, Ragni M, Gupta N, et al. Long-acting recombinant factor VIII Fc fusion protein (rFVIIIFc) for perioperative hemostatic management in severe hemophilia A. *Thromb Hemost*. 2016;116(1):1-8.
27. Powell JS, Apte S, Chambost H, et al. Long-acting recombinant factor IX Fc fusion protein (rFIXFc) for perioperative management of subjects with hemophilia B in the phase 3 B-LONG study. *Br J Haematol*. 2015;168:124-134.
28. Nolan B, Mahlangu J, Perry D, et al. Long-term safety and efficacy of recombinant factor VIII Fc fusion protein (rFVIIIFc) in subjects with hemophilia A. *Haemophilia*. 2016;22(1):72-80.
29. Pasi KJ, Fischer K, Ragni M, et al. Long-term safety and efficacy of extended-interval prophylaxis with recombinant factor IX Fc fusion protein (rFIXFc) in subjects with hemophilia B. *Thromb Hemost*. 2017;117(3):508-518.
30. International Conference on Harmonisation. International conference on harmonisation of technical requirements for registration of pharmaceuticals for human use. ICH harmonised tripartite guideline: Guideline for good clinical practice E6(R1). 1996. Accessed September 15, 2021. https://digicollections.net/medicinedocs/documents/s22154en/s22154en.pdf
31. World Medical Association. WMA declaration of Helsinki – Ethical Principles for Medical Research Involving Human Subjects. 1964. Accessed September 15, 2021. https://www.med.or.jp/dl-med/wma/helsinki2013e.pdf#:~:text=The%20World%20Medical%20Association%20%28WMA%29%20has%20developed%20the,a%20whole%20and%20each%20of%20its%20constituent%20paragraphs
32. Blanchette VS, Key NS, Ljung LR, Manco-Johnson MJ, van den Berg HM, Srivastava A. Definitions in hemophilia: communication from the SSC of the ISTH. *J Thromb Hemost*. 2014;12:1935-1939.
33. Kalairajah Y, Simpson D, Cossey AJ, Verrall GM, Spriggins AJ. Blood loss after total knee replacement. *J Bone Jt Surg Br*. 2005;87:1480-1482.
34. Carling MS, Jeppsson A, Eriksson BI, Brisby H. Transfusions and blood loss in total hip and knee arthroplasty: a prospective observational study. *J Orthop Surg Res*. 2015;10(1):48.
35. Gruppo R, López-Fernández M-F, Wynn TT, Engl W, Sharkhawy M, Tangada S. Perioperative hemostasis with full-length, PEGylated, recombinant factor VIII with extended half-life (rurioctocog alfa pegol) in patients with hemophilia A: final results of a multicentre, single-arm phase III trial. *Hemophilia*. 2019;25(5):773-781.
36. Tosetto A, Neff A, Lentz SR, et al. Turoctocog alfa pegol provides effective management for major and minor surgical procedures in patients across all age groups with severe hemophilia A: full data set from the pathfinder 3 and 5 phase III trials. *Haemophilia*. 2020;26(3):450-458.
37. Santagostino E, Lalezari S, Reding MT, et al. Safety and efficacy of BAY 94-9027, an extended-half-life factor VIII, during surgery in patients with severe hemophilia A: results of the PROTECT VIII clinical trial. *Thromb Res*. 2019;183:13-19.
38. Mahlangu J, Kuliczkowski K, Karim FA, et al. Efficacy and safety of rVIII-SingleChain: results of a phase 1/3 multicenter clinical trial in severe hemophilia A. *Blood*. 2016;128(5):630-637.
39. Négrier C, Abdul Karim F, Lepatan LM, et al. Efficacy and safety of long-acting recombinant fusion protein linking factor IX with albumin in hemophilia B patients undergoing surgery. *Haemophilia*. 2016;22(4):e259-e266.
40. Escobar MA, Tehranchi R, Karim FA, et al. Low-factor consumption for major surgery in hemophilia B with long-acting recombinant glycoPEGylated factor IX. *Haemophilia*. 2017;23(1):67-76.
41. Goddard NJ, Mann HA, Lee CA. Total knee replacement in patients with end-stage haemophilic arthropathy: 25-year results. *J Bone Jt Surg Br*. 2010;92(8):1085-1089.
42. Wiedel J, Stabler S, Geraghty S, Funk S. Joint replacement surgery in hemophilia. *World Feder Haemophilia*. 2010;50:1-17.
43. Collins PW, Quon DVK, Makris M, et al. Pharmacokinetics, safety and efficacy of a recombinant factor IX product, trenonacog alfa in previously treated hemophilia B patients. *Haemophilia*. 2018;24(1):104-112.
44. Martinowitz U, Luboshitz J, Bashari D, et al. Stability, efficacy, and safety of continuously infused sucrose-formulated recombinant factor VIII (rFVIII-FS) during surgery in patients with severe hemophilia. *Haemophilia*. 2009;15:676-685.
45. Musso R, Santagostino E, Faradji A, et al. Safety and efficacy of sucrose-formulated full-length recombinant factor VIII: experience in the standard clinical setting. *Thromb Hemost*. 2008;99(1):52-58.
46. Santagostino E, Lentz SR, Misgav M, et al. Safety and efficacy of turoctocog alfa (NovoEight®) during surgery in patients with hemophilia A: results from the multinational guardian™ clinical trials. *Haemophilia*. 2015;21(1):34-40.
47. Négrier C, Shapiro A, Berntorp E, et al. Surgical evaluation of a recombinant factor VIII prepared using a plasma/albumin-free method: efficacy and safety of Advate in previously treated patients. *Thromb Hemost*. 2008;100(2):217-223.
48. Ragni MV, Pasi KJ, White GC, et al. Use of recombinant factor IX in subjects with hemophilia B undergoing surgery. *Haemophilia*. 2002;8(2):91-97.
49. Windyga J, Rusen L, Gruppo R, et al. BDDrFVIII (Moroctocog alfa [AF-CC]) for surgical hemostasis in patients with hemophilia A: results of a pivotal study. *Haemophilia*. 2010;16(5):731-739.
50. Prasad N, Padmanabhan V, Mullaji A. Blood loss in total knee arthroplasty: an analysis of risk factors. *Int Orthop*. 2007;31(1):39-44.
51. National Hemophilia Federation. Physical therapy practice guidelines for persons with bleeding disorders: total Knee Replacement. 2015. Accessed September 15, 2021. https://www.hemophilia.org/sites/default/files/document/files/238pttotalkneereplacement.pdf
52. Ross D, Erkocak O, Rasouli MR, Parvizi J. Operative time directly correlates with blood loss and need for blood transfusion in total joint arthroplasty. *Arch Bone Jt Surg*. 2019;7(3):229-234.
53. Wu Y, Xue H, Zhang W, Wu Y, Yang Y, Ji H. Application of enhanced recovery after surgery in total knee arthroplasty in patients with hemophilia A: a pilot study. *Nurs Open*. 2020;8(1):80-86.
54. Chiasakul T, Buckner TW, Li M, Vega R, Gimotty PA, Cuker A. In-hospital complications and readmission in patients with hemophilia undergoing hip or knee arthroplasty. *JBJS Open Access*. 2020;5(2):e0085.

55. Lambert T, Recht M, Valentino LA, et al. Reformulated BeneFix: efficacy and safety in previously treated patients with moderately severe to severe hemophilia B. *Haemophilia*. 2007;13(3):233-243.
56. Shapiro AD, Di Paola J, Cohen A, et al. The safety and efficacy of recombinant human blood coagulation factor IX in previously untreated patients with severe or moderately severe hemophilia B. *Blood*. 2005;105(2):518-525.
57. Windyga J, Lissitchkov T, Stasyshyn O, et al. Efficacy and safety of a recombinant factor IX (Bax326) in previously treated patients with severe or moderately severe hemophilia B undergoing surgical or other invasive procedures: a prospective, open-label, uncontrolled, multicentre, phase III study. *Haemophilia*. 2014;20(5):651-658.
58. Patil VSC, Jijina F, Shetty S, Mohanty S. Wasekar N recombinant factor VIII FC fusion protein in surgeries in hemophilia A. *HemaSphere*. 2019;3:116.
59. Apte S, Phatale R, Joshi A, Subramanian K. Bilateral, simultaneous total knee replacement (TKR) surgery for hemophilia A with Eloctate (extended half life product) – a feasible and cost effective approach. *Blood*. 2018;132(Suppl. 1):4684.
60. Abraham A, Fouzia NA, Korula A, et al. W-P-008 (684) surgical prophylaxis using long acting factor concentrate in a cohort of hemophilia patients. *Haemophilia*. 2018;24:3-196.
61. O'Donovan M, Fosbury E, Clarke A, et al. Perioperative management with recombinant factor IX Fc fusion (rFIXFc): Irish and UK Experience. *Res Pract Thromb Hemost*. 2020;4(Suppl 1).
62. Lehtinen A, Baghaei F, Astermark J, Petrini P, Holme P. Surgical outcomes in patients with severe hemophilia receiving rFVIIIFc and rFIXFc: realworld experience in the Nordic countries. *Haemophilia*. 2020;26:27-181.
63. Bocchinfuso S, Singleton E, Benson J, et al. Perioperative management of patients with severe hemophilia A with recombinant factor VIII Fc fusion protein (rFVIIIFc). *Haemophilia*. 2021;27(S2):18-181.
64. Castet SCH, Fouassier M, Repesse Y, et al. Real-world effectiveness and usage of recombinant factor IX fc fusion protein (rFIXFc) for management of major/minor surgeries in patients with hemophilia B (HB) in France: results from the ongoing B-SURE study. *Haemophilia*. 2021;27(S2):18-181.
65. Iorio A, Edginton AN, Blanchette V, et al. Performing and interpreting individual pharmacokinetic profiles in patients with hemophilia A or B: rationale and general considerations. *Res Pract Thromb Hemost*. 2018;2(3):535-548.
66. Mann DM, Stafford KA, Poon M-C, Matino D, Stafford DW. The function of extravascular coagulation factor IX in hemostasis. *Haemophilia*. 2021;27(3):332-339.
67. Iorio A, Blanchette V, Blatny J, Collins P, Fischer K, Neufeld E. Estimating and interpreting the pharmacokinetic profiles of individual patients with hemophilia A or B using a population pharmacokinetic approach: communication from the SSC of the ISTH. *J Thromb Hemost*. 2017;15(12):2461-2465.
68. Lambert T, Benson G, Dolan G, et al. Practical aspects of extended half-life products for the treatment of hemophilia. *Ther Adv Hematol*. 2018;9(9):295-308.
69. Sommer JM, Sadeghi-Khomami A, Barnowski C, Wikén M, Willemze AJ. Real-world assay variability between laboratories in monitoring of recombinant factor IX Fc fusion protein activity in plasma samples. *Int J Lab Hematol*. 2020;42(3):350-358.
70. Kitchen S, Tiefenbacher S, Gosselin R. Factor activity assays for monitoring extended half-life FVIII and factor IX replacement therapies. *Semin Thromb Hemost*. 2017;43(3):331-337.

SUPPORTING INFORMATION

Additional supporting information can be found online in the Supporting Information section at the end of this article.

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