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ORIGINAL ARTICLE *Clinical haemophilia*

Efficacy and safety of long-acting recombinant fusion protein linking factor IX with albumin in haemophilia B patients undergoing surgery

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Introduction: Recombinant factor IX fusion protein (rIX-FP) has been developed to improve the pharmacokinetic (PK) profile of factor IX (FIX), allowing maintenance of desired FIX activity between injections at extended intervals, ultimately optimizing haemophilia B treatment. **Aim:** To determine the efficacy and safety of rIX-FP in the perioperative setting. **Methods:** Subjects were adult and paediatric patients with severe to moderately severe haemophilia B (FIX ≤ 2%) participating in three Phase III clinical trials and undergoing a surgical procedure. PK profiles were established prior to surgery for each patient. Haemostatic efficacy was assessed by the investigator for up to 72 h after surgery. Safety measurements during the study included adverse events and inhibitors to FIX. FIX activity was monitored during and after surgery to determine if repeat dosing was required. **Results:** Twenty-one, both major and minor, surgeries were performed in 19 patients. Haemostatic efficacy was rated as excellent ($n = 17$) or good ($n = 4$) in all surgeries. A single preoperative dose maintained intraoperative haemostasis in 20 of 21 surgeries. Nine major orthopaedic surgeries were conducted in eight patients with a mean of 7 (range: 6–12) rIX-FP injections during surgery and the 14-day postoperative period. Median rIX-FP consumption for orthopaedic surgeries was 87 IU kg^{-1} preoperatively and 375 IU kg^{-1} overall. No subject developed inhibitors to FIX or antibodies to rIX-FP. **Conclusion:** Recombinant factor IX fusion protein was well tolerated and effectively maintained haemostasis during and after surgery. Stable FIX activity was achieved with a prolonged dosing interval and reduced consumption compared to conventional or currently available long-acting recombinant FIX.

Keywords: albumin fusion proteins, factor IX, haemophilia B, orthopaedic surgery, recombinant fusion proteins

Introduction

During surgery, patients with haemophilia B are at an increased bleeding risk due to the underlying factor IX (FIX) deficiency; therefore, FIX replacement therapy is required to minimize bleeding and to maintain haemostasis. World Federation of Hemophilia (WFH) guidelines recommend FIX activity levels of 60–80 IU dL^{-1} in haemophilia B patients prior to major surgery. The guidelines recommend continued FIX replacement during the 14-day postoperative period; FIX activity should be maintained at 40–60 IU dL^{-1} in the first 3 days postsurgery, 30–50 IU dL^{-1} on day 4 through 6 and between 20 and 40 IU dL^{-1} from 7 to 14 days postsurgery [1].

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Currently available conventional recombinant and plasma-derived FIX replacement products have short half-lives (18–24 h), resulting in the need for frequent injections to maintain the FIX activity during the perioperative period [2,3]. Modified rFIX products with prolonged half-lives have therefore been developed to address this need [4,5]. rFIXFc (Alprolix®, Biogen Idec, Cambridge, MA, USA) is rFIX fused to the Fc domain of immunoglobulin G1. Its pharmacokinetic (PK) profile shows an average 2.4-fold increase in half-life over conventional therapies, and a clearance of 2.65 mL kg^{-1} h^{-1} in a subset of patients receiving 100 IU kg^{-1} [4]. Despite an improved PK profile compared to conventional therapies, rFIXFc still requires multiple doses on the day of surgery to maintain haemostasis [6]. rIX-FP, a recombinant fusion protein linking FIX to albumin, was developed with a prolonged half-life and reduced clearance of 102 h and 0.77 mL kg^{-1} h^{-1}, respectively, allowing for less frequent injections to maintain the FIX activity level during surgery [5]. Compared with marketed FIX replacement products, the prolonged half-life of rIX-FP, along with markedly reduced clearance and increased area under the curve, results in improved pharmacodynamic activity [5,7–10].

In the Phase III PROLONG-9FP clinical study, prophylactic injections of rIX-FP given once every 7, 10 or 14 days maintained FIX activity trough levels above 5 IU dL^{-1} and resulted in a median annualized spontaneous bleeding rate of 0.0. Ninety-nine percent of bleeding events were successfully treated with one or two injections of rIX-FP [5]. rIX-FP has been demonstrated to be safe and effective in 107 previously treated patients (PTPs) with no FIX inhibitor development or antibodies against rIX-FP [5,8,10]. Here, we report the safety and efficacy of rIX-FP in the perioperative setting, with a specific focus on nine major orthopaedic surgeries in eight subjects.

Methods

Study drug

Recombinant factor IX fusion protein is a recombinant fusion protein linking FIX with albumin manufactured in Chinese hamster ovary (CHO) cells. It is generated by the genetic fusion of human recombinant albumin to the C-terminus of rFIX via a cleavable linker, derived from the endogenous activation peptide in FIX [7].

Study design and participants

Subjects requiring non-emergency surgery participating in two Phase III studies, one in males aged 12–65 years old (NCT01496274 [3001]) and one in males <12 years old (NCT01662531 [3002]), or a Phase III extension study (NCT02053792 [3003]) were eligible to enrol in a surgical sub-study. New subjects could also be directly enrolled into the surgical sub-study (study 3003). Eligible patients were adult and paediatric PTPs with severe to moderately severe haemophilia B (FIX ≤ 2%) with no history of FIX inhibitors. Both major, defined as surgery that involved anaesthesia or respiratory assistance, and minor surgeries were assessed.

The study was approved by the institutional review board/ethics committee at each participating centre, registered and performed in accordance with good clinical practice, the Declaration of Helsinki and local regulatory requirements. Written informed consent was obtained from all patients or their legal guardians.

Concomitant medication

The use of blood products (packed red blood cells, whole blood, fresh frozen plasma or platelets) was allowed, if needed, during the perioperative period. Prior to surgery, the investigator determined if blood products were likely to be required, these were documented as planned transfusions. Any unplanned transfusions used during surgery were also documented by the investigator. In addition, heparin was allowed during the study to maintain patency of intravenous (IV) lines and was limited to 200 U day^{-1}. The following additional concomitant medications were allowed during the study: antifibrinolytic agents, antibiotics and antiviral agents, tranexamic acid or epsilon aminocaproic acid; local haemostatic measures (e.g. oxidized cellulose, fibrin glue); standard thrombosis prophylaxis. Marketed FIX replacement therapies were to be administered only in the event a rescue medication was needed and haemostasis was not achieved and maintained with rIX-FP. Postoperative pain was managed initially through IV morphine or other narcotic analgesics, followed by oral opioids. As pain decreased, paracetamol or acetaminophen was allowed.

Dosing and FIX activity assessment

All subjects were required to have a PK assessment with rIX-FP performed within the 12 months prior to surgery, during which subjects were given a single dose of 50 or 100 IU kg^{-1}, in accordance with the study protocol. The results of the PK assessment were used to determine individualized preoperative dosing in the study. A single bolus dose of rIX-FP was given preoperatively to a target FIX activity of 80–100 IU dL^{-1} for major surgeries. Intraoperative dosing of rIX-FP was dependent on FIX activity (measured locally prior to repeat dosing), and surgery type. Postoperative dosing, from wound closure up to

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14 days, was dependent on the type of surgery and local standard of care. Dosing was determined based on local laboratory results and investigators dosed to maintain FIX activity levels according to WFH postoperative guidelines. Throughout the perioperative period, samples were also sent to the central laboratory for FIX activity measurements using a validated one-stage clotting method as described previously [8]. Time points assessed during the perioperative period by the central laboratory included prior to dosing, and at specified minimum time points postoperatively (e.g. immediately after surgery, every 24 h up to 72 h).

After the surgical follow-up, all subjects began prophylaxis treatment with rIX-FP; subjects new to treatment were on weekly prophylaxis while those already enrolled in the clinical programme resumed their previous regimen. Subjects undergoing physical therapy were able to dose rIX-FP prior to therapy if needed, per protocol, once they were dosing on a weekly prophylaxis regimen. If subjects required dosing prior to physical therapy, it was to be a maximum of once a week during the first 3 months postsurgery.

Efficacy and safety assessments

Efficacy was rated immediately after surgery and every 24 h up to 72 h by the investigator using a 4-point scale for haemostatic efficacy (excellent, good, moderate, poor/no response) for the assessment of haemostasis adapted from WFH (Table 1). The estimated predicted blood loss during surgery, both average and maximum, as well as predicted transfusion requirements were based on a subject without haemophilia B undergoing a similar surgical procedure. These predicted values were then compared to the estimated actual blood loss and transfusion requirements. Additional efficacy assessments included re-bleeding events within 72 h of surgery, consumption of rIX-FP and number of rIX-FP injections during the 14-day perioperative period and median dose per injection.

Table 1. Investigator assessment of haemostatic efficacy.

Rating	Criteria
Excellent	Haemostasis clinically not significantly different from normal or estimated actual blood loss during surgery is not more than 20% higher than predicted blood loss for intended surgery
Good	Normal or mildly abnormal haemostasis in terms of quantity and/or quality or estimated blood loss is >20%, but <30% higher than the estimated predicted blood loss for the intended surgery
Moderate	Moderately abnormal haemostasis in terms of quantity and/or quality with estimated blood loss greater than what is defined as good
Poor/No response	Severely abnormal haemostasis in terms of quantity and/or quality and/or additional haemostatic intervention required with another Factor IX product for complete resolution

Safety was measured by the investigator who assessed adverse events (AEs) and serious adverse events (SAEs). In addition, development of inhibitors to FIX (Bethesda Units), measured by the Bethesda method using the Nijmegen modification [11], and antibodies against rIX-FP and CHO cell proteins, measured by enzyme-linked immunosorbent assays, were assessed prior to surgery and at the end of the surgical study period in each patient. Throughout the perioperative period, vital signs and haematology parameters were monitored.

Results

Subjects

Of the subjects who have participated in the PROLONG-9FP clinical programme to date, 21 surgeries have been documented in 19 subjects including nine major orthopaedic surgeries in eight subjects (Table 2). Six of the eight subjects who underwent orthopaedic surgery were enrolled into the surgical sub-study directly without previous exposure to rIX-FP treatment (study 3003). All eight subjects were over 18 years of age, reported haemophilic arthropathy in one or more joints prior to surgery and continued with rIX-FP prophylaxis after surgery as per protocol. One subject received low-molecular-weight heparin (LMWH) subcutaneously (60 mg daily) for approximately 2 weeks after joint replacement surgery. The same subject received 500 mg tranexamic acid every 8 h postoperatively for approximately 8 days. No other subjects were administered antifibrinolytic agents during the postoperative period.

In addition to the orthopaedic surgeries discussed, 12 additional major or minor surgeries have been performed with rIX-FP in 12 paediatric and adult patients and are detailed in Table 3. Of note, four of the surgeries were tooth extractions, two of which were in children aged 8 and 9 years of age. For both surgeries, multiple teeth were extracted and tranexamic acid was administered as concomitant medication. Both children returned to their routine prophylaxis regimen with rIX-FP postsurgery. The 8-year-old subject who had four teeth extracted was administered one additional treatment between his weekly routine prophylaxis doses.

Haemostatic efficacy

Haemostatic efficacy was rated as excellent ($n = 7$) or good ($n = 2$) by the investigator/surgeon for all orthopaedic surgeries (Table 2). For the remainder of the surgical procedures, both major and minor, haemostatic efficacy was rated as excellent ($n = 10$) or good ($n = 2$) by the investigator/surgeon in all surgeries (Table 3).

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Table 2. Haemostatic response to rIX-FP administered for major orthopaedic surgeries.

Subject	Age at screening, years	Surgical procedure	Rating of haemostatic response*	rIX-FP dose, IU kg^{-1}		Total rIX-FP consumption†, IU kg^{-1}	Number of rIX-FP doses†	Estimated blood loss (mL)		Unplanned transfusions
				Pre-op	Intra-op			Predicted‡	Actual	
1	43	Total knee replacement (L)	Excellent	127.7	None	380	7	1500–2000	500	None
		Total knee replacement (R)	Excellent	46.0	None	340	7	1500–2000	450	None
2	48	Total knee replacement	Good	83.7	41.4	458	9	300–400	500	None
3	50	Ankle arthroplasty	Excellent	87.2	None	339.5	6	250–300	250	None
4	51	Total knee replacement	Good	105.5	None	375	6	200–200	200	None
5	49	Total knee replacement	Excellent	80.6	None	295	7	30–100	50	None
6	37	Total knee replacement	Excellent	112.6	None	506	8	150–200	50	RBC
7	21	Total knee replacement	Excellent	100.0	None	430	7	150–200	55	RBC
8	57	Total knee replacement	Excellent	56.9	None	356	12	790–2000	600	None

L, left; R, right; RBC, red blood cells; rIX-FP, recombinant factor IX fusion protein.
*Where multiple assessments were done over the postoperative period, the lowest rating was used, regardless of time point.
†During the 14-day perioperative period, including preoperative dose and doses up to and including day 14.
‡Based on the preoperative predicted surgical blood loss for a subject without haemophilia undergoing the same type and extent of surgical procedure.

Table 3. Haemostatic response to rIX-FP administered for non-orthopaedic major and minor surgeries.

Subject	Study	Age at screening, years	Surgical procedure	Rating of haemostatic efficacy*
1	3001	43	Double mastectomy	Excellent
9	3003	56	Endoscopic mucosal resection	Excellent
10	3003	5	Excision of pigmental nevus	Excellent
11	3001	39	Haemorrhoidal ligation and rectopexy	Excellent
12	3003	19	Rhinoplasty; submucosal resection and inferior turbinectomy	Excellent
13	3001	42	Tooth extraction	Excellent
14	3001	14	Tooth extraction	Good
15	3002	9	Teeth extraction (2)†	Excellent
16	3002	8	Teeth extraction (4)†	Good
17	3001	31	Dental root canal	Excellent
18	3003	13	Circumcision	Excellent
19	3003	24	Circumcision	Excellent

rIX-FP, recombinant factor IX fusion protein.
*Where multiple assessments were done over the postoperative period, the lowest rating was used regardless of time point.
†Number of teeth extracted in brackets.

The estimated actual intraoperative blood loss was close to that predicted by the investigator/surgeon prior to the surgery for all major orthopaedic surgeries (Table 2). For the majority of surgeries ($n = 7$), no unplanned blood transfusions were required. Two subjects from the same surgical centre each undergoing total knee replacement, received three units of packed red blood cells after surgery that were not recorded as planned transfusions. Both subjects were new to treatment with rIX-FP, and both entered the study with low haemoglobin and haematocrit at the screening visit.

One subject received a single dose of 41 IU kg^{-1} rIX-FP intraoperatively. Results from the central laboratory, which were not available at the time of dosing, showed that FIX activity was 88 IU dL^{-1} prior to the intraoperative dose. The investigator estimated that the subject's actual blood loss was 500 mL, which is more than the investigator/surgeon had predicted (300–400 mL) for similar surgery in a patient without haemophilia B.

Two subjects undergoing a knee replacement reported a total of three postsurgical bleeding events at the joint replaced (2) or thigh muscle (1) during the 14-day postoperative period, all of which occurred more than 72 h postoperatively. Two of the three bleeding events were successfully treated with a single dose of rIX-FP. One bleeding event required two doses of rIX-FP to achieve haemostasis: the first dose of rIX-FP was given 48 h after the reported start of the bleeding event and a second dose of rIX-FP was given 4 days later.

Dosing and consumption of rIX-FP

Eight of the nine documented orthopaedic surgeries were successfully managed with a single preoperative dose of rIX-FP. In seven of the nine surgeries, the first postoperative dose of rIX-FP was administered more than 24 h after surgery. The median number of rIX-FP injections administered over the 14-day postoperative period was 7 (range: 6–12, mean 7.4) (Table 4). Overall consumption for orthopaedic surgeries over the 14-day surgical period was low (median: 375.3 IU kg^{-1}, mean: 386.7 IU kg^{-1}). The majority of patients were dosed approximately every 2 days

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Table 4. Perioperative consumption of rIX-FP during major orthopaedic surgeries.

	Consumption of rIX-FP during surgery (n = 9)*	
	Mean	Median (range)
Total number of injections	7.4	7 (6–12)
Preoperative, IU kg^{-1}	88.9	87.2 (46–128)
Intraoperative, IU kg^{-1}	4.6	0 (0–41.4)
Postoperative, IU kg^{-1}		
Day 1–3	67.5	54.0 (45.6–127.7)
Day 4–7	74.6	71.5 (26.9–122.0)
Day 8–14	150.8	161.2 (26.9–112.6)
Total consumption (14 days), IU kg^{-1}†	386.7	375.3 (295.5–506.7)

rIX-FP, recombinant factor IX fusion protein.
*Nine surgeries in eight patients.
†Includes preoperative and intraoperative dosing of rIX-FP (where applicable).

during the postoperative period to maintain the desired FIX activity level, though other approaches were taken to postoperative dosing. Dosing during the postoperative period varied with country standard of care and physician level comfort with rIX-FP dosing. While the majority of patients were dosed approximately every 2 days, one subject who underwent a knee replacement was dosed smaller amounts of rIX-FP more frequently (15–24 IU per kg daily) during the first 7 days postoperatively. This subject was also dosing LMWH daily. Consumption was not increased with more frequent dosing and the FIX activity levels remained within the WFH guidelines for major surgery. During the postoperative physical therapy, only two patients were dosed more than weekly, both from the same surgical centre.

For the 12 non-orthopaedic surgeries, the median number of injections administered over the 14-day postoperative period was 3 (range 2–4) with all subjects returning to prophylaxis with rIX-FP prior to the end of the 14 days. Haemostasis was successfully maintained for all surgeries with one dose of rIX-FP administered preoperatively.

Safety

Overall, eight AEs were reported in five subjects who underwent orthopaedic surgery: tachycardia, pyrexia (two events in a single subject), anaemia, urinary tract infection, postoperative wound infection and blisters (two events in a single subject). The subject for which the AE of anaemia was reported underwent two total knee replacements within 5 days. All AEs were mild or moderate, not considered to be related to rIX-FP and resolved. No SAEs were reported for any of the subjects undergoing surgical procedures, major or minor.

No FIX inhibitors or antibodies against rIX-FP were detected in any of the subjects that participated in the surgical sub-study. All subjects continued with rIX-FP prophylaxis treatment, and continued to be monitored for FIX inhibitors and antibodies against rIX-FP and CHO cell proteins. There were no reports of thrombotic events, hypersensitivity reactions or anaphylaxis in any of the study subjects.

Pharmacokinetics and FIX activity

The individual FIX measurements, as obtained by the one-stage assay via the central laboratory, for three representative surgeries as well as the time of rIX-FP dosing during the postsurgical period are shown in Fig. 1. Laboratory samples were taken for FIX measurements at random time points throughout the perioperative period and prior to rIX-FP dosing. All eight subjects maintained a FIX level within the WFH guidelines, with the majority of investigators choosing to dose subjects (n = 7) in approximately 48 h intervals. One subject was dosed more frequently with lower amounts of rIX-FP per injection as described.

Discussion

Recombinant factor IX fusion protein was used effectively for perioperative management in 21 surgeries in 19 subjects including nine major orthopaedic surgeries in eight subjects with a favourable safety profile in all. Intraoperative and postoperative blood loss was consistent with that expected for similar surgeries in patients without haemophilia for the majority of orthopaedic surgeries (n = 8). For one patient, the investigator reported intraoperative blood loss higher than predicted. This subject was the only subject dosed intraoperatively. It should be noted, however, that this subject's blood loss is within the ranges predicted for similar surgeries by other investigators in the rIX-FP clinical programme and the subject's intraoperative FIX level measured 88 IU dL^{-1} prior to dosing; however, these results were not available at the time of dosing. Similar efficacy and safety results were seen in 12 non-orthopaedic major and minor surgical procedures.

Factor IX replacement products currently marketed for use in perioperative management achieve the recommended preoperative FIX activity with a single preoperative dose. While this is also true for rIX-FP, it has the added benefit of a single preoperative dose being sufficient to complete the majority of surgical procedures without the need for intraoperative doses, as FIX levels are maintained intraoperatively and haemostasis is achieved. While conventional FIX replacement products such as pdFIX and rFIX are required to be dosed at least daily to maintain haemostasis during the postoperative period, rIX-FP maintains FIX levels within the WFH guidelines for major surgeries such that for most orthopaedic surgeries, dosing intervals of 48 h or longer during the

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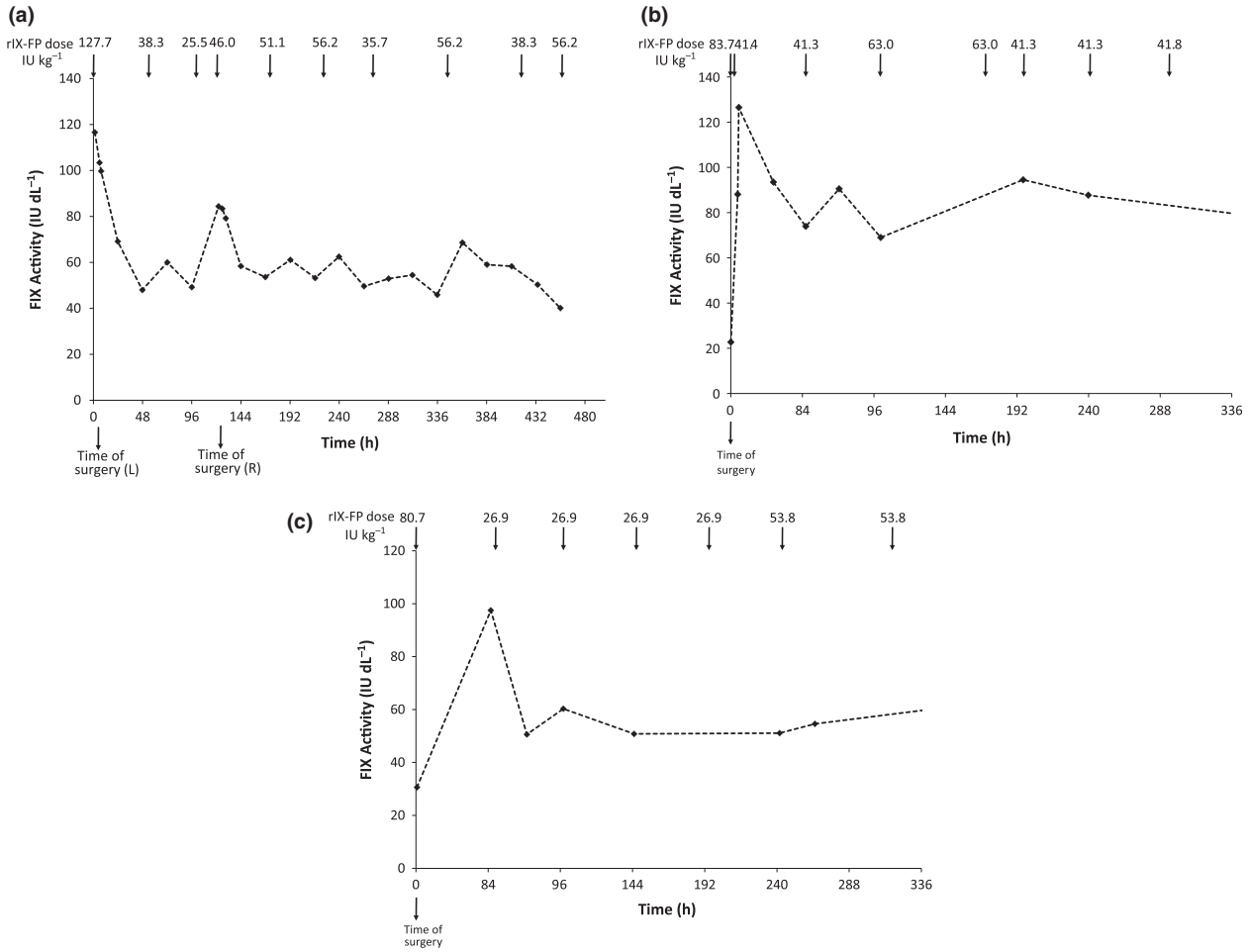

Fig. 1. Representative factor IX activity levels during the postoperative period for orthopaedic surgeries. Surgical dosing regimens and FIX activity over time are shown for Subject 1 (a) who underwent two total knee replacements [left (L) then right (R)] in 5 days, Subject 2 (b) who underwent a total knee replacement and Subject 5 (c) who also underwent a total knee replacement. FIX activity samples were taken at random time points throughout the surgical substudy and prior to dosing rIX-FP. rIX-FP, recombinant factor IX fusion protein.

postsurgical period are successful in maintaining the desired FIX activity. Although direct comparison is not possible, rIX-FP proved easy to administer for investigators and surgeons in the perioperative setting with the prolonged dosing schedule with FIX levels monitored at a local laboratory prior to dosing.

For another long-acting FIX replacement product, rFIXFc, the median preoperative dose for major surgery was 90 IU kg^{-1} dose which is comparable to the median preoperative dose (87.2 IU kg^{-1}) of rIX-FP used in major orthopaedic surgery. However, most subjects required one to three doses of rFIXFc on the day of surgery to maintain the desired FIX activity level, followed by two to three doses in the first 3 days postsurgery [6].

For rIX-FP, the mean number of doses over 14 days to maintain the desired FIX activity levels and haemostasis for orthopaedic surgeries was seven (including the presurgery dose), with a median total rIX-FP consumption of 375 IU kg^{-1} (range: 295–507 IU kg^{-1}). Although no direct comparison can be established, for the five major orthopaedic surgeries (all total knee replacements) treated with rFIXFc, the mean number of injections given over the 14 days was 10 and total consumption ranged from 500.4 to 1081.6 IU kg^{-1} [6].

No studies have clearly shown that surgery affects the PK properties of FIX in patients, while some data suggest that this may be true in factor VIII as well as factor VIIa-treated patients [12,13]. Therefore, the population PK models that were established using the general clinical population may be considered appropriate for determining dosing for surgical procedures. Consumption for the 14-day postoperative period for orthopaedic surgeries was lower for rIX-FP compared with conventional pdFIX and rFIX as well as more recently developed FIX therapies. In addition, conventional therapies such as rFIX often are administered via continuous infusion during surgery and the postoperative period in order to maintain the appropriate

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FIX levels [2]. In contrast, rFIXFc, which is a new long-acting rFIX with an extended half-life, does not need to be administered as a continuous infusion.

There were no SAEs reported for any subject who underwent major or minor surgery. For the orthopaedic surgeries, eight AEs were reported by five subjects (62.5%). All of the AEs were mild or moderate in severity, not related to study drug and resolved without any action taken with respect to rIX-FP treatment. No inhibitors to FIX or antibodies against rIX-FP were detected. All subjects are currently enrolled in the extension study on prophylaxis with rIX-FP, given weekly or at longer intervals.

In summary, rIX-FP had a favourable safety profile and was well tolerated when used in major or minor surgeries for perioperative management in patients with severe to moderately severe haemophilia B. rIX-FP, when used for perioperative management, allows for less consumption and prolonged dosing intervals than conventional FIX replacement therapies, while maintaining postoperative FIX levels as suggested by WFH. The flexibility in dosing also allows for shorter intervals with lower doses of rIX-FP to be used, at the investigator's discretion. The variability in dosing schedules postoperatively did not change the efficacy of rIX-FP, nor increase consumption during the postoperative period. rIX-FP provides a reliable convenient treatment option for patients with haemophilia B undergoing a surgical procedure allowing for less frequent dosing, and appropriate haemostatic control during and after surgery.

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Appendix

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