Long-acting recombinant factor IX Fc fusion protein (rFIXFc) for perioperative management of subjects with haemophilia B in the phase 3 B-LONG study


1University of California Davis, Sacramento, CA, USA,
2Department of Haematology, Sahyadri Hospital, Mahara, India,
3CTH, Service d’Hématologie Pédiatrique, Hopital d’Enfants La Timone, APHM, Aix Marseille Université, Marseille, France,
4Hematologie, Cliniques Universitaires Saint-Luc, Bruxelles, Belgium,
5Hemophilia Program of BC – Adult Division, St Paul’s Hospital, Vancouver, Canada,
6Puget Sound Blood Center, Seattle, WA, USA,
7Haemophilia Comprehensive Care Centre, University of the Witwatersrand, NHLS and Johannesburg Hospital, Johannesburg, South Africa;
8INCT do Sangue Hemocentro UNICAMP, Campinas, Brazil,
9Bleeding and Vascular Disorders, University Hospital Gasthuisberg, Leuven, Belgium,
10Barts and the London Comprehensive Care Centre, London,
11Addenbrooke’s Hospital, Cambridge, UK,
12University of Pittsburgh and the Hemophilia Center of Western Pennsylvania, Pittsburgh, PA, USA,
13Department of Haematology, Ruijin Hospital Shanghai Jiaotong University School of Medicine, Shanghai, China, and
14Biogen Idec, Cambridge, MA, USA

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Correspondence: Dr Brian Robinson, Biogen Idec, 225 Binney St, Cambridge, MA 02142, USA.
E-mail: brian.robinson@biogenidec.com

Summary

In the phase 3 B-LONG (Recombinant Factor IX Fc Fusion Protein [rFIXFc] in Subjects With Haemophilia B) study, rFIXFc demonstrated a prolonged half-life compared with recombinant factor IX (rFIX), and safety and efficacy for prophylaxis and treatment of bleeding in subjects with moderately-severe to severe haemophilia B. In this B-LONG sub-analysis, rFIXFc was evaluated for efficacy in subjects requiring major surgery. Dosing was investigator-determined. Assessments included dosing, consumption, bleeding, transfusions and haemostatic response. A population pharmacokinetics model of rFIXFc was used to predict FIX activity. Twelve subjects underwent 14 major surgeries (including 11 orthopaedic surgeries); most subjects (11/12) received rFIXFc prophylaxis before surgery (range, ~2 weeks–12 months). Investigators/surgeons rated haemostatic responses as excellent (n = 13) or good (n = 1). In most surgeries (85-7%), haemostasis from the pre-surgical dose until the end of surgery was maintained with a single rFIXFc infusion. Blood loss was consistent with similar surgeries in subjects without haemophilia. The strong correlation (R² = 0.9586, P < 0.001) between observed and population pharmacokinetic model-predicted FIX activity suggests surgery did not impact rFIXFc pharmacokinetics. No unique safety concerns or inhibitors were observed.

In conclusion, rFIXFc was safe and efficacious, with prolonged dosing intervals and low consumption, when used perioperatively in haemophilia B. Surgery did not appear to alter rFIXFc pharmacokinetics.

Keywords: clinical trial, phase 3, factor IX, haemophilia B, pharmacokinetics, surgery.

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Preoperative factor IX (FIX) levels of 60–80 iu/dl (60%–80%) are recommended for people with haemophilia B undergoing major surgery, with treatment continued in the postoperative period to maintain target FIX activity (Srivastava et al, 2013). Currently, frequent intravenous infusions or continuous infusion of FIX replacement are needed for perioperative management due to the relatively short half-lives of conventional products (White et al, 1997; National Haemophilia Foundation, 2007). Moreover, the lack of formal controlled studies of replacement therapy for perioperative management leads to variation in the standard of care. Possible complications associated with major surgery include infection, thromboses, development of inhibitors and potentially life-threatening bleeding. The surgical setting may also affect consumption of clotting factors, as observed in haemophilia A (Longo et al, 1989); however, this has not been reported for haemophilia B. For surgical prophylaxis, products with a prolonged half-life should help maintain FIX levels in circulation while reducing infusion frequency. It is important to fully evaluate and understand the surgical experience with new factor replacement products.

Results from the non-surgical arms of the multicentre phase 3 B-LONG [Recombinant Factor IX Fc Fusion Protein (rFIXFc) in Subjects With Haemophilia B] study demonstrated a prolonged half-life and lower consumption of recombinant FIX Fc fusion protein (rFIXFc), relative to rFIX, and the safety and efficacy of rFIXFc for treatment of bleeding and routine prophylaxis with dosing intervals of 1–2 weeks, which is longer than intervals seen with historical trials of rFIX (Powell et al, 2013; Powell et al, 2014). Here, we describe the surgical experience with rFIXFc in subjects with haemophilia B enrolled in B-LONG. Additionally, the effect of surgery on rFIXFc pharmacokinetics was assessed for the first time in haemophilia B, and the ability of a population pharmacokinetics model of rFIXFc (Diao et al, 2014) to predict FIX activity was evaluated.

Materials and methods

Study design

B-LONG was an open-label, non-randomized study to investigate the safety, efficacy, and pharmacokinetics of rFIXFc in male subjects with moderately-severe to severe haemophilia B (≤2 iu/dl FIX), aged ≥12 years with ≥100 previous exposure days (EDs) to any FIX product (Powell et al, 2013). Subjects with a history of inhibitors or anaphylaxis associated with FIX were excluded. Enrolled patients received rFIXFc weekly prophylaxis (Arm 1), individualized interval prophylaxis (Arm 2), episodic treatment (on-demand; Arm 3) or perioperative management (Arm 4). Allowed concomitant medications included thromboprophylaxis (e.g, heparin) and additional haemostatic treatment (e.g, tranexamic acid); however, blood products (except as required during surgery or acute clinical care) and any other FIX products were not permitted. All subjects, or their guardians, gave informed consent. The protocol was approved by institutional review boards/ethics committees at each location. The study was conducted in accordance with International Conference on Harmonization Guidelines for Good Clinical Practice, and ethical principles outlined in the Declaration of Helsinki and registered with ClinicalTrials.gov (ClinicalTrials.gov identifier: NCT01027364).

Surgical approach

Subjects requiring major surgery were enrolled in the perioperative management arm (Arm 4) from another treatment arm (Arms 1–3) or as new subjects. Subjects having surgery were required to have a negative inhibitor test after ≥4 EDs with rFIXFc. Major surgery was defined as any elective or emergent surgical procedure that usually involves general anaesthesia and/or respiratory assistance, in which a major body cavity is penetrated and exposed, or for which a substantial impairment of physical or physiological functions is produced, as determined by the investigator and based on guidance provided in the protocol. Minor surgery was defined as any elective or emergent surgical procedure that does not involve general anaesthesia and/or respiratory assistance. No new enrolments were allowed for minor surgery, and subjects were to remain in their assigned treatment arms.

A clinical dosing committee, composed of members of the sponsor study management team, monitored subject-level FIX activity and bleeding episodes. Before major surgery, the investigator and surgeon determined target plasma FIX levels for the surgical/rehabilitation period; perioperative rFIXFc regimens were recommended by the dosing committee chair and clinical pharmacologist to achieve these targets based on the subject’s clinical status, type of surgery and individual rFIXFc pharmacokinetic profile. Ultimately, the decision for initial dosing was made by the investigator. Additionally, dosing adjustments were made locally by the investigator as needed, based on clinical response and local laboratory measurements of FIX levels. A plasma archive was prepared for each blood sample drawn, so that FIX levels could also be measured later by the one-stage clotting assay at the central laboratory. Continuous infusion dosing was not allowed.

Samples to measure FIX activity were collected prior to the dose of rFIXFc given for the surgery and within 30 min following the end of the infusion. Blood was drawn again ~9 h following the end of infusion (or as determined by local standard of care). Additional perioperative sampling times (at a minimum of daily during hospitalization) were determined by the investigator and surgeon. Doses >100 iu/kg were allowed during the perioperative period to maintain target FIX activity and prevent bleeding. However, predicted maximum plasma FIX activity was not to exceed 150 iu/dl (normal range, 50–150 iu/dl FIX activity).
For all major surgeries, assessments included rFIXFc dosing, rFIXFc consumption, total blood loss as estimated by the investigator, transfusions and bleeding episodes (Table I). The analysis period for these endpoints was the day of surgery (Day 0; including the preoperative loading dose) and postoperative Days 1–14. Study endpoints also included investigator/surgeon assessment of surgical haemostasis based on a 4-point scale adapted from the World Federation of Haemophilia (WFH) guidelines and commonly used in haemophilia studies (Table II) (Ragni et al, 2002; Windyga et al, 2010, 2014; Srivastava et al, 2013). Although no specific objectives were specified for minor surgeries, information on the type of surgery and haemostatic response were collected.

Safety was evaluated by clinical assessments, routine laboratory tests and rFIXFc-specific safety assessments, including inhibitor development by the Nijmegen-modified Bethesda assay. An inhibitor test result of ≥0.6 Bethesda Units (BU)/ml, identified and confirmed by re-testing of a second sample obtained within 2–4 weeks, was required for a positive test result.

**Pharmacokinetic modelling**

A 3-compartmental rFIXFc population pharmacokinetics model was previously developed and validated based upon non-surgical FIX activity collected from the phase 3 study and phase 1/2a study of rFIXFc (Diao et al, 2014).

Using this model, pharmacokinetic parameters for individual surgery subjects were derived and used to predict FIX activities for each individual subject undergoing major surgery in B-LONG. Predicted and observed FIX activities were then compared.

**Statistical analysis**

Endpoints were summarized for all major surgeries using descriptive statistics. The investigator/surgeon assessment of the subject’s haemostatic response to rFIXFc was summarized as the number of surgeries at each rating.

**Results**

Of 123 participants in the B-LONG study, 12 underwent major surgery; 2 subjects underwent 2 surgeries each, giving a total of 14 major surgeries. As expected in individuals with haemophilia (Ragni et al, 2002; Hermans et al, 2009; Windyga et al, 2014), the most common major surgery type was orthopaedic (11/14; Table III). Baseline characteristics of subjects having major surgeries were reflective of the general haemophilia B population (Srivastava et al, 2013). Median age was 34.5 years (range, 17–61 years) and weight was 65.0 kg (range, 47.9–100.5 kg). No subjects had a family history of inhibitors. Positive tests for human immunodeficiency virus (HIV) and hepatitis C were documented in 2 (16.7%) and 7 (58.3%) subjects, respectively. Four subjects had 1 target joint and 4 subjects had >1 target joint; medical histories of the major surgery population overall were diverse and included arthropathy, indicating this was a severely affected population. There were 15 minor surgeries performed (mostly dental procedures).

Of the 12 subjects included in Arm 4, 2 enrolled in Arm 4 and moved into Arm 1 after surgery, 4 participated in Arm 4 only and 6 joined from Arm 1 (n = 5) or Arm 3 (n = 1). Individual rFIXFc pharmacokinetic parameters for these 12 subjects are shown in Table SI.

**Dosing**

Most subjects (11/12) received an initial rFIXFc prophylaxis regimen before surgery (range, ~2 weeks–12 months); the
Table III. Haemostatic response to surgical dosing (Major surgeries).

<table>
<thead>
<tr>
<th>Subject arm</th>
<th>Study arm</th>
<th>Type of surgery</th>
<th>Age at screening (years)</th>
<th>Investigator/surgeon rating of haemostatic response*</th>
<th>Preoperative rFIXFc loading dose (PK-based, iu/kg)</th>
<th>Total number of rFIXFc infusions Days 0–14</th>
<th>Total rFIXFc consumption Days 0–14 (iu/kg)</th>
<th>Estimated blood loss (ml)</th>
<th>Blood transfusions</th>
<th>Thromboprophylaxis</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>4</td>
<td>Total L knee replacement</td>
<td>32</td>
<td>Good</td>
<td>105.5</td>
<td>10</td>
<td>607.9</td>
<td>100</td>
<td>0</td>
<td>None</td>
</tr>
<tr>
<td>2</td>
<td>4</td>
<td>Total L knee replacement</td>
<td>38</td>
<td>Excellent</td>
<td>124.2</td>
<td>7</td>
<td>500.4</td>
<td>73</td>
<td>0</td>
<td>None</td>
</tr>
<tr>
<td>3</td>
<td>4</td>
<td>Total R knee replacement</td>
<td>61</td>
<td>Excellent</td>
<td>99.7</td>
<td>9</td>
<td>590.2</td>
<td>56</td>
<td>140</td>
<td>None</td>
</tr>
<tr>
<td>4</td>
<td>4</td>
<td>Total L knee replacement</td>
<td>34</td>
<td>Excellent</td>
<td>100.8</td>
<td>14</td>
<td>1081.6</td>
<td>&lt;100</td>
<td>75</td>
<td>None</td>
</tr>
<tr>
<td>5†</td>
<td>4</td>
<td>Total R knee replacement</td>
<td>30</td>
<td>Excellent</td>
<td>142.3</td>
<td>9</td>
<td>649.3</td>
<td>250</td>
<td>0</td>
<td>None</td>
</tr>
<tr>
<td>6</td>
<td>1</td>
<td>R knee arthroscopy</td>
<td>35</td>
<td>Excellent</td>
<td>79.3</td>
<td>11</td>
<td>597.7</td>
<td>10</td>
<td>Not provided</td>
<td>None</td>
</tr>
<tr>
<td>7</td>
<td>3</td>
<td>R ankle arthroscopic fusion</td>
<td>50</td>
<td>Excellent</td>
<td>122.8</td>
<td>10</td>
<td>754</td>
<td>&lt;5</td>
<td>0</td>
<td>None</td>
</tr>
<tr>
<td>8</td>
<td>4</td>
<td>External fixation of R knee</td>
<td>17</td>
<td>Excellent</td>
<td>120.2</td>
<td>9</td>
<td>787.2</td>
<td>100</td>
<td>0</td>
<td>None</td>
</tr>
<tr>
<td>9</td>
<td>1</td>
<td>R arm tendon transfer</td>
<td>54</td>
<td>Excellent</td>
<td>82.1</td>
<td>10</td>
<td>373.3</td>
<td>130</td>
<td>40</td>
<td>None</td>
</tr>
<tr>
<td>10†</td>
<td>4</td>
<td>Closure of intestinal fistula</td>
<td>43</td>
<td>Excellent</td>
<td>59.3</td>
<td>27</td>
<td>1348.7</td>
<td>300</td>
<td>500§</td>
<td>FFP, RBCs (3 total units)</td>
</tr>
<tr>
<td>11</td>
<td>1</td>
<td>Incision and drainage of dental abscess, with multiple extractions</td>
<td>24</td>
<td>Excellent</td>
<td>58.3</td>
<td>5</td>
<td>291.5</td>
<td>0</td>
<td>0</td>
<td>None</td>
</tr>
<tr>
<td>12†</td>
<td>1</td>
<td>Debridement, fracture dislocation, partial amputation**</td>
<td>22</td>
<td>Excellent</td>
<td>49.4††</td>
<td>12‡‡</td>
<td>684.8‡‡§</td>
<td>0</td>
<td>0</td>
<td>None</td>
</tr>
</tbody>
</table>

rFIXFc: recombinant factor IX Fc fusion protein; PK, pharmacokinetic; L, left; R, right; RBC, red blood cell; FFP, fresh frozen plasma.
*Assessment of haemostasis was to be recorded by surgeon/investigator approximately 24 h postoperatively, but some assessments were recorded days to a week after surgery.
†Subject continued on a postsurgical rFIXFc regimen into the extension study.
‡Subject received study-prohibited medication in the postoperative period and was discontinued from study.
§Early postoperative blood loss primarily owing to diffuse oozing from surgical wound; wound was closed by secondary intention.
¶Subject received 2 units intraoperatively, 5 units within 2 weeks of surgery.
**Emergency surgical procedure for trauma (all others were elective).
††Subject self-administered 106.2 iu/kg rFIXFc on day of surgery, before surgical loading dose; an unauthorized 98.7 iu/kg dose of rFIXFc was administered 2.8 h post-surgery.
‡‡Includes both surgeries and Days 0–17. Day 17 is 14 days after the second surgery.
§§Subject received tranexamic acid 1 g every day for 1 day and enoxaparin sodium 0.4 ml every day for 15 days.
¶¶Subject received dalteparin sodium 5000 units every day for 10 days, heparin 300 units as needed for 10 days and enoxaparin 40 mg twice a day for 44 days.
remaining subject received episodic treatment in Arm 3 before surgery. The most common prophylactic dosing interval was weekly (9/12 subjects) and the most common dose was 50 iu/kg (5/12 subjects). Overall, 12 of 14 (85.7%) major surgeries required only 1 infusion of rFIXFc to maintain haemostasis during the surgical period (the time of the presurgery dose to the end of surgery), and the median dose per infusion was 90.9 iu/kg (maximum concentration, ~90%). Most subjects received a total of 1–3 infusions on the day of surgery (including surgical period doses and any subsequent doses received on the same day of surgery). Additionally, most subjects received a total of 2–3 infusions during postoperative Days 1–3. In 9 of 13 surgeries with available dosing committee recommendations (69.2%), recommended and actual doses were generally concordant. In the other 4 surgeries, actual doses differed from recommend doses (e.g., higher or lower doses, more or less frequent dosing), at the discretion of the investigators. Individual subjects’ actual dosing regimens are shown in Table SII; the mean nominal dose of rFIXFc administered per day across all major surgery subjects is shown in Fig 1. For most subjects, the total daily dose of rFIXFc decreased during postoperative Days 4–14 compared with Days 1–3. No subject was dosed every day during the perioperative period (Days 0–14). Median total consumption on Days 1–14 was 432.3 iu/kg (range, 98.6–1084.7 iu/kg). For minor surgeries, most subjects required just 1 preoperative dose (range, 39.7–103.6 iu/kg).

### Haemostatic response

For 100% of major surgeries, haemostasis was rated excellent (13/14 surgeries) or good (1/14 surgeries) by the investigators/surgeons (Table III). Haemostasis also was rated as excellent for 10 of 12 minor surgeries for which an evaluation was available (Table IV); 1 minor surgery received a rating of good, and 1 received a rating of fair. Assessment of response was not provided for 3 minor surgeries.

<table>
<thead>
<tr>
<th>Subject</th>
<th>Type of surgery</th>
<th>Investigator/surgeon rating of haemostatic response</th>
</tr>
</thead>
<tbody>
<tr>
<td>Arm 1</td>
<td></td>
<td></td>
</tr>
<tr>
<td>1</td>
<td>Third molar extraction</td>
<td>Excellent</td>
</tr>
<tr>
<td>2</td>
<td>Surgical extraction of tooth 14</td>
<td>Good</td>
</tr>
<tr>
<td>3</td>
<td>Left ankle arthroscopic removal of osteophyte</td>
<td>Excellent</td>
</tr>
<tr>
<td>4</td>
<td>Dental extraction</td>
<td>Excellent</td>
</tr>
<tr>
<td>5</td>
<td>PCI with stenting</td>
<td>Excellent</td>
</tr>
<tr>
<td></td>
<td>Coronary angiography</td>
<td>Excellent</td>
</tr>
<tr>
<td>Arm 2</td>
<td></td>
<td></td>
</tr>
<tr>
<td>6</td>
<td>Wart removal</td>
<td>Not provided</td>
</tr>
<tr>
<td>7</td>
<td>Biopsy of alleged paratonsillar abscess</td>
<td>Excellent</td>
</tr>
<tr>
<td>8</td>
<td>Dental crown</td>
<td>Excellent</td>
</tr>
<tr>
<td>9</td>
<td>Dental extraction</td>
<td>Excellent</td>
</tr>
<tr>
<td></td>
<td>Dental extraction</td>
<td>Fair</td>
</tr>
<tr>
<td>Arm 3</td>
<td></td>
<td></td>
</tr>
<tr>
<td>10</td>
<td>Extraction of multiple teeth and alveoplasties</td>
<td>Excellent</td>
</tr>
<tr>
<td>11</td>
<td>Removal of 4 wisdom teeth</td>
<td>Excellent</td>
</tr>
<tr>
<td>12</td>
<td>Root canal treatment</td>
<td>Not provided</td>
</tr>
<tr>
<td>Arm 4</td>
<td></td>
<td></td>
</tr>
<tr>
<td>13</td>
<td>Extraction of teeth</td>
<td>Not provided</td>
</tr>
</tbody>
</table>

PCI, percutaneous coronary intervention.

Intraoperative and postoperative blood loss (Table III) were comparable to observations made in other major surgeries involving subjects without haematologic disorders (Prasad et al, 2007). The 2 subjects with the highest blood loss (Subjects 5 and 10) received transfusion of blood products during the postoperative period (Table III). Surgical haemostasis was rated as excellent for both subjects. Subject 5, who had double knee arthroplasties, received 3 total units of red blood cells on Day 3 post-surgery due to a low

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**Fig 1.** Mean nominal dose of rFIXFc administered per day across all subjects in Arm 4 (n = 12). [Some subjects received >1 dose on a given day, but means were calculated assuming independence (i.e., the denominator was the number of doses rather than the number of subjects)]. The mean nominal dose is represented by a solid black circle, and the standard deviation is represented by a dashed vertical line. rFIXFc, recombinant factor IX Fc fusion protein; SD, standard deviation.
postoperative haemoglobin level, as stated by the attending physician. This subject also had a low haemoglobin laboratory measurement on Day 8 post-surgery (across all subjects requiring major surgery, these were the only 2 haemoglobin laboratory measurements not within normal limits during the perioperative period). Subject 10 experienced 2 traumatic bleeding episodes at the surgical site, reported as related to surgery during the first 3 days and during the second week following intestinal fistula surgery; postoperative blood loss was primarily due to diffuse oozing from the surgical wound, which was closing by secondary intention. The subject was receiving rFIXFc doses every 1–2 days and had FIX activity levels of ~50 iu/dl approximately 1–3 h before the postoperative bleeding episodes. In addition, Subject 10 received 7 total units of fresh frozen plasma and red blood cells (2 units intraoperatively and an additional 5 units within 2 weeks of surgery). The subject was subsequently withdrawn from the study for receiving prohibited medication (prothrombin complex concentrate) during the postoperative period.

**Safety**

Overall, 10 (83.3%) of the 12 subjects who underwent major surgery reported ≥1 adverse event during the surgical/rehabilitation period. Each reported adverse event was experienced by 1 subject, except for anaemia and dizziness (n = 2 for each). Adverse events reported during the surgical and rehabilitation period were generally mild or moderate in severity; all were assessed by the investigators as unrelated to rFIXFc treatment. Three (25-0%) of the 12 subjects who underwent major surgery experienced ≥1 serious adverse event during the surgical/rehabilitation period. All 6 serious adverse events were assessed by the investigator as unrelated to rFIXFc treatment; all resolved, and no action was taken with the study treatment as a result. No subjects developed inhibitors to rFIXFc, and no subjects experienced anaphylactic or vascular thrombotic events during the study.

**Population pharmacokinetics modelling of surgical dosing regimens**

The individual pharmacokinetic parameters derived from the population pharmacokinetics model of rFIXFc (Diao et al., 2014) were utilized to model rFIXFc activity over time profiles (Fig 2A). Predicted FIX activity was then compared with observed FIX activity. There was excellent correlation ($R^2 = 0.9586, P < 0.001$) between observed (measured at the central laboratory) and predicted FIX activity (relative prediction error, −0.33% [95% confidence interval, −2.08% to 1.42%]) using FIX activities from all 14 major surgeries. For the individual subjects whose narratives are shown (i.e., Subjects 1, 2, and 3), representative plots of observed and predicted FIX activity from both central and local laboratory measurements are shown in Fig 2B. C. On an individual level and over the time-course of perioperative management, the majority of measured FIX activities were well predicted by the population pharmacokinetics model; consistency between observed and predicted FIX activity during the perioperative period was also seen for the other 9 subjects (data not shown).

**Surgery narratives**

Narratives for the same 3 representative subjects described in Fig 2 are included below; plots of the surgical rFIXFc dosing regimen and central laboratory FIX activity measurements for these subjects are shown in Fig 3. These 3 subjects underwent 3 major surgeries that, as orthopaedic surgeries, were representative of the types of surgeries observed in this clinical study and the general haemophilia B population (Ragni et al., 2002; Hermans et al., 2009; Windyga et al., 2014). Additionally, surgical outcomes of these subjects, assessed by investigator rating, encompassed the range of ratings observed for all surgeries. Narratives for the remaining 9 subjects who underwent major surgery are included in the Supporting Information.

Subject 1, a 32-year-old male, underwent total left knee replacement. The subject enrolled in Arm 4 60 days prior to surgery. Medical history of note included splenomegaly, right knee severe lateral compartmental arthritis and left knee tri-compartmental arthritis (and osteoarthritis in both knees). Prior to surgery, the subject received an initial rFIXFc prophylaxis regimen of ~55 iu/kg (actual dose) once weekly. The surgery was uneventful and haemostatic response was evaluated as ‘good’. Estimated intraoperative blood loss was 100 ml and postoperative blood loss was 0 ml. The surgical dosing regimen (actual and recommended) for this subject is described in Fig 3A. No serious adverse events were reported during the postoperative period.

Subject 2, a 38-year-old male, underwent total left knee replacement. The subject enrolled in Arm 4 82 days (~3 months) prior to surgery. Medical history of note included hepatitis C, nephritic colic (i.e., pain resulting from kidney stones), arthropathy of both ankles and elbows and atrophy of the left quadriceps. Prior to surgery, the subject received an initial prophylaxis regimen of ~55 iu/kg (actual dose) once weekly. The subject experienced 2 spontaneous bleeding episodes during the period prior to surgery and was treated for these in accordance with the protocol. The surgery was uneventful and haemostatic response was evaluated as ‘excellent’. Estimated intraoperative blood loss was 75 ml and postoperative blood loss was 0 ml. The surgical dosing regimen (actual and recommended) for this subject is described in Fig 3B. No serious adverse events were reported during the postoperative period.

Subject 3, a 61-year-old male, underwent total right knee arthroplasty. The subject enrolled in Arm 4 38 days prior to surgery. Medical history of note included HIV, hepatitis C and B, liver cirrhosis with portal hypertension, osteoporosis, chronic pain, depression, bipolar disorder, Bowen disease,
Fig 2. Surgical pharmacokinetic profiles. (A) Predicted FIX activity using the population pharmacokinetics model. In all 14 major surgeries, there was an excellent correlation ($R^2 = 0.9586; P < 0.001$) between central laboratory observed FIX activity and that predicted by the pharmacokinetics model (relative prediction error, 0.332% (95% confidence interval, –2.08% to 1.42%)). The solid line represents unity, and the dashed line represents the regression line. (B) Central laboratory measurements of FIX activity over time for 3 representative subjects. (C) Local laboratory measurements of FIX activity over time for 3 representative subjects. FIX, factor IX.
Fig 3. Surgical dosing regimen and FIX activity over time for 3 representative subjects: (A) Subject 1, (B) Subject 2 and (C) Subject 3. Target trough levels varied with the type of procedure and local standard of practice. Solid data points and connecting lines indicate FIX activity over time as measured by the central laboratory. Arrows at the top of the plot indicate timing and actual dose in iu/kg; the dosing regimen (iu/kg) recommended by the dosing committee is also noted above the horizontal line at the top of each panel. FIX, factor IX; rFIXFc, recombinant factor IX Fc fusion protein; ND, no dose.
arthropathy, iron and methadone allergy and deep vein thrombosis. Surgical history included left breast lumpectomy, partial right hip replacement with a later revision, left total knee arthroplasty, bilateral femur fracture, femoral pin removal (following the procedure to fix a fracture), and recent intrathecal pump procedure. Prior to surgery, the subject received 4 prophylaxis doses ranging from ~40 to ~80 iu/kg with varied intervals of 1–6 days. The surgery was uneventful and haemostatic response was evaluated as ‘excellent’. Estimated intraoperative blood loss was 56 ml and postoperative blood loss was approximately 140 ml. The surgical dosing regimen (actual and recommended) for this subject is described in Fig 3C. No serious adverse events were reported during the initial postoperative period. During prolonged rehabilitation, the subject underwent minor dental surgery (minor surgery Subject 13 in Table IV) that was complicated by serious adverse events of bacterial sepsis (2 events) and tachycardia with possible sources being an intra­theal pump and vascular access port. The events were severe, resolved with treatment, and were considered unrelated to the study drug by the investigator.

In all 3 subjects, perioperative haemostasis was maintained with prolonged dosing intervals and decreased factor consumption compared with those reported in the literature for other FIX therapies used during similar surgeries (Ragni et al, 2002; Quon & Logan, 2011).

Discussion
In this study, rFIXFc effectively controlled perioperative bleeding in 14 major surgeries, with similar results in minor surgeries. Surgical blood loss was consistent with that expected for similar surgeries involving subjects without haemophilia (Prasad et al, 2007). rFIXFc was well tolerated and no subject developed inhibitors. This is the first report of FIX activity pharmacokinetics modelling during surgery. Observed FIX activity during the perioperative period closely followed predictions from population pharmacokinetics-based modelling. It is understood that local laboratories use a variety of one-stage clotting assay methodologies (e.g., reagents, instruments) and a recent field study showed some variability in FIX activity measurements for both rFIX and rFIXFc (Sommer et al, 2014). Importantly, local and central laboratory results were sufficiently concordant in the present B-LONG sub-study to enable safe and effective perioperative dosing regimens, consistent with prior experience with FIX products, and investigators successfully managed subjects undergoing major surgery using local laboratory monitoring for FIX activity. These results, combined with those demonstrating a positive clinical outcome with rFIXFc prophylaxis (Powell et al, 2013), suggest that rFIXFc may also provide benefit for maintaining sufficiently protective FIX levels during the surgical rehabilitation period, potentially with lower consumption and less frequent dosing than historically reported for other FIX therapies. Assessment of the efficacy of rFIXFc during the surgical rehabilitation period will require further analyses.

It has been hypothesized by clinicians that consumption of clotting factor replacements may be higher as a result of perioperative bleeding, as has been observed for some patients with haemophilia A treated with FVIII products during the perioperative period (Longo et al, 1989). A possible effect of surgery on the pharmacokinetics of rFIXFc was evaluated in this study by assessing the ability of a population pharmacokinetics model that was developed from nonsurgical data to predict FIX activity during the perioperative period. The comparison of predicted with observed FIX activity during the perioperative period showed excellent correlation and low relative prediction error; because these predictions utilized a model that was based upon nonsurgical data, these results indicate that the surgical procedures performed during the phase 3 study had no significant impact on the pharmacokinetics of rFIXFc. Instead, surgery has been reported to affect the consumption of FVIII products (Longo et al, 1989), as well as recombinant factor VIIa (Klitgaard & Nielsen, 2008).

Importantly, the close agreement between actual and predicted FIX activities suggests that a population pharmacokinetics model (Diao et al, 2014) can be used to formulate general dosing guidance to achieve the target plasma FIX activity levels recommended for perioperative management in people with haemophilia B.

Dosing was recommended based on individual subjects’ baseline pharmacokinetic data; however, investigators were not required to follow these recommendations and could adjust dosing if clinically appropriate and based on local standard of care. For some subjects, rFIXFc was administered up to 2 times on the day of surgery; long-acting FIX products are predicted to require less frequent dosing during surgery (Collins et al, 2012), and there are several possible explanations for this observed dosing frequency for rFIXFc. WFH guidelines suggest a preoperative target FIX activity level of 60 to 80 iu/dl for patients with haemophilia B undergoing major surgery (Srivastava et al, 2013); however, some investigators targeted a higher level due to regional or institutional practices, as suggested by measured FIX activity levels >100 iu/dl for some subjects. Additionally, in many cases, dosing on the day of surgery may have been pre-determined by the investigator. Thus, because these surgeries were the first instances in which rFIXFc was administered perioperatively, these investigators may have dosed cautiously (based on their prior experience with conventional FIX products with shorter half-lives) due to considerations related to major surgery in people with severe or moderately-severe haemophilia B. While most subjects had progressively longer dosing intervals postoperatively, only Subject 10, whose incision was left open post-surgery, was dosed more than once per day during the postoperative period.

Overall, the amount of rFIXFc used to maintain haemo­stasis during the perioperative period was less than that
observed in historical studies of conventional FIX products (Rudowski et al., 1987; Ragni et al., 2002; Quon & Logan, 2011). In B-LONG, the mean dose on the day of surgery (Day 0) was 84-16 IU/kg; mean doses on subsequent days (Days 1–14) ranged from 49.12–64.61 IU/kg. No subject was dosed every day during the perioperative period (Days 0–14). In a study of recombinant FIX (Benefix®, Pfizer Inc., New York, NY, USA) in 28 subjects with haemophilia B of varying degrees of severity, undergoing major (n = 23) or minor (n = 13) surgery, the mean preoperative dose was 63.1 IU/kg for bolus dosing; however, it is important to note that this included both major and minor surgeries and not all subjects had severe haemophilia (Ragni et al., 2002). The study also used continuous infusion, with a mean dose of 6.4 IU/kg/h (range, 4.3–8.6) over a mean of 4.9 days (range, 1–11) (Ragni et al., 2002), which would translate into ~154 IU/kg/day and is substantially higher than the doses used in the present study. In a retrospective analysis of plasma-derived coagulation FIX (AlphaNine®, SD, Grifols Biologicals Inc, Los Angeles, CA, USA) in 20 subjects with haemophilia B undergoing major surgery, the average FIX dose on the day of surgery was 254.9 IU/kg (representing a combination of continuous and bolus dosing) (Quon & Logan, 2011), considerably higher than the present study. It is important to note that the present study did not allow continuous infusion dosing. The administration of rFIXFc when dosed by continuous infusion during surgery will require further research.

The primary limitations of this analysis were the small number of subjects and treatment differences due to the local standard of care. Because sampling time points were not uniform across surgical subjects, it is not possible to comment on median peak plasma FIX activities in the preoperative or early postoperative periods. Such evaluations in controlled studies with larger numbers of subjects may illuminate the mechanisms behind investigator ratings of ‘excellent’ haemostatic response with rFIXFc.

In conclusion, these results support the safety and efficacy of rFIXFc, with prolonged dosing intervals, for perioperative haemostasis in people with moderately-severe to severe haemophilia B; data additionally indicate that perioperative consumption with long-acting rFIXFc may be lower than with conventional FIX therapies. Further, they suggest that rFIXFc pharmacokinetics are not altered during surgery and demonstrate the utility of the rFIXFc population pharmacokinetics model for formulating dosing guidance to achieve the target plasma FIX activity levels recommended for effective perioperative management.

Disclosures and competing interests


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Supporting Information

Additional Supporting Information may be found in the online version of this article:
Table S1. Individual rFIXFc Pharmacokinetic Parameters Determined Using Compartmental Analysis (Major Surgeries).

Table SII. Individual Subjects’ rFIXFc Surgical Dosing Regimens.

Data S1. Additional surgery narratives.

References


