Long-acting recombinant factor VIII Fc fusion protein (rFVIIIFc) for perioperative haemostatic management in severe haemophilia A

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Summary
The Phase 3 A-LONG and Kids A-LONG studies demonstrated the prolonged half-life of rFVIIIFc compared with rFVIII, and the safety and efficacy of rFVIIIFc in subjects with severe haemophilia A. Eligible subjects from A-LONG and Kids A-LONG continued rFVIIIFc treatment by enrolling in ASPIRE, an ongoing extension study. Based on combined data from the primary studies and ASPIRE interim data, the safety and efficacy of rFVIIIFc in subjects requiring surgery were evaluated. Perioperative dosing regimens were determined by investigators with guidance based on pharmacokinetic data and recommendations from a clinical dosing committee. In addition to dosing frequency, factor consumption, blood loss, transfusions, bleeding episodes, and haemostatic response were assessed. Across studies, 21 subjects underwent 23 evaluable major surgeries, including 19 orthopaedic surgeries; 41 subjects underwent 52 minor surgeries, including 30 dental procedures. No major and 10 minor surgeries were performed in paediatric subjects. Of the major (n = 22) and minor (n = 32) surgeries assessed for haemostatic response, all were rated as excellent or good by the investigator/surgeon. During most major surgeries (95.7 %), haemostasis was maintained with one rFVIIIFc infusion. Blood loss in major surgeries was consistent with similar surgeries in subjects without haemophilia. Across studies, rFVIIIFc was well tolerated; no subject developed an inhibitor.

Keywords
Phase 3 trial, factor VIII, haemophilia A, haemostasis, surgery

Introduction
Surgical intervention in people with haemophilia poses a haemostatic risk associated with perioperative bleeding (1). This bleeding risk is generally managed by raising the level of deficient factor in the perioperative period to prevent bleeding and to facilitate healing and postoperative rehabilitation (2). In individuals with severe haemophilia A, the most common indication for major surgery is arthroplasty to treat haemophilic arthropathy secondary to repeated joint bleeding (1, 3). Arthroplasty surgeries are performed more often in adults with haemophilia than in children due to cumulative joint damage caused by years of recurrent bleeding; joint damage is particularly prevalent in patients not on prophylactic factor infusion (4, 5).

The phase 3 A-LONG study demonstrated the prolonged half-life of recombinant factor VIII Fc fusion protein (rFVIIIFc) relative to recombinant FVIII (rFVIII), and the safety and efficacy of rFVIIIFc for prevention and treatment of bleeding episodes in adults and adolescents with severe haemophilia A (6). These results were confirmed in paediatric subjects in the Phase 3 Kids A-LONG study (7). Eligible subjects from A-LONG and Kids A-LONG continued treatment with rFVIIIFc in ASPIRE, an ongoing extension study (8). The objective of the current analysis is to describe the surgical experience from these three studies in adults, adolescents, and children receiving rFVIIIFc during major or minor surgery.

Materials and methods
Subjects and study design
This report includes data from surgeries performed in A-LONG, Kids A-LONG, and the ongoing ASPIRE study. A-LONG was an open-label, multicentre, Phase 3 study that evaluated the pharmacokinetics, safety, and efficacy of rFVIIIFc (6). Eligible subjects had severe haemophilia A (<1 IU/dl [<1 %] endogenous FVIII activity), were ≥12 years of age, and had ≥150 prior exposure days (EDs) to any FVIII product. The study included three treatment
arrows (Arm 1, individualised prophylaxis; Arm 2, weekly prophylaxis; and Arm 3, episodic treatment). Kids A-LONG was an open-label, multicentre, Phase 3 study that evaluated the safety, efficacy, and pharmacokinetics of rFVIIIFc in previously treated paediatric subjects (7). Eligible subjects had severe haemophilia A, were <12 years of age, and had ≥50 prior EDs to a FVIII product. All study subjects received prophylaxis with rFVIIIFc. ASPIRE is an ongoing, open-label, multicentre, extension study to evaluate the long-term safety and efficacy of rFVIIIFc. Subjects who completed A-LONG or Kids A-LONG were eligible to enroll in ASPIRE (8). Data from major and minor surgeries were collected from any treatment arm during all three studies. Subjects in A-LONG must have had ≥12 EDs to rFVIIIFc prior to major surgery. The analysis presented here includes surgeries performed in ASPIRE up to the time of the interim analysis (cut-off date January 6, 2014), in addition to those performed in A-LONG and Kids A-LONG.

Study protocols were approved by institutional review boards and/or ethics committees at participating institutions. Subjects, or their guardians, provided written informed consent prior to participation in the studies; if appropriate, 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 (9) and ethical principles that comply with the Declaration of Helsinki (10), and are registered with ClinicalTrials.gov (ClinicalTrials.gov identifier: NCT01181128, NCT01458106, NCT01454739).

**Surgical approach**

Surgeries were classified as either major or minor. Major surgery was defined as any elective or emergent surgical procedure that usually, but not always, involved general anaesthesia and/or respiratory assistance in which a major body cavity is penetrated or exposed, or for which a substantial impairment of physical or physiological functions is produced. Surgeries not meeting the above criteria were classified as minor.

For major surgery, the preoperative period began with the first dose of rFVIIIFc given just prior to surgery onset; the intraoperative period was defined as the time the surgery began until the time the surgery was completed; and the postoperative period was defined as the period (up to 14 days) following the completion of the surgery through the last dose of rFVIIIFc given to prevent bleeding, as judged by the investigator/surgeon. Continuous infusion dosing of replacement factor was not allowed. Subjects undergoing major or minor surgery were treated with rFVIIIFc according to the local standard of care (i.e. treatment based on the type of surgery and the clinical status and pharmacokinetic profile of the subject), in consultation with the sponsor medical monitor as required; dosing regimens were ultimately selected by the investigator. Concomitant medications for additional haemostatic treatment (e.g. tranexamic acid) and thromboprophylaxis (e.g. heparin) were allowed in all studies as per local practice.

### Table 1: Subject demographics and baseline characteristics

<table>
<thead>
<tr>
<th>Major surgery population&lt;sup&gt;a&lt;/sup&gt;</th>
<th>Minor surgery population&lt;sup&gt;d&lt;/sup&gt;</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>&lt;12 years old (n = 10)</td>
</tr>
<tr>
<td>Age, years, median (min, max)</td>
<td>40.0 (21, 62)</td>
</tr>
<tr>
<td>Weight, kg, median (min, max)</td>
<td>75.5 (52.0, 104.0)</td>
</tr>
<tr>
<td>Family history of inhibitors, n (%)</td>
<td>1 (4.8)</td>
</tr>
<tr>
<td>HIV-positive, n (%)</td>
<td>5 (23.8)</td>
</tr>
<tr>
<td>HCV-positive, n (%)</td>
<td>12 (57.1)</td>
</tr>
<tr>
<td>≥1 target joints, n (%)</td>
<td>14 (66.7)</td>
</tr>
</tbody>
</table>

HCV, hepatitis C virus; HIV, human immunodeficiency virus; rFVIIIFc, recombinant factor VIII Fc fusion protein.<sup>a</sup>Each subject was counted once; subjects may have undergone major and minor surgery and were included in both cohorts.<sup>b</sup>Baseline data were collected at the time of entry into the parent study (i.e. A-LONG or Kids A-LONG).<sup>c</sup>Excludes one subject who underwent major surgery but did not receive rFVIIIFc treatment for the surgery; subject received a non-study FVIII product.<sup>d</sup>Excludes three subjects who underwent minor surgery but did not receive additional rFVIIIFc treatment for the surgery; these subjects were receiving rFVIIIfc prophylaxis in the studies.
Table 2: Summary of rFVIIIFc consumption during the perioperative period for major surgeries by type of surgery.

<table>
<thead>
<tr>
<th>Type of surgery</th>
<th>n</th>
<th>Median loading dose, IU/kg</th>
<th>Mean consumption on the day of surgery, IU/kg/day&lt;sup&gt;a&lt;/sup&gt;</th>
<th>Mean consumption on Days 1–3, IU/kg/day&lt;sup&gt;a&lt;/sup&gt;</th>
<th>Mean consumption on Days 4–14, IU/kg/day</th>
<th>Mean consumption on the day of surgery, IU/kg/day&lt;sup&gt;a&lt;/sup&gt;</th>
<th>Total number of infusions on day of surgery, n</th>
</tr>
</thead>
<tbody>
<tr>
<td>Ankle fusion</td>
<td>3</td>
<td>74.54 (55.33, 101.3)</td>
<td>103.2 (76.07, 126.6)</td>
<td>50.63 (36.88, 54.47)</td>
<td>29.19 (21.87, 37.97)</td>
<td>2 (2, 2)</td>
<td></td>
</tr>
<tr>
<td>Appendectomy</td>
<td>1</td>
<td>65.79</td>
<td>65.79</td>
<td>15.26</td>
<td>11.78</td>
<td>1</td>
<td></td>
</tr>
<tr>
<td>Arthroscopy</td>
<td>2</td>
<td>50.87, 75.53</td>
<td>75.53, 77.52</td>
<td>50.35, 56.52</td>
<td>23.92, 44.24</td>
<td>1, 2</td>
<td></td>
</tr>
<tr>
<td>Endoscopic third ventriculotomy</td>
<td>1</td>
<td>40.63</td>
<td>115.6</td>
<td>25.00</td>
<td>16.76</td>
<td>3</td>
<td></td>
</tr>
<tr>
<td>Laparoscopic inguinal hernia repair</td>
<td>2</td>
<td>50.00, 53.76</td>
<td>68.75, 86.02</td>
<td>29.17, 53.76</td>
<td>14.06, 35.19</td>
<td>2, 2</td>
<td></td>
</tr>
<tr>
<td>Spinal surgery</td>
<td>2</td>
<td>50.78, 101.6</td>
<td>50.78, 101.6</td>
<td>23.44, 44.27</td>
<td>0.00, 17.86</td>
<td>1, 1</td>
<td></td>
</tr>
<tr>
<td>Unilateral elbow arthroplasty</td>
<td>1</td>
<td>68.97</td>
<td>107.8</td>
<td>40.23</td>
<td>15.47</td>
<td>2</td>
<td></td>
</tr>
<tr>
<td>Unilateral hip arthroplasty</td>
<td>1</td>
<td>59.52</td>
<td>84.33</td>
<td>23.15</td>
<td>16.25</td>
<td>2</td>
<td></td>
</tr>
<tr>
<td>Unilateral knee arthroscopy</td>
<td>1</td>
<td>58.82</td>
<td>58.82</td>
<td>13.07</td>
<td>33.87</td>
<td>1</td>
<td></td>
</tr>
<tr>
<td>Bilateral knee arthroplasty</td>
<td>1</td>
<td>60.34</td>
<td>77.59</td>
<td>37.36</td>
<td>36.05</td>
<td>2</td>
<td></td>
</tr>
<tr>
<td>Unilateral knee arthroplasty</td>
<td>7</td>
<td>56.37 (49.57, 76.92)</td>
<td>80.55 (73.28, 115.4)</td>
<td>44.83 (22.99, 79.10)</td>
<td>32.67 (15.37, 66.26)</td>
<td>2 (2, 2)</td>
<td></td>
</tr>
<tr>
<td>Amputation</td>
<td>1</td>
<td>58.33</td>
<td>80.56</td>
<td>44.44</td>
<td>22.22</td>
<td>2</td>
<td></td>
</tr>
</tbody>
</table>

rFVIIIFc, recombinant factor VIII Fc fusion protein. *Data are reported for each individual surgery for surgery types with n ≥2. Data are presented as median (min, max) for surgery types with n >2; within each surgery type, mean rFVIIIFc consumption was assessed for each individual surgery and the median of these values is shown. # Included the loading dose, even if the loading dose was administered the day before surgery.

mined by their investigators/surgeons using a four-point scale (i.e. excellent, good, fair, poor/none) consistent with the World Federation of Hemophilia (WFH) guidelines (11). Because the perioperative management period represents a unique clinical situation, adverse events reported during this period for subjects in the major surgery subgroups were reviewed separately. Safety was evaluated throughout the studies by clinical assessments, routine laboratory tests, and rFVIIIFc-specific safety assessments, including inhibitor development by the Nijmegen-modified Bethesda assay. A positive inhibitor was defined as a neutralising antibody test result of ≥0.6 Bethesda units per millilitre (BU/ml), identified and confirmed by re-testing of a second sample obtained within 2–4 weeks.

Statistics
Endpoints were summarised using descriptive statistics. The investigator/surgeon assessment of a subject’s haemostatic response to rFVIIIFc was summarised as the number of surgeries at each rat- ing on the four-point scale (i.e. excellent, good, fair, poor/none).

Results
Subjects
Demographics and baseline characteristics for subjects who underwent major or minor surgery in all three studies (A-LONG, Kids A-LONG, and ASPIRE) were representative of a population with severe haemophilia A (Table 1).

Major surgeries
Across the three studies, 22 subjects underwent 24 major surgeries; of these surgeries, one was not evaluable because the subject received a non-study drug and was not treated with rFVIIIFc during the surgical period. In the A-LONG study, nine subjects underwent nine major surgeries. In the ASPIRE study, 13 subjects underwent 15 major surgeries (incl. one surgery that was not evaluable, as noted above). No major surgeries were performed after the first rFVIIIFc dose in the Kids A-LONG study. The most common types of major surgery were unilateral knee arthroplasty (n = 7) and ankle fusion (n = 3; Table 2). This is in agreement with previous reports of subjects with haemophilia in which the most common type of surgery was arthroplasty (1).

Minor surgeries
Across studies, 41 subjects underwent a total of 52 minor surgeries. Ten minor surgeries were performed in paediatric subjects (Kids A-LONG, n = 7; ASPIRE, n = 3). The other 42 minor surgeries were performed in adults and adolescents. rFVIIIFc was not administered for three of the 42 surgeries (no dose was given either on the day of surgery or as treatment related to the surgery);
these three subjects were on rFVIIIFc prophylaxis regimens in the studies. For the 49 minor surgeries across the three studies for which subjects were administered rFVIIIFc, the most common types were dental procedure (n = 30), endoscopy (n = 7), and port placement or removal (n = 5).

**rFVIIIFc dosing**

**Major surgeries**

Twenty-two of 23 evaluable major surgeries required a single infusion of rFVIIIFc to maintain haemostasis during surgery (defined as the loading dose until the end of surgery) and the remaining surgery required two infusions. In total, each subject received one to three infusions on the day of surgery (▶Table 2). Additionally, the number of subjects requiring an infusion for major surgery decreased in the days following surgery (▶Figure 1).

Among the 23 evaluable major surgeries, haemostasis was maintained with a median rFVIIIFc dose per infusion (including loading dose) of 58.3 IU/kg (range 45, 102) and a median total dose (including loading dose) of 58.8 IU/kg (range 50, 102) during the preoperative and intraoperative periods. The mean total dose of rFVIIIFc administered per day from the day of surgery through the perioperative period ending on Day 14 is shown in Figure 1. Of the evaluable major surgeries, 12 different types of surgery were performed. For each type of surgery, mean rFVIIIFc consumption per day on the day of surgery, Days 1–3, and Days 4–14 are shown in ▶Table 2. In general, consumption tended to decrease in the days following surgery (e.g. mean daily consumption on Days 4–14 was less than on Days 1–3). Use of thromboprophylaxis and tranexamic acid varied across the different surgery types per investigator discretion (▶Table 2). Plots of the surgical rFVIIIFc dosing regimen and local laboratory FVIII activity measurements for three representative major surgeries are shown in Suppl. Figure 1 (available online at www.thrombosis-online.com). These three adult subjects underwent three orthopaedic surgeries that were representative of the types of surgeries observed in this study and in the general population of subjects with severe haemophilia A (1).

**Minor surgeries**

For the 49 minor surgeries across the three studies, the median number of infusions on the day of surgery was 1 (range 1, 3). For the 39 surgeries in adolescents and adults, the median number of infusions on the day of surgery was 1 (range 1, 2). For the 10 minor surgeries in paediatric subjects, the median number of infusions on the day of surgery was 2 (range 1, 3).

For the 49 minor surgeries across the three studies, the median total dose required to maintain haemostasis on the day of surgery was 62.50 IU/kg (range 23.28, 188.68). For the 39 surgeries in adolescents and adults, the median total dose required to maintain haemostasis on the day of surgery was 52.08 IU/kg (range 23.28, 100.62). For the 10 minor surgeries in paediatric subjects, the median total dose required to maintain haemostasis on the day of surgery was 86.87 IU/kg (range 60.98, 188.68).

**Assessment of haemostatic response to treatment with rFVIIIFc**

**Major surgeries**

Haemostatic response to rFVIIIFc treatment during surgery and the postoperative period was assessed by investigators/surgeons for 22 major surgeries; 100% were rated as excellent (n = 19) or good (n = 3; ▶Table 3).

Figure 1: Mean nominal total dose of rFVIIIFc per day in subjects with evaluable major surgeries*. rFVIIIFc, recombinant factor VIII Fc fusion protein; SD, standard deviation. *Some subjects received more than one dose on a given day. On Day 0 (day of surgery), each subject received one to three infusions.
Minor surgeries

For 32 of 49 minor surgeries, investigator ratings of haemostatic response to rFVIIIFc were available during surgery and postoperatively. Of these, 100% were rated as excellent (n = 25) or good (n = 7). For the 23 of 39 minor surgeries that were assessed for haemostatic response in adolescent and adult subjects, 18 were rated as excellent and five were rated as good. In the subgroup of paediatric subjects, haemostasis was rated for nine of 10 minor surgeries; haemostatic response to rFVIIIFc treatment was rated as excellent (n = 7) or good (n = 2) for 100% of surgeries with ratings available.

Blood loss

Major surgeries

Intraoperative and postoperative blood losses were comparable to those observed in other major surgeries involving subjects without

Minor surgeries

For 32 of 49 minor surgeries, investigator ratings of haemostatic response to rFVIIIFc were available during surgery and postoperatively. Of these, 100% were rated as excellent (n = 25) or good (n = 7). For the 23 of 39 minor surgeries that were assessed for haemostatic response in adolescent and adult subjects, 18 were rated as excellent and five were rated as good. In the subgroup of paediatric subjects, haemostasis was rated for nine of 10 minor surgeries; haemostatic response to rFVIIIFc treatment was rated as excellent (n = 7) or good (n = 2) for 100% of surgeries with ratings available.

Blood loss

Major surgeries

Intraoperative and postoperative blood losses were comparable to those observed in other major surgeries involving subjects without
haematologic disorders (12–16). For evaluable major surgeries with available data, estimated blood loss during surgery ranged from 0 to 1200 ml (n = 20 surgeries; 1200 ml blood loss occurred during attempted total left knee arthroplasty which evolved into an above-the-knee amputation), and estimated postoperative blood loss ranged from 0 to 1100 ml (n = 20 surgeries; 1100 ml blood loss occurred for bilateral knee arthroplasty under general anaesthesia; ►Table 3). In the subgroup of unilateral knee arthroplasties (n = 7, excluding the surgery that evolved into an amputation), the median intraoperative and postoperative blood losses were 50 ml (range 0, 600) and 200 ml (range 0, 750), respectively, consistent with those reported in the literature for knee arthroplasties in patients without haemophilia (12).

Minor surgeries

Blood loss was estimated for five of the 49 minor surgeries, all of which were performed in adolescents and adults. For three tooth extractions, estimated blood losses during surgery and postoperatively for each surgery were 0.5 ml and 0.5 ml; 1 ml and 0 ml; and 0 ml and 0 ml, respectively. For the remaining two minor surgeries, blood loss was estimated during surgery only; for surgical extraction of a complete bony impacted tooth, blood loss was estimated to be 5 ml, and for a wisdom tooth extraction, blood loss was estimated to be 30 ml.

Number of transfusions

In three of the 23 evaluable major surgeries in three subjects, packed red blood cell transfusion was required during the perioperative period (►Table 3). For one major surgery (bilateral knee arthroplasty), the subject required transfusion of two units of packed red blood cells (one unit each on Days 3 and 4 following surgery). The estimated blood loss in this surgery was 500 ml intraoperatively and an additional 550 ml per knee from surgical drains postoperatively. Haemostatic response in this surgery was evaluated by the investigator as excellent. A left total knee arthroplasty scheduled in an adult subject required transfusion of packed red blood cells (400 ml) on Day 1 following surgery. The estimated blood loss was 610 ml intraoperatively and 290 ml postoperatively, and haemostatic response was evaluated by the investigator as excellent. No blood transfusions were required for any of the minor surgeries.

Incidence of postoperative bleeding episodes

During the postoperative period for a major surgery, one subject reported a bleeding episode. This subject experienced a post-procedural haemorrhage one day after a left knee revision arthroplasty. The surgery was performed at a non-study site and the haemorrhage resolved the next day. The subject received a single dose of non-study product to treat this bleeding episode in the postoperative period and did not require a blood transfusion. This bleeding episode occurred on Day 76 of the study (following surgery on Day 75). No postoperative bleeding episodes were reported for minor surgeries.

Safety

As of the January 6, 2014 data cut-off date for ASPIRE, none of the subjects who underwent major surgery in A-LONG or ASPIRE developed an inhibitor to rFVIIIFc. No subjects experienced anaphylaxis or a serious hypersensitivity reaction to rFVIIIFc, and no serious vascular thrombotic events were reported. One subject experienced a nonserious perianal venous thrombosis during the postoperative period that was treated with topical lidocaine ointment. The event was considered mild by the investigator and unrelated to the study drug; the data suggest the event was likely a rectal haemorrhoid. Across studies, 18 adverse events were reported during the perioperative management period for major surgeries, none of which were assessed by the investigators as related to treatment with rFVIIIFc. Of these 18 adverse events, one was assessed as serious by the investigator (postoperative haemorrhage described in the previous section), but required no change in the rFVIIIFc treatment regimen, and the event resolved one day after onset. Adverse events were not assessed separately for minor surgeries and were included in the primary safety analyses for the A-LONG, Kids A-LONG, and ASPIRE studies, which have been reported previously (6–8).

Discussion

This analysis demonstrates that rFVIIIFc is well tolerated and efficacious for the management of perioperative haemostasis across a wide spectrum of major and minor surgeries in subjects with severe haemophilia A. These results are consistent with the primary results of the A-LONG and Kids A-LONG studies, which demonstrated the safety and efficacy of rFVIIIFc for the prevention and treatment of bleeding episodes (6, 7, 17). Administration of rFVIIIFc controlled perioperative bleeding in all surgeries with available assessments. All major and minor surgeries evaluated for haemostatic response were rated as excellent (19 major surgeries and 25 minor surgeries) or good (three major surgeries and seven minor surgeries) by the investigator/surgeon based on a commonly used four-point scale. The positive assessments of haemostatic response to rFVIIIFc during the perioperative period are as expected for an efficacious FVIII replacement therapy and are similar to those that have been reported for other FVIII products (18–21). Dosing on the day of minor surgery appeared to be higher in paediatric subjects than in adult and adolescent subjects; this likely reflects previously-reported FVIII pharmacokinetic differences between adults and children (e.g. shorter half-life of FVIII...
replacement therapy in children) and/or a conservative dosing of paediatric patients (i.e. higher initial dose or greater tendency to provide a second infusion to prevent bleeding) (22, 23). Patients without haemophilia undergoing arthroplasty surgery have been observed to require transfusions as often as 69% of the time (24). In the present analysis, two of the nine (22%) arthroplasty surgeries required transfusion. Furthermore, surgical blood loss was consistent with that expected for similar surgeries in subjects without haemophilia (12–14). The safety results for surgical data from the three studies (i.e. A-LONG, Kids A-LONG, and ASPIRE) show that rFVIIIfc was generally well tolerated and no subjects undergoing major surgery developed an inhibitor.

With the advent of novel replacement therapies utilizing bolus dosing, it is important to comment on FVIII consumption with these new long-acting therapies and to compare them with conventional FVIII products. There are, however, no head-to-head studies to allow for direct comparisons. Consumption of a rFVIII product with a prolonged half-life during surgery may be expected to be less than that of conventional rFVIII products. While direct comparisons between studies are difficult due to differences in study designs, where it was possible to draw inferences from the literature, rFVIIIfc consumption during major surgeries (including loading dose) tended to be generally similar to or lower than that of conventional rFVIII products.

In a study of rFVIII (NOVOEIGHT®, Novo Nordisk, Bagsvaerd, Denmark), mean factor consumption on the day of surgery ranged from 27 to 153 IU/kg; in the first six days following surgery, the total daily dose of rFVIII was ~60 IU/kg/day or greater (19). In another study of full-length rFVIII (ADVATE™, Baxter, Deerfield, IL, USA), median consumption in the first seven days following major orthopaedic surgery was 65.2 IU/kg/day for bolus injection and 66.2 IU/kg/day for continuous infusion (21). In a study of sucrose-formulated rFVIII (KOGENATE® SF, Bayer, Berkeley, CA, USA), knee arthroplasty surgeries received a mean dose of 54.3–61.2 IU/kg/day of rFVIII, greater than that seen with rFVIIIfc when used for similar procedures (Table 2) (20). Mean consumption of sucrose-formulated rFVIII per day for surgeries judged to be major ranged from 21.4–170.7 IU/kg/day; five of 12 major surgeries reported a mean consumption per day of >100 IU/kg (20). In a study of B-domain-deleted (BDD) rFVIII (XYN-THA™, Pfizer Inc., New York, NY, USA), mean ± standard deviation (SD) consumption per day for those receiving continuous infusion was reported to be 3.7 ± 0.9 IU/hour and 2.8 ± 0.9 IU/kg/hour during the intraoperative and initial postoperative periods; assuming a constant rate of infusion, this would translate into ~88.8 IU/kg/day and ~67.2 IU/kg/day for these two time periods (18).

An important consideration with the use of any factor replacement therapy during surgery is the ability to accurately monitor FVIII activity using the variety of methodologies and reagents in use at local laboratories. In the present study, surgical dosing regimens were adjusted based upon local practice and FVIII activity results from local laboratories. A recent field study of rFVIIIfc showed that for both rFVIIIfc and ADVATE, FVIII activity levels could be accurately monitored by either the one-stage clotting assay or the chromogenic assay using any of the commercial assay reagents and FVIII standards found in 30 different laboratories, without the need for a product-specific standard (25). These findings were confirmed in an independent study of multiple FVIII products (26). In contrast, this was not shown for at least one other pegylated long-acting FVIII replacement therapy in development (27).

Limitations of this study include the variable dosing regimens and time intervals in perioperative management, thus limiting the interpretation of aggregate FVIII activity levels, as well as treatment differences due to the local standard of care. Strengths of this study include the prospective study design and the inclusion of a broad age range of subjects (3–62 years) undergoing a variety of major and minor surgeries typical for a population of subjects with severe haemophilia A; however, it is important to note that no paediatric subjects underwent major surgery. Furthermore, because dosing regimens were not prespecified, but determined by individual investigators, the data are more representative of a real-world patient population.

In conclusion, together with previously published results (6–8), the data shown here indicate that rFVIIIfc is safe and efficacious for the maintenance of perioperative haemostasis and for surgical prophylaxis in both major and minor surgery in individuals with severe haemophilia A.

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Author contributions
G.F. Pierce contributed to the design and conceptualization of the research, design of data analyses, interpretation of data, and drafting and revising the manuscript. J. Mahlangu, M. Ragni, N. Gupta, S. Rangarajan, R. Klamroth, J. Oldenburg, K. Nagomi, and G. Young contributed to the data collection, interpretation of data, and drafting and revising the manuscript. G. Allen and L.M. Cristiano contributed to the design of data analyses, data collection, interpretation of data, and drafting and revising the manuscript. B. Robinson contributed to the design of data analyses, interpretation of data, and drafting and revising the manuscript. Y. Dong contributed to the design of data analyses, performed the statistical analyses, and contributed to the interpretation of data and revision of the manuscript.

Conflicts of interest
J. Mahlangu: grant/research support from Bayer, Biogen, CSL Behring, Novo Nordisk, and Inspiration Biopharmaceuticals; paid consultant for Amgen, Bayer, Novo Nordisk, Pfizer, and Roche; speakers’ bureau for Bayer, Biogen, and Novo Nordisk. M. Ragni: grant/research support from Baxter Bioscience, Baxter Healthcare,
What is known about this topic?

- The prolonged half-life and the safety and efficacy of rFVIIIfc for the prevention and treatment of bleeding episodes in subjects with severe haemophilia A has been demonstrated in Phase 3 studies.
- There are limited data in the literature on the use of long-acting coagulation factors during surgery in subjects with haemophilia A.

What does this paper add?

- This analysis was based on combined data from surgeries performed in the Phase 3 A-LONG and Kids A-LONG studies, and the ongoing ASPIRE extension study.
- Findings from this analysis demonstrate that rFVIIIfc is well tolerated and efficacious for the management of perioperative haemostasis in adults, adolescents, and children with haemophilia A undergoing major or minor surgery.

References