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Results of a randomized phase III/IV trial comparing intermittent bolus versus continuous infusion of antihaemophilic factor (recombinant) in adults with severe or moderately severe haemophilia A undergoing major orthopaedic surgery

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Abstract

Introduction: In patients with haemophilia A undergoing surgery, factor VIII (FVIII) replacement therapy by continuous infusion (CI) may offer an alternative to bolus infusion (BI).

Aim: To compare the perioperative haemostatic efficacy and safety of antihaemophilic factor (recombinant) (ADVATE®; Baxalta US Inc., a Takeda company, Lexington, MA, USA) CI or BI administration.

Methods: In this multicentre, phase III/IV, controlled study (NCT00357656), 60 previously treated adult patients with severe or moderately severe disease undergoing elective unilateral major orthopaedic surgery (knee replacement, *n* = 48; hip surgery, *n* = 4; other, *n* = 8) requiring drain placement were randomized to receive antihaemophilic factor (recombinant) CI (*n* = 29) or BI (*n* = 31) through postoperative day 7. Primary outcome measure was cumulative packed red blood cell (PRBC)/blood volume in the drainage fluid within 24 h after surgery, used to establish non-inferiority of CI to BI.

Results: CI:BI ratio of cumulative PRBC volume in the 24-h drainage fluid was 0.92 (*p*-value <.001 for non-inferiority; 95% confidence interval, 0.82–1.05). Total antihaemophilic factor (recombinant) dose per kg body weight received in the combined trans- and postoperative periods was similar with CI and BI to maintain targeted FVIII levels during/after surgery. Treatment-related adverse events (AEs) were reported in five patients treated by CI (eight events) and five treated by BI (six events), including two serious AEs in each arm.

Conclusion: CI administration of antihaemophilic factor (recombinant) is a viable alternative to BI in patients with haemophilia A undergoing major orthopaedic surgery, providing comparable efficacy and safety.

KEYWORDS
clinical trial, haemophilia A, intravenous infusion, orthopaedic surgery, recombinant factor VIII

1 | INTRODUCTION

Antihaemophilic factor (recombinant), plasma/albumin-free method (ADVATE®; Baxalta US Inc., a Takeda company, Lexington, MA, USA), is a recombinant human coagulation factor VIII (FVIII) indicated for the treatment and prophylaxis of bleeding, including perioperative management, in patients of all ages with haemophilia A.[1,2] When used perioperatively, antihaemophilic factor (recombinant) is typically administered by bolus infusion (BI) at time points dictated by its pharmacokinetic (PK) profile.

Continuous infusion (CI) was developed to reduce the wide variations in plasma FVIII levels that usually accompany BI and decrease the quantity of infused FVIII concentrate.[3–9] CI during and/or after surgery [1,10] may stabilize FVIII levels, eliminating the deep troughs characteristic of BI that may increase bleeding risk. Several cohort and non-controlled studies have indicated that FVIII CI is well tolerated and efficacious for providing perioperative haemostasis for patients with haemophilia A; some studies have suggested that CI may also reduce FVIII consumption compared with BI.[3,7,8,11–13]

Continuous infusion and BI in the same type of intervention have not been compared in a prospective, controlled setting. The objective of this prospective, randomized phase III/IV study in patients with severe or moderately severe haemophilia A was to assess the perioperative haemostatic efficacy and safety of antihaemophilic factor (recombinant) administered via CI and intermittent BI.

2 | MATERIALS AND METHODS

2.1 | Patients

Eligible previously treated patients (18–70 years of age) had severe or moderately severe haemophilia A at screening (FVIII level ≤2 IU/dl) and were scheduled for elective unilateral major orthopaedic surgery requiring drain placement. Protocol amendments raised the maximum age (previously 65 years) and expanded the type of surgery (previously unilateral primary total knee replacement only). Major orthopaedic surgery was defined as requiring moderate or deep sedation, general anaesthesia, or major nerve conduction blockade and had a significant risk of large-volume blood loss or blood loss into confined anatomical space. Patients provided written informed consent and were required to have had prior exposure to FVIII concentrates for ≥150 days. Patients were excluded if they met any of the following criteria: detectable FVIII inhibitors at screening (by the central laboratory), history of inhibitors (>0.4 Bethesda units [BU] by Nijmegen modification of the Bethesda assay), scheduled for any other minor or major surgery, laboratory evidence of abnormal haemostasis from causes other than haemophilia A, and current or planned receipt of an immunomodulatory drug other than antiretroviral therapy.

2.2 | Study design

This phase III/IV, prospective, multicentre, randomized, controlled study was divided into three periods: (1) a preoperative period, including a PK evaluation; (2) an intraoperative and postoperative period, from loading dose to postoperative day 7; and (3) a safety follow-up period, from postoperative day 8 to the end-of-study visit (6 weeks following surgery). The study was conducted in accordance with the principles of the Declaration of Helsinki, and the protocol, informed consent form and all amendments were approved by the ethics committee at each study site. The trial is registered at ClinicalTrials.gov (NCT00357656).

Pharmacokinetic analysis was performed before surgery to establish individual FVIII recovery and clearance (CL) values. In the preoperative period (≤60 days before the surgery), patients who had completed a washout of 72 h and were not actively bleeding were infused with antihaemophilic factor (recombinant) 50 ± 5 IU/kg of body weight and had 10 postinfusion samples taken within 48 h. If PK data suggested the presence of subclinical inhibitors (FVIII half-life <8 h, incremental recovery (IR) <1.5 (IU/dl)/(IU/kg), or CL >5.0 ml/(kg × h), patients were excluded from further participation in the study.

Patients who completed the preoperative PK phase were randomized 1:1 to treatment by CI or BI through postoperative day 7. Patients were stratified by type of surgery (unilateral knee replacement, hip surgery and shoulder/elbow/ankle/knee [except knee replacement] surgery). Randomization was separate and independent for each stratum. Randomization lists were prepared in blocks with a block size >2 using the random number generator algorithm of Wichmann and Hill [14] as modified by McLeod.[15] Patients in each group had blood drawn once every 24 h for measurement of FVIII activity. Patients stayed in hospital until postoperative day 7 to receive study treatment per protocol. Patients were discharged from hospital according to site practice.

Patients randomized to CI could continue on CI or switch to intermittent BI starting on postoperative day 8, at the discretion of the investigator. During the period from postoperative day 8 until 6 weeks ±3 days following surgery, treatment (including mechanical or pharmacologic thrombosis prophylaxis) was also at the discretion of the investigator, depending on current practice of the site during physical rehabilitation.

Antihaemophilic factor (recombinant) doses during the perioperative period (until postoperative day 7) were based on the PK profile determined before surgery. Within 60 min before surgery, patients received a loading dose of antihaemophilic factor (recombinant) to maintain a minimum FVIII level of at least 80% of normal. The formulas for determining the initial weight-adjusted loading dose differed, depending on whether the patient was randomized to receive antihaemophilic factor (recombinant) as BI or CI for subsequent management:

- BI loading dose and subsequent BIs (IU/kg) = ([target FVIII level {IU/dl} × $2^{I/t}$ − preinfusion level {IU/dl}]/IR [{IU/dl}/{IU/kg}]), where

'I' is the infusion interval (in hours) at which the target FVIII level shall be maintained and 't' is the estimated FVIII half-life (in hours);

- CI loading dose (IU/kg) = ([target FVIII level {IU/dl} − preinfusion level {IU/dl}] / IR [{IU/dl} / {IU/kg}]).

The loading dose was given intravenously over up to 5 min at a maximum infusion rate of 10 ml/min. If the blood sample drawn ~15 min after infusion showed that the desired FVIII level had not been reached or the activated partial thromboplastin time (aPTT) had not normalized, a supplemental loading dose could be given. Surgery could be started only after normalization of the aPTT. To compensate for intraoperative blood loss and increased FVIII consumption, patients received an additional bolus of study drug in the recovery room sufficient to raise the FVIII level by 50 IU/dl. CI was to be started before surgery, immediately following the loading dose; study product was administered at a rate (IU/[kg × h]) calculated according to the following formula: CL × target FVIII level. The infusion was administered using a syringe pump according to this regimen, but always ≥0.4 ml/h. BI treatment started with the loading dose; treatment frequency varied according to the patient's PK profile, but typically included three infusions per 24 h during the first 72 h following the loading dose, infusions every 12 h from postoperative day 3 to 7, and daily infusions from postoperative day 8 to 14. For both CI and BI, FVIII trough levels were to be maintained above 80 IU/dl for the initial 72 h, at 50–100 IU/dl through postoperative day 7 and >30 IU/dl for postoperative days 8–14.

2.3 | Primary and secondary efficacy outcome measures

The primary study objective was to compare the perioperative haemostatic efficacy of antihaemophilic factor (recombinant) CI versus intermittent BI. The primary efficacy outcome measure was the cumulative packed red blood cell (PRBC)/blood volume in the drainage fluid (based on haematocrit values) assessed during the first 24 h after surgery determined from drainage fluid samples using the red blood cell counting method used at the local laboratory. Secondary efficacy outcome measures included postoperative blood loss until drain removal, number of bleeding episodes through postoperative day 7 and number of units of PRBCs transfused. The trigger for initiating a blood transfusion was determined by each clinician for each patient.

2.4 | Safety outcome measures

Safety was a secondary objective. The numbers of adverse events (AEs) and serious AEs (SAEs) were assessed, as well as their relationship to treatment and the incidence of FVIII antibody formation. AEs were grouped by the Medical Dictionary for Regulatory Activities system organ class and classified by severity (mild, moderate, severe). Inhibitor testing was performed at screening, at the rescreen visit after the pretreatment phase (if applicable) and at the end-of-study visit according to the Nijmegen modification of the Bethesda assay in the central laboratory. FVIII inhibitors could be determined at the local laboratory and verified by the central laboratory.

2.5 | Additional exploratory outcome measures

Exploratory outcome measures included total weight-adjusted antihaemophilic factor (recombinant) dose through postoperative day 7, PK assessments (IR, CL) through postoperative day 7, total haemoglobin in cumulative drainage fluid during the first 24 h after surgery and until drain removal, rate of clinically relevant postoperative haematomas, and Global Hemostatic Efficacy Assessment (GHEA).

The GHEA was based on three categories (Table 1), added to form the GHEA score (excellent, 7–9 [with no category <2]; good, 5–7 [with no category <1]; fair, 2–4 [with no category <1]; none, 0–1). For a score of 7 to be rated 'excellent', each individual assessment score had to be ≥2; otherwise, a score of 7 was to be rated 'good'.

2.6 | Statistics

Descriptive statistics were provided for baseline characteristics and summarized by treatment regimen. A sample size of 60 divided equally between the CI and BI arms was selected for the study. To establish non-inferiority of CI to BI, the ratio of the mean PRBC volumes of the drainage fluids in the CI arm to the BI arm was compared to a non-inferiority margin of 200%. This was equivalent to the upper 95% confidence limit for the ratio being below 200%. The sample size requirements for establishing non-inferiority by *t*-test at a non-inferiority limit of 200% were calculated and a sample size of 50–60 was determined to provide adequate power. In addition, at least 15 patients in each treatment group were required to have baseline FVIII levels <1%. Pearson's chi-squared test with Monte Carlo simulation was used for comparison of patients with bleeding episodes and for patients who required transfusions.

3 | RESULTS

3.1 | Patients

The study started on 29 May 2006 and was completed on 9 December 2015. Of 85 patients enrolled at 22 sites (in the United States, European Union, Norway and Russia), 72 received the infusion of antihaemophilic factor (recombinant) in the preoperative period for PK determination. Of these, 63 met the criteria for perioperative treatment and were randomized to receive CI (n = 32) or BI (n = 31). Of the patients who received CI, 23 had severe haemophilia A (baseline FVIII level <1 IU/dl) and six had moderately severe haemophilia A (baseline FVIII level 1 to <2 IU/dl). Of the patients who received BI, 26 had severe haemophilia A and five had moderately

TABLE 1 GHEA scoring categories[a]

Category 1. Intraoperative haemostatic efficacy	
0	Uncontrolled blood loss necessitating the use of another FVIII replacement product
1	Intraoperative blood loss >150% of that expected for surgery but haemostasis achieved and maintained
2	Intraoperative blood loss up to 50% more than expected for surgery
3	Intraoperative blood loss less than or equal to that expected for surgery
Category 2. Volume of blood loss in drains at 24 h following surgery	
0	Uncontrolled blood loss necessitating the use of another FVIII replacement product or surgical reintervention
1	Volume in drain >150% of that expected for surgery but haemostasis achieved and maintained
2	Volume in drain up to 50% more than expected for surgery
3	Volume in drain less than or equal to that expected for surgery
Category 3. Haemostatic efficacy at postoperative day 8	
0	Bleeding episode that was the result of an inadequate therapeutic response in the face of proper dosing, necessitating a change in the therapeutic regimen
1	Postoperative haemostasis clearly less than optimal for surgery but maintained without the need for a change in therapeutic regimen
2	Postoperative haemostasis achieved was probably as good as that observed with other licensed FVIII concentrates for the surgery
3	Postoperative haemostasis achieved was unequivocally as good as or better than that observed with other licensed FVIII concentrates for the surgery

Abbreviation: GHEA, Global Hemostatic Efficacy Assessment.

[a]Categories 1 and 2 determined by the operating surgeon; category 3 determined by the investigator. The scores from the three categories were added to form the total GHEA score (excellent, 7–9 [with no category <2]; good, 5–7 [with no category <1]; fair, 2–4 [with no category <1]; none, 0–1). Scores of 7 were rated as 'excellent', if each individual assessment score was ≥2; otherwise, a score of 7 was rated as 'good'.

severe haemophilia A. Three patients randomized to CI did not undergo surgery and were not treated. Thus, 60 patients received treatment and comprised the per-protocol analysis set (CI, *n* = 29; BI, *n* = 31). The safety analysis set included all 72 patients who received at least one dose of antihaemophilic factor (recombinant). Patient disposition is summarized in Figure 1. Each patient underwent one procedure: unilateral knee replacement surgery (*n* = 48; 24 CI, 24 BI), hip surgery (*n* = 4; two CI, two BI) or shoulder/elbow/ankle/knee surgery (*n* = 8; three CI, five BI). All patients were male. Demographic and clinical characteristics were similar between groups; the medians and ranges of age were nearly identical (Table 2). Four patients received enoxaparin or nadroparin as thrombosis prophylaxis.

3.2 | Efficacy and exploratory outcomes

Information on drainage fluid PRBC was not available for six patients (three CI, three BI) at 24 h after surgery, but the cumulative PRBC/blood volume in the drainage fluid (ie RBC, MCV and haematocrit) during the first 24 h following surgery was comparable between the CI and BI groups (Table 3; Table 4 [by type of surgery]), with a ratio of 0.92 (95% confidence interval for mean, 0.82–1.05; median, 3.4×10^{12} RBCs/l for CI and 3.5×10^{12} RBCs/l for BI). The one-sided *p*-value against the null hypothesis of ratio ≥200% was <.001, confirming the non-inferiority of CI to BI with a 5% type I error (as the upper confidence limit did not exceed 200%).

Total blood loss until drain removal, adjusted for expected blood loss, was slightly higher in the CI group than the BI group (Table 3). The mean (95% confidence interval) ratio of blood loss volume for CI versus BI was estimated to be 1.3 (0.8–2.1), and the one-sided *p*-value against the null hypothesis of ratio ≥200% was .041. Most bleeding episodes occurred in patients receiving BI; of four reported bleeding episodes (one episode per patient), three occurred in patients receiving BI and one in a patient receiving CI (Table 3). None of the bleeding episodes was considered by the investigator to be 'the result of inadequate therapeutic response in the face of proper dosing, necessitating a change in therapeutic regimen'. Patients receiving CI were given more PRBC transfusions than patients receiving BI. PRBC transfusions were required in 18/29 and 13/31 patients receiving CI and BI, respectively, with a mean (range) of 1.3 (1–5) units in patients receiving CI and a mean (range) of 0.9 (1–3) units in patients receiving BI.

The total amount of haemoglobin in the cumulative drainage fluid during the first 24 h after surgery and until drain removal (if drainage continued) was comparable between patients who received CI and BI. In the stratum of patients who underwent unilateral knee replacement (CI, *n* = 24; BI, *n* = 24), the point estimate for the mean was 98.21 g/l (95% confidence interval for mean, 89.68–107.56 g/l) for CI and 97.63 g/l (86.07–110.74 g/l) for BI. The ratio of CI to BI was estimated to be 1.01.

Clinically relevant postoperative haematomas were observed in two patients receiving CI and two receiving BI (three haematomas per group, for a total of six). Two patients (one CI, one BI) had undergone knee replacement and two patients (one CI, one BI) had undergone hip surgery.

The total antihaemophilic factor (recombinant) dose (per kg body weight) administered in the combined transoperative and postoperative periods was similar in the CI and BI groups (Table 3). The global haemostatic efficacy of antihaemophilic factor (recombinant) administered by CI was assessed to be at least as good as that administered by BI. As shown in Table 5, scores of 'excellent' were evenly distributed among patients who received CI and patients who received BI. All patients receiving CI had a score of 'excellent' or 'good'.

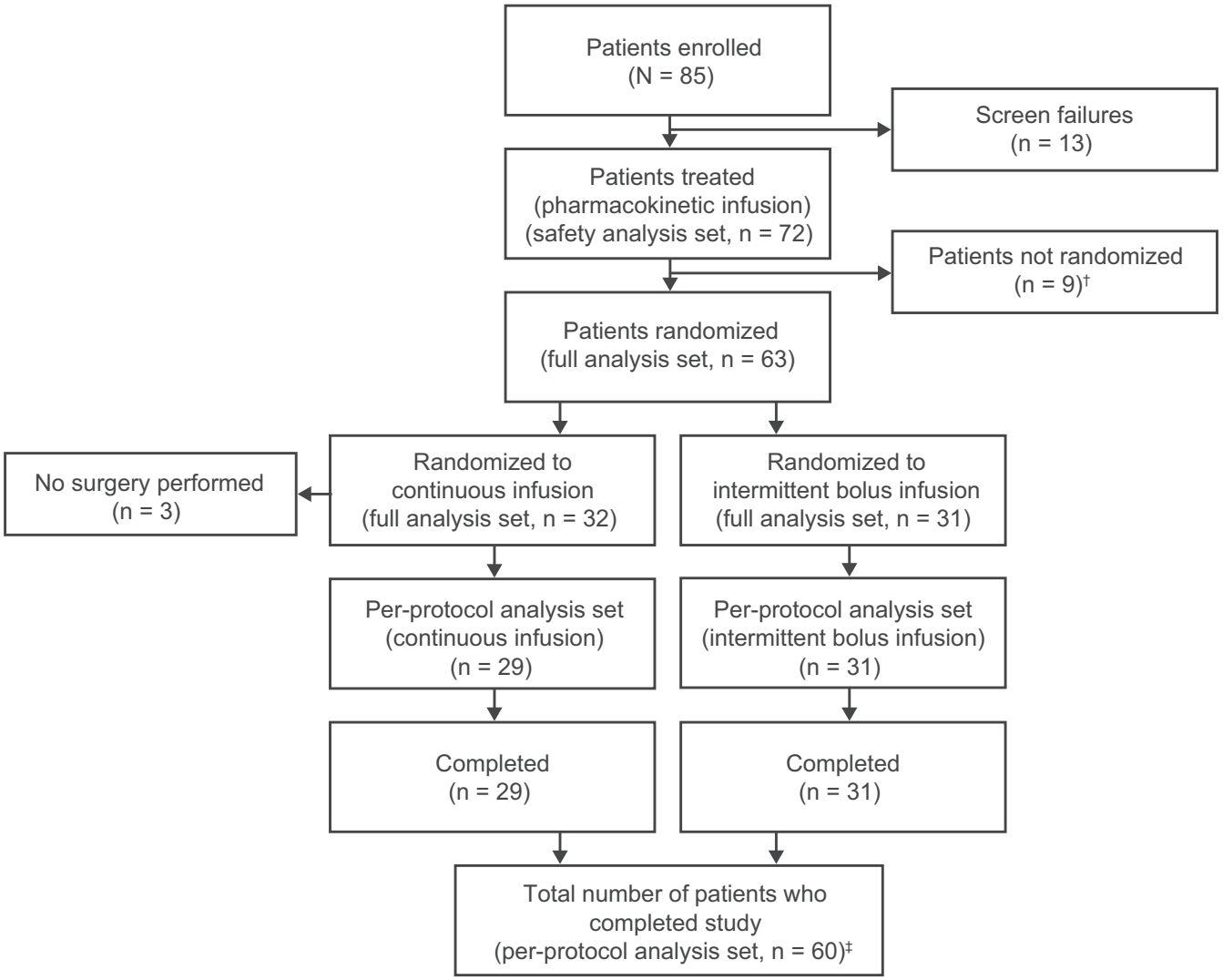

FIGURE 1 Disposition of patients. †Nine patients were not randomized for the following reasons: excluded because of pharmacokinetics (*n* = 4), screen failures (*n* = 2), physician decision (*n* = 1), sponsor decision (*n* = 1) and death (*n* = 1).‡Three patients randomized to receive continuous infusion did not undergo surgery and were therefore not treated. Thus, 60 patients received treatment and comprised the per-protocol analysis set (continuous infusion, *n* = 29; bolus infusion, *n* = 31)

Incremental recovery over time could be analysed only for the BI arm, as BIs in the CI arm were rare. Compared to the value at the loading dose on day 0, the median IR decreased by ~20% after the first week following surgery (day 7), with high variability across individual patients. During the second week, many patients were discharged from hospital and not enough samples were available for analysis. CL could be analysed for the CI arm, but not the BI arm because of insufficient data. The determination of CL used the observed FVIII level as the steady-state level. This assumption was questionable for days 1 and 4 due to the additional postsurgical BIs and the reduction in infusion rate scheduled at day 3. For days 2, 3 and 5, an increase of ~20% in median CL was observed compared with that from the presurgical full PK analysis. Only at days 6 and 7 was the median CL below the initial value, but high variability in individual patient values was seen throughout the first week. Second-week data were insufficient for analysis.

3.3 | Safety outcomes

Adverse events observed are summarized in Table 6. In the safety population (*N* = 72), 230 AEs were reported in 51 patients (70.8%). A total of 14 treatment-related AEs were reported in 10 patients: five patients treated by CI had eight AEs and five patients treated by BI had six AEs. Ten of the 14 treatment-related AEs were classified as non-serious (reported in six patients): anaemia (*n* = 5), headache (*n* = 2), allergic dermatitis (*n* = 1), pruritus (*n* = 1) and pyrexia (*n* = 1).

Ten SAEs were reported in ten patients. Of these, four SAEs of FVIII inhibitor development (two patients in each group) were considered related to treatment; all four patients had severe haemophilia A, and none required treatment with a bypassing agent. The two patients receiving CI developed high-titre inhibitors (up to 20.8 and 10.7 BU, respectively, on study days 63 and 57), which later decreased to the low-titre range in both patients (1.0 and 1.7 BU,

TABLE 2 Patient demographic and clinical characteristics in the per-protocol analysis set

Characteristic	Continuous infusion (*n* = 29)	Bolus infusion (*n* = 31)
Age at screening (years)		
Median	35.0	36.0
Range	18–58	22–59
Weight (kg)		
Median	78.0	74.8
Range	49–110	55–122
Height (cm)		
Median	173.0	175.0
Range	164–191	162–186
Race, *n* (%)		
Asian	0	1 (3)
White	29 (100)	30 (97)
Surgical procedure (all were unilateral), *n* (%)		
Knee replacement	24 (82.8)	24 (77.4)
Hip surgery	2 (6.9)	2 (6.5)
Shoulder/elbow/knee/ankle surgery	3 (10.3)	5 (16.1)

TABLE 3 Key efficacy parameters in the per-protocol analysis set[a]

Parameter	Continuous infusion	Bolus infusion
Primary efficacy outcome		
Cumulative PRBC volume in drainage fluid at 24 h (10^{12} RBCs/l), mean (SD)	3.38 (0.63)[b] (*n* = 26)	3.63 (0.97)[b] (*n* = 28)
Secondary efficacy outcomes		
Actual postoperative blood loss until drain removal (ml), mean (SD)	929 (168)[c] (*n* = 28)	767 (182)[c] (*n* = 30)
Number of patients with bleeding episodes through postoperative day 7	1[d]	3[d]
Number of bleeding episodes, mean (SD)	0.03 (0.186) (*n* = 29)	0.10 (0.301) (*n* = 31)
Number of patients receiving PRBC transfusions	18[e]	13[e]
Number of PRBCs transfused, mean (SD)	1.3 (1.4) (*n* = 29)	0.9 (1.2) (*n* = 31)
Exploratory outcome		
Antihaemophilic factor (recombinant) dose administered (safety analysis set) (total IU/kg)[f]	53,960.6 (*n* = 32)	49,314.9 (*n* = 31)

Abbreviations: BI, bolus infusion; CI, continuous infusion; PRBC, packed red blood cell; SD, standard deviation.

[a]Data shown are from patients in the per-protocol analysis set, unless otherwise specified. The patient numbers shown for the different parameters vary because some patients did not have all data available.

[b]The one-sided *p*-value (against the null hypothesis of the CI:BI ratio ≥200%) was <.001.

[c]The one-sided *p*-value (against the null hypothesis of the CI:BI ratio ≥200%) was .041.

[d]Not statistically significant by a post hoc Pearson's chi-squared test ($p_{\text{two-sided}}$ = .612, using Monte Carlo simulation with 10^6 replicates).

[e]Not statistically significant by a post hoc Pearson's chi-squared test ($p_{\text{two-sided}}$ = .132, using Monte Carlo simulation with 10^6 replicates).

[f]Trans- and postoperatively combined.

respectively). One patient was a 35-year-old male who had undergone hip surgery; he had received plasma-derived FVIII products and had weakly positive Lupus anticoagulants of unknown clinical relevance. The other was a 30-year-old male who had undergone left knee replacement. Of the two patients receiving BI who developed FVIII inhibitors, one was a 35-year-old male who had undergone left primary total knee replacement and developed a low-titre inhibitor (transient; maximum 0.89 BU that later decreased to 0.17 BU) on study day 30. The other was a 50-year-old male who developed a low-titre inhibitor on study day 36 with a maximum titre of 3 BU that later decreased to 2.4 BU. The other six SAEs (febrile infection, joint swelling, haemarthrosis, pseudomembranous colitis, multiorgan failure and muscle haemorrhage) were considered to be unrelated to treatment.

One patient died during the study. Death was due to multiorgan failure attributed to codeine toxicity. The patient had received antihaemophilic factor (recombinant) only for PK evaluation and was not randomized to treatment by CI or BI and therefore did not undergo surgery.

4 | DISCUSSION

These results demonstrate that treatment by CI was non-inferior to treatment by BI in terms of haemostatic efficacy and safety in patients undergoing elective unilateral major orthopaedic surgery that required drain placement. Although prior studies have evaluated CI of FVIII in patients with haemophilia A undergoing surgical procedures,[3,8,11–13] this was the first controlled trial to compare CI and BI of FVIII in the studied population.

The same concentrate used in the present study was also used in surgical patients in the pivotal study reported by Négrier et al.[13] In that prospective, open-label, uncontrolled clinical trial, the efficacy and safety of CI and BI of antihaemophilic factor (recombinant) was examined in 58 patients undergoing 65 surgical procedures, of which 22 were associated with major haemorrhagic risk.[13] CI (with or without supplemental BIs) was used in 18 procedures and BI alone was used in 47 procedures. Intraoperative haemostatic efficacy, as well as postoperative haemostatic efficacy rated at the time of discharge, was assessed as 'excellent' or 'good' for all procedures; treatments were well tolerated, and no development of FVIII inhibitors was reported.[13] The median (range) total FVIII consumption during hospitalization for all major surgeries was 822 (401–2014) IU/kg per surgery with CI (including any supplemental BI) and 910 (228–1825) IU/kg per surgery with BI alone. Among

TABLE 4 Cumulative PRBC volume in drainage fluid at 24 h (10^{12} RBCs/l) by type of surgery

Type of surgery	Continuous infusion	Bolus infusion
Unilateral knee replacement	*n* = 23	*n* = 22
Mean (SD)	3.35 (0.62)	3.72 (0.98)
Median	3.39	3.52
Range	1.86–4.25	2.48–6.57
Hip surgery	*n* = 1	*n* = 2
Mean (SD)	3.40 (NA)	2.86 (1.73)
Median	3.40	2.86
Range	NA	1.63–4.08
Shoulder/elbow/ankle/knee (except knee replacement) surgery	*n* = 2	*n* = 4
Mean (SD)	3.82 (1.10)	3.55 (0.58)
Median	3.82	3.50
Range	3.04–4.60	2.90–4.30

Abbreviations: NA, not applicable; SD, standard deviation.

TABLE 5 GHEA score

GHEA score[a]	Continuous infusion (*n* = 29)	Bolus infusion (*n* = 31)
Excellent	21	21
Good	8	4
Fair	0	0
None	0	0
Not evaluated[b]	0	6

Abbreviation: GHEA, Global Hemostatic Efficacy Assessment.

[a]Values represent numbers of patients with reported GHEA scores.

[b]The GHEA score at postoperative day 8 was missing for six patients.

those undergoing orthopaedic procedures, the median daily FVIII consumption during the first seven postoperative days was similar with CI (66.2 IU/kg/day) and BI (65.2 IU/kg/day).[13] Similarly to the current study, Négrier et al. concluded that antihaemophilic factor (recombinant) administered via CI or BI was effective and safe for perioperative haemostasis, although that study was not designed to compare CI with BI.

Based on the findings of earlier studies, which reported good haemostatic efficacy and total FVIII doses 19%–36% lower with CI versus BI,[3,7,8,11,12] it was hypothesized that CI might be similarly or even more effective for preventing postoperative bleeding but with a reduced consumption of antihaemophilic factor (recombinant) compared with BI. However, in our study, the use of antihaemophilic factor (recombinant) was higher for CI versus BI on postoperative days 1–14 and higher for BI versus CI intraoperatively, on postoperative day 0, and from postoperative day 15 to study end. These findings may be due in part to the study protocol and design, which specified dosing, permitted patients to switch from CI to BI from day 8 onwards and focused on reducing variations in plasma factor levels rather than reducing

TABLE 6 Summary of AEs in the safety population[a] and by treatment arm

Type of AE, *n* (%)	Overall safety population (*N* = 72)	Continuous infusion (*n* = 32)	Bolus infusion (*n* = 31)
Treatment-related AEs	10 (13.9)	5 (15.6)	5 (16.1)
Treatment-related SAEs[b]	4 (5.6)	2 (6.3)	2 (6.5)
SAEs unrelated to treatment	6 (8.3)[c]	4 (12.5)	1 (3.2)

Abbreviations: AE, adverse event; SAE, serious adverse event.

[a]The safety population included nine patients who were not randomized to receive continuous or bolus infusion; no AEs were recorded in these patients.

[b]All treatment-related SAEs were development of FVIII inhibitors.

[c]One SAE unrelated to treatment occurred in a patient who died before randomization.

the amount of product used. When transoperative and postoperative usage was combined, the total factor consumption was similar in the CI and BI groups, which mirrors the findings of Négrier et al.[13]

This study provided the unique opportunity to compare the safety of CI versus BI. Although administration by CI provides the advantage of achieving more stable FVIII levels without the troughs that usually accompany BI and place the patient at risk of bleeding, the use of CI during and after surgery has raised concerns about an increased risk of inhibitor formation, particularly in patients with mild or moderate haemophilia.[16–18] However, no increase in inhibitor risk was seen in a large retrospective survey of 1079 procedures[19] and no inhibitors were detected in a prospective study of CI use in 46 previously treated patients with severe haemophilia A.[20] The development of inhibitors is a multifactorial process associated with a variety of genetic and environmental risk factors.[21] In the current study of patients with severe or moderately severe haemophilia A (baseline FVIII ≤2 IU/dl) and prior FVIII exposure of ≥150 days, 4 of 60 (6.7%) patients developed FVIII inhibitors, with no difference in frequency between the two groups (observed in two patients receiving CI and two receiving BI). Both patients with CI developed high-titre inhibitors that evolved to low titre, whereas the two patients with inhibitors during BI had low-titre inhibitors. Due to the limited number of affected patients, it is not possible to determine whether this difference was related to the study drug, method of administration, or potential confounding factors (eg the presence of high-risk FVIII mutations and other genetic risk factors, which were not assessed in this study, or variability in tissue damage related to the surgical procedure). Although patients had been previously exposed to cryoprecipitates, fresh frozen plasma and/or plasma-derived or recombinant FVIII concentrates, we cannot comment on how tolerant they were to FVIII due to a lack of an accurate record of prestudy FVIII usage. In the separate study of the present study drug (Négrier et al. mentioned above), surgical patients previously treated with antihaemophilic factor (recombinant) did not develop FVIII inhibitors.[13] In addition, the risk of inhibitors was not found to

be elevated in a postmarketing surveillance study of patients previously treated with antihaemophilic factor (recombinant).[22]

During the first week after surgery, a decrease in IR and an increase in CL were observed in the current study, although the limited data available prevent meaningful analysis and interpretation of these results, which should be considered in the context of varying results reported in the literature. Although Batorova and Martinowitz saw a significant decrease in CL during the 1–2 weeks following surgery,[11] others have described variable changes in CL following major surgical procedures,[23] and recent reports indicate substantial intraindividual variation in IR and poor reproducibility of CL, with numerous factors affecting IR and CL.[23,24]

Limitations of this study include the necessity to enrol patients undergoing orthopaedic surgeries other than unilateral knee replacement, difficulty in estimating PRBC volumes in drainage fluid, lack of information on the drainage fluid PRBC for six patients, and variability in surgical techniques and practices at the participating sites, which could only be partially addressed per study protocol. Another limitation inherent to the study design is the use of PK assessment before surgery and central dosing recommendations, which differ from conditions in real-world clinical practice. On the other hand, this study has inherent strengths as a multicentre randomized study with a large number of patients with balanced surgical procedures in the two arms.

5 | CONCLUSION

The administration of antihaemophilic factor (recombinant) by CI resulted in comparable efficacy and safety outcomes and is a viable alternative to intermittent BI in the perioperative haemostatic management of patients with haemophilia A undergoing major orthopaedic surgery. Taking into account the complexity of CI versus BI, it is useful to know that these types of FVIII administration showed non-inferiority, such that treatment may be optimized for individual patients. These findings may help inform perioperative haemostatic management of these patients, with the goal of maintaining stable FVIII levels during and after surgery, whether by the use of CI or BI regimens.

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DISCLOSURES

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*A member of the Takeda group of companies.

AUTHOR CONTRIBUTIONS

All authors reviewed/revised the manuscript critically for intellectual content and gave their final approval for it to be published. Ingrid Pabinger was a study investigator and contributed to the design of the study and interpretation of the data and study content. Vasily Mamonov and Jerzy Windyga were study investigators and contributed to the interpretation of the data and study content. None of the authors received honoraria for the writing of this manuscript. Werner Engl and Bruce Ewenstein contributed to the conception, design, analysis and interpretation of the clinical trial. Jennifer Doralt, Srilatha Tangada and Gerald Spotts contributed to the analysis and interpretation of the data, and study conduct.

All authors agree to be accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved.

DATA AVAILABILITY STATEMENT

The datasets, including the redacted study protocol, redacted statistical analysis plan, and individual participants' data supporting the results reported in this article, will be made available within 3 months from initial request, to researchers who provide a methodologically sound proposal. The data will be provided after its de-identification, in compliance with applicable privacy laws, data protection and requirements for consent and anonymization. Data requests should follow the process outlined in the Data Sharing section on: www.takeda.com/what-we-do/research-and-development/takeda-clinical-trial-transparency/

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