PB0939

Surgical Experience from the Phase III STASEY Trial of Emicizumab Prophylaxis in Persons with Hemophilia A (PwHA) with FVIII Inhibitors: Data from the Second Interim Analysis

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SUMMARY

- The management and outcomes of PwHA who underwent surgical procedures during emicizumab studies are of clinical interest.
- PwHA with FVIII inhibitors receiving emicizumab prophylaxis as part of the Phase III STASEY trial underwent minor and unplanned major surgeries, managed at the investigator's discretion.
- Overall, minor and major surgeries were safely performed in the STASEY trial with few post-operative bleeds.

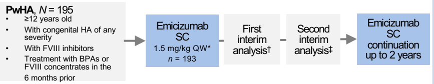
INTRODUCTION

- Emicizumab, a subcutaneously administered, bispecific monoclonal antibody, bridges activated factor (F)IX and FX replacing the function of missing activated FVIII in PwHA, thereby restoring hemostasis.[1]
- The Phase IIIb STASEY trial (NCT03191799) assessed the safety and efficacy of emicizumab prophylaxis in PwHA with FVIII inhibitors; an interim analysis revealed that no new safety signals were identified.[2]
- Here we present the surgical experience in PwHA with FVIII inhibitors enrolled in the STASEY trial.

METHODS

In the STASEY trial (Figure 1), minor and unplanned major surgeries were managed per the investigator's discretion.

Figure 1. STASEY trial design.


PwHA, N = 195
≥12 years old
With congenital HA of any severity
With FVIII inhibitors
Treatment with BPAs or FVIII concentrates in the 6 months prior
Emicizumab SC 1.5 mg/kg QW* n = 193
First interim analysis†
Second interim analysis‡
Emicizumab SC continuation up to 2 years

*Maintenance dose. Emicizumab was administered at a loading dose of 3.0 mg/kg QW for 4 weeks prior to maintenance dosing.
†Scheduled when approximately 100 patients had received treatment for at least 24 weeks.
‡Scheduled when at least 100 patients had received treatment for at least 1 year.
BPA, bypassing agents; F, factor; HA, hemophilia A; PwHA, persons with hemophilia A; QW, once weekly; SC, subcutaneous.

- Surgeries were categorized as minor or major as defined by Santagostino E, et al. (2015)[3]
- Details of procedures (type and number), use of any additional coagulation factor, adverse events, and management of post-operative bleeds were captured.

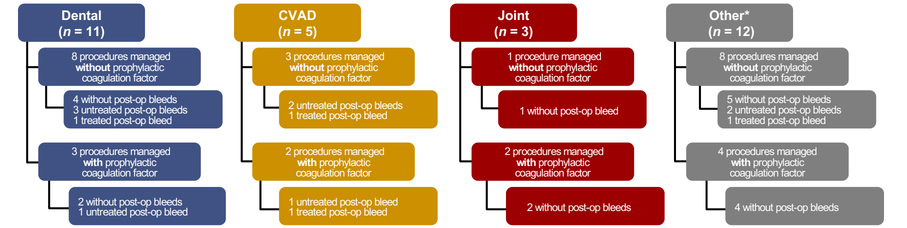
RESULTS

As of 20 May 2019, 31 minor and nine major surgeries were performed in 22 and eight participants, respectively.

- Two-thirds (20/31; 64.5%) of minor surgeries were managed without additional prophylactic coagulation factor; of these, only 3/20 (15.0%) required post-operative treatment for bleeds (**Figure 2**; **Table 1**).
- One of 11 (9.1%) minor surgeries managed with additional prophylactic coagulation factor required post-operative treatment for a bleed.
- Case details of a minor arthroscopic knee surgery are shown in **Table 2**.

RESULTS CONTINUED

Figure 2. Outcomes of minor surgeries (*n* = 31).


Dental (n = 11)
8 procedures managed without prophylactic coagulation factor
4 without post-op bleeds
3 untreated post-op bleeds
1 treated post-op bleed
3 procedures managed with prophylactic coagulation factor
2 without post-op bleeds
1 untreated post-op bleed
CVAD (n = 5)
3 procedures managed without prophylactic coagulation factor
2 untreated post-op bleeds
1 treated post-op bleed
2 procedures managed with prophylactic coagulation factor
1 untreated post-op bleed
1 treated post-op bleed
Joint (n = 3)
1 procedure managed without prophylactic coagulation factor
1 without post-op bleed
2 procedures managed with prophylactic coagulation factor
2 without post-op bleeds
Other* (n = 12)
8 procedures managed without prophylactic coagulation factor
5 without post-op bleeds
2 untreated post-op bleeds
1 treated post-op bleed
4 procedures managed with prophylactic coagulation factor
4 without post-op bleeds

*Other minor surgeries were: skin (*n* = 8), blood vessel (*n* = 2), chemocauterization, epistaxis (*n* = 1), and laser eye surgery (*n* = 1).
N refers to the number of surgeries. Categories defined by manual review. One minor skin surgery (skin graft) is not included here as it was part of a combined major surgery (arthrodesis)
CVAD, central venous access device; post-op, post-operative..

Table 1. Outcomes of cases of interest in PwHA undergoing minor surgery.

	Surgery type			
	Tooth extraction	Cutaneous biopsy	CVAD insertion	Tooth extraction*
Age, years†	21	42	75	64
Prophylactic coagulation factor, yes/no	No	No	Yes	No
Cumulative prophylactic factor administered	-	-	48 μg/kg rFVIIa	-
Bleed, yes/no Type/location of bleed Treated/untreated	Yes Mouth Treated	Yes Skin wound/right calf Treated	Yes Chest Untreated	Yes Mouth Untreated
Cumulative factor for post-op bleed	15 μg/kg rFVIIa	88 μg/kg rFVIIa	-	-
Hemostatic grading	Good, fair	Excellent	Excellent	Good, fair

*Patient also received tranexamic acid. †Age at study entry.
CVAD, central venous access device; PwHA, persons with hemophilia A; rFVIIa, recombinant activated factor VII.

- Dental interventions with anti-fibrinolytics were uncomplicated with the exception of one case where an additional dose of 90 ug/kg FVIIa was added; the combined use of anti-fibrinolytics and FVIIa led to formation of a hypertrophic clot at the extraction site, which required surgical removal.
- Overall, 8/9 (89%) major surgeries were managed with prophylactic coagulation factor, resulting in four treated post-operative bleeds, two untreated bleeds, and two resulting in no bleeds (**Table 3**). One major surgery, coronarography for myocardial ischemia, was managed without prophylactic coagulation factor and did not lead to a post-operative bleed.
  - Case details of a total hip replacement are shown in **Table 4**.

Table 2. Case details of a semi-acute arthroscopic knee surgery due to infected prosthesis (minor surgery).

Patient characteristics

- 47-year-old male with HA and long-lasting high titer FVIII inhibitors (292 BU).

Pre-operative treatment

- Bolus 85 μg/kg rFVIIa was administered 1 hour pre-operation.

Peri- and post-operative treatment

- 60 μg/kg rFVIIa every 4 hours for 5 days.

Case details

- The PwHA presented with an active infection of the knee; two punctures (intra-articular and in the surrounding tissue) were covered by two bolus injections of 60 μg/kg rFVIIa given 3 hours apart.
- Cultures were positive for *Klebsiella Pneumoniae*; the PwHA was admitted and treated with antibiotics.
- The arthroscopic knee surgery was uneventful and there was no evidence of TMA; the patient was discharged on Day 4 after surgery.

BU, Bethesda units; F, factor; HA, hemophilia; PwHA, person with hemophilia A; rFVIIa, recombinant activated factor VII; TMA, thrombotic microangiopathy.

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Emicizumab is subject to additional safety monitoring requirements in many countries. Healthcare professionals are asked to report any suspected adverse reactions to the regulatory authorities in your country according to your national requirements.

Table 3. Case details and outcomes of major surgeries/procedures in PwHA.

Surgery	Age, years*	Type of additional prophylaxis	Post-op bleed (treated/untreated)
Arthroplasty			
Hip arthroplasty	33	aPCC†	No
Hip arthroplasty	50	rFVIIa	Yes, untreated
Arthroplasty, leg amputation	55	rFVIIa	Yes, treated
Femur fracture treatment	17	rFVIIa	Yes, treated
Open reduction of femur fracture	18	rFVIIa	Yes, untreated
Joint			
Arthrodesis	61	rFVIIa	Yes, treated
Arthrodesis	61	rFVIIa	Yes, treated
Other			
Hemorrhoid operation, polypectomy§	58	FVIII‡	No
Coronarography for MI‖	55	-	No

*Age at study entry. †Monitoring for development of thrombotic events should be undertaken when emicizumab is administered in combination with aPCC >100 U/kg/24 hours for ≥24 hours.[4] ‡Short-acting. §Considered major because of surgical rather than laser removal. ‖As this participant was fully anti-coagulated, this is considered a major procedure.
aPCC, activated prothrombin complex concentrate; FVIII, factor VIII; MI, myocardial infarction; PwHA, persons with hemophilia A; rFVIIa, recombinant activated factor VII.

Table 4. Case details of a total hip replacement (major surgery).

Patient characteristics

- 50-year-old* male with hemophilia A with high-responding FVIII inhibitors.

Pre-operative treatment

- Bolus 90 μg/kg rFVIIa was administered at the start of surgery.

Peri- and post-operative treatment

- During surgery, 80 μg/kg rFVIIa was administered every 3 hours; post-operatively, 80 μg/kg rFVIIa dosing was administered every 4 hours (Days 1–3); every 6 hours (Days 4–7); and every 8 hours (Days 8–11).
- TA (3 g/24 hours) and prophylactic LMW heparin were administered for the entire post-operative period.

Case details

- The surgeon rated hemostasis as 'good to excellent'; the lowest hemoglobin (99 g/L) was recorded on Day 2.
- The patient had no signs of TMA and was discharged in good health on Day 11.

*Patient was aged 51 years at time of surgery.
LMW, low molecular weight; rFVIIa, recombinant activated factor VII; TA, tranexamic acid; TMA, thrombotic microangiopathy.

CONCLUSIONS

- In PwHA with FVIII inhibitors receiving emicizumab prophylaxis, most minor surgical procedures were performed without additional prophylactic coagulation factor and did not result in post-operative treated bleeds.
  - Emicizumab alone may provide adequate hemostatic coverage for patients undergoing certain types of minor surgery.
- Major surgeries were safely performed with additional coagulation prophylaxis.
- Peri-operative management of surgeries with rFVIIa did not result in TE or TMA.

ACKNOWLEDGMENTS

The authors would like to thank the study participants and their families, as well as the study investigators and site personnel. This study was sponsored by F. Hoffmann-La Roche Ltd. Statistical support for this analysis was provided by Vanessa Lestang of Cytel, Inc. Third-party medical writing support for this poster was provided by Alex Coulthard, BSc, of Gardiner-Caldwell Communications and was funded by F. Hoffmann-La Roche Ltd.