Poster No. 1786

A Phase IV, Multicenter, Open-label Study of Emicizumab Prophylaxis in Persons with Hemophilia A with or Without FVIII Inhibitors Undergoing Minor Surgical Procedures

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Acknowledgments

This study was sponsored by F. Hoffmann-La Roche Ltd and Genentech, Inc. Third party medical writing assistance, under the direction of the authors, was provided by Alex Coulthard, BSc, of Gardiner-Caldwell Communications and was funded by F. Hoffmann-La Roche Ltd and Genentech, Inc.

Disclosures

ME: has provided consultancy to BioMarin, Pfizer, Novo Nordisk, CSL Behring, Kedrion, Genentech, Inc., Sanofi, Takeda and the National Hemophilia Foundation, and received research funding from Pfizer, Novo Nordisk, Sanofi, Takeda and UniQure; **AD**: has provided consultancy to Genentech, Inc. and UniQure, received honoraria from Spire and Medscape, received research funding from BioMarin, Takeda and the American Thrombosis and Hemostasis Network, and is on a Board of Directors/Advisory Committee for the World Federation of Hemophilia USA; **DQ**: has received honoraria from Bayer, BioMarin, Bioverativ/Sanofi, Genentech, Inc. and F. Hoffmann-La Roche Ltd, Novo Nordisk and Octapharma and acted as a speaker for BioMarin, Bioverativ/Sanofi, Genentech, Inc. and F. Hoffmann-La Roche Ltd, Novo Nordisk and Shire/Takeda; **BT**: employee of and holder of stocks in Genentech, Inc.; **LL** and **RHK**: employees of Genentech, Inc. and holders of stocks in F. Hoffmann-La Roche Ltd; **SLC**: has received honoraria from Kedrion, Novo Nordisk and Genentech, Inc., has received research funding from CSL Behring and Shire, is on a Board of Directors/Advisory Committee for the American Thrombosis and Hemostasis Network and the Hemostasis and Thrombosis Research Society, and is on the PREP Heme/Onc Editorial Board of the American Academy of Pediatrics.

Key takeaways

- In this study of people with hemophilia A receiving emicizumab prophylaxis, minor surgeries were safely performed
- The majority of participants did not have excessive bleeding at the surgical site and did not receive bypassing agent/factor VIII post-operatively

Accepted as a Poster Presentation at the 62nd ASH Annual Meeting and Exposition

This study evaluated the safety and efficacy of emicizumab prophylaxis in PwHA undergoing minor surgical procedures

Background

- Emicizumab is a bispecific, humanized, monoclonal antibody that restores the function of missing FVIIIa in PwHA[1,2]
- The management of PwHA undergoing surgery while receiving emicizumab is of clinical interest

Study design

- A multicenter, Phase IV, single-arm study (NCT03361137)

Study population

- PwHA of any age, with/without FVIII inhibitors, were eligible to participate, provided that they:
  - had received ≥4 loading doses of emicizumab
  - were scheduled to undergo a minor surgical procedure
  - were scheduled to receive emicizumab 1.5 mg/kg weekly, 3 mg/kg every 2 weeks, or 6 mg/kg every 4 weeks for ≥1 month after surgery

Endpoints

- Included incidence of excessive bleeding* intra-operatively and until discharge from surgery, use of BPAs or FVIII to control bleeding, and AEs

- The study was terminated early due to low enrollment and the limited variety of types of surgery

*Excessive bleeding, as assessed by the healthcare professional performing the surgery, was defined as a rating of fair to poor on the hemostatic rating scale[3] and translates to an intra- and/or post-operative blood loss of ≥25% over expectation for a patient without hemophilia prior to discharge from surgery.
AE, adverse event; BPA, bypassing agent; FVIII, factor VIII; FVIIIa, activated factor VIII; PwHA, persons with hemophilia A.

1. Kitazawa T, et al. *Nat Med* 2012;18:1570–74;
2. Shima M, et al. *N Engl J Med* 2016;374:2044–53;
3. Blanchette VS, et al. *J Thromb Haemost* 2014;12:1935–39.

The majority of participants were <18 years of age and all surgeries were either CVAD removal or dental procedures

	Participants with FVIII inhibitors (n=11)	Participants without FVIII inhibitors (n=3)
Age, years		
Mean (SD)	12.7 (5.6)	16.7 (17.2)
<18, n (%)	9 (81.8)	2 (66.7)
≥18–<65, n (%)	2 (18.2)	1 (33.3)
BMI, kg/m² (mean [SD])	20.5 (6.4)	20.3 (3.7)
Ethnicity, n (%)		
Hispanic or Latino	4 (36.4)	1 (33.3)
Not Hispanic or Latino	7 (63.6)	2 (66.7)
Race, n (%)		
Asian	1 (9.1)	0
Black or African American	1 (9.1)	1 (33.3)
White	6 (54.5)	1 (33.3)
Multiple	2 (18.2)	0
Unknown	1 (9.1)	1 (33.3)
Surgical procedure, n (%)		
Removal of CVAD	9 (81.8)	2 (66.7)
Simple dental extraction	1 (9.1)	1 (33.3)
Not performed within study dates due to COVID-19	1 (9.1)*	0

- In total, 10 PwHA with FVIII inhibitors and 3 PwHA without FVIII inhibitors underwent minor surgery

*This participant did not undergo surgery within the scheduled dates and is therefore not included in the surgery population.

BMI, body mass index; COVID-19, coronavirus disease 2019; CVAD, central venous access device; FVIII, factor VIII; PwHA, persons with hemophilia A; SD, standard deviation.

Few participants had bleeding events or received treatment with rFVIIa or FVIII either during surgery or post-operatively

- Overall, 7/10 (70%) and 3/3 (100%) PwHA with and without FVIII inhibitors, respectively, did not have excessive bleeding at the surgical site and did not receive rFVIIa/FVIII post-operatively
  - Of 10 PwHA with FVIII inhibitors, 1 person had excessive bleeding during surgery with a need for rFVIIa treatment and 3 PwHA had post-operative bleeding with a need for rFVIIa treatment
  - Of 3 PwHA without FVIII inhibitors, none had excessive bleeding necessitating FVIII treatment during surgery or until discharge; one PwHA had a post-operative bleed that did not require treatment

Participants with bleeding due to surgery who received intra-operative or post-operative treatment with rFVIIa or FVIII

Participant	Procedure	Excessive bleeding* during surgery	rFVIIa or FVIII use during surgery	Post-operative bleeding	rFVIIa or FVIII post-operatively
Participants with FVIII inhibitors					
#1	Simple dental extraction	✖	✖	✓	70.4 µg/kg rFVIIa
#2	CVAD removal	✓	74.9 µg/kg rFVIIa	✓	74.9 µg/kg rFVIIa
#3	CVAD removal	✖	91.7 µg/kg rFVIIa	✓	91.7 µg/kg rFVIIa
#4	CVAD removal	✖	84.3 µg/kg rFVIIa	✖	✖
Participants without FVIII inhibitors					
#5	Simple dental extraction	✖	✖	✓	✖

*Excessive bleeding, as assessed by the healthcare professional performing the surgery, was defined as a rating of fair to poor on the hemostatic rating scale[1] and translates to an intra- and/or post-operative blood loss of ≥25% over expectation for a patient without hemophilia prior to discharge from surgery.
CVAD, central venous access device; FVIII, factor VIII; PwHA, persons with hemophilia A; rFVIIa, recombinant activated factor VII.

1. Blanchette VS, et al. *J Thromb Haemost* 2014;12:1935–39.

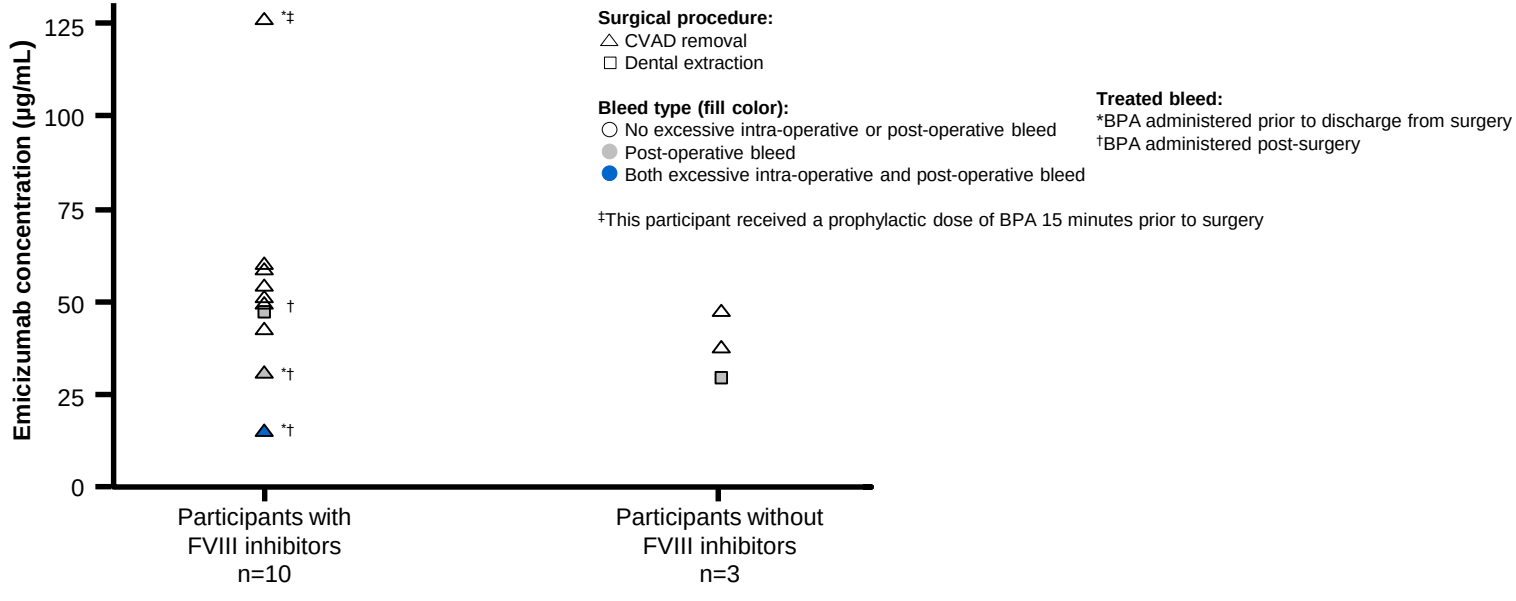
Overall, 3 PwHA undergoing surgery received antifibrinolytics peri-operatively

Details of participants who received peri-operative treatment with antifibrinolytics

Antifibrinolytic	Dose	Duration	Excessive bleeding during surgery or post-operative bleeding
Participants with FVIII inhibitors			
Aminocaproic acid	53 mg/kg QID 80 mg/kg QID	4 days 7 days	Post-operative bleed requiring rFVIIa
Tranexamic acid	1300 mg TID	8 days	×
Participants without FVIII inhibitors			
Aminocaproic acid	28 mg/kg QID	8 days	×

FVIII, factor VIII; PwHA, persons with hemophilia A; QID, four times a day; rFVIIa, recombinant activated factor VII; TID, three times a day.

Emicizumab concentrations prior to surgery and outcomes



- One participant with FVIII inhibitors, who had both excessive intra-operative and post-operative bleeding, had an emicizumab plasma concentration of ~15 µg/mL[§]

[§]This participant was receiving emicizumab 1.5 mg/kg weekly (to which there were no adherence issues) and was Day 5 post-dose on the day of the blood draw. The patient received one dose of rFVIIa intra-operatively and one dose post-surgery for a non-severe bleed with resolution of bleeding one hour later.

Emicizumab plasma concentrations may or may not represent trough levels.

BPA, bypassing agent; CVAD, central venous access device; FVIII, factor VIII; rFVIIa, recombinant activated factor VII.

The majority of participants did not report AEs; all reported AEs were low-grade, non-serious and unrelated to emicizumab

n	Participants with FVIII inhibitors (n=10)	Participants without FVIII inhibitors (n=3)
Any AE	4	0
Treatment-related AE	0	0
Grade 3–5 AE	0	0
AE leading to dose modification or interruption	0	0
AE leading to withdrawal from treatment	0	0
Serious AE	0	0
Thromboembolic event	0	0
Thrombotic microangiopathy event	0	0
Complication requiring hospitalization or return to surgery	0	0

- A total of 6 AEs were reported in 4 participants: headache (n=2), constipation, procedural pain, adhesiolysis, and hematoma (all n=1)

AE, adverse event; FVIII, factor VIII.

Conclusions

- In this small study of PwHA with/without FVIII inhibitors receiving emicizumab prophylaxis, minor surgeries were safely performed; the majority of participants did not have excessive bleeding at the surgical site and did not receive BPA/FVIII during surgery or post-operatively
- The data suggest that consideration be given to the maintenance of emicizumab concentration levels prior to surgery
- There were no serious AEs, thromboembolic events, thrombotic microangiopathy events or deaths
- These data are consistent with findings from previous studies; further analyses assessing surgical outcomes in PwHA with/without FVIII inhibitors are ongoing[1,2]

AE, adverse event; BPA, bypassing agent; FVIII, factor VIII; PwHA, persons with hemophilia A.

1. Santagostino E et al. *Res Pract Thromb Haemost* 2019;3:1–228; OC 60.1;
2. Castaman G et al. *Res Pract Thromb Haemost* 2020;4(Suppl 1): PB0939.

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