Emicizumab Prophylaxis in People with Haemophilia A: Summary of 10 Years of Safety Data on Thromboembolic Events and Thrombotic Microangiopathy

Authors: Katayon Sarouei,[1] Simona Barlera,[2] Letizia Polito,[3] Guillermo Tobaruela,[3]* Juliana ML Biondo[1]

**Email: william.tobaruela@roche.com*

Affiliations: [1]Genentech, Inc., South San Francisco, CA, USA; [2]Parexel International, Milan, Italy; [3]F. Hoffmann-La Roche Ltd, Basel, Switzerland

Summary

An updated safety evaluation of **thrombotic events (TEs) and thrombotic microangiopathies (TMAs)** was conducted in people with congenital haemophilia A receiving emicizumab

The reporting rate for TEs without concomitant activated prothrombin complex concentrate **remains low** as more people are treated with emicizumab

No new safety concerns were observed since the last data cut-off and the benefit–risk profile remains positive in this summary of 10 years of safety data

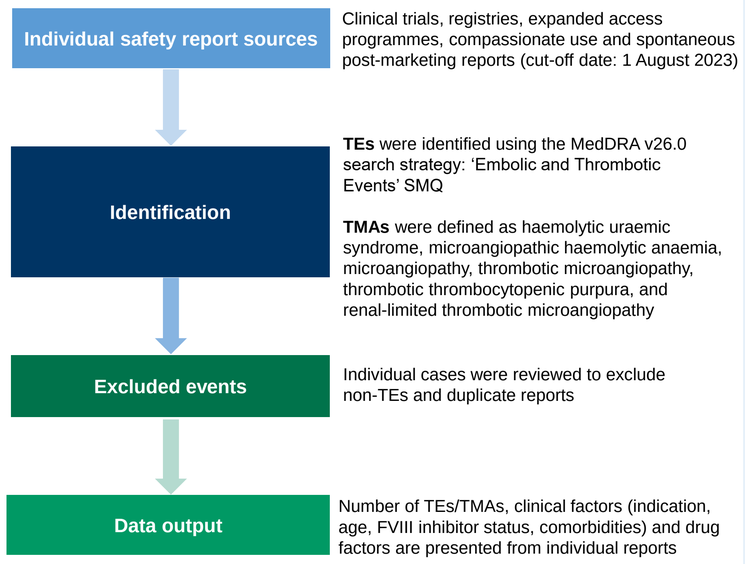
Health authorities **no longer require special expedited safety reporting** of TE's/TMAs for emicizumab

Background

- As of July 2023, more than 24,000 people have been treated with emicizumab worldwide, with this number continually growing.[1]
- In 2017, the HAVEN 1 clinical trial outlined thrombotic events (TEs) and thrombotic microangiopathies (TMAs) as risks when taking emicizumab alongside activated prothrombin complex concentrate (aPCC) at doses of >100U/kg/24 hours for ≥24 hours in people with haemophilia A (HA).[2]
- Subsequently, these events have been monitored on an ongoing basis in all individuals receiving emicizumab, with or without concurrent aPCC, and routine risk minimisation activities have been included in the label.
- This poster presents an updated safety evaluation of emicizumab prophylaxis, focusing on TEs and TMAs.

Methods

Figure 1. Methodology



F, factor; MedDRA, Medical Dictionary for Regulatory Activities; SMQ, Standardised Medical Query.

Results

- From 28 June 2012 to 1 August 2023, 155 events in 137 patients meeting the search criteria were identified, from 24 countries, in the Roche Global Safety Database (**Figure 2**).
- In people with congenital HA and other non-approved indications, there were 18 clinical trial events in 18 patients, 112 post-marketing events in 97 patients, and 25 non-interventional study events in 22 patients.
- Of these, 97 events were identified in people with congenital HA (34 since the previous analysis[3]): two TEs and five TMAs associated with aPCC, and 90 TEs not associated with aPCC use.

Figure 2. Summary of TEs and TMA events

*Includes off-label or unknown indication. †Excluded case reports include intracranial haemorrhage (n=6), blood clot in urine (n=1), duplicate report (n=1), and invalid case report (n=1). ‡One new TMA case reported since last analysis.[3]
Blue shading in the figure indicates congenital haemophilia A.
AHA, acquired haemophilia A; VWD, Von Willebrand disease.

One new TMA associated with aPCC was reported since the last analysis[3]

- The new TMA event observed since the previous data cut (15 May 2022[3]) was from a report in the Roche Global Safety Database in October 2022
  - A patient with severe HA was given aPCC above the dosage specified in the treatment guidelines in a risk–benefit decision to treat a diverticular haemorrhage. The patient subsequently recovered.

A total of 81 non-aPCC-associated and non-device-associated TEs were reported in people with congenital HA receiving emicizumab

- Characteristics of non-aPCC-associated and non-device-associated TEs are described in **Table 1**.
- The median (range) age at event was 48 (0.8–84) years.
- A total of 71 (87.7%) TEs were medically confirmed and 10 (12.3%) were consumer reported; sources included spontaneous (44 TEs), non-interventional studies (13 TEs), literature (4 TEs), and clinical trials (8 TEs).
- Twenty-three (28.4%) TEs occurred in 16 people with HA with known FVIII inhibitors.
- There was a new fatality since the previous analysis,[3] a cerebrovascular event in a person with multiple cardiovascular risk factors.

Table 1. Characteristics of people with congenital HA who experienced non-device-associated TEs

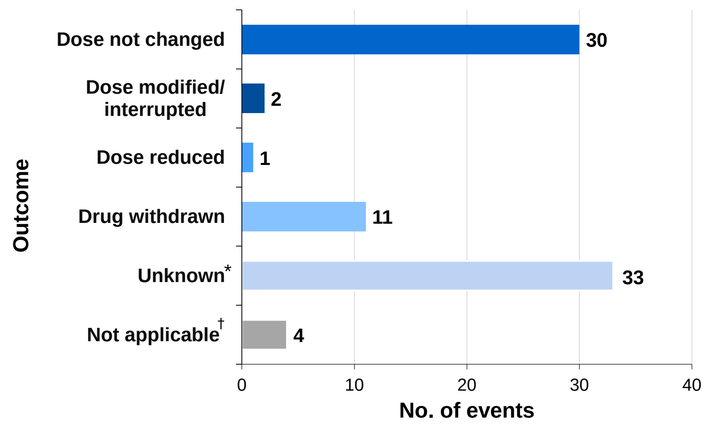
	Non-aPCC-associated and non-device-associated TEs N=81
Median (range) age at event, years	48 (0.8–84)*
Medically confirmed, n (%) **Consumer reported, n (%)**	71 (87.7) 10 (12.3)
Sources, n (%) Post-marketing† Non-interventional study Clinical trials‡	 48 (59.3) 13 (16.0) 8 (9.9)
Presence of FVIII inhibitors, n (%)	23 (28.4)
Associated with ≥1 CV risk factor§ or other risk factor for thrombosis,¶ n (%)	55 (67.9)
Led to discontinuation of emicizumab, n (%)	11 (13.6)
TEs with fatal outcome, n (%)**	5 (6.2)

*Age was provided for 50 of 69 cases. †Post-marketing events included 44 spontaneous reports and 4 events reported in the literature. ‡Clinical trial events included six SAEs: acute myocardial infarction (MO39129), acute coronary syndrome (BH37001), acute myocardial infarction (BH37001), myocardial infarction (unknown study, patient-reported), venous limb thrombosis (YO39309), cerebrovascular accident (YO39309), and two non-serious AEs: haemorrhoids thrombosed (BO41423) and renal infarct (BO41423). §Previous myocardial infarction, ischaemic heart disease, coronary artery disease, hypertension, hyperlipidaemia, smoking, advanced age. ¶Sepsis/bacteraemia, coinciding injury, hepatitis C, thrombosis.[4,5] **Two myocardial infarctions and one cerebrovascular event in three people with multiple risk factors; two disseminated intravascular coagulation events related to pneumonia in two people >70 years old.
CV, cardiovascular; SAEs, serious adverse events.

Among people with HA who had dose modification data available and experienced a non-aPCC-associated and non-device-associated TE, most had no change to emicizumab prophylaxis

- Emicizumab prophylaxis was modified, interrupted, reduced, or withdrawn in 14/81 (17.3%) events of people with HA receiving emicizumab without concomitant aPCC experiencing a TE (**Figure 3**).
- There were no dose modifications in 30/81 (37.0%) events of people with HA experiencing a non-aPCC-associated TE; data are unknown for 33 events.

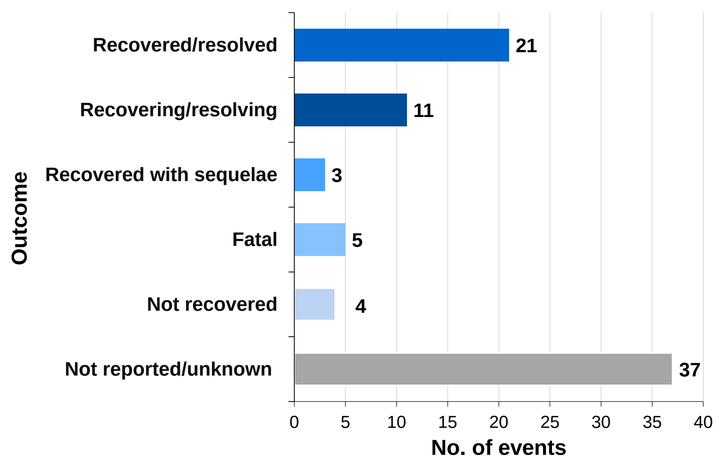
Figure 3. Dose modifications in people with congenital HA who experienced non-aPCC-associated TEs



*Includes two fatal TEs; †Three fatal TEs and one non-fatal case of myocardial infarction that was incorrectly coded.

A total of 32/81 non-aPCC-associated and non-device-associated TEs were recovered or resolving at the time of data cut

Figure 4. Reported outcomes of TEs at the time of analysis



Clinical trial incidence and real-world data analyses

- The incidence rate for serious TEs (excluding aPCC-related serious AEs) in clinical trials with people with congenital HA receiving emicizumab is 0.17 events per 100 person-years (based on data from 850 patients with a median emicizumab exposure of 108 weeks; 95% confidence interval [CI]: 0.05–0.43).[1]
- TE frequency is also monitored in numerous key emicizumab clinical trials, Phase IV HA studies, and ongoing registries including: HAVEN 1–7, STASEY, AOZORA, ACE002JP, ATHN 7/ATHN Transcends, EUHASS, PedNET, HEMNOR, and UKHCDO.
- Real-world data in the overall population of people with HA, irrespective of treatment, including incidence risk for arterial, venous and device-related TEs, is shown in **Table 2**.

Table 2. Real-world data analyses using the US-based Market Scan claims database for people with HA irrespective of treatment[6]

Events	Incidence rate ratio (95% CI)	Crude incidence rate/ 100 person-years (95% CI)
Arterial events		
Myocardial infarction	0.80 (0.53–1.12)	0.23 (0.15–0.32)
Ischaemic stroke*	1.03 (0.72–1.39)	0.29 (0.20–0.39)
Venous events		
Deep vein thrombosis*	0.89 (0.60–1.23)	0.25 (0.17–0.35)
Pulmonary embolism	0.29 (0.14–0.49)	0.08 (0.04–0.14)
Device-related thrombosis	1.60 (1.21–2.05)	0.46 (0.35–0.58)

*Excludes device-related thrombosis.

Limitations of data collection through pharmacovigilance initiatives

- Pharmacovigilance initiatives exist for the purpose of monitoring and reporting on adverse events.
- Due to the potential underreporting of events in this context, making conclusions based on incidence rates is discouraged, especially given that many events are reported in the literature for the emicizumab clinical trial programme.
- Reporting events with greater detail outside clinical trials can continue to support understanding of TEs and TMA events.

Conclusions

- No new safety concerns were observed since the last data cut-off and the risk–benefit profile remains positive.
- All TMAs were associated with concomitant use of aPCC at >100U/kg/24 hours for ≥24 hours.
- Most TEs (67.9%) were associated with pre-existing cardiovascular risk factors and/or risk factors for thrombosis.
- This analysis continues to support that TEs and TMAs without concomitant aPCC at doses of >100U/kg/24 hours for ≥24 hours are not an identified risk for people with HA receiving emicizumab prophylaxis.
- Health authorities no longer require special expedited safety reporting for emicizumab worldwide. However, monitoring and reporting of safety data are still ongoing.

Presented at The European Association for Haemophilia and Allied Disorders (EAHAD) 2024 Annual Meeting | 6–9 February 2024 | Frankfurt, Germany

References

1. Roche, data on file.
2. Oldenburg J, et al. N Engl J Med 2017;377(9):809–18.
3. Koparkar S, et al. Presented at EAHAD 2023.
4. Anderson FA, Jr. and Spencer FA. Circulation 2003;107(23 Suppl. 1):I9–16.
5. Mozaffarian D, et al. Circulation 2016;133:e38–360.
6. Faghmous I, et al. J Comp Eff Res 2021;10(18):1323–36.

Acknowledgements

This analysis was sponsored by F. Hoffmann-La Roche Ltd/Genentech, Inc. Third party medical writing assistance, under the direction of all authors, was provided by Jake Hunter, MSc, of Ashfield MedComms, an Inizio company, and was funded by F. Hoffmann-La Roche Ltd/Genentech, Inc.

Disclosures

KS: Shareholder of: F. Hoffmann-La Roche Ltd, Employee of: Genentech, Inc.; **SB**: None Declared; **LP**: Shareholder and employee of: F. Hoffmann-La Roche Ltd; **GT**: Shareholder of: F. Hoffmann-La Roche Ltd, Employee of: F. Hoffmann-La Roche Ltd; **JB**: Employee of: Genentech, Inc.

Download this presentation: https://ter.li/2624v2