Evaluation of the safety of emicizumab prophylaxis in people with haemophilia A: an updated summary of thrombotic events and thrombotic microangiopathies

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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 (aPCC) **remains low** as exposure increases

The evidence does not support a causal relationship between TEs and emicizumab, and the benefit–risk profile of emicizumab **remains positive**

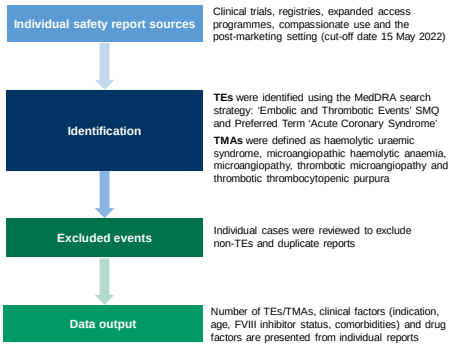
All four TMAs identified in this analysis were associated with concomitant aPCC, and **no new TMAs** have been reported since the previous analysis[6]

Background

- As of March 2022, more than 15,000 people had been treated with emicizumab worldwide, with this number continually growing.[1]
- The HAVEN 1–4 trials identified thrombotic events (TEs) and thrombotic microangiopathies (TMAs) as risks when emicizumab is used alongside activated prothrombin complex concentrate (aPCC) at doses of >100U/kg/24 hours for ≥24 hours in people with haemophilia A (HA).[2–5]
- 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 and beyond. This poster presents an updated safety evaluation of emicizumab prophylaxis, focusing on TEs and TMAs.

Methods

Figure 1. Methodology

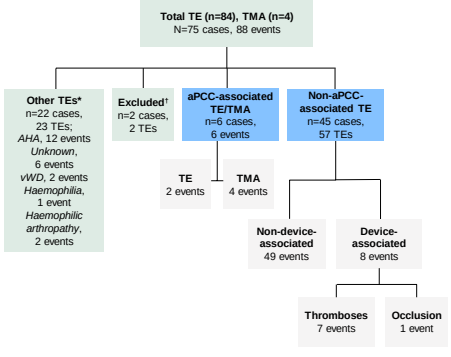


F, factor; MedDRA, Medical Dictionary for Regulatory Activities; SMQ, Standardised Medical Query

Results

- As of the data cut-off (15 May 2022), 75 cases (88 events) meeting the search criteria were identified on the Roche Global Safety Database (**Figure 2**).
- There were 11 clinical trial cases (11 events), 51 post-marketing cases (63 events), and 13 non-interventional study cases (14 events), across approved and unapproved indications, including off-label use.
- Of these, 63 events were identified in people with congenital HA: two TEs and four TMAs associated with aPCC, and 57 TEs not associated with aPCC use.

Figure 2. Summary of TEs and TMA events



*Includes off-label or unknown indication. †Excluded case reports include one duplicate and one hemiparesis event not related to TEs but captured by SMQ. Blue shading in the figure indicates congenital haemophilia A.
AHA, acquired haemophilia A; SMQ, Standardized Medical Query; vWD, von Willebrand disease

No new TEs or TMAs associated with aPCC have been reported since the last analysis (data cut-off 15 May 2021)

- At last analysis, two TEs and four TMAs associated with aPCC were reported;[6] this updated analysis reports no new aPCC-associated TEs or TMAs.

A total of 49 non-device-associated and non-aPCC-associated TEs were reported in people with congenital HA receiving emicizumab

- Characteristics of non-device-associated and non-aPCC-associated TEs are described in **Table 1**.
- The median age at event was 48 (range 0.8–84) years.
- A total of 46 (94.0%) TEs were medically confirmed and three (6.0%) were consumer reported; sources included spontaneous (27 TEs), non-interventional studies (10 TEs), literature (8 TEs), and clinical trials (4 TEs).
- Sixteen (32.7%) TEs occurred in people with HA with known FVIII inhibitors.

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

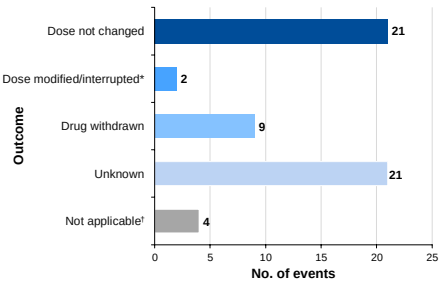
	Non-device-associated TEs N=49
Median (range) age at event, years	48 (0.8–84)*
Medically confirmed, n (%) **Consumer reported, n (%)**	46 (93.9) 3 (6.1)
Sources, n (%) Post-marketing† Non-interventional study Clinical trials‡	 35 (71.4) 10 (20.4) 4 (8.2)
Presence of FVIII inhibitors, n (%)	16 (32.7)
Associated with ≥1 CV risk factor§ or other risk factor for thrombosis¶, n (%)	41 (83.7)
Led to discontinuation of emicizumab, n (%)	9 (18.4)
TEs with fatal outcome, n (%)**	4 (8.2)

*Age was provided for 33 events and unknown for nine events. †Post-marketing events include 27 spontaneous events and eight events reported in the literature. ‡Clinical trial events included: three SAEs with acute myocardial infarction (MO39129), acute coronary syndrome (BH37001), acute myocardial infarction (BH37001) and non-serious AE of haemorrhoids thrombosed (BO41423). §Previous myocardial infarction, ischaemic heart disease, coronary artery disease, hypertension, hyperlipidaemia, smoking, advanced age. ¶Sepsis/bacteraemia, device use, coinciding injury, hepatitis C, thrombosis.
**Two myocardial infarctions in medically complex individuals; two DIC events in people >70 years of age with pneumonia.
CV, cardiovascular, DIC, disseminated intravascular coagulation

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

- Emicizumab prophylaxis was modified, interrupted, or withdrawn in 11/57 (19.3%) events of people with HA receiving emicizumab without concomitant aPCC experiencing a TE (**Figure 3**).
- There were no dose modifications in 21/57 (36.8%) events of people with HA experiencing a non-aPCC-associated TE, and data are unknown for 21 events.

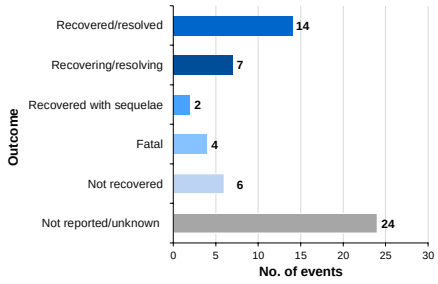
Figure 3. Dose modifications in people with congenital HA who experienced non-aPCC-associated TEs



*One person received 1.5mg/kg emicizumab once per week and then, following two TEs, received 240mg once per week as reported; †TEs with fatal outcome.

A total of 23/57 non-aPCC-associated TEs were recovered or resolving at the time of data cut

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



A total of 41 non-aPCC-associated TEs were associated with ≥1 CV risk factor or other risk factor for thrombosis*

- All non-aPCC-associated and non-device-associated TEs for which data were available (41/49 events) were associated with a CV or other thrombosis risk factor
  - CV risk factors included previous myocardial infarction, ischaemic heart disease, coronary artery disease, hypertension, hyperlipidaemia, smoking, and advanced age (>50 years)
  - Risk factors for thrombosis included sepsis/bacteraemia, device use, coinciding injury, and hepatitis C infection.
- A total of 27 TEs were associated with ≥3 CV risk factors or other risk factors for thrombosis.

*Risk factors are defined as per Anderson FA, Jr., Spencer FA. 2003[7] and Mozaffarian D, et al. 2016.[8]

Clinical trial incidence and real-world data analyses

- The incidence rate for serious TEs in clinical trials with people with congenital HA receiving emicizumab is 0.15 events per 100 person-years (95% CI: 0.03–0.44).[2–5,9–12]
- Key clinical trials, Phase IV HA studies, and ongoing registries measuring TE frequency include: HAVEN 1–7, STASEY, ATHN 7/ATHN Transcends, EUHASS, PedNET, HEMNOR, and UKHCDO.
- Real-world data in the overall population of people with HA, including incidence risk for arterial, venous and device-related TEs, is shown in **Table 2.**

Table 2. Real-world data analyses using the Market Scan claims database[13]

Events	Incidence risk, % (95% CI)	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.

Conclusions

- The reporting rate for TEs without concomitant aPCC remains low as emicizumab exposure increases.
- All TMAs were associated with concomitant use of aPCC, and no new TMAs have been reported since the previous analysis.
- Most cases with adequate information available were associated with pre-existing CV risk factors and/or risk factors for thrombosis.
- This analysis continues to support that TEs and TMAs without concomitant aPCC are not an identified risk for people with HA receiving emicizumab prophylaxis. The benefit–risk profile of emicizumab remains positive.

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Disclosures

SK: employment: Genentech Inc.; shareholder: Genentech Inc.; **SB**: nothing to disclose; **FN**: employment: F. Hoffmann-La Roche Ltd; shareholder: F. Hoffmann-La Roche Ltd; **RHK**: employment: Genentech Inc.; shareholder: Genentech Inc.; **GT**: employment: F. Hoffmann-La Roche Ltd; shareholder: F. Hoffmann-La Roche Ltd.