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Evaluation of the Safety of Emicizumab Prophylaxis in People with Hemophilia A (PwHA): An Updated Summary of Thrombotic Events and Thrombotic Microangiopathies

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Summary

Safety reports up to 15 May 2021 were collated and analyzed for TEs and TMAs in PwHA receiving emicizumab

No new TMAs and no new TEs associated with aPCC were reported since the last update

TEs and TMAs without concomitant aPCC were not identified as a risk for PwHA receiving emicizumab prophylaxis

51.4% PwHA had TEs that were recovered/resolving. In most cases, no changes in emicizumab prophylaxis were made as a result of the event

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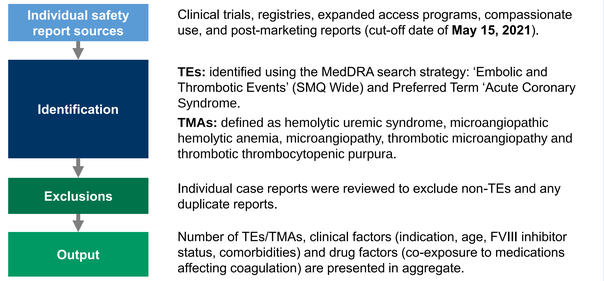
Background

- Emicizumab, a bispecific monoclonal antibody that substitutes for the function of factor (F)VIII, is indicated for routine prophylaxis in people with congenital hemophilia A (PwcHA) with/without FVIII inhibitors in >100 and >80 countries, respectively, and has been used by >11,400 people across the globe (data cut-off May 15, 2021).[1]
- The pivotal HAVEN 1–4 trials established the efficacy and safety of emicizumab prophylaxis; however, the HAVEN 1 trial identified an increased risk of thrombotic events (TEs) and thrombotic microangiopathies (TMAs) when emicizumab was used in conjunction with >100U/kg/24 hours of activated prothrombin complex concentrate (aPCC) for ≥24 hours.[2]
- Here we report an **updated safety evaluation** of emicizumab prophylaxis through May 15, 2021, focusing on reported TEs and TMAs.

Safety reports until May 15, 2021 were collated and analyzed for TEs and TMAs in people receiving emicizumab prophylaxis

Figure 1. Methodology for identification of TEs and TMAs in people treated with emicizumab

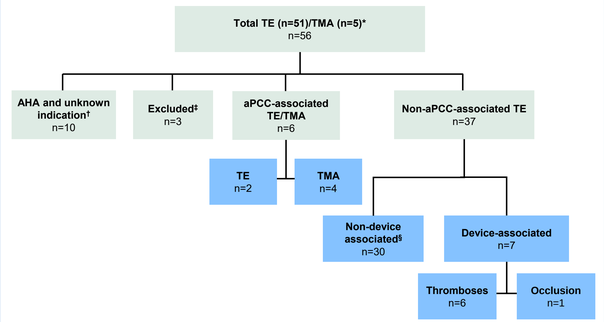


FVIII, factor eight; MedDRA, Medical Dictionary for Regulatory Activities; SMQ, standardized medical query; TEs, thrombotic events; TMAs, thrombotic microangiopathies

A total of 56 events met search criteria, 43 of which were identified after review

- In total, 52 cases (56 events) meeting search criteria were identified on the Roche Global Safety Database as of May 15, 2021 (**Figure 2**). Cases were defined as reports of PwHA experiencing TEs and/or TMAs; an event was defined as an occurrence of a TE or TMA.
- After review, 39 cases (43 events) were reported in PwcHA, while 10 cases were determined to be off-label/of unknown indication, two cases were determined to be duplicates, and one case of 'hemiparesis' was identified through SMQ review but did not fit the clinical definition of a true TE. In this case, the patient developed an intracerebral bleed and, as a consequence, also developed weakness of the left side (hemiparesis).
- In total, 33 cases (37 events; **37 TEs, no TMAs**) were not associated with concomitant aPCC use.

Figure 2. Summary of TE and TMA events in people receiving emicizumab



*One TMA occurred in a duplicate case report and was therefore excluded from this analysis. †Includes off-label use. Further evaluation of off-label/unknown indication is not provided in this abstract. ‡Excluded case reports include two duplicates and one hemiparesis event not related to TEs but captured by SMQ (n=1). §Includes case reports with preferred terms (verbatim terms) of thrombosis (thrombosis), cerebral infarction (multiple cerebral infarction), thrombophlebitis migrans (Trousseau's syndrome) considered one event. Previous safety update was January 2020.
Blue shading indicates congenital hemophilia A.
AHA, acquired hemophilia A; aPCC, activated prothrombin complex concentrate

No new TMAs or TEs associated with aPCC have been reported since the last update[3]

- At the previous safety evaluation (January 2020), only one TMA was reported outside of clinical trials, which was associated with concomitant aPCC above the recommended dosage.[3]
  - This was the only reported case of TMA following the issuing of risk minimization measures to provide guidance on bypassing agent use in combination with emicizumab.[3]
- No new TMA cases have been reported since the previous safety evaluation, demonstrating the continuing efficacy of the risk minimization measures.
- Since the previous safety evaluation, 24 TEs not associated with aPCC use have been reported.[3]
- **No TMAs have been reported without concomitant use of aPCC, and no new TMAs or TEs associated with aPCC use** were reported since the last update.[3]

A total of 37 TEs not associated with aPCC were reported in people with congenital hemophilia A

- Characteristics of the TEs not associated with aPCC are reported in **Table 1**.
- In total, **7 of these TEs (18.9%) were associated with central venous access devices (CVADs)** while 30 (81.1%) were not (**Table 1**)
  - Of the CVAD-related events, **4 were reported as resolving/recovering** at the last report.
- In **six of the 30 non-CVAD-associated cases** (20%), the event led to the discontinuation of emicizumab.
- An evaluation of latency or duration of treatment did not reveal any patterns or trends.

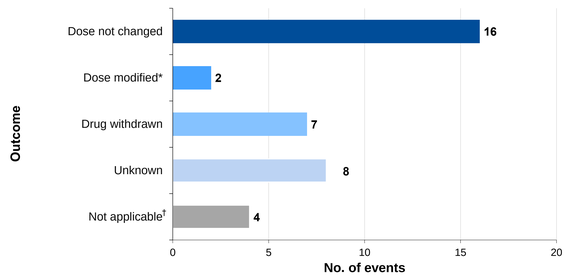
Table 1. Characteristics of PwcHA with TEs not associated with aPCC

	TEs reported in PwcHA (n=37)
Age at time of event, years	
Median	49
Range	0.42–84
Emicizumab treatment duration at time of event, days	
Median	330
Range	0–1076
TE report type, n (%)	
Medically confirmed	36 (97.3)
Patient reported	1 (2.7)
TEs occurring in PwcHA with FVIII inhibitors, n (%)	17 (45.9)
TEs associated with CVADs, n (%)	7 (18.9)
Resolving/recovering at last report	4
TEs associated with ≥1 CV risk factors* or other risk factors for thrombosis†, n (%)	34 (91.9)

*e.g. previous myocardial infarction, ischemic heart disease, coronary artery disease, hypertension, hyperlipidemia, smoking, advanced age >50 years; †e.g. sepsis/bacteremia, device use, coinciding injury, hepatitis C.
CV, cardiovascular; CVADs, central venous access devices; FVIII, factor eight; PwcHA, people with congenital hemophilia A

No changes to emicizumab prophylaxis were made in most patients who experienced a TE

Figure 3. Changes to emicizumab prophylaxis as a result of TE



*One patient received 1.5mg/kg emcizumab QW and then, following two TE events, received 240mg once per week; †TEs with fatal outcome.

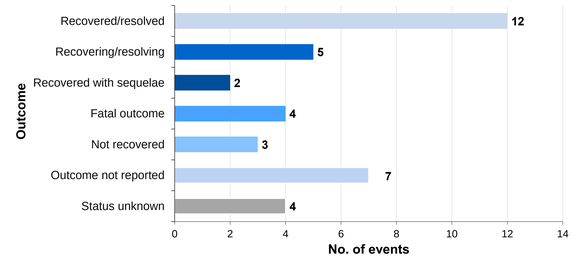
Four TEs with fatal outcome occurred in medically complex patients and people with advanced age

- **Four patients with TEs** not associated with aPCC had a fatal outcome (**Figure 4**):
  - Two myocardial infarctions in medically complex* patients.
  - Two disseminated intravascular coagulation events in people >70 years of age with pneumonia.

*One patient had multiple conditions including type 2 diabetes mellitus, hepatic cirrhosis, anemia, and upper gastrointestinal hemorrhage; another patient had assisted ambulation due to arthropathies. Both patients had hepatitis C.

The majority of TEs were recovered or resolving at the cut-off date

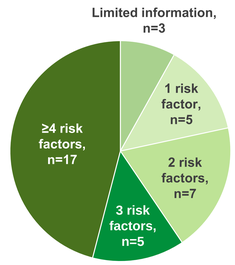
Figure 4. Reported outcomes of TEs at time of analysis



34/37 non-aPCC-related TEs were associated with ≥1 CV risk factor or other risk factors for thrombosis

- Almost all non-aPCC-related TEs in congenital HA (34/37) were associated with a history of CV disease or risk factors for thrombosis (**Figure 5**). In the other 3 events, there was not enough information to determine association with risk factors.
- CV risk factors included previous myocardial infarction, ischemic heart disease, coronary artery disease, hypertension, hyperlipidemia, smoking, and advanced age (>50 years).
- Risk factors for thrombosis included sepsis/bacteremia, device use, coinciding injury, and hepatitis C infection.

Figure 5. Association of TEs with CV and/or thrombosis risk factors*



*Risk factors are defined as per Anderson FA, Jr., Spencer FA. 2003[4] and Mozaffarian D, et al. 2016[5]

Conclusions

- The evaluation of TEs without concomitant aPCC remains similar to previous analyses as exposure increases.
- All TE cases with adequate information available were associated with CV risk factors and/or risk factors for thrombosis.
- All TMAs were associated with concomitant use of aPCC, and no new events were reported since the last update.
- This post-marketing analysis supports that TEs and TMAs without concomitant aPCC are not an identified risk for PwcHA receiving emicizumab prophylaxis. The risk–benefit profile of emicizumab remains unchanged.

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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.

References

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Disclosures

MH: employment and equity: Roche; **DM**: employment: Pro Unlimited; **FS**: employment and stockholder: Roche; **RHK**: employment, equity and stockholder: Genentech; **FN**: employment and stockholder: Roche; consultancy: Novartis and Actelion.