Summary of Thrombotic Events or Thrombotic Microangiopathy Events in Persons Taking Emicizumab▼

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▼ This medicinal product is subject to additional monitoring. This will allow quick identification of new safety information. Healthcare professionals are asked to report any suspected adverse reactions. These should be reported to the Regulatory Authorities in your country according to your national requirements.

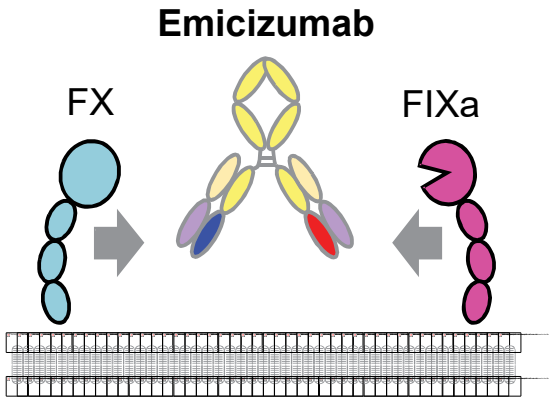
Disclosure

- Disclosure for Dr Richard H. Ko: Employee of Genentech, Inc.

Clinical data established the safety and efficacy of emicizumab prophylaxis for PwHA and it is being used globally

Emicizumab:

- Is a subcutaneously administered, bispecific, humanised monoclonal antibody that replaces the function of missing activated FVIII and restores haemostasis in PwHA[1,2]
- Is indicated for routine prophylaxis in PwHA with or without FVIII inhibitors[3*]
- Is approved in 95 countries for use in PwHA with FVIII inhibitors and 70 without;[4†] and has been used by >6100 persons across the globe, through 31 Dec 2019[5]
- Had safety and efficacy established in the HAVEN 1–4 clinical trials for persons with congenital HA[6–10]
  - TE and TMA events were identified as risks when emicizumab was used with aPCC on average >100 U/kg/24 hours for ≥24 hours[5,3]



*In the EU, approved for use in persons without FVIII inhibitors only in those with severe HA. †As of 14 Jan 2020.

aPCC, activated prothrombin complex concentrate; F, factor; HA, haemophilia A; PwHA, persons with haemophilia A; TE, thrombotic events; TMA, thrombotic microangiopathy.

1. Kitazawa T, et al. *Nat Med* 2012;18:1570–1574; 2. Sampei Z, et al. *PLoS One* 2013;8:e57479; 3. HEMLIBRA® SmPC 2018 (https://www.ema.europa.eu/en/documents/product-information/hemlibra-epar-product-information_en.pdf); 4. Roche. Data on file; 5. HEMLIBRA https://www.emicizumabinfo.com/ Accessed 16 Jan 2020; 6. Callaghan M, et al. Presentation at ISTH 2019; 7. Oldenburg J, et al. *N Engl J Med* 2017;377:809–818; 8. Young G, et al. *Blood* 2019;134:2127–2138; 9. Mahlangu J, et al. *N Engl J Med* 2018;379:811–822; 10. Pipe SW, et al. *Lancet Haematol* 2019;6:e295–e305.

Risk of TEs in persons with congenital HA has not been well established

- TEs occur in persons with coagulation disorders, however, the true incidence of TEs in congenital HA is unknown[1]
  - Further studies on the occurrence of TEs in PwHA are needed
  - While reported incidence varies in the literature, CV risks are common in congenital HA[2]
  - A recent analysis indicated that MI risk for congenital HA is similar to that of a age/sex-matched population without HA[3]
- Thrombosis is a known risk of high plasma levels of FVIII (FVIII> ~200%)[4]
- Emicizumab is thought to confer a mild-to-moderate phenotype in persons with severe HA[5]

No evidence of a different risk of MI in PwHA relative to non-HA counterparts in a RWD study[3]

Crude incidence rate (95% CI)		
People with congenital HA (n=3144)	**Matched cohort of individuals without HA (n=15,673)**	**Adjusted incidence rate ratio (aIRR)***
0.25 (0.15–0.34)	0.22 (0.18–0.27)	1.31 (0.85–2.00)

*A Poisson regression model was fitted to estimate the aIRR; the model was adjusted for all baseline covariates as well as HIV and hepatitis C status, with age as a time-varying covariate.

CI, confidence interval; CV, cardiovascular; HIV, human immunodeficiency virus; MI, myocardial infarction; RWD, real-world data.

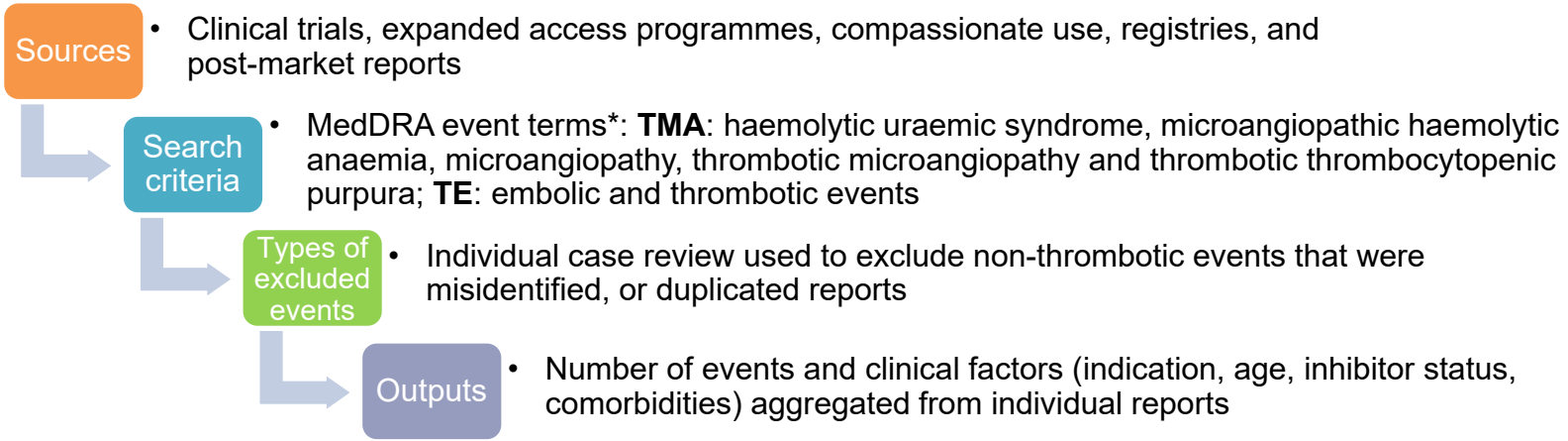
1. Pocoski J, et al. *Haemophilia* 2014;20:472–478; 2. Sood SL, et al. *Blood Adv* 2018;2:1325–1333; 3. Faghmous I, et al. Poster presented at ASH 2019, P-1133; 4. Kyrle PA, et al. *N Engl J Med* 2000;343:457–462; 5. MASAC Document #255 https://www.hemophilia.org/sites/default/files/document/files/255Emicizumab.pdf Accessed 16 Jan 2020.

Identification of TEs and TMA events

Aim

- To present available data on TEs and TMA events in persons treated with emicizumab through 31 Dec 2019

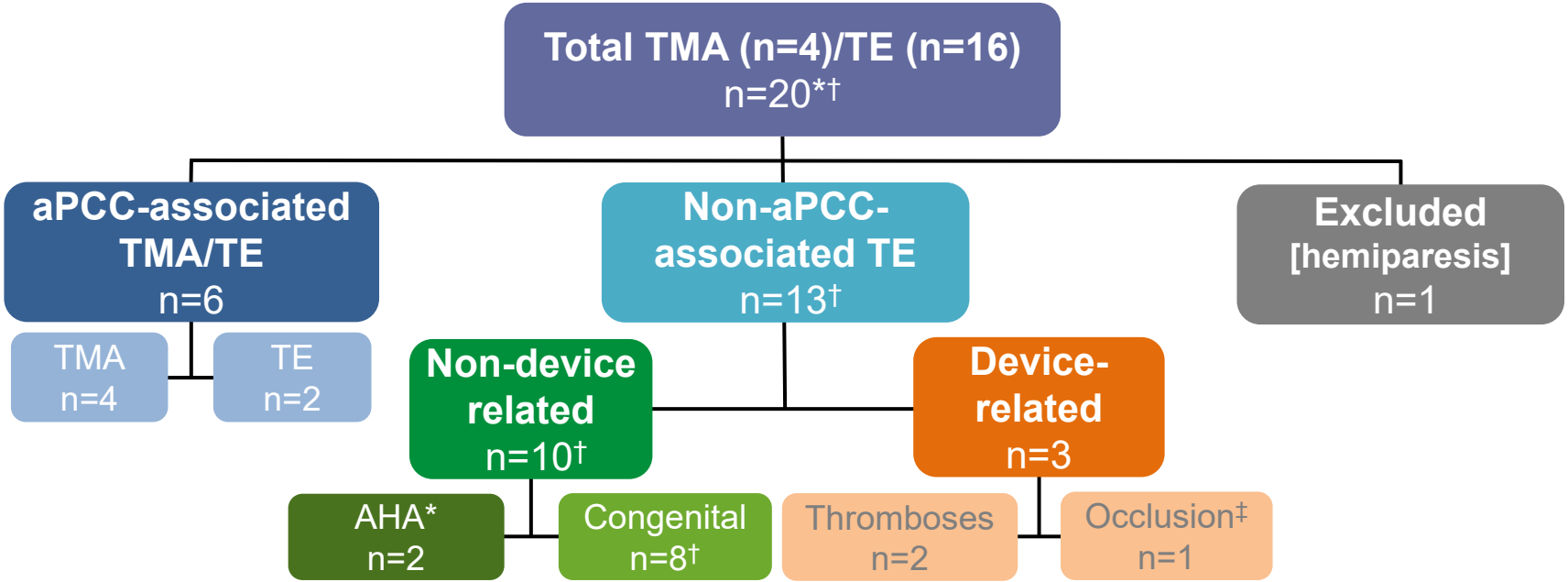
Approach to identify TEs and TMA events in those treated with emicizumab



Note: limited data are available in post-market cases

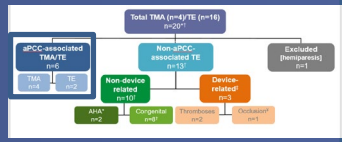
The safety events herein align with those in the Roche emicizumab global safety database.
*MedDRA (Medical Dictionary for Regulatory Activities) version 21.1 event terms are used;
TE search criteria used SMQ, standardised MedDRA queries (wide).

Summary of TMA events and TEs across all persons treated with emicizumab*

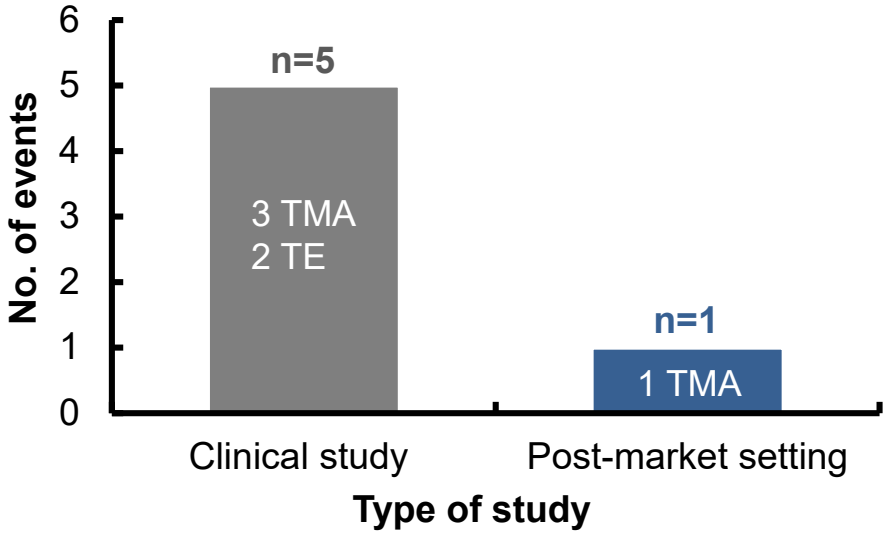


*Includes off-label use; †Two events occurred in one person; ‡Captured TE event through SMQ review, however does not fit the clinical definition of TE.
AHA, acquired haemophilia A.

Only one TMA associated with the known risk[1,2] of concomitant aPCC has been reported since guidance was issued



TMA and TEs associated with emicizumab + aPCC >100 U/kg/24hrs for ≥24 hours[1]



Risk minimisation measures in place to provide guidance on bypassing agent use[2]

- HCP, patient and caregiver education
- Warnings and precautions (Boxed warning in US; black triangle in EU)

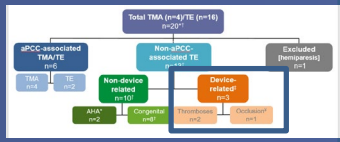
Post-market monitoring of aPCC-related TEs and TMA events

- Ongoing safety monitoring in clinical studies
- Studies[3] to look at frequency of TEs/TMA events

HCP, healthcare professional.

1. HEMLIBRA® SmPC 2018 https://www.ema.europa.eu/en/documents/product-information/hemlibra-epar-product-information_en.pdf Accessed 13 Jan 2020; 2. Hemlibra. https://www.emicizumabinfo.com/ Accessed 13 Jan 2020;
3. US FDA 2020 https://www.fda.gov/drugs/postmarket-requirements-and-commitments/postmarketing-requirements-and-commitments-reports Accessed 13 Jan 2020.

CVAD-related thrombosis is a common complication among patients requiring central venous access[1]



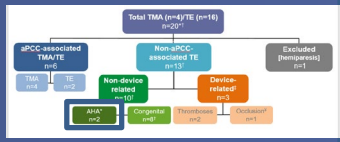
- CVAD-related (venous) thromboses, n=2
  - **Outcomes:**
    - Both recovered/resolving
    - No reported change to emicizumab prophylaxis
    - One published case was managed with CVAD removal followed by anticoagulation therapy while continuing emicizumab[2]

- CVAD occlusion, n=1
  - **Outcomes:**
    - Recovered/resolving
    - No change to emicizumab prophylaxis

CVAD, central venous access device.

1. Rajasekhar A and Streiff MB. *Blood* 2017;129:2727–2736;
2. George N, et al. *Blood* 134(Supplement_1):4938–4938; Presented at ASH 2019.

Risk factors for TE were present in both AHA cases



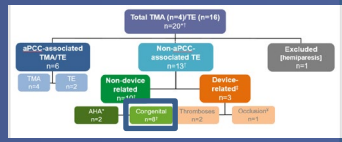
- Case 1: Elderly adult female with severe comorbidities and having major abdominal surgery, experienced multiple small cerebral TEs while taking emicizumab[1]
  - Occurred after the 3rd dose of emicizumab in association with rhFVIIa

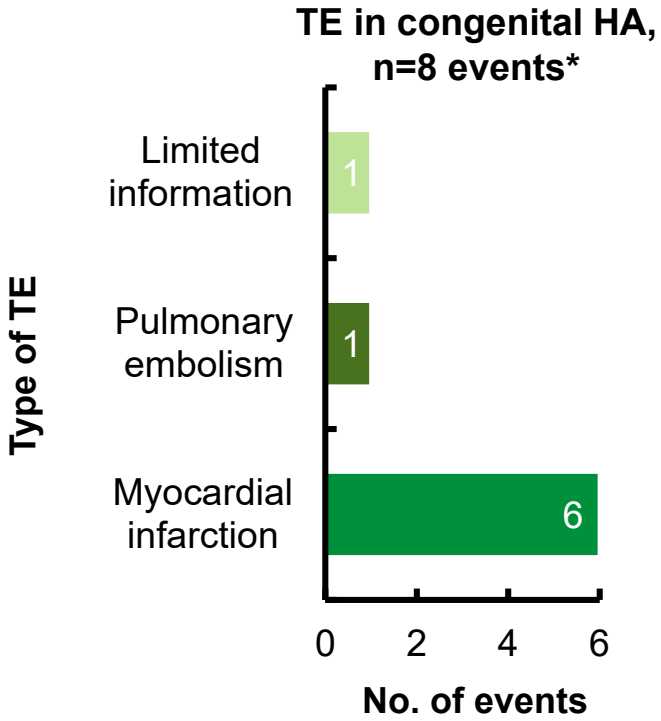
- Case 2: Adult female with a complicated medical history and at least 2 risk factors for VTE[2] had a TE while taking emicizumab

rhFVIIa, activated recombinant human factor VII.

1. Knoebl P, et al. Oral presented at ISTH 2019;
2. Anderson FA, Jr. and Spencer FA. *Circulation*. 2003;107:I9–16.

All non-aPCC-related TEs in congenital HA were associated with a history of CV disease or risk factors for thrombosis





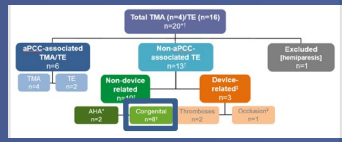
- Median age for cases of TE in congenital HA: 53 years
- One PwHA had 2 events: PE and MI[1]
  - History of VTE; smoker
- One MI case is unconfirmed, follow-up pending

*Seven PwHA, but 8 TEs, as 2 events occurred in 1 person.

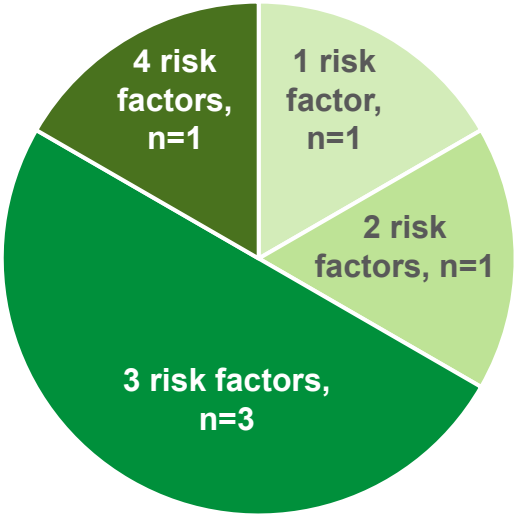
PE, pulmonary embolism; VTE, venous thromboembolism.

1. Gundabolu K, et al. *Haemophilia* 2020;26:e5–e8.

All reported events of MI were associated with known CV risk factors



Number of events categorised by number of reported risk factors in those with MI, n=6



No MI events occurred in those with no CV risk factors

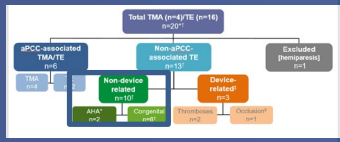
Risk factors* were present in all cases of MI in congenital HA

- CV risk factors included: hypertension, hyperlipidaemia, ischaemic heart disease, smoking, and advanced age[1,2]
- 2 events occurred in clinical trials; 4 in the post-market setting

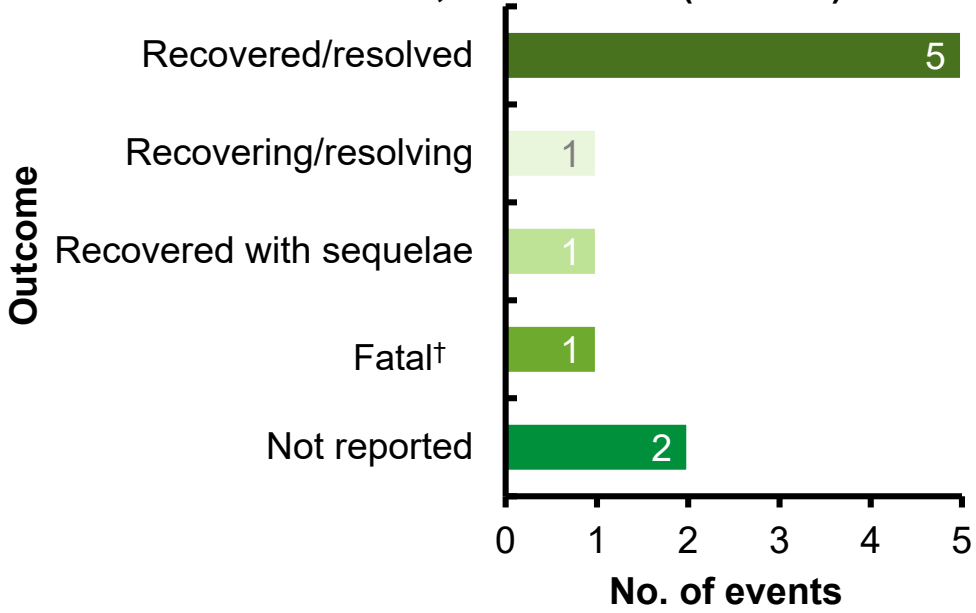
*Risk factors did not include family history of cardiovascular disease in a first degree relative.

1. Anderson FA, Jr., Spencer FA. *Circulation*. 2003;107(23 Suppl 1):I9–16;
2. Mozaffarian D, et al. *Circulation*. 2016;133(4):e38–360.

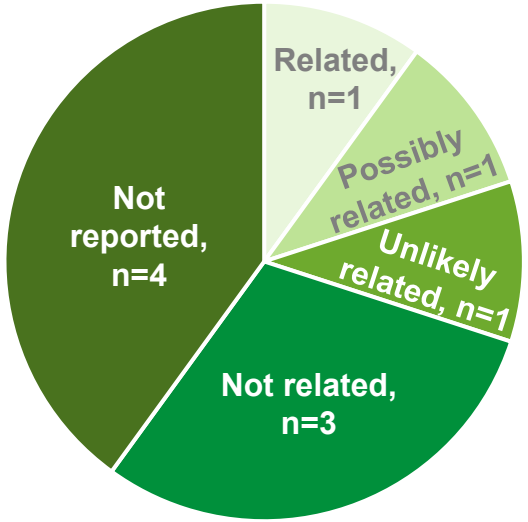
The majority of persons treated with emicizumab with TEs recover and few TEs were reported as related to emicizumab



Reported event outcomes of non-device associated TEs, n=10 events (9 PwHA)*



Reporter assessment of causality of non-device-related TEs, n=10 events (9 PwHA)



In 7/9 patients, there was no reported change to emicizumab prophylaxis as a result of the event

*2 events occurred in 1 person.

†TE occurred concurrent to other life-threatening events, critical illnesses, and/or critical conditions.

Conclusions

- TMA events and TEs with concomitant emicizumab and aPCC >100 U/kg/24hrs for ≥24 hours are known risks being managed with boxed warnings and risk minimisation measures
- All other TEs in persons treated with emicizumab were associated with known co-morbidities or pre-existing risk factors
- Roche continues to evaluate TEs and TMA events in post-marketing studies and registries[1]
  - Detailed, timely case information is essential to evaluate evidence of risk
- The incidence rate of arterial and venous TEs in the current HA population needs to be established, regardless of therapeutic approach[2]

1. Hemlibra. https://www.emicizumabinfo.com/ Accessed Jan 13, 2020;
2. Pocoski J, et al. *Haemophilia*. 2014;20:472–478.

Acknowledgments

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