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# Disorders of Hemostasis

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# Disclosures

*In compliance with ACCME policy, ASH requires disclosures to the session audience:*

## Speakers

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## Disclosures

**Honoraria:** Takeda

**Membership on a Board or Advisory Committee:** Abbvie; Astellas; Bristol Myers Squibb; Daiichi Sankyo; Jazz Pharmaceuticals; Servier Pharmaceuticals; Syndax Pharmaceuticals



# Learning Objectives

Upon participation in this activity, attendees will be able to:

- Review evidence for prophylaxis of patients with acquired hemophilia A with Emicizumab and immunosuppression using rituximab and bortezomib
- Review safety and efficacy of Emicizumab in patients with hemophilia A, including in infants



# Case 1

- A 79 yo man with multiple medical comorbid conditions presents with new onset bruising over the past three weeks and a painful swollen right forearm, with decreased pulses and bluish discoloration. He had received a COVID-19 mRNA booster 4 weeks before presentation.
- Hemoglobin 6.5 g/dL (12 months ago 10.8g/dL), White cell and platelet count normal. Prothrombin (pt) time normal. Activated partial thromboplastin time (aPTT) 89 sec (normal 25-35). aPTT 50/50 mix 46 sec immediately, 59 sec at 1 hour incubation at 37 C
- FVIII activity <1%. Bethesda Inhibitor titer 135 BU



# Case 1

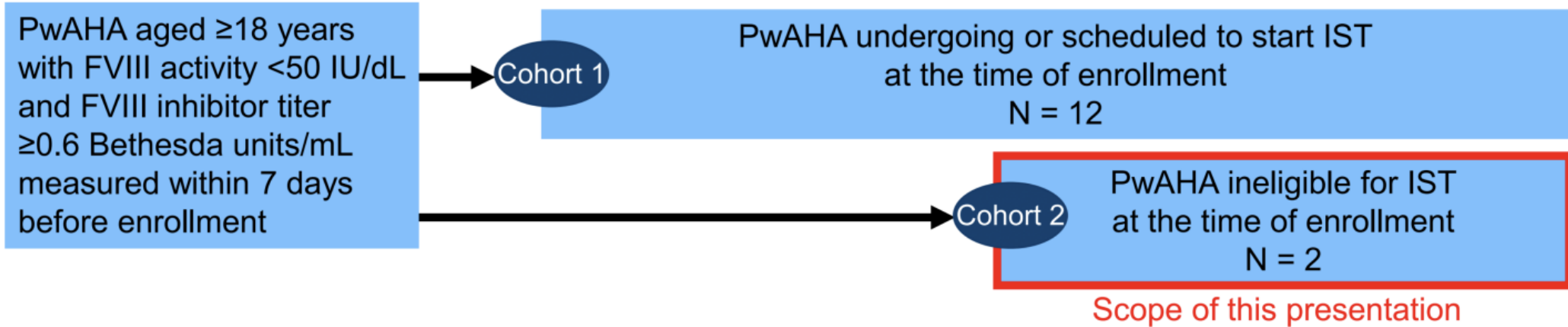
- The patient is treated with aPCC at 100u/kg q12 h, but after the third dose, develops atrial fibrillation with rapid ventricular response, chest pain and a troponin elevation
- What hemostatic agent would you use next?
  - A. Recombinant FVIIa
  - B. Recombinant porcine FVIII
  - C. aPCC at a lower dose
  - D. Emicizumab plus / minus recombinant porcine FVIII
  - E. Other

# Acquired Hemophilia A

- Autoimmune bleeding condition caused by development of antibodies to FVIII
  - Bleeding often more severe than corresponding factor VIII levels would suggest
- Diagnosis with an isolated prolonged aPTT which fails to correct on mixing studies
  - FVIII activity levels invariably low with a detected inhibitor (Bethesda titer)
- Treatment consists of
  - Hemostasis including with bypassing agents such as recombinant FVIIa or aPCC, or recombinant porcine FVIII.
  - Immunosuppression
- Efficizumab
  - Subcutaneous bispecific antibody which binds to FIXa and FX.
  - Approved for prophylaxis against bleeding in people with Hemophilia A with or without inhibitors



# Phase III study of Emicizumab in patients with acquired hemophilia A (AGEHA study)



- Emicizumab was administered subcutaneously at **6 mg/kg on Day 1** and **3 mg/kg on Day 2** followed by **1.5 mg/kg once weekly from Day 8 onwards** to rapidly maximize the potential of emicizumab to prevent bleeds.
- Emicizumab administration was to be completed when both of the following criteria were met: (1) FVIII activity exceeded 50 IU/dL and (2) more than 72 hours had passed since the last use of coagulation factor products for the last bleed requiring treatment in order to assure hemostasis.
- No restriction was set on IST use during the study.

\*FVIII, factor eight; IST, immunosuppressive therapy; PwAHA, patients with acquired hemophilia A.



# AGEHA Study (Presented 2022 ISTH)

## Results

- Enrolled 12 people on immunosuppressive therapy. 11 of them (91.7%) had finished initial emicizumab treatment.
  - Prior to treatment: 6 (50.0%) people experienced 30 treated bleeds (27 major bleeds)
  - On treatment: 5 bleeds occurred in 2 (16.7%) people (0 major bleeds)

## Conclusion

- Emicizumab was well tolerated with no treatment discontinuation.
- One asymptomatic DVT reported during emicizumab treatment.
- No patients developed significant anti-emicizumab antibodies



# Two additional people presented

- Patient 13

- 82-year-old woman diagnosed with acquired Hemophilia A 6 days before enrollment
- Judged ineligible for immunosuppressive therapy due to uncontrolled diabetes and poor performance status
- After starting Emicizumab, bleeding symptoms resolved.
- With improving condition, therapy with prednisone and cyclophosphamide initiated
- During Emicizumab therapy, only one non-major bleed occurred

- Patient 14

- 59-year-old woman with acquired hemophilia A of long duration on aPCC prophylaxis
- Immunosuppressive therapy stopped due to infections complications
- During aPCC prophylaxis, 1 bleed requiring treatment occurred.
- During Emicizumab therapy, no bleeds requiring treatment occurred



# Emicizumab in Acquired Hemophilia A

Literature review: 12 studies (8 full text and 4 conference abstracts) reported on the use of Emicizumab in 33 people with acquired Hemophilia A

- **Population**

- Median age 74 years (21–93) 1
- ~24% (8/33) male
- Bleeding sites: hematoma formation, mucocutaneous bleeds and surgical site bleeds.
- The inhibitor titers ranged between 3.5 and 2000 Bethesda units
- 91% (30/33) initiated on Emicizumab for active/recurrent bleeding events

- **Treatments**

- *Loading dose*
  - 17 pts were initiated on the standard loading dose regimen of 3 mg/kg weekly for 4 weeks,
  - 14 pts received a modified loading do
- *Maintenance: 24/33*
  - 9 on a standard treatment
  - 15 modified treatment



# Emicizumab in Acquired Hemophilia A

- **Therapy Duration 20days – 10 months**
  - Treatment ongoing in 4/33 people at time of submission
  - FVIII levels at time of discontinuation ranged from 10% to 86% with different protocols (ranging from endogenous FVIII levels of 10% to normalization and clearance of inhibitor).
- **Clinical response 100%**
  - No spontaneous bleeding
  - 3 people had surgical procedures with bleeding
    - Tooth extraction required 1 week of rFVIIa
    - Perisurgical rFVIIa to close a surgical wound
    - Recurrent hematuria from bladder defect requiring embolization.
- **Complications**
  - 2 deaths likely unrelated to Emicizumab treatment (arrhythmia and peritonitis)
  - 1 stroke on day 16 after 3 doses Emicizumab
  - 1 person experienced atopic eczema



# Case 1 (continued)

- Our 79-year-old male is started on immunosuppression with prednisone (1mg/kg) which results in marked hyperglycemia, hallucinations, and mania requiring a 1-to-1 sitter
- What would you do now?
  - A. Continue prednisone alone
  - B. Continue prednisone, add cyclophosphamide
  - C. Stop prednisone and start Cyclophosphamide
  - D. Stop prednisone and start Rituximab
  - E. Stop prednisone and start Rituximab and Bortezomib



## Rituximab and Bortezomib for Patients with Newly Diagnosed Acquired Haemophilia: Single Arm, Single Center, Prospective Phase 2 Study

- **Dosing**
  - Rituximab 375mg/m<sup>2</sup> IV on day 0 and Bortez 1.3 mg/m<sup>2</sup> SQ on days 1, 4, 8, and 10
- **30 patients enrolled, all completed treatment**
  - 9 experienced bleeding after initiation of treatment
  - Response: Complete response 80% (24/30) Partial response 17% (5/30)
  - Median time to complete response 74 days (12 – 179)
  - 1 person relapsed 2 months after achieving CR (median follow-up 39 months (3-50 months))
- **Toxicities**
  - 1 death from cardiac event 3 months after last dose of bortezomib
  - Grade 1-2 neutropenia (30%), grade 1-2 peripheral neuropathy (16.7%), grade 1-2 thrombocytopenia (13.3%) and grade 1-2 fever (13.3%).

# Acquired Hemophilia after Vaccination: A Systematic Review.

## Abstract 2473: Parmar K, et al

- **Acquired hemophilia**
  - 21 case reports in literature
  - 13 cases in Vaccine Adverse Event Reporting System (VAERS) (2 of acquired hemophilia B)
  - 2 deaths reported (retroperitoneal bleeding and sepsis)
- **Vaccines**
  - Pfizer (53%), Moderna (28%), and Astra Zeneca (19%)
- **Timing**
  - 28% after 1<sup>st</sup> dose, 47% after second dose
  - Average duration for onset of symptoms from SARS COVID-19 vaccination was 2 weeks 4 days
- **Causality**
  - Timing suggest possible
  - Given large number of vaccinations, this is a very rare complication



# Case 2 and 3

- **Case 2:** 61-year-old with severe hemophilia A (levels <1%) and type II diabetes and coronary artery disease with stent placement, on aspirin 81mg daily
  - Established severe arthropathy
  - On prophylaxis with extended half-life factor VIII twice weekly
  - Break-through bleeding ~twice monthly and poor venous access
  - He is concerned about thrombosis risk with Emicizumab
- **Case 3:** His daughter is currently pregnant with her second child.
  - She had previously given birth to a male child with severe hemophilia A who suffered an intracranial hemorrhage at 6 weeks of age.
  - Prenatal testing shows the fetus to be a male with severe hemophilia A.



# Whom would you treat with Emicizumab?

- A. The 67-year-old man
- B. The newborn, but only after age 1
- C. The newborn shortly after birth
- D. The daughter (obligate hemophilia A carrier)
- E. A and C

# Safety of Emicizumab

- **Abstract 189:** Abbatista et al, Hemorrhagic and Thrombotic Adverse Events Associated with Emicizumab and Extended Half-Life FVIII Replacement Drugs in Patients with Hemophilia A: Data from the Eudravigilance Database



# Thrombotic risk in Hemophilia A

- Few available data on patients treated with Emicizumab

## **HAVEN 1** clinical trial

Oldenburg J, NEJM 2017

aPCC >100 U/kg

3 MAHA

2 venous thrombosis

rFVIIa

No thrombotic events

## **EUHASS**

Shang A, Blood 2020

No thrombotic event on 148 PwHA treated with Emicizumab

## **Roche Global Safety Database**

(discontinued on May 2021)

Howard M, Blood 2021

43 thrombotic events (6 with aPCC)

**EUHASS** data reported by **Roche** showed 4 thrombotic events on 985 PwHA (abstract #192)

- Data available on safety of extended half-life products are minimal



# Objectives

Comparative analysis of Hemorrhagic and Thrombotic Adverse Drug Reaction (**ADR**) reported during treatment with **Emicizumab** and **EHL FVIII products** by evaluating post-marketing data gathered during **2021**, from the **EudraVigilance** database.



# Results

## Adverse Events reported in 2021

Total	EMICIZUMAB 406	EHL products 376	ROR (95%CI)
Hemorrhagic	232 (57%)	275 (73%)	0.49 (0.36-0.66)
Thrombotic	24 (6%)	9 (2.4%)	2.56 (1.18-5.59)



# Thrombotic ADR

## EMICIZUMAB

1 DIC\*

1 microangiopathy\*

8 venous thrombosis\*\*

14 arterial thrombosis \*\*\*

(5 MI, 3 stroke, 2 peripheral artery occlusion, 1 TIA, 1 renal infarct, 1 mesenteric artery occlusion)

## EHL products

1 DIC

3 venous thrombosis\*\*

5 arterial thrombosis (5 MI)

9\* (27%) thrombotic ADR during concomitant treatment with bypassing agent

→ All but one were reported with concurrent **FVIIa**



# Conclusion

- A lower reporting frequency of hemorrhagic ADR and a higher reporting frequency of thrombotic ADR for Emicizumab compared to extended half-life FVIII products
- About one-third of thrombotic ADR were reported with concomitant use of emicizumab and bypassing agents
- Risk – benefit profile requires a detailed evaluation of both bleeding and thrombotic risk
- Accurate pharmaco-surveillance is required for a long-term safety evaluation



# Emicizumab Prophylaxis for the Treatment of Infants with Severe Hemophilia A without Factor VIII Inhibitors: Results from the Interim Analysis of the HAVEN 7 Study on behalf of the HAVEN 7 Study Investigators

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# Background

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- Currently, many infants with severe HA do not receive prophylaxis until at least one year of age, due to the **challenges of FVIII administration** in pediatric patients:<sup>1,2</sup>



- Venous access issues
- Central venous access - associated risks



- Emicizumab is **approved** in infants, and enables **initiation of prophylaxis** from HA diagnosis via subcutaneous administration, and may **mitigate risks** including:



- spontaneous and traumatic bleeding
- intracranial hemorrhages
- FVIII inhibitor development

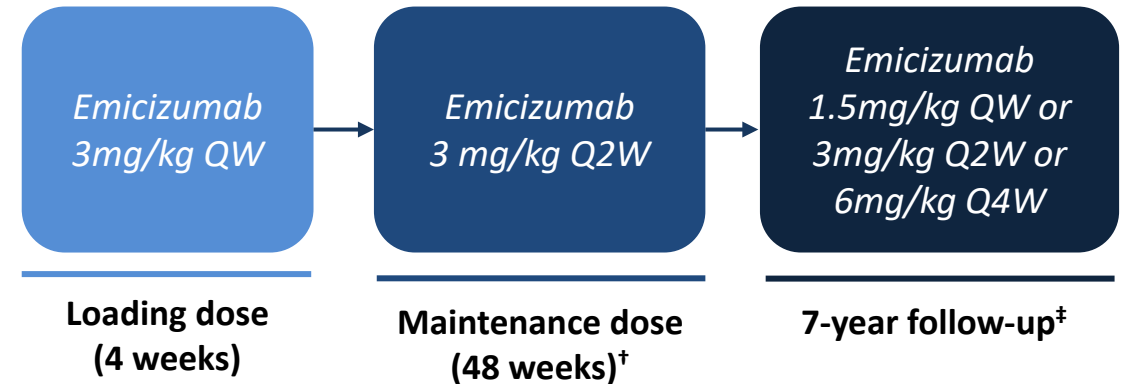
This interim analysis of **HAVEN 7** (NCT04431726) aims to evaluate the efficacy, safety, PK and PD of emicizumab in infants  $\leq 12$  months of age with severe HA without FVIII inhibitors



# Study design

- At data cut-off, **54 participants** were exposed to emicizumab for a median (min, max) duration of **42.1 (1–60) weeks** (mean exposure duration: 34.4 weeks)
- **Key inclusion criteria:**
  - PUPs or MTPs\* from **birth to ≤12 months of age** with **severe HA without FVIII inhibitors**
  - No evidence of ICH at enrolment
- Endpoints included:
  - **Efficacy:** ABRs for treated bleeds, all bleeds, treated spontaneous bleeds, treated joint bleeds
  - **Safety:** AEs, AESIs including TEs and TMAs, immunogenicity
  - **PK:** Plasma trough emicizumab concentrations
  - **Biomarkers:** FIX and FX antigen concentrations and effect of emicizumab on aPTT, among others

## A phase IIIb, multi-center, open-label study of emicizumab in infants aged ≤12 months with severe HA without FVIII inhibitors



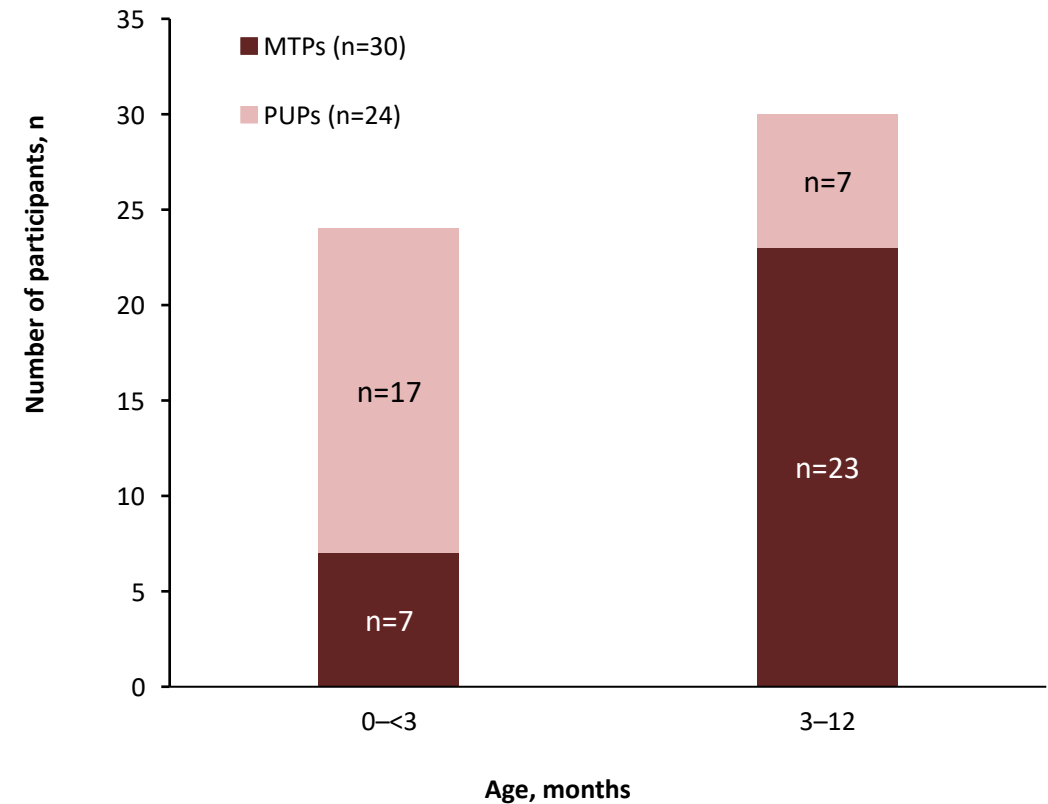
At the interim analysis cut-off, no participants were up-titrated

\*Defined as a participant with ≤5 exposure days to FVIII. †The primary analysis will be performed when the last patient has completed 52 weeks in the study, is lost to follow-up, or has withdrawn from study treatment, whichever occurs first. ‡The 7-year follow-up will include MRI analysis to evaluate long-term joint health. Recruitment was completed on 20 May 2022 with 55 participants. Interim analysis cut-off occurred when the 10th patient aged <3 months at the time of informed consent completed 24 weeks in the study, was lost to follow-up, or was withdrawn from study treatment, whichever occurred first; CCOD: 31 March 2022. ABR, annualized bleeding rate; AE, adverse event; AESI, adverse event of special interest; CCOD, clinical cut-off date; F, factor; HA, hemophilia A; IA, interim analysis; ICH, intracranial hemorrhage; MRI, magnetic resonance imaging; MTP, minimally treated patient; PK, pharmacokinetic; PUP, previously untreated patient; QW, every week; Q2W, every 2 weeks; Q4W, every 4 weeks; TE, thrombotic event; TMA, thrombotic microangiopathy

# Baseline characteristics

Emicizumab (N=54)	
<b>Age*, months</b>	
Mean (SD)	5.1 (3.9)
Median	4.5
Min, Max	9 days, 11 months
<b>Age group, months</b>	
0–<3	24 (44.4)
3–12	30 (55.6)
<b>Status, n (%)</b>	
MTP <sup>†</sup>	30 (55.6)
PUP	24 (44.4)
<b>Historical bleeding episodes prior to first dose of emicizumab, n (%)</b>	
Zero bleeds	18 (33.3)
≥1 bleed	36 (66.7)
<b>Family history of HA, n (%)</b>	40 (74.1)

Participant status and age at time of informed consent



\*At time of informed consent. †Defined as a participant with ≤5 exposure days to FVIII  
 HA, hemophilia A; MTP; minimally treated patient; PUP, previously untreated patient; SD, standard deviation

# No new safety signals were identified at interim analysis

	Emicizumab (N=54)
Participants with ≥1 AE, n (%)	50 (92.6)
Total number of AEs, n	314
Total number of deaths, n	0
Withdrawal due to AE, n	0
<b>Total number of participants with ≥1</b>	
AE with fatal outcome, n	0
SAEs*, n (%) [events]	8 (14.8) [12]
<b>Related AE, n (%) [events]</b>	<b>9 (16.7) [23]</b>
Grade ≥3 AE, n (%) [events]	12 (22.2) [16]
<b>AEs of special interest, n</b>	
Systemic hypersensitivity reactions and anaphylactic / anaphylactoid reactions	0
TEs and hypercoagulation	0
Microangiopathic hemolytic anemia or TMA	0



**No AEs** led to withdrawal or dose modification or interruption

All related AEs were **ISRs**; no SAEs were considered related to treatment

**No ICHs** were reported



Of the 48 participants evaluable for immunogenicity, **none tested positive for ADAs to emicizumab**

CCOD: 31 March 2022.

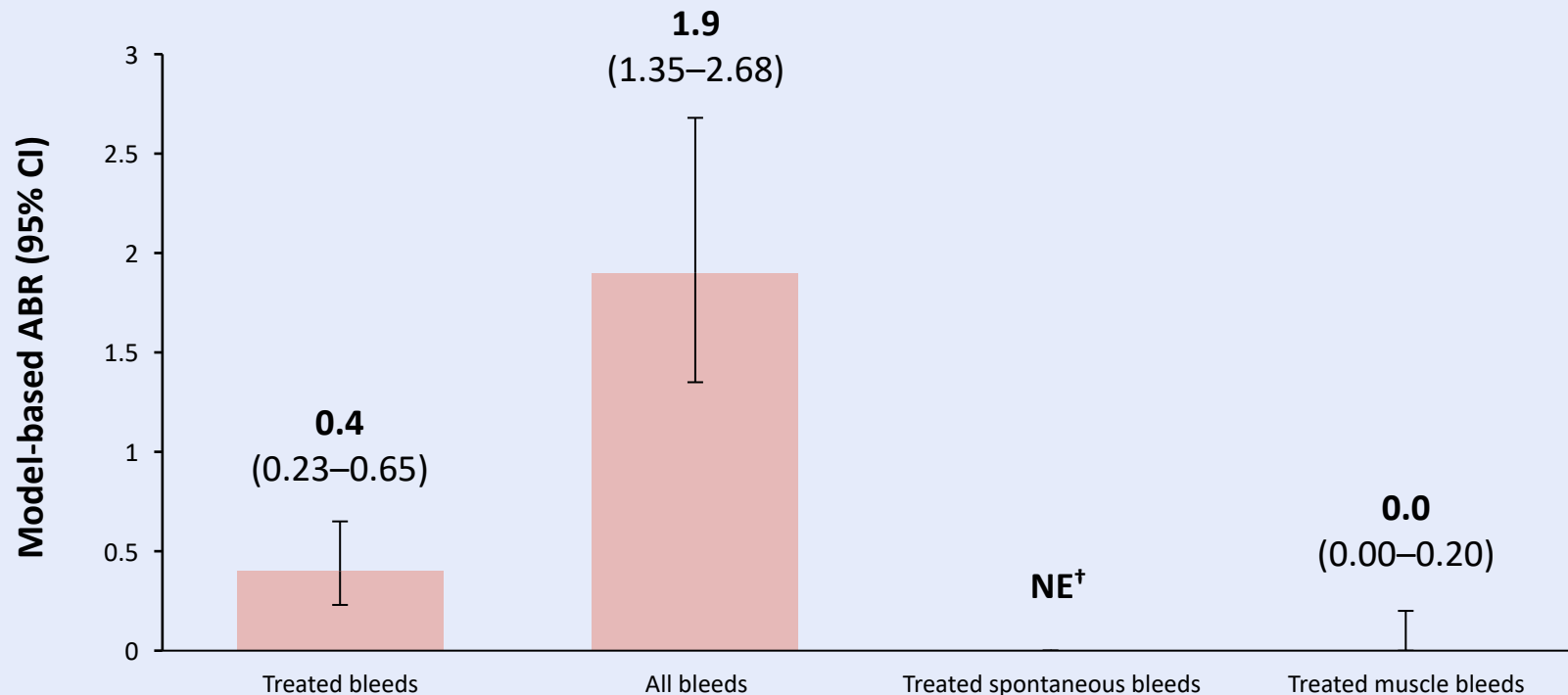
\*8 participants reported 12 SAEs: 3 cases of head injury, 2 cases of fall, 2 cases of bronchiolitis, and one case each of bronchitis, tonsillitis, URTI, UTI, and viral infection.

ADA, anti-drug antibodies; ICH, intracranial hemorrhage; ISR, injection site reaction; URTI, upper respiratory tract infection; UTI, urinary tract infection



# Emicizumab demonstrated consistent efficacy across bleeding endpoints

## Model-based\* ABRs across bleed categories



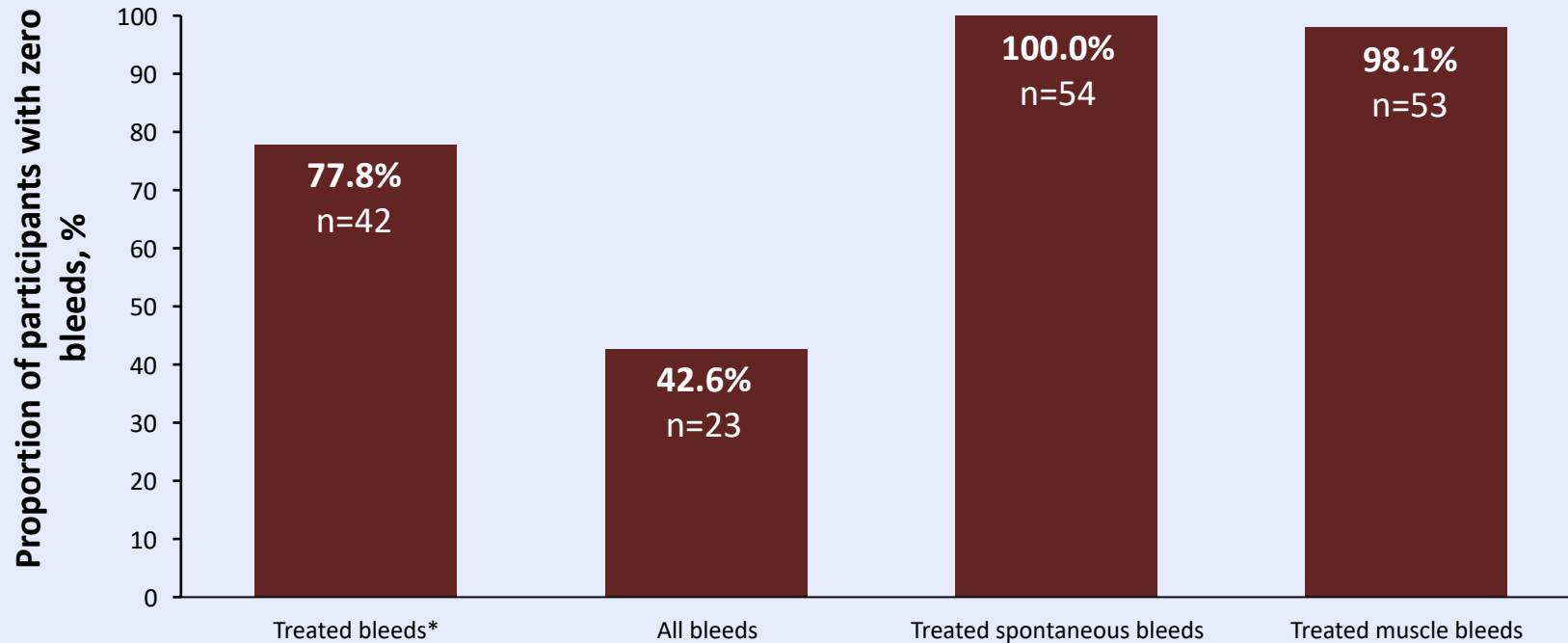
Median (min, max) age at IA: 16 (1, 26) months (N=54)

All treated bleeds were categorized as traumatic<sup>‡</sup>

\*Model-based ABRs were assessed with aid of a negative binomial regression model. †All treated bleeds were traumatic, hence ABRs for treated spontaneous bleeds are not estimable. ‡Bleeds were classified as traumatic if parents/caregivers recorded a bleed with a known or believed reason for the bleed. ABR, annualized bleeding rate; IA, interim analysis; NE, not estimable

# Emicizumab demonstrated consistent efficacy across bleeding endpoints

Participants with zero bleeds across bleed categories



Median (min, max) age at IA: 16 (1, 26) months (N=54)

\*All treated bleeds were traumatic  
IA, interim analysis

# Conclusions

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Effective mean trough concentrations of emicizumab were **achieved and maintained**



Emicizumab prophylaxis was well tolerated, and **no new safety signals** were observed as of the interim analysis



Participants had low model-based ABRs, and **all participants had zero treated spontaneous bleeds**; all treated bleeds were traumatic



This interim analysis suggests that emicizumab is **efficacious and well tolerated in infants with HA** without FVIII inhibitors

# Emicizumab Pearls

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- Hemostasis is similar to having a factor VIII level of 10% - 20%
  - Spontaneous bleeding rare.
  - Provoked bleeding can and does happen
- Laboratory monitoring
  - Shortened aPTT **DOES NOT** reflect increased factor VIII activity
  - Measuring factor VIII levels
    - **CANNOT** use standard assay with human reagents
    - Must use chromogenic assay with bovine reagents (reference laboratory or send-out)
    - Measuring inhibitor titer (Bethesda assay) requires similar techniques (reference laboratory or send-out)



# Summary-Case1

- In acquired hemophilia A, treatment with emicizumab may offer reasonable hemostasis allowing for outpatient therapy
- Acquired hemophilia A occurs after vaccination against SARS-CoV2 but is likely a vanishingly rare complication
- Steroid-free Immunosuppression for acquired hemophilia A has been successful using the regimen of bortezomib and Rituximab



# Summary Cases 2/3

- Emicizumab is safe and effective in people with hemophilia
  - Bleeding less common than with extended half-life factor VIII products
  - Thrombosis more common than with extended half-life factor VIII products
  - Loss of immune tolerance in people with a prior history of acquired factor VIII inhibitors reported
- Emicizumab is safe and effective in infants below the age of 12 months
  - Bleeding related to trauma only
  - Ongoing study to refine risks and benefits