

Final Analysis of the STASEY Trial: A Single-arm, Multicenter, Open-label, Phase III Clinical Trial Evaluating the Safety and Tolerability of Emicizumab Prophylaxis in Persons with Hemophilia A with Factor VIII Inhibitors

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Summary



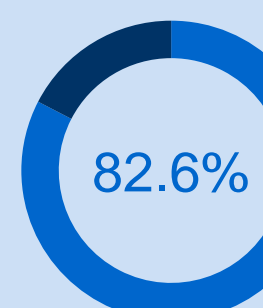
The safety and efficacy of emicizumab was assessed in persons with hemophilia A (PwHA) with factor VIII inhibitors

No new or unexpected safety concerns were identified during the study



The findings of the STASEY trial provide further evidence of the positive risk-benefit profile of emicizumab

Most participants had zero treated bleeds



PwHA with zero treated bleeds



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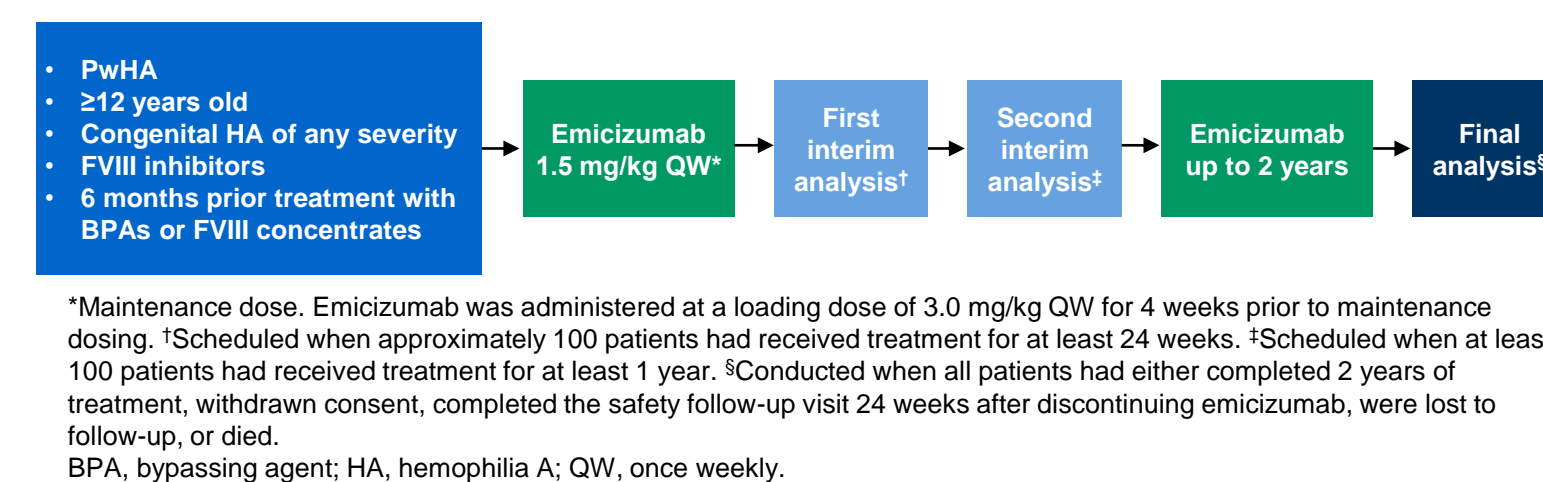
Background

- Emicizumab, a bispecific monoclonal antibody, substitutes for the function of missing activated factor (F)VIII in persons with hemophilia A (PwHA) by bridging FX and activated FIX, thereby restoring hemostasis.¹
- Emicizumab was demonstrated to be safe and efficacious during the HAVEN program and is indicated for routine prophylaxis in PwHA with FVIII inhibitors and those with severe HA (FVIII activity <1%) without FVIII inhibitors.²⁻⁶
- STASEY (NCT03191799) is a phase IIIb study assessing the safety and efficacy of emicizumab prophylaxis in PwHA with FVIII inhibitors.
- Here, we present the results of the final analysis of the STASEY trial.

The STASEY trial enrolled PwHA ≥12 years old with FVIII inhibitors

- STASEY was a Phase IIIb, single-arm, open-label, multicenter study (Figure 1).
- Informed consent and ethics committee approval were obtained.

Figure 1. STASEY trial design



- Primary endpoint**
 - To evaluate the safety of emicizumab, including the incidence and severity of adverse events (AEs), inclusive of thromboembolic events (TEs), thrombotic microangiopathies (TMAs), and hypersensitive reactions.
- Key secondary endpoints**
 - To evaluate the efficacy of emicizumab assessed by annualized bleed rates (ABRs).
 - To assess the incidence and clinical significance of anti-drug antibodies (ADAs).

A total of 193 PwHA were included in the safety-evaluable population

- At the date of the last patient's last visit on 19 November 2020, 193 PwHA had received ≥1 dose of emicizumab, forming the safety-evaluable population (Table 1).
- The median (interquartile range) treatment duration was 103.1 (103.1–105.1) weeks.

Table 1. Baseline characteristics (safety-evaluable population)

	Total N=193
Median age (range), years	28 (12–80)
Male, n (%)	193 (100.0)
Hemophilia severity at baseline, n (%)	
Mild	3 (1.6)
Moderate	9 (4.7)
Severe	181 (93.8)
Hemophilia treatment history, n (%)	
Prophylactic only	67 (34.7)
Episodic only	114 (59.0)
Both episodic and prophylactic	12 (6.2)
Highest historical inhibitor titer,* median BU/mL (range)	85 (0–32700)
Prior immune tolerance induction treatment, n (%)	100 (51.8)
No. of bleeds in 24 weeks prior to trial entry, median (range)	4 (0–49)
Target joints at baseline, n (%)	127 (65.8)

*Nineteen participants had FVIII inhibitor titer <5 BU/mL; 1 participant had unknown titer. BU, Bethesda unit.

References

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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.

Emicizumab was well tolerated and no new safety concerns were identified during the STASEY trial

- The most common AEs were arthralgia (33/193, 17.1%), nasopharyngitis (30/193, 15.5%), and headache (29/193, 15.0%) (Table 2).
- No new TEs were reported since the two in the interim analyses (myocardial infarction in a participant aged 55 years with several risk factors, and a hypertrophic clot in a participant aged 29 years following a tooth extraction).
- Emicizumab-related AEs were reported in 35/193 (18.1%) PwHA.
 - Injection-site reactions (ISRs) were the most common emicizumab-related AE (19/193, 9.8%).
- Further to the fatality reported at the first interim analysis (polytrauma with fatal head injury; unrelated to emicizumab), one death was reported (abdominal compartment syndrome in a participant aged 59 years) and deemed unrelated to emicizumab.
- Five PwHA received activated prothrombin complex concentrate (aPCC) and 56 PwHA received recombinant FVIIa, with no associated TMAs or TEs.

Table 2. Summary of safety

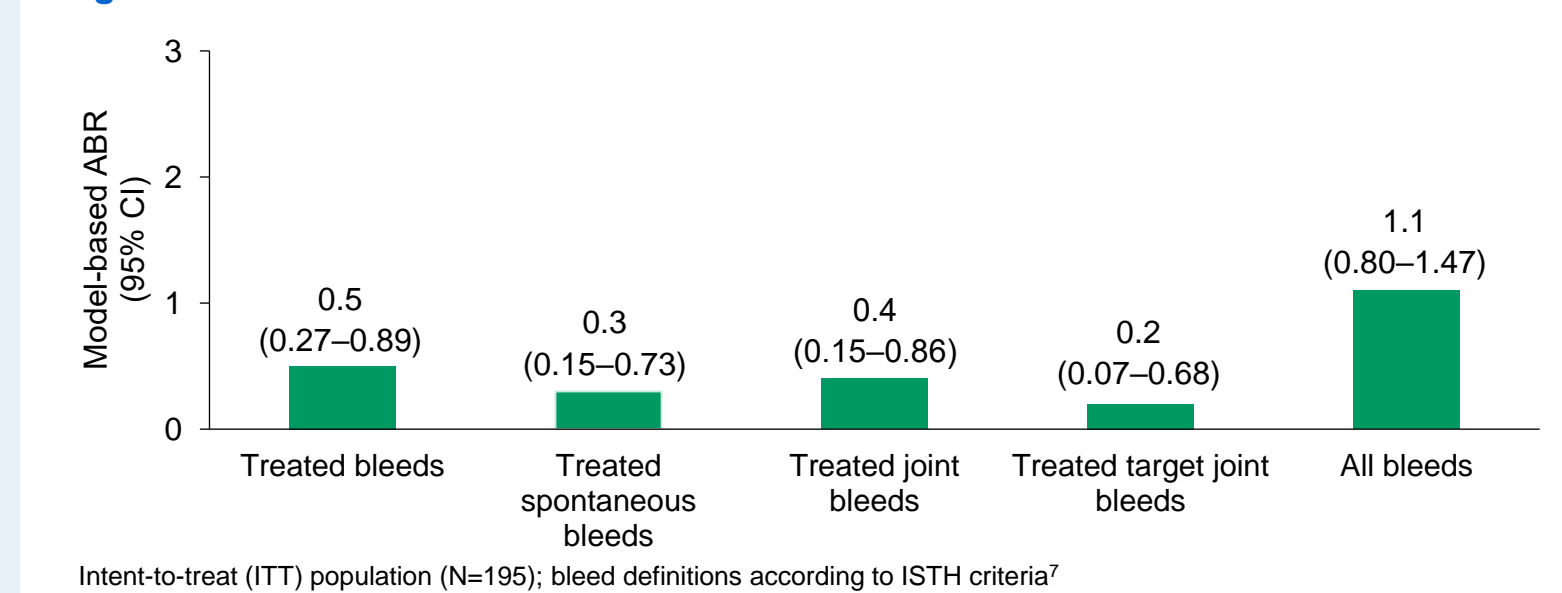
	Total N=193
Total number of AEs	800
Number of PwHA with ≥1 event, n (%)	163 (84.5)
Fatal AE*	2 (1.0)
Serious AE	31 (16.1)
AE leading to treatment withdrawal†	1 (0.5)
AE leading to dose modification or interruption‡	4 (2.1)
AE leading to trial discontinuation§	1 (0.5)
Grade ≥3 AE	39 (20.2)
Study treatment-related AE¶	35 (18.1)
ISR**	19 (9.8)
AEs of special interest, n (%)	
Systemic hypersensitivity/anaphylactic/anaphylactoid reaction	0
TE††	2 (1.0)
TE associated with aPCC and emicizumab‡‡	0
TMA	0
TMA associated with aPCC and emicizumab‡‡	0
Most common AEs (≥10% of PwHA), n (%)	
Arthralgia	33 (17.1)
Nasopharyngitis	30 (15.5)
Headache	29 (15.0)
ISR§§	22 (11.4)
Pyrexia	21 (10.9)

*Polytrauma with fatal head injury, unrelated to emicizumab, previously reported in the first interim analysis (n=1); abdominal compartment syndrome, unrelated to emicizumab (n=1). †Nephrotic syndrome was experienced by one participant and led to withdrawal from treatment, based only on AE data; the physician assessed the causality of nephrotic syndrome and deemed it not related to emicizumab and likely related to the concurrent condition of type 1 diabetes mellitus. ‡Dose modifications or interruptions occurred in four participants due to the following AEs: exacerbation of chronic pancreatitis Grade 2, exacerbation of hepatitis C, syncope during first emicizumab administration, and nasopharyngitis and ear congestion; none were deemed related to emicizumab. §Pneumonia aspiration was experienced by one participant leading to study discontinuation, based only on AE data; however, abdominal compartment syndrome occurred in the same participant, resulting in fatality. ¶Other than ISRs, the most common treatment-related AEs included pruritus (n=2), somnolence (n=2), and fatigue (n=1). **Treatment-related ISRs were of mild severity in 17 participants and moderate in two participants. ††ST-elevation myocardial infarction due to thrombus in a coronary artery in one PwHA, and hypertrophic clot at site of tooth extraction in one PwHA who was receiving a combination of anti-fibrinolytics together with activated FVIIa; both events were deemed unrelated to emicizumab; the latter event is a known complication of tooth extractions. ‡‡No TEs or TMAs were observed in any participant receiving concomitant aPCC alongside emicizumab prophylaxis. Guidance regarding aPCC (no more than 50 U/kg to be given as an initial dose and avoid doses of >100 U/kg/24 hours for more) in PwHA who had received at least one dose of emicizumab was followed by 4/5 participants. §§Three participants had ISRs that were not related to study treatment.

Effective bleed control was achieved with emicizumab prophylaxis

- The model-based ABR for treated bleeds was low, at 0.5 (95% confidence interval [CI]: 0.27–0.89; calculated using negative binomial regression; Figure 2).

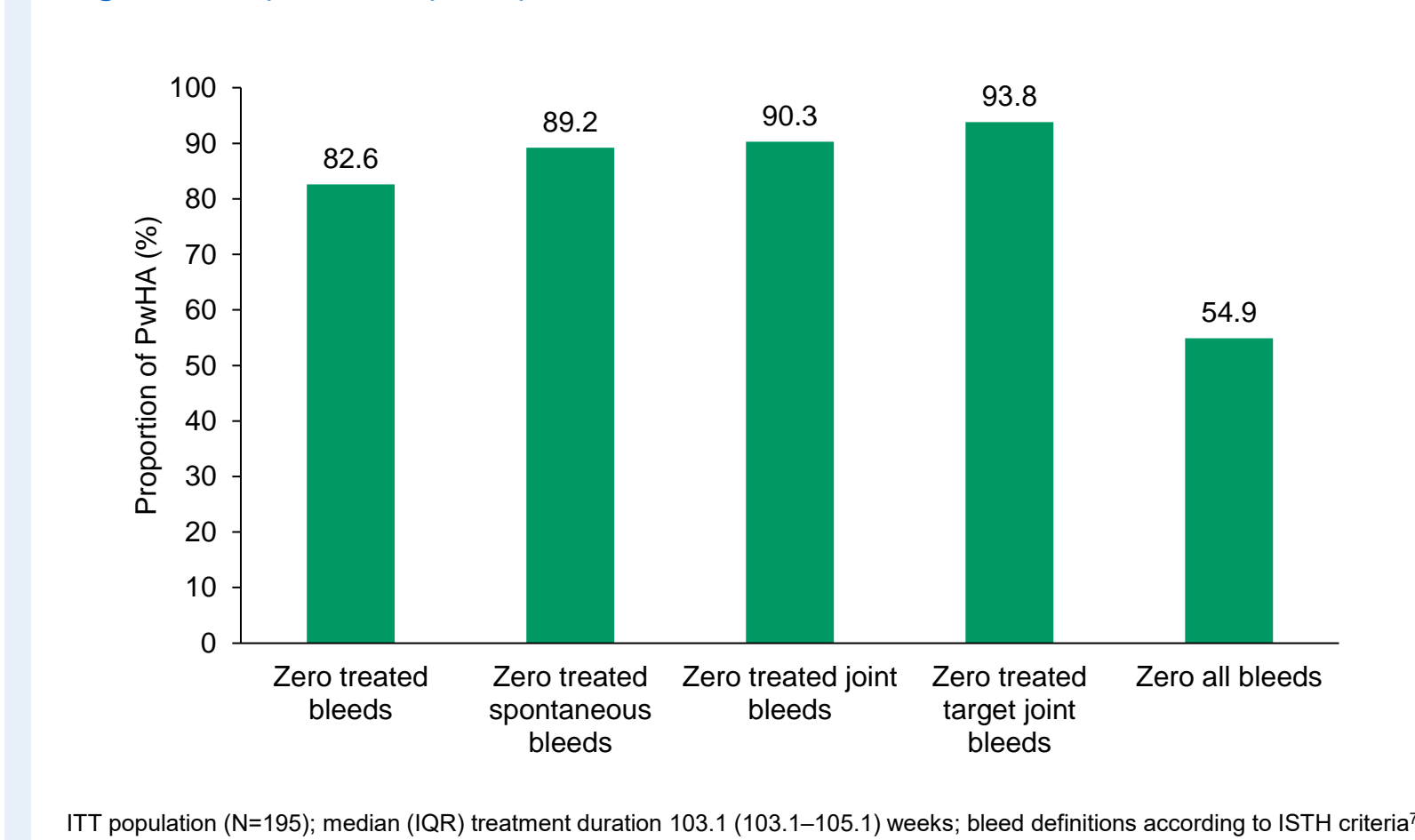
Figure 2. Model-based ABRs



The majority of PwHA experienced zero treated bleeds

- High proportions of participants experienced zero treated bleeds during the study (Figure 3).
- When including all bleeds, over half of participants experienced zero bleeds.

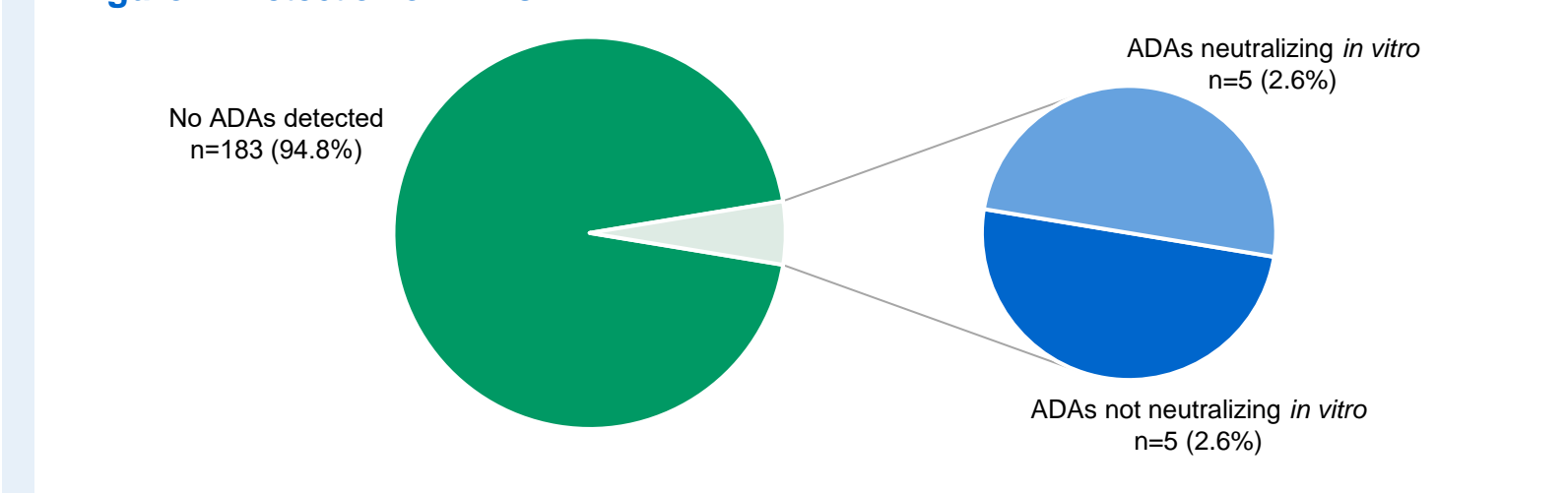
Figure 3. Proportions of participants with zero bleeds



The proportion of PwHA who developed ADAs was low

- Ten (5.2%) of 193 evaluable participants developed ADAs (Figure 4).
 - Eight participants (4.1%) had treatment-induced responses, and two participants (1.0%) had treatment-boosted responses. Five (2.6%) of the participants had neutralizing ADAs *in vitro*.
- The majority of ADAs were of low titer and/or transient (single occurrence) or of short duration.
- The development of ADAs was not associated with a change in safety profile.
- No cases of anaphylaxis or hypersensitivity were reported in ADA-positive participants.
- The presence of ADAs, including neutralizing ADAs, did not impact pharmacokinetics.
- None of the 10 ADA-positive PwHA experienced a treated bleed.
- No participant discontinued emicizumab due to the presence of ADAs.
- All participants tested negative for ADAs at their last visit.

Figure 4. Detection of ADAs



Conclusions

Results from the final analysis of the STASEY trial corroborate the favorable safety profile of emicizumab, as demonstrated in the HAVEN program.

Effective bleed control was achieved with emicizumab prophylaxis.

ADAs were infrequent, the majority were of low titer and/or transient and, regardless of their neutralizing capacity *in vitro*, they did not impact the efficacy or safety of emicizumab.

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