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Second Interim Analysis Results from the STASEY Trial: A Single-arm, Multicenter, Open-label, Phase III Clinical Trial to Evaluate the Safety and Tolerability of Emicizumab Prophylaxis in People with Hemophilia A (PwHA) with FVIII Inhibitors

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SUMMARY

- While the efficacy and safety of emicizumab prophylaxis in PwHA has been demonstrated during the HAVEN clinical trial program,[1–4] it is important to continue to assess safety in a broad population for an extended time for a new treatment.
- Results from the second interim analysis of the STASEY trial demonstrate that emicizumab prophylaxis is well tolerated and effective in preventing bleeds in a large cohort of PwHA with factor (F)VIII inhibitors.

INTRODUCTION

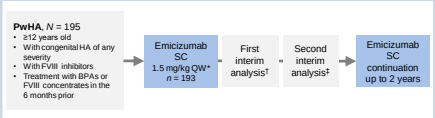
- Emicizumab, a subcutaneously administered, bispecific monoclonal antibody, bridges activated FIX and FX, replacing the function of missing activated FVIII in PwHA, thereby restoring hemostasis.[5]
- STASEY (NCT0319799) is a Phase IIIb, single-arm, open-label, multicenter trial to evaluate the safety and tolerability of emicizumab in PwHA with FVIII inhibitors.[6]
- This report provides results of the second interim analysis from STASEY.

METHODS

Participants for the STASEY trial were enrolled globally.

- PwHA aged ≥12 years with FVIII inhibitors were recruited (**Figure 1**).
  - Following ethics committee approval and informed consent, 195 participants across 24 countries formed the intent-to-treat population, 193 of whom received emicizumab.

Figure 1. STASEY trial design.



*Maintenance dose. Emicizumab was administered at a loading dose of 3.0 mg/kg QW for 4 weeks prior to maintenance dosing.
†Scheduled when approximately 100 patients had received treatment for at least 24 weeks.
‡Scheduled when at least 100 patients had received treatment for at least 1 year.
BPA, bypassing agent; F, factor; PwHA, persons with hemophilia A; QW, once weekly; SC, subcutaneous.

Objectives for the STASEY trial focused on the safety of emicizumab in a post-marketing setting.

- Primary endpoints evaluated the safety of emicizumab, comprising: incidence and severity of all adverse events (AEs), including thromboembolic events (TEs) or thrombotic microangiopathies (TMAs), systemic hypersensitivity, anaphylaxis, and anaphylactoid events as well as changes in physical examination findings, vital signs, and laboratory parameters.
- Bleed and medication data were collected as previously reported.[7]
  - Secondary endpoints evaluated the efficacy of emicizumab, including: number of bleeds over time, quality of life, treatment burden, and patient preference.
  - An additional immunogenicity endpoint evaluated the development of anti-drug antibodies (ADAs).

RESULTS

Table 1. Demographics and baseline characteristics (safety-evaluable population).

	n = 193
Age, years	
Median (range)	28.0 (12–80)
≥12–<18, *n* (%)	39 (20.2)
≥18–<65, *n* (%)	145 (75.1)
≥65, *n* (%)	9 (4.7)
Male, *n* (%)	**193 (100)**
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 (59.1)
Both episodic and prophylactic	12 (6.2)
Highest historical inhibitor titer,* median BU/mL (range)	114.0 (1–32700)
Prior ITI treatment, *n* (%)	100 (51.8)
No. bleeds in 24 weeks prior to trial entry, median (range)	4 (0–49)
Target joints at baseline, *n* (%)	127 (65.8)

*Eight patients had FVIII inhibitor titer <5 BU; 24 patients had unknown titer.
BU, Bethesda units; F, factor; ITI, immune tolerance induction.

Results presented here are from a second interim analysis of the STASEY trial.

- At data cut-off (20 May 2019), 193 PwHA (**Table 1**) had received emicizumab and were evaluable for safety.
- Median (range) treatment duration was 50.9 (1.1–88.1) weeks.

No new safety signals were identified for emicizumab in the primary outcomes.

- Emicizumab was well tolerated (**Table 2**).
- Two AEs were classed as TEs.
  - One ST-elevation myocardial infarction in a 55-year-old who had several risk factors, including a history of smoking, hypertension, and family history of coronary heart disease. He did not receive concomitant bypassing agents and continued emicizumab without dose adjustment; the treating physician assessed the event as unrelated to emicizumab.
  - One hypertrophic clot formation following tooth extraction, during which the individual received multiple doses of anti-fibrinolytic combined with recombinant activated FVII (rFVIIa).
- Emicizumab-related AEs were reported in 33/193 (17.1%) PwHA.
  - Injection-site reactions were most common (22/193; 11.4%).
- One fatality was reported (polytrauma), assessed as unrelated to emicizumab.
- Three PwHA received activated prothrombin complex concentrate and 32 received rFVIIa, with no associated TMA or arterial/venous TEs.

Table 2. Safety summary (safety-evaluable population).

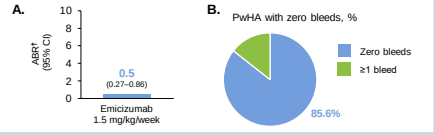
	n = 193
AEs, *n* (%)	
Total number of AEs	**551**
Number of PwHA with ≥1 event	**145 (75.1)**
Fatal AE	1 (0.5)†
Serious AE	19 (9.8)
AE leading to treatment withdrawal	1 (0.5)
AE leading to dose modification or interruption	3 (1.6)
AE leading to trial discontinuation	0
Grade ≥3 AE	22 (11.4)
Trial treatment-related AE	33 (17.1)
Injection-site reaction	22 (11.4)
AEs of special interest	
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)	
Nasopharyngitis	24 (12.4)
Headache	23 (11.9)
Injection-site reaction	22 (11.4)

*Polytrauma with fatal head injury, unrelated to emicizumab, previously reported in first interim analysis.
†STEMI due to thrombus in a coronary artery in one PwHA, and hypertrophic clot at site of tooth extraction in one PwHA who was receiving anti-fibrinolytics. The latter is a known complication of tooth extraction,[8] with the clot not being vessel based. Coded using MedDRA Version 21.1.
AE, adverse event; aPCC, activated prothrombin complex concentrate; MedDRA, Medical Dictionary for Regulatory Activities; PwHA, people with hemophilia A; STEMI, ST-elevation myocardial infarction; TE, thromboembolic event; TMA, thrombotic microangiopathy.

Secondary outcomes were as expected based on the HAVEN clinical trial program.

- Overall, 10/193 (5.2%) participants developed ADAs; in two participants, these were transient.
- No ADAs had neutralizing potential (by pharmacokinetic/clinical assessment).
  - The presence of ADAs was not associated with a change in safety profile or anaphylactic or hypersensitivity reactions.
- Annualized bleed rates (ABRs) remained low (**Figure 2**; **Table 3**), as seen in the HAVEN clinical trial program.[1–4]
  - Treated joint bleeds and treated target joint bleeds were rare (model-based ABRs, 0.3 [95% confidence interval (CI), 0.13–0.67] and 0.2 [95% CI, 0.06–0.68], respectively), with the majority of participants having no bleeds into their joints.

Figure 2. Treated bleeds* (intent-to-treat population).



*Treated bleeds were defined as a bleed directly followed by a hemophilia medication reported as a treatment for bleed, without an intervening bleed and irrespective of the time between the treatment and the preceding bleed. If multiple bleeds occurred on the same calendar day, the subsequent treatment was considered to apply to each of these multiple bleeds. Bleeds due to surgery/procedure are excluded.
†Calculated using negative binomial regression method.
ABR, annualized bleed rate; CI, confidence interval; PwHA, people with hemophilia A.

Table 3. Summary of additional bleed endpoints (intent-to-treat population).

ABR	*N* = 195
All bleeds	
ABR* (95% CI)	1.3 (0.95–1.80)
Median ABR, calculated (IQR)	0.0 (0.00–1.14)
PwHA with zero bleeds, *n* (%)	121 (62.1)
Treated spontaneous bleeds†	
ABR* (95% CI)	0.3 (0.13–0.67)
Median ABR, calculated (IQR)	0.0 (0.00–0.00)
PwHA with zero bleeds, *n* (%)	179 (91.8)
Treated joint bleeds†‡	
ABR* (95% CI)	0.3 (0.12–0.84)
Median ABR, calculated (IQR)	0.0 (0.00–0.00)
PwHA with zero bleeds, *n* (%)	182 (93.3)
Treated target joint bleeds†	
ABR* (95% CI)	0.2 (0.06–0.68)
Median ABR, calculated (IQR)	0.0 (0.00–0.00)
PwHA with zero bleeds, *n* (%)	186 (95.4)

*Calculated using negative binomial regression method.
†Treated bleeds were defined as a bleed directly followed by a hemophilia medication reported as a treatment for a bleed, without an intervening bleed and irrespective of the time between the treatment and the preceding bleed. If multiple bleeds occurred on the same calendar day, the subsequent treatment was considered to apply to each of these multiple bleeds. Bleeds due to surgery/procedure are excluded.
‡Joint bleeds are defined as bleeds with type reported as 'joint' in combination with ≥1 of the following symptoms: increased swelling or warmth of skin over the joint; increasing pain; decreased range of motion or difficulty in using the joint compared with baseline.
ABR, annualized bleed rate; CI, confidence interval; IQR, interquartile range; PwHA, people with hemophilia A.

CONCLUSIONS

- **Results from the second interim analysis of the STASEY trial found no new safety signals, confirming that emicizumab was well tolerated.**
  - **Emicizumab prophylaxis was effective for PwHA with FVIII inhibitors, with the majority of PwHA having zero treated bleeds during the trial.**
- **These findings expand on data supporting the use of emicizumab prophylaxis as a safe and effective way to prevent bleeding for PwHA.**

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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.