Pharmacokinetics and Coagulation Biomarkers in Persons with Hemophilia A (PwHA) and FVIII Inhibitors Receiving Emicizumab in the Phase IIIb STASEY Study

PB0942

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SUMMARY

- Emicizumab, a novel therapy for prophylaxis of hemophilia A (HA), has demonstrated safety and efficacy in PwHA with and without factor (F)VIII inhibitors in Phase III studies (HAVEN 1–4),[1–4] with reduced treatment burden through subcutaneous and less frequent dosing (once every week, 2 weeks, or 4 weeks).[5]
- While emicizumab mimics FVIII cofactor activity, it has fundamental differences from FVIII in terms of pharmacokinetics (PK) and biochemical and pharmacological properties.[6]
- STASEY is a single-arm, multicenter Phase IIIb study to further evaluate the safety of emicizumab in PwHA with FVIII inhibitors.[7]
- The STASEY study demonstrates that the PK and coagulation biomarker profiles of emicizumab in this large population of PwHA with FVIII inhibitors (*n* = 193) are consistent with those reported in other emicizumab studies.[8,9]

INTRODUCTION

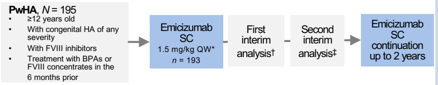
- HA results from a deficiency of coagulation FVIII, leading to risks of frequent and/or prolonged bleeds: spontaneously or related to trauma or surgery.[10]
- Emicizumab is a novel recombinant, humanized, bispecific antibody that restores the function of missing activated FVIII in PwHA by bridging activated FIX and FX.[11]
  - Emicizumab showed a favorable safety profile and clinically meaningful bleed prevention in PwHA with FVIII inhibitors in the STASEY study (NCT03191799).[12]
- This analysis aims to present the PK of emicizumab prophylaxis in PwHA with FVIII inhibitors, as well as their biomarkers of coagulation observed during STASEY.

METHODS

PK and coagulation biomarkers of 193 PwHA with FVIII inhibitors were assessed throughout emicizumab exposure (median 51 weeks) in the STASEY study (Figure 1).

- Emicizumab levels were measured with a validated ELISA assay.
- Two PD markers were assessed: FVIII activity (FVIII:C) using a validated chromogenic assay containing human FIXa and FX (Hyphen Biomed) and activated partial thromboplastin time (aPTT).
- Prothrombin time (PT, international normalized ratio [INR]) and D-dimer were measured using standard assays.
- FVIII inhibitor titers were measured using a chromogenic Bethesda assay containing bovine reagents.

Figure 1. STASEY trial design.


PwHA, N = 195
≥12 years old
With congenital HA of any severity
With FVIII inhibitors
Treatment with BPAs or FVIII concentrates in the 6 months prior
Emicizumab SC
1.5 mg/kg QW*
n = 193
First interim analysis†
Second interim analysis‡
Emicizumab SC continuation up to 2 years

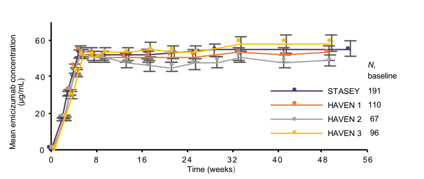
*Maintenance dose. Emicizumab was administered at a loading dose of 3.0 mg/kg QW for 4 weeks prior to maintenance dosing.
†Scheduled when approximately 100 patients had received treatment for at least 24 weeks.
‡Scheduled when at least 100 patients had received treatment for at least 1 year.
BPA, bypassing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

RESULTS

Emicizumab trough plasma concentrations reached a therapeutic level by Week 5 and were sustained throughout maintenance dosing.

- Mean steady-state emicizumab trough plasma concentrations reached >50 µg/mL by Week 5 and were sustained thereafter (data cut-off: 20 May 2019; **Figure 2**).
- The emicizumab levels in the STASEY study are consistent with previous studies of weekly maintenance dosing.

Figure 2. Mean (95% CI) steady-state trough emicizumab concentrations for participants given 1.5 mg/kg QW maintenance doses across STASEY and HAVEN 1–3 studies.

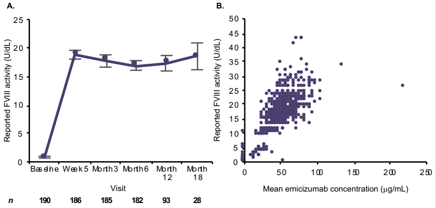


Time has been staggered by 0.2 intervals between STASEY and HAVEN studies to enhance distinction between the overlapping data.
Data from participants who up-titrated to 3 mg/kg QW emicizumab were included in the descriptive statistics until up-titration.
CI, confidence interval.

PD markers demonstrated on-target activity of emicizumab.

- Mean reported FVIII:C activity increased to ~19 U/dL by Week 5 and was maintained throughout the study (**Figure 3**).
- Reported FVIII:C activity correlated with emicizumab concentration, similar to HAVEN studies.[9]

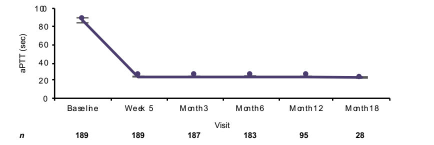
Figure 3 A. Mean (95% CI) FVIII:C activity across the STASEY study period; **B.** FVIII:C activity versus emicizumab concentration (*n* = 193).



FVIII activity values reported as '<1.00%' are inputted as 0.5 (lower limit of quantification/2).
For all patients who were up-titrated, data shown only before up-titration.
CI, confidence interval; F, factor.

- aPTT was normalized by the first post-emicizumab dose assessment, and subsequently remained at or just below the normal range (**Figure 4**).

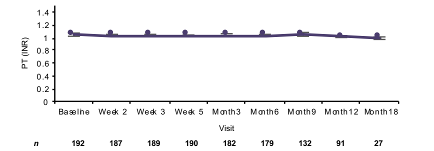
Figure 4. Mean (95% CI) aPTT over the STASEY study period (*n* = 193).



For all patients who were up-titrated, data shown only before up-titration.
aPTT, activated partial thromboplastin time; CI, confidence interval.

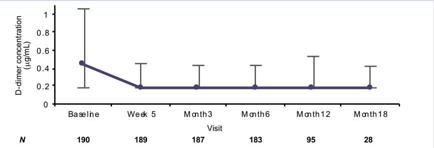
Emicizumab did not affect PT (Figure 5) or concentrations of safety markers of activated coagulation (D-dimer; Figure 6), similar to HAVEN studies.[9]

Figure 5. Mean (95% CI) PT time (INR) over the STASEY study period (*n* = 193).



For all patients who were up-titrated, data shown only before up-titration.
CI, confidence interval; INR, international normalized ratio; PT, prothrombin time.

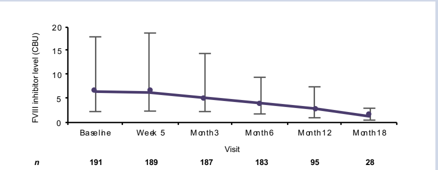
Figure 6. Median (Q1–Q3) D-dimer concentration over the study period (*n* = 193).



D-dimer values reported as '0.36' are inputted to 0.18 (lower level of quantification/2).
For all patients who were up-titrated, data shown only before up-titration.

- Participants' FVIII inhibitor titers remained stable or declined slightly over time (**Figure 7**).
  - 26 participants had titers <0.6 CBU at their last available evaluation (study days 183–547).

Figure 7. Median (Q1–Q3) FVIII inhibitor titer over the STASEY study period (*n* = 193).



FVIII inhibitor values reported as '>45' are inputted as 45 (the upper limit of quantification).
CBU, chromogenic Bethesda unit; F, factor.

CONCLUSIONS

- **The PK and coagulation biomarker profiles and PK/pharmacodynamic relationship of emicizumab in the STASEY study were consistent with those from HAVEN 1–4 studies.[8,9]**

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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.

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