PB0521

# 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

Victor Jiménez-Yuste,[1] Flora Peyvandi,[2] Robert Klamroth,[3] Giancarlo Castaman,[4] Chandrakala Shanmukhaiah,[5] Savita Rangarajan,[6] Jaime García Chavez,[7] Raul Martinez,[8] Gili Kenet,[9] Hazaa Alzahrani,[10] Susan Robson,[11] Christophe Schmitt,[11] Anna Kiialainen,[11] Oliver Meier,[11] Margareth Ozelo[12]

## 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

Most participants had zero treated bleeds

82.6%

PwHA with zero treated bleeds

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

***Pushed for time?***

*Receive a copy of this poster: https://bit.ly/3vq7Ubb*

[1]Hospital Universitario La Paz, Autónoma University, Madrid, Spain; [2]IRCCS Fondazione Ca' Granda Ospedale Maggiore Policlinico, Angelo Bianchi Bonomi Hemophilia and Thrombosis Center and Department of Pathophysiology and Transplantation, University of Milan, Milan, Italy; [3]Comprehensive Care Haemophilia Treatment Centre, Vivantes Klinikum, Berlin, Germany; [4]Careggi University Hospital, Florence, Italy; [5]Department of Haematology, Seth GS Medical College and King Edward Memorial Hospital, Mumbai, India; [6]Fortis Hospitals Ltd, Mumbai, India; [7]Unidad de Investigación en Enfermedades Hematologicas, Hospital de Especialidades CMN La Raza, IMSS, Mexico City, Mexico; [8]UMAE Hospital De Especialidades CMNSXXI, Mexico City, Mexico; [9]Sheba Medical Center, Tel Hashomer, Israel; [10]King Faisal Specialist Hospital and Research Centre, Riyadh, Saudi Arabia; [11]F. Hoffmann-La Roche Ltd, Basel, Switzerland; [12]Hemocentro UNICAMP, University of Campinas, Campinas, SP, Brazil.

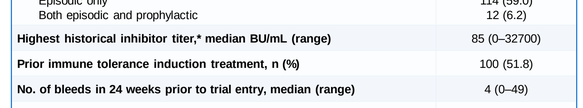
## Background

- 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




*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. §Conducted when all patients had either completed 2 years of treatment, withdrawn consent, completed the safety follow-up visit 24 weeks after discontinuing emicizumab, were lost to follow-up, or died.
BPA, bypassing agent; HA, hemophilia A; QW, once weekly.

- **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.

## 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

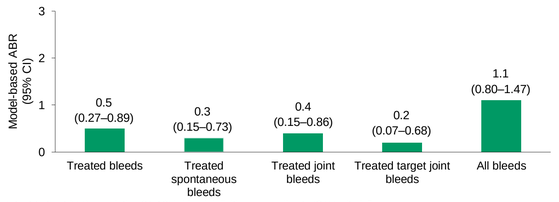
| | Total N=193 |
|---|---|
| **Total number of AEs** | 800 |
| **Number of PwHA with ≥1 event, n (%)** | 163 (84.5) |
| Fatal AE* | 2 (1.0) |
| Serious AE | 31 (16.1) |
| AE leading to treatment withdrawal† | 1 (0.5) |
| AE leading to dose modification or interruption‡ | 4 (2.1) |
| AE leading to trial 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 24 hours or 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

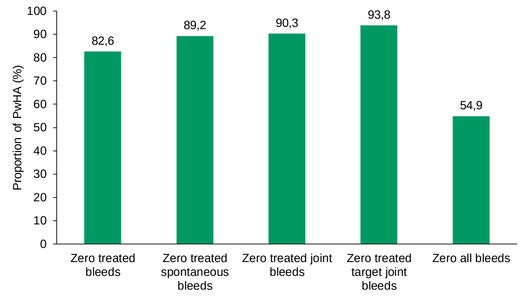



Intent-to-treat (ITT) population (N=195); bleed definitions according to ISTH criteria[7]

## 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

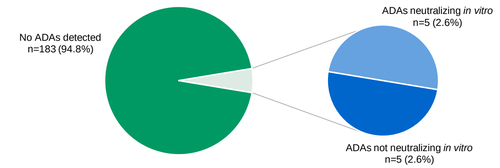



ITT population (N=195); median (IQR) treatment duration 103.1 (103.1–105.1) weeks; bleed definitions according to ISTH criteria[7]

## 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.

**Presented at the XXIX Congress of the International Society on Thrombosis and Haemostasis (ISTH) | 17–21 July 2021**

▼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.

**References**

1. Kitazawa T, et al. *Thromb Haemost* 2017;117:1348–57; 2. Oldenburg J, et al. *N Engl J Med* 2017;377:809–18; 3. Young G, et al. *Blood* 2019;134:2127–38; 4. Mahlangu J, et al. *N Engl J Med* 2018;379:811–2; 5. Pipe S, et al. *Lancet Haematol* 2019;6:E295–E305; 6. European Medicines Agency. Hemlibra solution for injection, Summary of Product Characteristics 2018; available from: https://www.ema.europa.eu/en/documents/product-information/hemlibra-epar-product-information_en.pdf; accessed June 2021; 7. Blanchette VS, et al. *J Thromb Haemost* 2014;12:1935–9.

**Acknowledgments**

The authors would like to thank the study participants and their families, as well as the study investigators, research coordinators and nurses. Statistical support for the development of this poster was provided by Constanze Schulz, of Cytel. Medical writing support for the development of this poster, under the direction of the authors, was provided by Georgia Pangratiou, PhD, of Ashfield MedComms, an Ashfield Health company, and funded by F. Hoffmann-La Roche Ltd.

**Disclosures**

VJ-Y: consultation fees (Sobi, F. Hoffmann-La Roche Ltd, Novo Nordisk, Grifols, Bayer, Pfizer, BioMarin, CSL Behring, Takeda, Sanofi); research funding (Sobi, F. Hoffmann-La Roche Ltd, Novo Nordisk, Grifols, Pfizer, Takeda). FP: honoraria (Sanofi, Sobi, F. Hoffmann-La Roche Ltd, Takeda, Grifols); consultation fees (Sanofi, Sobi); travel expenses (Sanofi, Sobi, F. Hoffmann-La Roche Ltd, Takeda, Grifols). RK: honoraria (Bayer, Biotest, BioMarin, CSL Behring, Daiichi Sankyo, LEO Pharma A/S, Novo Nordisk. Octapharma, Pfizer, F. Hoffmann-La Roche Ltd, Chugai Pharmaceutical Co., Ltd, Sanofi, TakedaShire, Sobi); consultation fees (Bayer, Biotest, BioMarin, Novo Nordisk, Octapharma, Pfizer, F. Hoffmann-La Roche Ltd, Chugai Pharmaceutical Co., Ltd, Sanofi, TakedaShire, Sobi); speakers bureau (Bayer, Biotest, BioMarin, CSL Behring, Daiichi Sankyo, LEO Pharma A/S, Novo Nordisk, Octapharma, Pfizer, F. Hoffmann-La Roche Ltd, Chugai Pharmaceutical Co., Ltd, Sanofi, TakedaShire, Sobi); research funding (Bayer, LEO Pharma A/S); travel expenses (Bayer, Biotest, BioMarin, CSL Behring, Daiichi Sankyo, LEO Pharma A/S, Novo Nordisk, Octapharma, Pfizer, F. Hoffmann-La Roche Ltd, Chugai Pharmaceutical Co., Ltd, TakedaShire, Sobi). GC: consultation fees (UniQure, CSL Behring, F. Hoffmann-La Roche Ltd, Bayer, Novo Nordisk, Sobi, Sanofi, Takeda, Kedrion Biopharma Inc., Werfen); research funding (Sobi, CSL Behring). CSh: honoraria (Takeda, Novo Nordisk); consultation fees (Novo Nordisk); speakers bureau (Novo Nordisk, Intas Pharmaceuticals Ltd, Zydus). SRa: consultation fees (Reliance Life Sciences, Pfizer, Sanofi); speakers bureau (TakedaShire); research funding (Sangamo); travel expenses (TakedaShire, Reliance Life Sciences). JGC: honoraria (Novo Nordisk, F. Hoffmann-La Roche Ltd, Bayer); consultation fees (LFB, Novo Nordisk); expert testimony (Novo Nordisk, F. Hoffmann-La Roche Ltd, Bayer). RM: honoraria (F. Hoffmann-La Roche Ltd). GK: consultation fees (OPKO Biologics, Bayer, Pfizer, Alnylam Pharmaceuticals, CSL Behring, Sanofi, Takeda, F. Hoffmann-La Roche Ltd, Novo Nordisk, BioMarin, UniQure); speakers bureau (Bayer, Pfizer, CSL Behring, Shire, Novo Nordisk, F. Hoffmann-La Roche Ltd); research funding (OPKO Biologics, Bio Products Laboratory Ltd, Shire, Bayer, Pfizer, Alnylam Pharmaceuticals, F. Hoffmann-La Roche Ltd). HA: honoraria (F. Hoffmann-La Roche Ltd, Pfizer, Sanofi, Sobi, Bayer); consultation fees (F. Hoffmann-La Roche Ltd, Pfizer, Sanofi, Sobi, Bayer); travel expenses (F. Hoffmann-La Roche Ltd, Pfizer, Sanofi, Sobi, Bayer). SRo: employment (F. Hoffmann-La Roche Ltd). CSc, AK and OM: employment and stocks/shares (F. Hoffmann-La Roche Ltd). MO: consultation fees (Bayer, BioMarin, Novo Nordisk, Pfizer, F. Hoffmann-La Roche Ltd, Sanofi, Takeda); speakers bureau (Bayer, BioMarin, Novo Nordisk, F. Hoffmann-La Roche Ltd, Takeda); research funding (BioMarin, Novo Nordisk, Pfizer, F. Hoffmann-La Roche Ltd, Sanofi, Takeda); travel expenses (Novo Nordisk, F. Hoffmann-La Roche Ltd, Takeda).