Poster No. 1800

Safety and Efficacy of Emicizumab in Persons with Hemophilia A With or Without FVIII Inhibitors: Pooled Data from Four Phase III Studies (HAVEN 1–4)

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*See full manuscript for all authors' disclosures.

Key takeaways

- In long-term follow-up, emicizumab maintained low bleed rates in persons with hemophilia A
- Emicizumab remained well tolerated, with no new safety concerns

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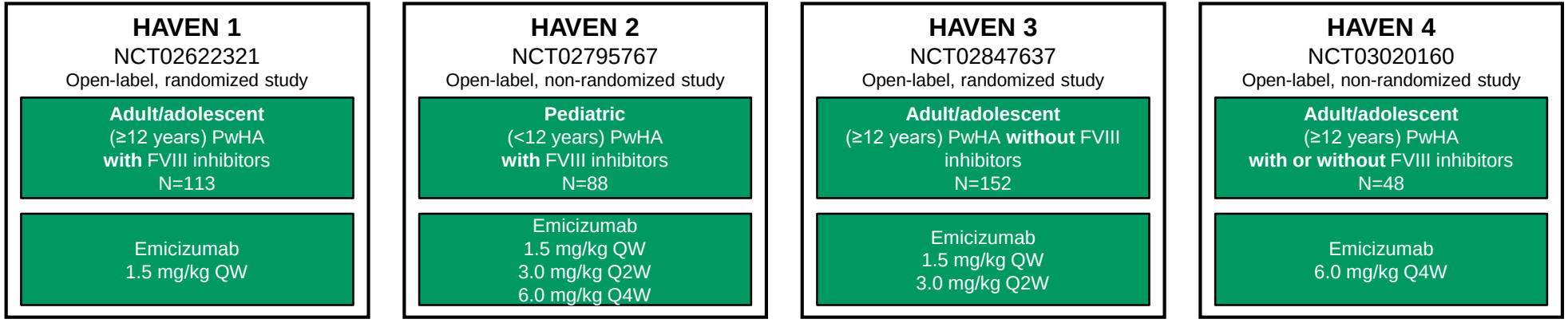
Data from HAVEN 1–4 Phase III studies were pooled to establish the long term efficacy and safety of emicizumab in hemophilia A

Background

- Emicizumab is a subcutaneously administered, bispecific, humanized, monoclonal antibody that promotes effective hemostasis in PwHA[1,2]

Methods

- The HAVEN 1–4 studies were designed to assess the efficacy and safety of emicizumab prophylaxis in PwHA; this analysis pools data from:[3–6]



- Efficacy endpoints included ABRs and percentages of participants with zero and 1–3 treated bleeds
- Safety endpoints included incidence of AEs and AEs of special interest

AE, adverse event; ABR, annualized bleed rate; FVIII, factor VIII; PwHA, persons with hemophilia A; QW, once weekly; Q2W, once every 2 weeks; Q4W, once every 4 weeks.

1. Kitazawa T, et al. *Nat Med*. 2012;18:1570–4; 2. Shima M, et al. *N Engl J Med*. 2016;374:2044–53; 3. Oldenburg J, et al. *N Engl J Med*. 2017;377:809–18; 4. Young G, et al. *Blood*. 2019;134:2127–38; 5. Mahlangu J, et al. *N Engl J Med*. 2018;379:811–22; 6. Pipe SW, et al. *Lancet Haematol*. 2019;6:e295–e305.

Demographics, baseline characteristics and emicizumab exposure in the pooled population (data cut-off May 15, 2020)

	Analysis populations
Participants enrolled, n	401
Participants in ITT group (efficacy population), n*	400
Participants treated with emicizumab (safety population), n*	399

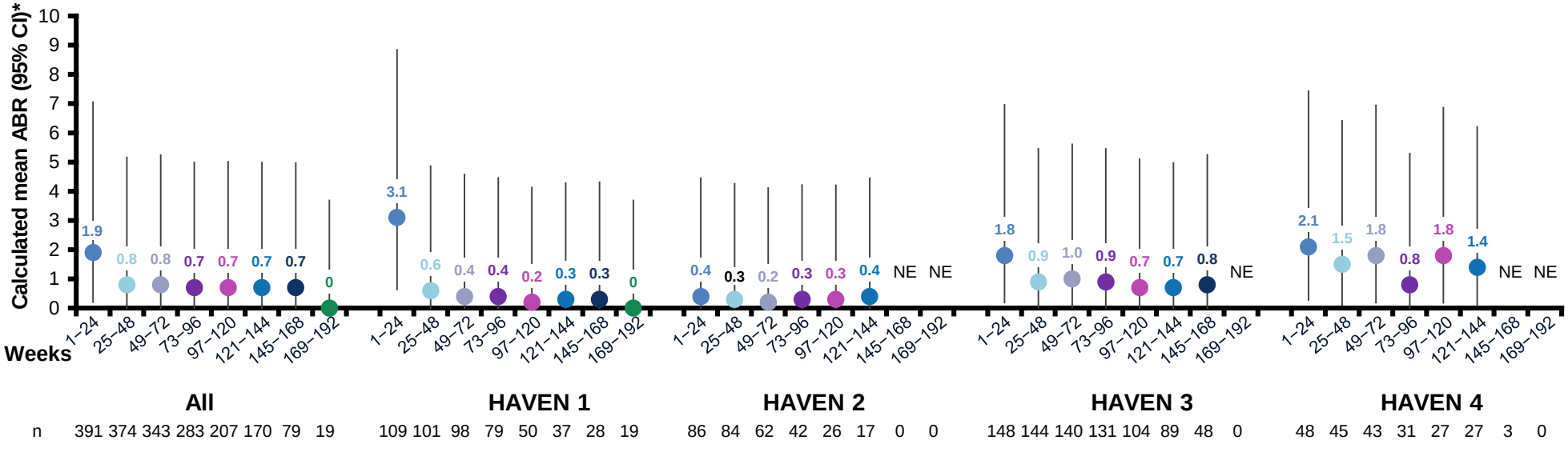
	Total population (N=401)
Median (IQR) duration of exposure, weeks	120.4 (89.0–164.4)
Total participant years of emicizumab exposure	970.3
Age	
Median, years (range)	28.0 (1–77)
<18 years, n (%)	132 (32.9)
≥65 years, n (%)	13 (3.2)
Race, n (%)	
White	267 (66.6)
Asian	76 (19.0)
Black/African American	32 (8.0)
Other or unknown	26 (6.5)

	Total population (N=401)
Previous treatment regimen, n (%)†	
Episodic	192 (48.0)
Prophylactic	208 (52.0)
FVIII inhibitors at baseline, n (%)	
Yes	209 (52.1)
No	192 (47.9)
Previously undergone immune tolerance induction therapy, n (%)	127 (31.7)
Median no. of bleeds in 24 weeks prior to study entry (IQR)	8.0 (5.0–15.0)
Presence of target joints‡[1] at baseline, n (%)	244 (61.0)

*One participant in HAVEN 3 assigned to 'no prophylaxis' was lost to follow-up prior to the switch to emicizumab and was therefore not treated; hence excluded from the efficacy and safety analyses. Another participant in HAVEN 1 assigned to an active arm, discontinued prior to first emicizumab treatment and was excluded from the safety analyses. The demographics table is based on those who enrolled (N=401). Participants included in the efficacy analysis only were N=400; participants included in the safety analysis only were N=399; †For ITT population. ‡In line with International Society on Thrombosis and Haemostasis definition,[1] target joints were defined as major joints (e.g., hip, elbow, wrist, shoulder, knee, and ankle) in which ≥3 spontaneous bleeding events occurred over a 24-week treatment period. FVIII, factor VIII; IQR, interquartile range; ITT, intent-to-treat.

1. Blanchette VS, et al. *J Thromb Haemost.* 2014;12:1935–9.

The pooled mean ABR decreased over the first year and remained below 1 in the following 24-week treatment intervals

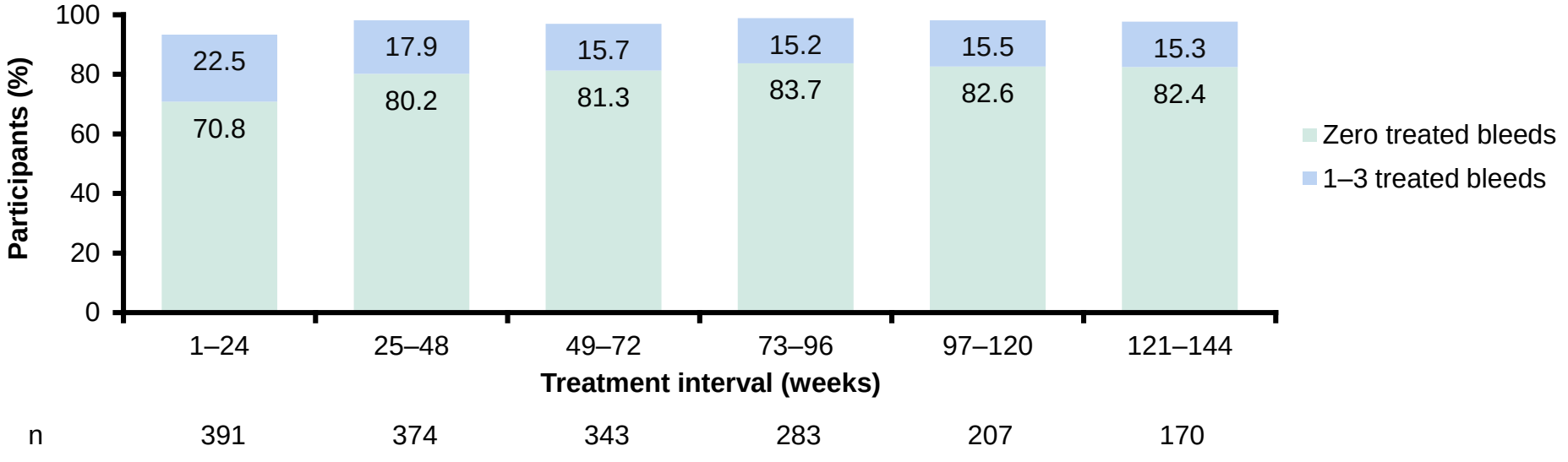


- Across HAVEN 1–4, the ABR* for treated bleeds over the entire study period was 1.4 (95% CI, 1.1–1.7)
- Slightly higher ABRs in HAVEN 4 may be attributable to an outlier with 18 bleeds and the relatively small number of other PwHA[1]

*This result was calculated using a negative-binomial regression model.
ABR, annualized bleed rates; CI, confidence interval; NE, not estimated.

1. Pipe SW, et al. *Lancet Haematol*. 2019;6:e295–e305.

The percentage of participants with zero treated bleeds increased over the first year and remained above 80% thereafter



After week 24, at least 97% of participants had ≤3 bleeds in each treatment interval

At clinical cut off, >95% of target joints in evaluable PwHA were resolved* with emicizumab prophylaxis

Among 226 evaluable PwHA who had at least one target joint at baseline and received at least 52 weeks of emicizumab prophylaxis:

95.1% (504/530) target joints resolved*

89.4% (202/226) PwHA had zero target joint bleeds

***Target joint resolution**: ≤2 spontaneous or traumatic bleeding events in a 12-month period[1]

Clinical cut off date: May 15, 2020.

1. Blanchette VS, et al. *J Thromb Haemost.* 2014;12:1935–9.

During 970 patient-years of exposure, emicizumab had a favorable long-term safety profile with no new or unexpected signals

All AEs	Total population (N=399)
At least one AE, n (%)	381 (95.5%)
Local injection-site reaction, n (%)	111 (27.8%)
Treatment-related AE, n (%)	139 (34.8%)*
Grade ≥3 AE†, n (%)	87 (21.8%)
AE leading to withdrawal from treatment, n (%)	5 (1.3%)
Serious AE, n (%)	93 (23.3%)
AE with fatal outcome, n (%)	1 (0.3%)‡[1]

AEs of special interest	Total population (N=399)
Systemic hypersensitivity/anaphylactic reaction§	1 (0.3%)
All thromboembolic events	4 (1.0%)¶¥
Associated with concomitant aPCC use	2 (0.5%)
Device occlusion of a peripherally inserted central catheter	1 (0.3%)¶
Myocardial infarction	1 (0.3%)¥
All thrombotic microangiopathy events	3 (0.8%)€
Associated with concomitant aPCC use	3 (0.8%)

- No participants discontinued due to AEs beyond the 5 previously described in the primary analyses[1-4]
- The device occlusion and MI events¶¥ were assessed by the Investigators as unrelated to emicizumab, both resolved, and each individual continued emicizumab

*One participant in HAVEN 4 was missing data on AE relationship to treatment. †Adverse events were graded according to the World Health Organization toxicity grading scale. ‡Death of one participant in HAVEN 1 was caused by rectal hemorrhage.[5] §Assessed using Sampson criteria and includes all participants who experienced indicative symptoms. One participant was identified through algorithmic analysis as potentially having a systemic hypersensitivity/anaphylactic/anaphylactoid reaction (he had experienced symptoms of abdominal pain and cough); however, medical review of the case showed that Sampson criteria were not met. ¶The person with the non-serious device occlusion had a history of device-related thrombosis before receiving emicizumab. ¥The person with MI was >65 years, had previously undiagnosed coronary artery disease, was treated for the event, and recovered with reduced heart function. €No new cases of thrombotic microangiopathy have been reported since the primary study analyses. aPCC, activated prothrombin complex concentrate; AE, adverse event; MI, myocardial infarction.

1. Oldenburg J, et al. *N Engl J Med.* 2017;377:809–18;
2. Young G, et al. *Blood.* 2019;134:2127–38;
3. Mahlangu J, et al. *N Engl J Med.* 2018;379:811–22;
4. Pipe SW, et al. *Lancet Haematol.* 2019;6:e295–e305;
5. Khoo L, et al. *Haemophilia.* 2020; DOI: 10.1111/hae.14110.

Conclusions

- With nearly 3 years of follow-up, emicizumab maintained low bleed rates in PwHA of all ages, with/without FVIII inhibitors
- ABRs decreased over time and the proportion of participants with zero treated bleeds increased; almost all target joints resolved
- Emicizumab remains well tolerated over long-term follow-up, and no new safety concerns were identified in this analysis
- Long-term safety and efficacy data for emicizumab are consistent with the findings of the primary analyses and indicate continued reductions in bleeding with long-term treatment

Please see full publication in *Blood* for further details

ABR, annualized bleed rate; FVIII, factor VIII; PwHA, persons with hemophilia A.

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