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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

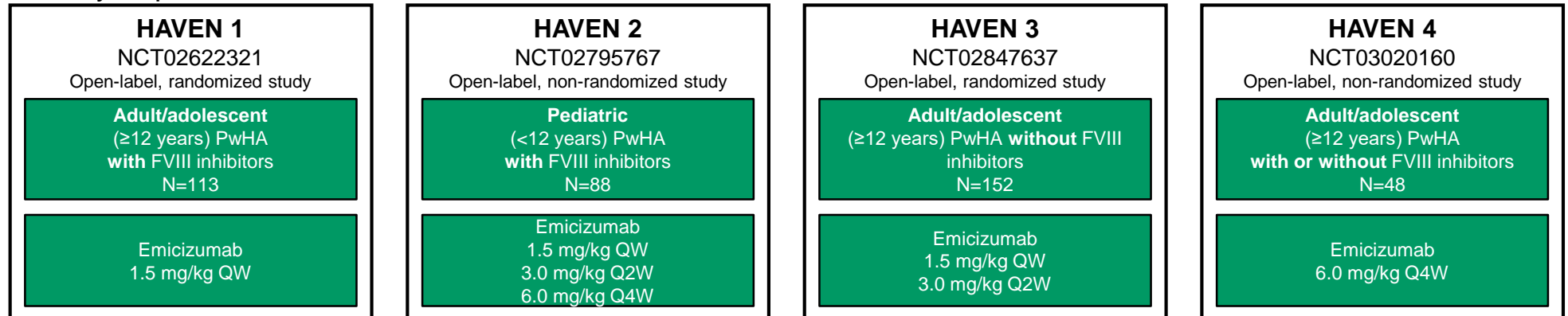
Data from HAVEN 1–4 Phase III studies were pooled to establish the long term efficacy and safety of emicizumab in hemophilia A

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}



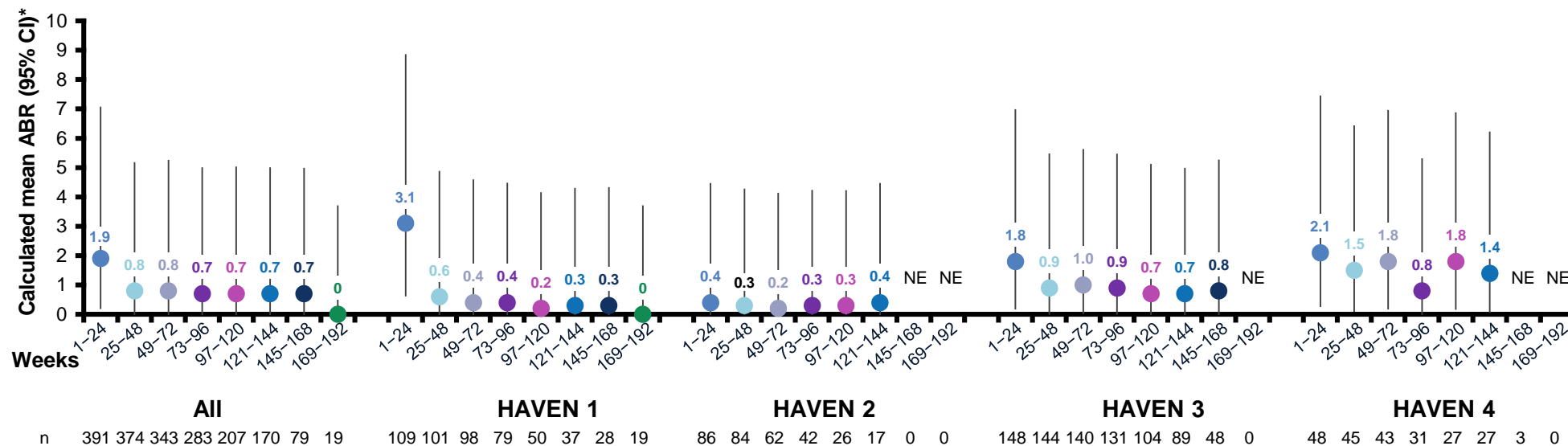
- Efficacy endpoints included ABRs and percentages of participants with zero and 1–3 treated bleeds
- Safety endpoints included incidence of AEs and AEs of special interest

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

Analysis populations		Total population (N=401)		Total population (N=401)	
Participants enrolled, n	401	Median (IQR) duration of exposure, weeks	120.4 (89.0–164.4)	Previous treatment regimen, n (%)[†]	
Participants in ITT group (efficacy population), n*	400	Total participant years of emicizumab exposure	970.3	Episodic	192 (48.0)
Participants treated with emicizumab (safety population), n*	399	Age		Prophylactic	208 (52.0)
		Median, years (range)	28.0 (1–77)	FVIII inhibitors at baseline, n (%)	
		<18 years, n (%)	132 (32.9)	Yes	209 (52.1)
		≥65 years, n (%)	13 (3.2)	No	192 (47.9)
		Race, n (%)		Previously undergone immune tolerance induction therapy, n (%)	127 (31.7)
		White	267 (66.6)	Median no. of bleeds in 24 weeks prior to study entry (IQR)	8.0 (5.0–15.0)
		Asian	76 (19.0)	Presence of target joints^{‡1} at baseline, n (%)	244 (61.0)
		Black/African American	32 (8.0)		
		Other or unknown	26 (6.5)		

*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.

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

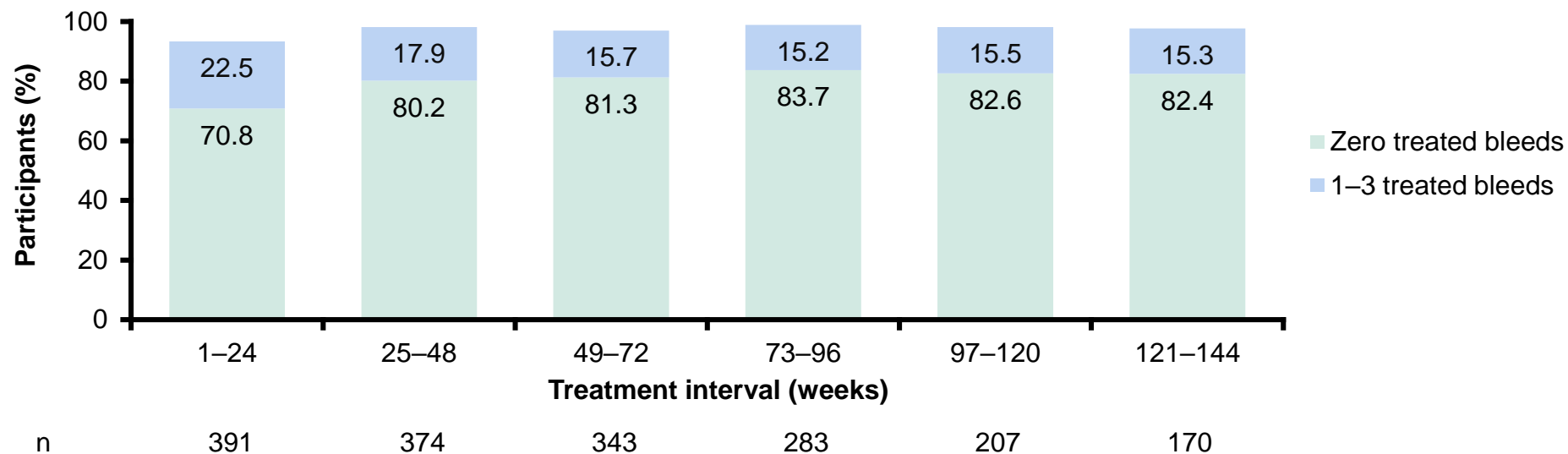


- Across HAVEN 1–4, the ABR* for treated bleeds over the entire study period was 1.4 (95% CI, 1.1–1.7)
- Slightly higher ABRs in HAVEN 4 may be attributable to an outlier with 18 bleeds and the relatively small number of other PwHA¹



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

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 period¹

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 analyses¹⁻⁴
- 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. [§]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.

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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



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