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A Randomized, Multicenter, Open-label, Phase III Clinical Trial to Evaluate the Efficacy, Safety, and Pharmacokinetics of Prophylactic Emicizumab Versus No Prophylaxis in Persons with Hemophilia A in the Asia-Pacific Region (HAVEN 5)

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SUMMARY

- Prophylaxis is standard of care for persons with hemophilia A (PwHA).[1] However, breakthrough bleeding can continue to occur despite adherence to factor prophylaxis,[2] which itself is associated with a high treatment burden.
- In the Asia-Pacific region access to prophylaxis is limited, thus exposing PwHA to greater disease- and treatment-related burdens.[3–5]
- HAVEN 5 (NCT03315455) demonstrated that subcutaneous emicizumab prophylaxis offers a highly efficacious, well-tolerated, and flexible treatment option for PwHA from China and other Asia-Pacific countries.

INTRODUCTION

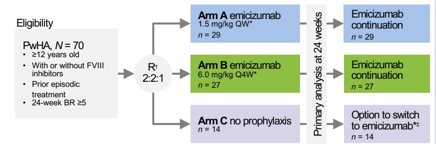
- Emicizumab (HEMLIBRA®), a bispecific, humanized, monoclonal antibody, bridges activated factor (F)IX and FX to restore hemostasis in PwHA.[6]
- HAVEN 5 is a randomized, multicenter, open-label, Phase III study designed to evaluate the efficacy, safety, and pharmacokinetics (PK) of subcutaneous emicizumab prophylaxis compared with no prophylaxis in adults and adolescents with hemophilia A regardless of FVIII inhibitor status. Here we present results from the primary analysis—at the time all participants had completed 24 weeks on study.

METHODS

HAVEN 5 enrolled PwHA from China and other countries in the Asia-Pacific region aged ≥12 years with and without FVIII inhibitors.

- PwHA eligible for randomization were those who had received episodic bypassing agents or replacement FVIII prior to study entry, and who had experienced ≥5 bleeds in the 24 weeks prior to study entry (**Figure 1**).
  - Participants who were randomized to Arm C could switch to receiving emicizumab prophylaxis (6.0 mg/kg once every 4 weeks [Q4W]) after completing 24 weeks in the study.

Figure 1. HAVEN 5 study design.


Eligibility
PwHA, N = 70
• ≥12 years old
• With or without FVIII inhibitors
• Prior episodic treatment
• 24-week BR ≥5
R†
2:2:1
Arm A emicizumab
1.5 mg/kg QW*
n = 29
Arm B emicizumab
6.0 mg/kg Q4W*
n = 27
Arm C no prophylaxis
n = 14
Primary analysis at 24 weeks
Emicizumab continuation
n = 29
Emicizumab continuation
n = 27
Option to switch to emicizumab*‡
n = 14

Cut-off date: 21 June 2019

Primary endpoint: ABR for treated bleeds, calculated using a negative binomial regression model

Secondary endpoints: additional bleed-related endpoints, AEs, and PK

*Maintenance doses. Emicizumab was administered at a loading dose of 3.0 mg/kg QW for 4 weeks prior to maintenance dosing indicated.
†Randomization stratified based on the number of bleeds in the 6 months prior to study start: <9 or ≥9.
‡Emicizumab 6.0 mg/kg Q4W maintenance dosing.
ABR, annualized bleeding rate; AE, adverse event; BR, bleed rate; F, factor; PK, pharmacokinetics; PwHA, persons with hemophilia A; QW, once weekly; Q4W, once every 4 weeks; R, randomization.

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RESULTS

Demographics and characteristics are balanced between arms.

- The median (range) age of participants was 29.0 (12–66) years, and 50% of participants reported two or more target joints at baseline (**Table 1**).

Table 1. Demographics and clinical characteristics.

	Arm A Emicizumab 1.5 mg/kg QW *n* = 29	Arm B Emicizumab 6.0 mg/kg Q4W *n* = 27	Arm C No prophylaxis *n* = 14	Total *N* = 70
Age, years				
Median (range)	31.0 (12–57)	28.0 (13–66)	26.5 (13–46)	29.0 (12–66)
<18, *n* (%)	3 (10)	6 (22)	2 (14)	11 (16)
≥18, *n* (%)	26 (90)	21 (78)	12 (86)	59 (84)
≥65, *n* (%)	0 (0)	1 (4)	0 (0)	1 (1)
Race, *n* (%)				
Chinese	25 (86)	21 (78)	14 (100)	60 (86)
Other Asian	4 (14)	6 (22)	0 (0)	10 (14)
FVIII inhibitor status, *n* (%)				
Positive	6 (21)	7 (26)	3 (21)	16 (23)
Negative	23 (79)	20 (74)	11 (79)	54 (77)
Bleeds in 24 weeks prior to study entry				
Median	14.0	14.0	19.5	14.5
<9, *n* (%)	7 (24)	6 (22)	3 (21)	16 (23)
≥9, *n* (%)	22 (76)	21 (78)	11 (79)	54 (77)
Target joints				
Yes, *n* (%)	20 (69)	20 (74)	12 (86)	52 (74)
>1, *n* (%)	13/20 (65)	14/20 (70)	8/12 (67)	35/52 (67)

F, factor; QW, once weekly; Q4W, once every 4 weeks.

Emicizumab was well tolerated and demonstrated a favorable safety profile.

- The most common AEs were upper respiratory tract infection (Arm A, 31%; Arm B, 19%; Arm C, 36%) and injection-site reaction (Arm A, 14%; Arm B, 19%; Arm C, 0%) (**Table 2**).
- No fatalities, thrombotic microangiopathies (TMAs), or thrombotic events (TEs) were reported.
- Anti-emicizumab antibodies (ADAs) were detected in 8/64 (13%) participants. Of these, only one participant (1/64, 2%) had ADAs with neutralizing potential, which were transient.

Table 2. Safety summary.

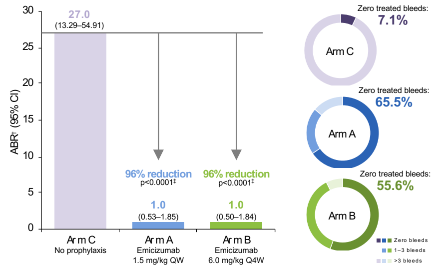
	Arm A Emicizumab 1.5 mg/kg QW *n* = 29	Arm B Emicizumab 6.0 mg/kg Q4W *n* = 27	Arm C* Emicizumab 6.0 mg/kg Q4W *n* = 14
Median (range) duration of exposure, weeks	43.14 (28.1–60.1)	44.14 (20.1–56.6)	18.29 (4.1–32.1)
Total number of AEs	109	76	26
Participants with ≥1 AE, *n* (%)	25 (86)	19 (70)	10 (71)
AE with fatal outcome	0 (0)	0 (0)	0 (0)
SAE	2 (7)	1 (4)	0 (0)
AE leading to withdrawal	0 (0)	0 (0)	0 (0)
AE leading to dose modification/interruption	2 (7)	0 (0)	2 (14)
Grade ≥3 AE	3 (10)	1 (4)	0 (0)
Related AE	12 (41)	10 (37)	5 (36)
Local injection-site reaction	4 (14)	5 (19)	0 (0)
AEs of special interest			
Systemic hypersensitivity/anaphylactic/anaphylactoid reaction†	0 (0)	1 (4)	0 (0)
TE	0 (0)	0 (0)	0 (0)
TMA	0 (0)	0 (0)	0 (0)

*Includes emicizumab prophylaxis period only.
†Assessed using the Samson Criteria and includes all participants that experienced indicative symptoms. One participant in Arm B experienced indicative symptoms; upon medical review, this case was not considered a true hypersensitivity/anaphylactic/anaphylactoid reaction event.
AE, adverse event; QW, once weekly; Q4W, once every 4 weeks; SAE, serious adverse event; TE, thrombotic event; TMA, thrombotic microangiopathy.

Emicizumab QW and Q4W significantly reduced treated ABRs by 96% versus no prophylaxis (Figure 2).

- Similar reductions were observed in all secondary bleed-related endpoints (**Table 3**).
- In Arms A and B, **65.5%** (19/29) and **55.6%** (15/27) of participants had zero treated bleeds, respectively, versus just one participant (1/14; **7.1%**) in Arm C (no prophylaxis).
- The median (interquartile range [IQR]) efficacy period was 43.71 (36.14–48.43) weeks for Arm A, 46.14 (36.71–49.29) weeks for Arm B, and 24.00 (24.00–24.29) weeks for Arm C (no prophylaxis).

Figure 2. Randomized comparison of treated* bleeds.


ABR† (95% CI)
30
25
20
15
10
5
0
27.0
(13.29–54.91)
96% reduction
p<0.0001‡
1.0
(0.53–1.85)
96% reduction
p<0.0001‡
1.0
(0.50–1.84)
Arm C
No prophylaxis
Arm A
Emicizumab
1.5 mg/kg QW
Arm B
Emicizumab
6.0 mg/kg Q4W
Zero treated bleeds:
7.1%
Arm C
Zero treated bleeds:
65.5%
Arm A
Zero treated bleeds:
55.6%
Arm B
Zero bleeds
1–3 bleeds
>3 bleeds

*Treated bleeds are defined as a bleed followed by treatment for a bleed. Bleeds due to surgery/procedure are excluded.
†Model-based ABR. Median (IQR): Arm C, 45.3 (21.74–70.49); Arm A, 0.0 (0.00–1.23); Arm B, 0.0 (0.00–2.26).
‡p-values are obtained via a global model with a three-level categorical effect for treatment.
ABR, annualized bleed rate; CI, confidence interval; IQR, interquartile range; QW, once weekly; Q4W, once every 4 weeks.

Table 3. HAVEN 5 secondary bleed-related endpoints.

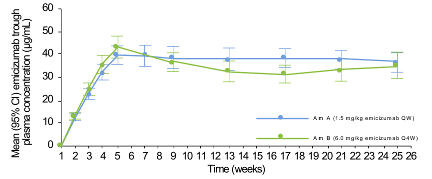
	Arm A Emicizumab 1.5 mg/kg QW *n* = 29	Arm B Emicizumab 6.0 mg/kg Q4W *n* = 27	Arm C* No prophylaxis *n* = 14
Median (IQR) efficacy period, weeks	43.71 (36.14–48.43)	46.14 (36.71–49.29)	24.00 (24.00–24.29)
All bleeds			
ABR† (95% CI)	1.9 (1.23–2.97)	2.1 (1.33–3.26)	41.1 (26.37–64.19)
% reduction (RR) vs Arm C, p-value	95%, p<0.0001	95%, p<0.0001	-
% participants with 0 bleeds (95% CI)	37.9 (20.7–57.7)	33.3 (16.5–54.0)	0 (0.0–23.2)
Treated‡ spontaneous bleeds			
ABR† (95% CI)	0.4 (0.18–0.96)	0.5 (0.20–1.12)	23.6 (9.28–60.03)
% reduction (RR) vs Arm C, p-value	98%, p<0.0001	98%, p<0.0001	-
% participants with 0 bleeds (95% CI)	82.8 (64.2–94.2)	74.1 (53.7–88.9)	14.3 (1.8–42.8)
Treated‡ joint bleeds			
ABR† (95% CI)	0.7 (0.36–1.46)	0.6 (0.28–1.22)	17.7 (8.33–37.57)
% reduction (RR) vs Arm C, p-value	96%, p<0.0001	97%, p<0.0001	-
% participants with 0 bleeds (95% CI)	75.9 (56.5–89.7)	59.3 (38.8–77.6)	7.1 (0.2–33.9)
Treated‡ target joint bleeds			
ABR† (95% CI)	0.4 (0.18–1.09)	0.3 (0.12–0.85)	8.6 (3.15–23.42)
% reduction (RR) vs Arm C, p-value	95%, p<0.0001	96%, p<0.0001	-
% participants with 0 bleeds (95% CI)	82.8 (64.2–94.2)	70.4 (49.8–86.2)	28.6 (8.4–58.1)

*'No prophylaxis' period only. Arm C has a shorter efficacy period as most participants took the option to switch to emicizumab after 24 weeks on study.
†Calculated using a negative binomial regression model.
‡Treated bleeds are defined as a bleed followed by treatment for a bleed. Bleeds due to surgery/procedure are excluded.
ABR, annualized bleed rate; CI, confidence interval; IQR, interquartile range; QW, once weekly; Q4W, once every 4 weeks; RR, rate ratio.

QW or Q4W emicizumab dosing regimens achieved sustained effective trough concentrations (Figure 3).

- Trough plasma concentrations increased with loading doses until Week 5, then were maintained at approximately 37 μg/mL and 33 μg/mL with QW and Q4W dosing, respectively.
- Exposure was around 22% lower than that observed in previous HAVEN studies,[7–10] although this does not appear to be clinically significant.
- No cause for this difference has been identified despite comprehensive investigations. Based on similar PK investigations in Chinese and Caucasian participants,[11] and Asian and Caucasian participants,[12] it is unlikely to be associated with ethnicity. Rather, these results are likely to be a study-specific phenomenon.

Figure 3. Emicizumab trough plasma concentrations over time.



QW, once weekly; Q4W, once every 4 weeks; SD, standard deviation.

CONCLUSIONS

- **Emicizumab prophylaxis QW or Q4W achieved highly effective bleed control with a significant 96% reduction of treated bleeds versus no prophylaxis in this population.**
- **Emicizumab was well tolerated, with no fatalities, TEs, TMAs, or new safety signals.**
- **Lower emicizumab exposure seen in this study did not influence the efficacy and safety profiles of emicizumab in PwHA from the Asia-Pacific region, which are consistent with those seen in previous HAVEN trials.[7–10]**

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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.