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Exploratory analysis from HAVEN 1–4 to further contextualize injection-site reactions among people with hemophilia A receiving emicizumab

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Summary

This exploratory analysis of long-term follow-up of HAVEN 1–4 examines injection-site reactions (ISRs) associated with emicizumab prophylaxis in people with hemophilia A (PwHA)

Overall, 0.75% of over 42,000 emicizumab injections were associated with an ISR

The results from this analysis expand our understanding of the tolerability of emicizumab injections in PwHA

Symptoms associated with ISRs trended down over time across all four studies, and the type and incidence of symptoms were similar irrespective of emicizumab dosing regimen

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Background

- Emicizumab is a recombinant, humanized bispecific monoclonal antibody that is indicated for routine prophylaxis in people with hemophilia A (PwHA) with or without factor (F)VIII inhibitors.
- Long-term data from the Phase III HAVEN 1–4 clinical studies showed that subcutaneous emicizumab prophylaxis maintained low bleed rates and was well tolerated across all four studies.[1]
- Almost all respondents to a treatment-preference survey in the HAVEN 3 and HAVEN 4 studies favored emicizumab prophylaxis over their previous episodic or prophylactic FVIII regimens.[2]
- In the long-term follow-up of the HAVEN 1–4 studies, over a median emicizumab duration of 130.3 weeks, the most common treatment-related adverse events (AEs) were injection-site reactions (ISRs), as classified by The Medical Dictionary for Regulatory Activities preferred terms.[1,3]
- This exploratory analysis further contextualizes ISRs across HAVEN 1–4 to inform on the tolerability of emicizumab injections.

PwHA with or without FVIII inhibitors who received emicizumab in the HAVEN 1–4 studies were included in this exploratory analysis

- Long-term data from four multicenter, open-label Phase III studies (NCT02622321, NCT02795767, NCT02847637, NCT03020160) were pooled to evaluate ISRs associated with emicizumab treatment; study designs have been previously published and are summarized in **Table 1**.[4–7]
- For all four studies, the data cut-off for this analysis was 15 May 2020.
- Data from participants in the total safety population with ≥1 post-baseline assessment were included in this analysis.
- The schedule of clinic visits was similar across the HAVEN 1–4 studies until Week 49 (HAVEN 2) or Week 73 (HAVEN 1, 3 and 4); following this, the schedule of follow-up visits were every 12 weeks (HAVEN 1, 2, and 4) or every 24 weeks (HAVEN 3).
- Exploratory outcomes included the proportion of participants with ISRs over 24-week intervals, the proportion of total emicizumab injections associated with an ISR, and the type and incidence of ISR-related symptoms.

Table 1. Overview of the HAVEN 1–4 studies

	HAVEN 1	HAVEN 2	HAVEN 3	HAVEN 4
Study design	Open-label, randomized	Open-label, non-randomized	Open-label, randomized	Open-label, non-randomized
Age of participants	≥12 years	<12 years*	≥12 years	≥12 years
FVIII inhibitor status	With	With	Without	With or without
Emicizumab dosing regimen†	1.5mg/kg QW	1.5mg/kg QW 3.0mg/kg Q2W 6.0mg/kg Q4W	1.5mg/kg QW 3.0mg/kg Q2W	6.0mg/kg Q4W

*Adolescents aged 12–17 years weighing <40 kg were also permitted to enroll.
†Dosing regimen is the maintenance dose. Apart from the HAVEN 4 PK run-in cohort (n=7), all maintenance doses were preceded by loading doses of 3.0mg/kg QW for 4 weeks.
F, factor; PK, pharmacokinetics; QW, once weekly; Q2W, once every 2 weeks; Q4W, once every 4 weeks.

In total, 399 participants were included in this pooled analysis

- PwHA who received emicizumab in the safety populations of HAVEN 1–4 were included in this analysis; baseline characteristics are summarized in **Table 2**.
- The median (range) emicizumab duration was 130.3 weeks (3.4–221.1), and 389 participants (97.5%) had a duration >52 weeks.

Table 2. Baseline characteristics

	HAVEN 1	HAVEN 2	HAVEN 3	HAVEN 4	Total
Participants enrolled, n*	113†	88	152‡	48	401
Age (years)					
Median (range)	29 (12–75)	7 (1–15)	38 (13–77)	38 (14–68)	28 (1–77)
<18, n (%)	32 (28.3)	88 (100)	8 (5.3)	4 (8.3)	132 (32.9)
≥65, n (%)	5 (4.4)	0	5 (3.3)	3 (6.3)	13 (3.2)
Previous treatment regimen, n (%)					
Episodic	64 (56.6)	22 (25.0)	88 (58.3)	18 (37.5)	192 (48.0)
Prophylactic	49 (43.4)	66 (75.0)	63 (41.7)	30 (62.5)	208 (52.0)
FVIII inhibitor at baseline, n (%)					
Yes	113 (100)	88 (100)	0	8 (16.7)	209 (52.1)
No	0	0	152 (100)	40 (83.3)	192 (47.9)

*The table includes all enrolled participants (N=401).
†One participant discontinued prior to first emicizumab treatment and was excluded from this analysis.
‡One participant was not treated and was excluded from this analysis.
F, factor.

Overall, 112 participants (28.1%) reported ≥1 ISR

- The proportion of participants reporting ISRs was similar across all dosing regimens (**Table 3**).

Table 3. Summary of ISRs reported in the total safety population

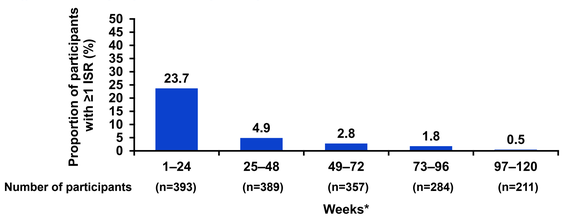
	Emicizumab dosing regimen			
	1.5mg/kg QW	3.0mg/kg Q2W	6.0mg/kg Q4W	Total
Participants <18 years old	n=107	n=11	n=14	N=132
Total number of ISRs, n	72	7	22	101
Number (%) of participants with ISRs				
≥1 events	34 (31.8)	2 (18.2)	8 (57.1)	44 (33.3)
1 event	15 (14.0)	0	5 (35.7)	20 (15.2)
2 events	11 (10.3)	1 (9.1)	1 (7.1)	13 (9.8)
>5 events	1 (0.9)	0	2 (14.3)	3 (2.3)
Number of ISRs per participant (overall)				
Mean (SD [range])	0.67 (1.32 [0–8])	0.64 (1.57 [0–5])	1.57 (2.65 [0–9])	0.77 (1.54 [0–9])
Number of ISRs per participant with ISRs	n=34	n=2	n=8	n=44
Mean (SD)	2.12 (1.55)	3.50 (2.12)	2.75 (3.06)	2.30 (1.90)
Median (range)	2 (1–8)	3.50 (2–5)	1 (1–9)	2 (1–9)
Mean (SD) number of ISRs per 100 emicizumab doses				
Overall participants	0.62 (1.23)	1.22 (2.75)	6.22 (12.07)	1.27 (4.38)
Participants with ISRs	1.96 (1.46)	6.73 (1.20)	10.88 (14.58)	3.80 (6.98)
Participants ≥18 years old	n=172	n=51	n=44	N=267
Total number of ISRs, n	123	33	60	216
Number (%) of participants with ISRs				
≥1 events	48 (27.9)	12 (23.5)	8 (18.2)	68 (25.5)
1 event	24 (14.0)	6 (11.8)	2 (4.5)	32 (12.0)
2 events	14 (8.1)	2 (3.9)	3 (6.8)	19 (7.1)
>5 events	5 (2.9)	1 (2.0)	3 (6.8)	9 (3.4)
Number of ISRs per participant (overall)				
Mean (SD [range])	0.72 (1.98 [0–14])	0.65 (1.88 [0–12])	1.36 (4.59 [0–23])	0.81 (2.58 [0–23])
Number of ISRs per participant with ISRs	n=48	n=12	n=8	n=68
Mean (SD)	2.56 (3.08)	2.75 (3.14)	7.50 (8.77)	3.18 (4.34)
Median (range)	1.50 (1–14)	1.50 (1–12)	2 (1–23)	2 (1–23)
Mean (SD) number of ISRs per 100 emicizumab doses				
Overall participants	0.50 (1.25)	1.17 (3.18)	5.12 (18.07)	1.39 (7.65)
Participants with ISRs	1.81 (1.81)	4.96 (5.04)	28.18 (35.53)	5.47 (14.48)

ISR, injection-site reaction; QW, weekly; Q2W, every 2 weeks; Q4W, every 4 weeks; SD, standard deviation.

The proportion of participants who experienced an ISR declined over time to <1%

- Over time, the proportion of participants who had an ISR declined from 23.7% in the first 24 weeks, to 4.9% at 25–48 weeks, 2.8% at 49–72 weeks, 1.8% at 73–96 weeks, and 0.5% at 97–120 weeks (**Figure 1**).
- No participant discontinued emicizumab because of an ISR.

Figure 1. The proportion of participants with ≥1 ISR over 24-week intervals

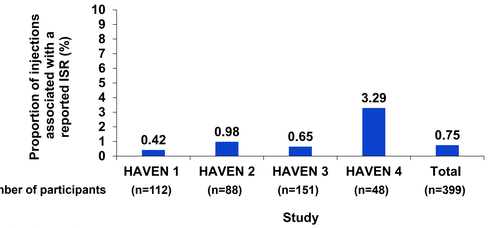


*Data are only shown up to week 120 due to small numbers of participants included in the later time intervals, mostly due to switching to commercial emicizumab.
ISR, injection-site reaction.

Overall, <1% of emicizumab injections were associated with an ISR

- In total, 317 ISRs occurred out of over 42,000 injections, corresponding to 0.75% of injections being associated with a reported ISR (**Figure 2**).
- When split by study, the percentage of ISRs by total injections was highest in HAVEN 4 at 3.29%.

Figure 2. Proportion of ISRs by total number of injections across studies



ISR, injection-site reaction.

The type and incidence of ISR-associated symptoms were similar irrespective of dosing regimen and age

- The top three most common recorded symptoms associated with ISRs were: erythema, occurring in 52 participants; pain, occurring in 18 participants; and swelling, which occurred in 16 participants (**Table 4**).
- All ISRs were reported as being non-serious and mild to moderate in intensity.

Table 4. ISR-related symptoms in the total safety population

	Emicizumab dosing regimen			
	1.5mg/kg QW	3.0mg/kg Q2W	6.0mg/kg Q4W	Total
Participants <18 years old	n=107	n=11	n=14	N=132
Number (%) of participants with ≥1 ISR	34 (31.8)	2 (18.2)	8 (57.1)	44 (33.3)
Number (%) of participants with ISR-related symptoms				
Erythema	12 (11.2)	1 (9.1)	3 (21.4)	16 (12.1)
Pain	5 (4.7)	0	1 (7.1)	6 (4.5)
Swelling	8 (7.5)	0	1 (7.1)	9 (6.8)
Pruritus	2 (1.9)	1 (9.1)	0	3 (2.3)
Hemorrhage	8 (7.5)	0	0	8 (6.1)
Rash	4 (3.7)	1 (9.1)	2 (14.3)	7 (5.3)
Urticaria	3 (2.8)	0	3 (21.4)	6 (4.5)
Participants ≥18 years old	n=172	n=51	n=44	N=267
Number (%) of participants with ≥1 ISR	48 (27.9)	12 (23.5)	8 (18.2)	68 (25.5)
Number (%) of participants with ISR-related symptoms				
Erythema	24 (14.0)	5 (9.8)	7 (15.9)	36 (13.5)
Pain	9 (5.2)	2 (3.9)	1 (2.3)	12 (4.5)
Swelling	4 (2.3)	2 (3.9)	1 (2.3)	7 (2.6)
Pruritus	10 (5.8)	1 (2.0)	1 (2.3)	12 (4.5)
Hemorrhage	3 (1.7)	1 (2.0)	0	4 (1.5)
Rash	3 (1.7)	2 (3.9)	0	5 (1.9)
Urticaria	3 (1.7)	1 (2.0)	2 (4.5)	6 (2.2)

Note: shown are events that occurred in ≥3% of all participants.
ISR; injection-site reaction; QW, weekly; Q2W, every 2 weeks; Q4W, every 4 weeks.

Conclusions

- In this exploratory analysis of long-term data pooled from the HAVEN 1–4 studies, 0.75% of over 42,000 emicizumab injections were associated with ISRs.
- These data show that the proportion of participants experiencing an ISR declined over time; however, the study is limited by changes in visit schedules beyond the main phase of the studies, which may introduce a reporting bias.
  - Due to their mild severity, participants receiving emicizumab may become accustomed to the ISRs over time and cease reporting them.
- This analysis provides a comprehensive overview of ISRs occurring with emicizumab injections over time and across different dosing regimens; the information conveyed here supports better administration education to patients and providers, optimizing understanding of patient experience with the subcutaneous injection of emicizumab.

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