P1214

# Bleed patterns in infants, from birth to 12 months of age, with hemophilia A treated with emicizumab: exploratory analysis of the HAVEN 7 study

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## Summary

This HAVEN 7 exploratory bleed patterns analysis describes **the types and locations of bleeds** that occurred in previously **untreated/minimally treated infants** with severe hemophilia A receiving treatment with emicizumab

Emicizumab was effective at **maintaining low annualized bleeding rates** in infants up to 12 months of age at informed consent

The bleeding patterns observed in this 52-week period of emicizumab treatment may be **similar to typical patterns of bruising/injury observed in non-hemophilic infants**

Infants treated with emicizumab **experienced no treated spontaneous bleeds, and had a low joint bleed rate**; no intracranial hemorrhage occurred

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## Background

- Emicizumab, a bispecific monoclonal antibody, replaces the function of deficient activated factor (F)VIII to improve hemostasis in people with hemophilia A (HA)
  - Early initiation of emicizumab may mitigate risks of spontaneous and traumatic bleeding, including intracranial hemorrhage (ICH), as well as FVIII inhibitor development, and has been recommended by the National Bleeding Disorders Foundation's Medical and Scientific Advisory Council (MASAC) for infants since 2020, prior to HAVEN 7 study initiation.[1]
- HAVEN 7 (NCT04431726) was designed to evaluate the safety, efficacy, pharmacokinetics and pharmacodynamics of emicizumab in infants aged 0–12 months with severe HA without FVIII inhibitors
  - After 52 weeks of treatment, emicizumab demonstrated effective bleed control and was well tolerated.[2]
- This poster presents the results of an exploratory analysis of HAVEN 7, investigating bleed patterns of infants enrolled in the study.

## HAVEN 7 is a phase 3b, multicenter, open-label study, details of which have been published previously[2]

- Eligible participants had no history of, or minimal exposure (≤5 days) to hemophilia-related treatments containing FVIII. Participants were excluded if they had any prior use of emicizumab or evidence of ICH.
- Participants received subcutaneous loading doses of emicizumab 3mg/kg weekly for 4 weeks, followed by maintenance doses of 3mg/kg every 2 weeks.
- Annualized bleeding rates (ABRs) (95% confidence interval [CI]) were estimated using a negative binomial regression model and excluded surgical bleeds.
- This exploratory analysis investigated the type and location of bleeds, and bleed patterns relative to age.
- A new bleed was defined as a bleed occurring >72 hours after the last treatment for the original bleed. Any symptoms of bleeding that occurred ≤72 hours after the last treatment in the same location were considered the same bleed.[3]

## At clinical cutoff (May 22, 2023), 55 male infants were enrolled in the study, and had completed 52 weeks of emicizumab treatment

- Median treatment duration was 100.3 weeks (range: 52–118).
- At informed consent, median participant age was 4.0 months (range: 9 days–11 months 30 days; **Table 1**).

**Table 1. Baseline characteristics.**

| | Participants (N=55) |
|---|---|
| **Age at informed consent (months)** | |
| Mean (SD) | 5.0 (3.9) |
| Median | 4.0 |
| Min–max | 9 days – 11 months 30 days |
| **Male, n (%)** | **55 (100)** |
| **Prior treatment status, n (%)** | |
| MTP* | 30 (54.5) |
| PUP | 25 (45.5) |
| **Family history of HA, n (%)** | **41 (74.5)** |
| Family history of FVIII inhibitors | 7 (12.7) |
| **Number of participants with ≥1 bleed prior to emicizumab initiation†, n (%)** | **36 (65.5)** |
| Number of bleeds, n | 77 |
| Spontaneous bleeds | 25 (32.5%) |
| Traumatic bleeds | 19 (24.7%) |
| Procedural/surgical bleeds | 33 (42.9%) |
| **Age at first bleed,† weeks** | |
| Median | 1.0 |
| Min–max | 0–49 |

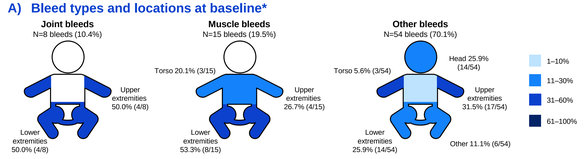
*Defined as a participant with ≤5 EDs to hemophilia-related treatments containing FVIII, such as plasma-derived FVIII, recombinant FVIII, fresh/frozen plasma, cryoprecipitate, or whole blood products; †Data on bleeds prior to the study (since birth) were collected retrospectively. ED, exposure days; F, factor; HA, hemophilia A; max, maximum; min, minimum; MTP, minimally treated participant; PUP, previously untreated participant; SD, standard deviation.

## A total of 195 bleeds (treated and untreated) were reported in 46 participants during the study

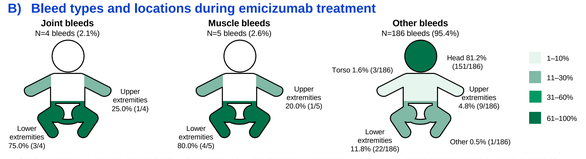
- Prior to study entry, most bleeds had occurred at the lower extremities (26/77 [33.8%]), with 25 (32.5%), 14 (18.2%) and 6 (7.8%) occurring at the upper extremities, the head and the torso, respectively (**Figure 1A**).
- During the study, most bleeds occurred on the head (151/195 [77.4%]), and 29 (14.9%), 11 (5.6%) and 3 (1.5%) occurred at the lower and upper extremities and the torso, respectively (**Figure 1B**).

**Figure 1. Bleed types and locations at baseline and during the study.**

A) Bleed types and locations at baseline*




B) Bleed types and locations during emicizumab treatment



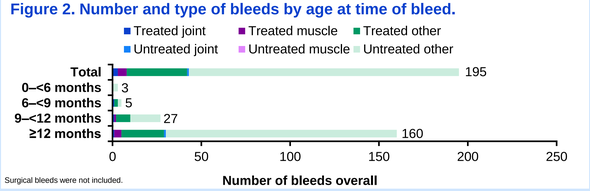

A) *Historical bleeds were captured through medical history records and therefore may be underrepresented. Overall percentages are based on a total number of 77 bleeds at baseline. Bleed location percentages are calculated using the number of each bleed type as the denominator. Joint bleeds included upper extremities (elbow, shoulder and fingers/thumb) and lower extremities (hip, ankle and knee); muscle bleeds included torso (chest, upper back and upper abdomen), upper extremities (upper arm, back of upper arm and forearm) and lower extremities (thigh); other bleeds included head (mouth, top of head, back of head, cheek/face, eye, forehead) torso (genitals), upper extremities (back of hand, fingers/thumb, upper arm, forearm, palm, and elbow) and lower extremities (sole/heel, thigh, knee and hip) and other (other, stool and vomit).

B) Overall percentages are based on a total number of 195 bleeds during emicizumab treatment. Bleed location percentages are calculated using the number of each bleed type as the denominator. Joint bleeds included upper extremities (elbow) and lower extremities (knee and ankle); muscle bleeds included upper extremities (wrist) and lower extremities (thigh and buttock); other bleeds included head (mouth, nose, forehead, cheek/face, top of head, eye, back of head, gum in mouth, chin and ear), torso (lower abdomen, lower back and side), upper extremities (fingers/thumb, forearm and palm), lower extremities (knee, foot, shin, toes and buttock) and other (bruising location cannot be recalled).

## Zero treated spontaneous bleeds were reported during the study

- Model-based ABRs (95% CI) for treated bleeds and all bleeds were 0.40 (0.30–0.63) and 2.0 (1.49–2.66), respectively.
- Overall, 3/195 (1.5%) bleeds occurred in participants aged 0–<6 months at time of bleed; 5 (2.6%), 27 (13.8%), and 160 (82.1%), occurred at ages 6–<9, 9–<12, and ≥12 months, respectively (**Figure 2**).
- There were 42 treated bleeds in 25/46 (54.3%) participants, all traumatic
  - Zero (0%) occurred in participants aged 0–<6 months at time of bleed, and 3 (7.1%), 10 (23.8%), and 29 (69.0%) at ages 6–<9, 9–<12, and ≥12 months, respectively (**Figure 2**).

**Figure 2. Number and type of bleeds by age at time of bleed.**

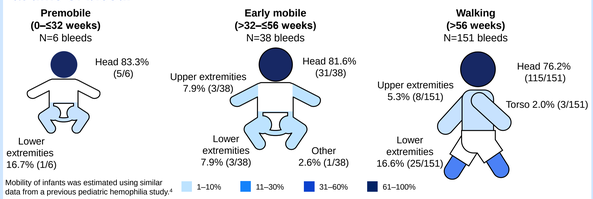



Surgical bleeds were not included.

## Bleeding patterns observed were similar to bruising/injury patterns in non-hemophilic infants

- The majority of bleeds occurred in participants aged >56 weeks (**Figure 3**), consistent with motor development and also bruising/injury patterns observed in non-hemophilic infants.[4,5]

**Figure 3. Number of bleeds (treated and untreated) by location and mobility at time of bleed.**

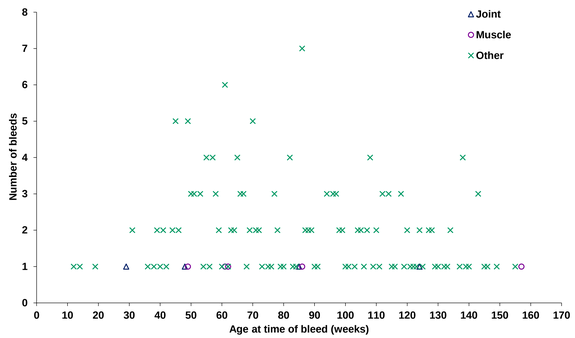



## Most traumatic and non-surgical bleeds occurred on the head

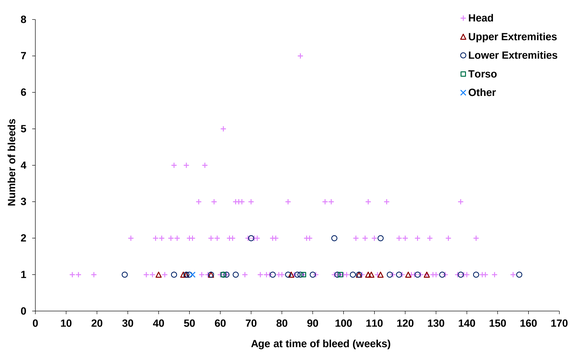
- Four (2.1%) joint and 5 (2.6%) muscle bleeds occurred, all at >6 months of age (**Figure 4A**).
- Most spontaneous and traumatic bleeds occurred on the head (151/195 [77.4%]; **Figure 4B**); the most common were mouth bleeds (57/151 bleeds [37.7%]; 12 treated) and nose bleeds (37/151 bleeds [24.5%]; all untreated).
- No ICH occurred.

**Figure 4. Number of treated and untreated bleeds.**

A) Distribution of joint, muscle and other bleeds by age at time of bleed




B) Distribution of all bleeds by location and age at time of bleed




Surgical bleeds were not included.

- The median (range) numbers of FVIII exposure days per participant and FVIII infusions per bleed during emicizumab treatment were 0.0 (0.0–4.0) and 1.0 (1.0–3.0), respectively.[6]
- Two infants aged 10 and 11 months at informed consent contributed to 24.6% of overall bleeds. One infant had 27 (13.8%) bleeds; 23 on the head, mostly nose bleeds. The other infant had 21 (10.7%) bleeds; 14 bleeds on the head, primarily mouth bleeds.

## Conclusions

- This is one of the first analyses describing in detail bleeding patterns in infants with HA receiving emicizumab.
- At the primary analysis of HAVEN 7, no treated spontaneous bleeds were reported during emicizumab treatment, and joint and muscle bleed rates were low.
- All treated bleeds reported were traumatic and bleed events increased with age as infants gained mobility and motor development.
- No ICH was reported with emicizumab prophylaxis; HAVEN 7 was not designed to investigate ICH.
- In this exploratory analysis, the pattern and location of bleeding displayed during emicizumab treatment were similar to previously published analyses of bruising and injury in infants without a bleeding disorder.[4,5]

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**Disclosures**

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