P1238

Pharmacodynamic Biomarkers in Infants with Hemophilia A Receiving Emicizumab in HAVEN 7

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Summary

Background:
The developing coagulation system in infants may be expected to impact the pharmacodynamics (PD) of emicizumab prophylaxis. HAVEN 7 investigates emicizumab in infants with hemophilia A (HA) from birth to ≤12 months of age

Methods:
PD was assessed by activated partial thromboplastin time (aPTT), factor (F)VIII-like activity and by FXIa-triggered thrombin generation (TG) assay. Plasma antigen levels of FIX and FX were also determined

Conclusions:
The PD profiles of emicizumab in infants with HA were consistent with those previously observed in older children and adults with HA

Results:
FVIII-like activity and TG increased, and aPTT was shortened, after starting emicizumab prophylaxis. FVIII-like activity increased with age up to ~3–4 months old, and FIX and FX levels increased with age up to ~9 months old

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Background

- Emicizumab, a bispecific antibody that mimics the cofactor function of activated factor (F)VIII, demonstrated a favorable safety and efficacy profile in infants with severe hemophilia A (HA) without FVIII inhibitors in HAVEN 7 (NCT04431726).[1–3]
- It is known that some coagulation factors, including FIX and FX, the binding targets of emicizumab, have lower plasma levels during the first 6 months of life.
- This research investigates whether the developing coagulation system impacts the pharmacodynamics (PD) of emicizumab prophylaxis in infants with HA enrolled to HAVEN 7 from birth to ≤12 months of age.

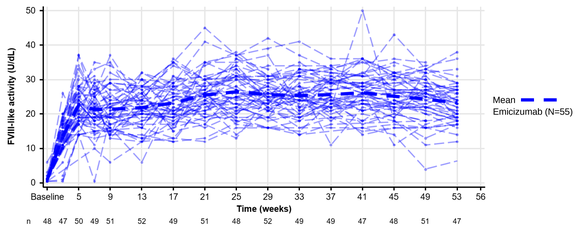
Methods

- Informed consent from the parents/legally authorized representative and ethics approval were obtained.
- Trough plasma concentrations of emicizumab were measured by validated enzyme-linked immunosorbent assay.
- PD was assessed by activated partial thromboplastin time (aPTT), FVIII activity using a chromogenic assay containing human FIX and FX (considered FVIII-like activity), and by FXIa-triggered thrombin generation (TG) assay.
- Plasma antigen levels of FIX and FX were determined using immunoassays.
- Plasma samples from 110 healthy infants collected separately were also measured to generate age-matched reference ranges.

Results: PD biomarkers, and FIX and FX plasma levels, were assessed in 55 participants during the first 52 weeks of emicizumab treatment (data cut-off: May 22, 2023).

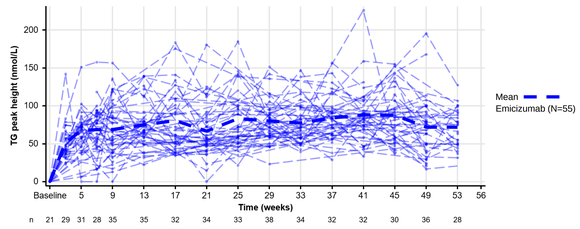
- By the first post-baseline visit (Week 3), aPTT was shortened to the age-matched reference range in most participants and was then generally maintained in the normal range throughout the treatment period.
- Mean (standard deviation [SD]) FVIII-like activity increased to 22.5 (6.1) U/dL at Week 5 after the emicizumab loading doses and was sustained at 21–26 U/dL thereafter (**Figure 1**).
- Mean (SD) TG peak height increased to 67.4 (27.2) nmol/L at Week 5 and was sustained at 67–88 nmol/L throughout the treatment period (**Figure 2**).
- Mean plasma FIX and FX concentrations were not affected by emicizumab treatment.

Figure 1. Mean and individual FVIII-like activity over time.



For the participant whose dose was up-titrated, only data before up-titration are included. Values reported as <1 U/dL are replaced with 0.5 (lower limit of quantification). FVIII, factor VIII.

Figure 2. Mean and individual TG peak height over time.

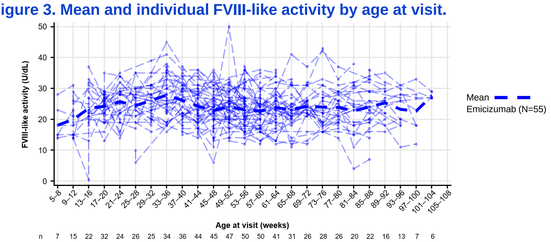


For the participant whose dose was up-titrated, only data before up-titration are included. TG, thrombin generation.

Results: PD biomarkers as a function of age group.

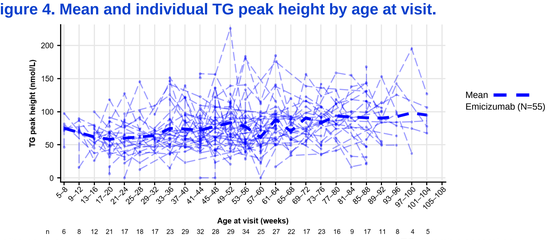
- The loading period (first 4 weeks) was excluded and only “steady state” measurements were considered for the PD markers.
- Mean (SD) FVIII-like activity of 18.1 (5.4) U/dL in the youngest participants (1–2 months old) increased to 23.6 (7.6) U/dL at 3–4 months old and was similar (23–28 U/dL) in the older age groups (**Figure 3**).
- Age did not have a notable impact on mean TG peak height (**Figure 4**).
- There was no age effect on aPTT.

Figure 3. Mean and individual FVIII-like activity by age at visit.



For the participant whose dose was up-titrated, only data before up-titration are included. Values reported as <1 U/dL are replaced with 0.5 (lower limit of quantification). FVIII, factor VIII.

Figure 4. Mean and individual TG peak height by age at visit.

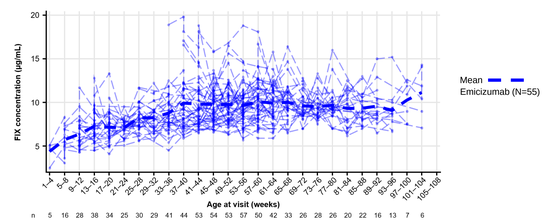


For the participant whose dose was up-titrated, only data before up-titration are included. TG, thrombin generation.

Results: FIX and FX plasma levels as a function of age group.

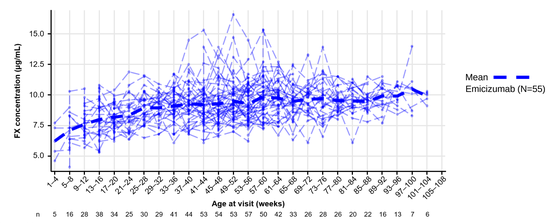
- All measurements were considered for FIX and FX plasma levels.
- Mean (SD) plasma FIX and FX antigen concentrations were 4.40 (1.09) µg/mL (**Figure 5**) and 6.24 (1.29) µg/mL (**Figure 6**) in the <1-month-old participants, increased progressively with age until about 9 months old, and then stayed around 9–10 µg/mL thereafter for both FIX and FX.

Figure 5. Mean and individual FIX concentration by age at visit.



FIX, factor IX.

Figure 6. Mean and individual FX concentration by age at visit.



FX, factor X.

Results: Biomarkers in age-matched healthy infants.

- Plasma samples from 110 healthy infants (0–3 months old, n=42; >3–24 months old, n=68) were collected separately to generate age-matched reference ranges.
- Lower plasma levels of FIX and FX, as well as FVIII activity, were observed in the healthy infants ≤3 months versus >3 months of age (**Table 1**).
- There was no statistically significant difference in TG between ≤3 months versus >3 months of age in healthy infants.

Table 1. Biomarker reference ranges by age in healthy infants.

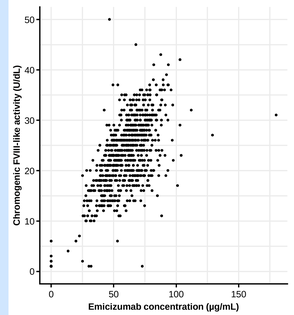
	0–3 months	>3–24 months
aPTT, mean (range), sec	55.1 (23.9–100.0); n=26*	34.7 (23.9–50.0); n=64
FVIII:C, mean (range), %	42.1 (0–100.0); n=40	89.1 (30.0–162.0); n=64
TG peak height, mean (range), nmol/L	257.0 (148.0–419.9); n=45	
FIX, mean (range), µg/mL	7.1 (0–13.4); n=40	11.0 (6.6–17.3); n=58
FX, mean (range), µg/mL	5.8 (0–9.9); n=41	9.3 (5.2–13.5); n=63

*14 samples were above upper limit of quantification (>255 sec) and were excluded from calculations. Some samples were clotted and there was not sufficient volume to conduct all analyses with all samples. aPTT, activated partial thromboplastin time; FIX, factor IX; FVIII:C, factor VIII activity; FX, factor X; sec, seconds; TG, thrombin generation.

Results: Pharmacokinetic/PD relationships.

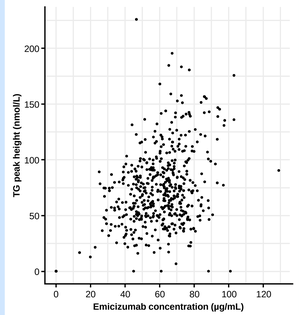
- FVIII-like activity increased with increasing emicizumab concentrations in a linear fashion up to emicizumab concentrations of 100 µg/mL (**Figure 7**)
  - Hence, the lower FVIII-like activity in the youngest participants could be partially explained by lower mean “steady state” trough emicizumab concentrations of 48.3 µg/mL at 1 month of age, which then increased to approximately 60 µg/mL at 4–5 months of age and older.
- TG peak height increased with increasing emicizumab concentrations but showed high variability (**Figure 8**).

Figure 7. Individual FVIII-like activity by emicizumab concentration.



Values reported as <1 U/dL are replaced with 0.5 (lower limit of quantification). FVIII, factor VIII.

Figure 8. Individual TG peak height by emicizumab concentration.



TG, thrombin generation.

- Lower FIX and FX plasma levels during the first 9 months of age may also have an impact on the PD results. Even though the levels were lower in the youngest participants, increases in FVIII-like activity and TG were seen at “steady state” emicizumab in all age groups, as expected based on previous studies of emicizumab.

Conclusions

- FVIII-like activity and thrombin generation increased, and aPTT was shortened, after starting emicizumab prophylaxis in HAVEN 7.
- FVIII-like activity was observed to increase with age up to ~3–4 months old, and FIX and FX levels were observed to increase with age up to ~9 months old.
- The PD profiles of emicizumab in infants with HA were consistent with those previously observed in older children and adults with HA.[4–8]
- Hence, even with lower levels of FIX and FX observed in the youngest participants, emicizumab showed the expected PD response.

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