Post ASH 2023

Haemophilia - emicizumab

Haemophilia A
Portfolio

M-CZ-00003744

Agenda of ASH 2023 - emicizumab

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- **Special population**
  - ✓ ***HAVEN 7 primary analysis (Oral presentation 505)*** *– Pipe S, et al. – Emicizumab prophylaxis in infants with severe hemophilia A without factor VIII inhibitors: Results from the primary analysis of the HAVEN 7 study*
  - ✓ ***HAVEN 7 biomarkers (Poster P1238) –*** *Kiialainen A, et al. – Pharmacodynamic biomarkers in infants with hemophilia A receiving emicizumab in HAVEN 7*
  - ✓ ***Physical activity (Oral presentation 663)*** *– Mancuso ME, et al. – Physical activity, bleedings and quality of life in patients with haemophilia a without inhibitors - a multicenter, observational Italian study with a wearable device*
  - ✓ ***Bone health (Poster P2620)*** *– Lyu T, et al. – Bone health of hemophilia A patients using emicizumab*

- **Real World Data (RWD) – long term efficacy and safety**
  - ✓ ***Canada (Poster P1240)*** *– Poon MC, et al. – Experience with emicizumab among people with hemophilia A in the Canadian hemophilia bleeding disorders registry*

- **Quality of life**
  - ✓ ***United States - ATHN7 (Poster P3998)*** *– Buckner TW, et al. – Quality of life in emicizumab-treated people with hemophilia A in the ATHN 7 hemophilia natural history study – An assessment of baseline PROMIS®-29 Scores*

Emicizumab prophylaxis in infants with severe hemophilia A without factor VIII inhibitors: Results from the primary analysis of the HAVEN 7 study

Upraveno podle ústní prezentace 505 přednesené na kongresu Americké hematologické společnosti (ASH), 9. – 12. prosince 2023

Abstrakt je dostupný na: https://ash.confex.com/ash/2023/webprogram/Paper177963.html

Background

- Starting prophylaxis early in life should be the standard of care
- However, many infants with severe HA do not receive prophylaxis until ≥1 year of age, owing to the **challenges of FVIII administration**:
  - Venous access issues
  - CVAD-associated risks

- Emicizumab can be administered subcutaneously from HA diagnosis, enabling **early initiation of prophylaxis**, and **may mitigate risks of**:
  - Untreated spontaneous and traumatic bleeding, which accrues damage
  - Intracranial hemorrhages, of which there is a substantial risk in the first year of life
  - FVIII inhibitor development, due to reduced use of FVIII products

The primary analysis of **HAVEN 7** (NCT04431726) evaluates the efficacy, safety, PK (and PD, reported in Poster 1238) of emicizumab in infants ≤12 months of age with severe HA without FVIII inhibitors

CVAD, central venous access device; F, factor; HA, hemophilia A; PD, pharmacodynamics; PK, pharmacokinetics.

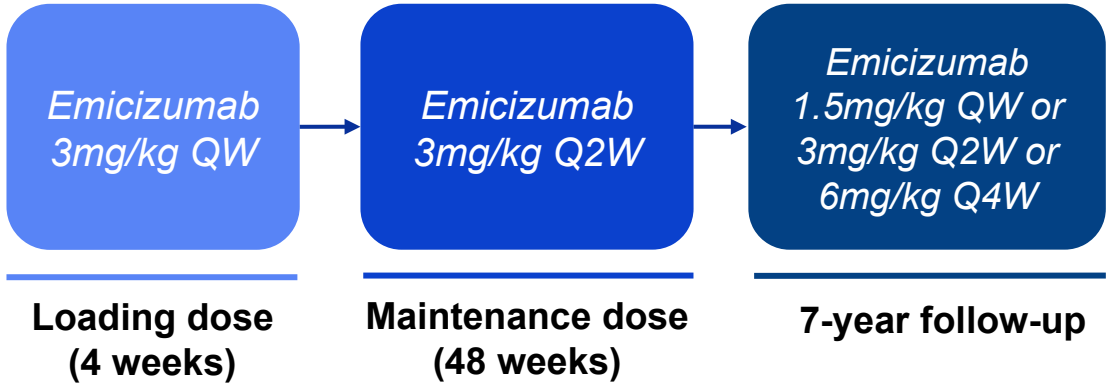
Pipe S, et al. ASH 2023; ústní prezentace 505.

Study design

- At data cut-off, **55 participants** were exposed to emicizumab for a median (range) duration of **100.3 (52–118) weeks***
- **Key inclusion criteria:**
  - PUPs or MTPs† from **birth to ≤12 months of age** with **severe HA without FVIII inhibitors**
  - No evidence of ICH at enrollment

- Endpoints included:
  - **Efficacy:** ABRs for treated bleeds, all bleeds, treated spontaneous bleeds, treated joint bleeds
  - **Safety:** AEs, AESIs including TEs and TMAs, immunogenicity including ADAs and FVIII inhibitors
  - **PK:** Plasma trough emicizumab concentrations
  - **PD:** Biomarker data, reported in Poster 1238

A Phase IIIb, multi-center, open-label study of emicizumab in infants aged ≤12 months with severe HA without FVIII inhibitors



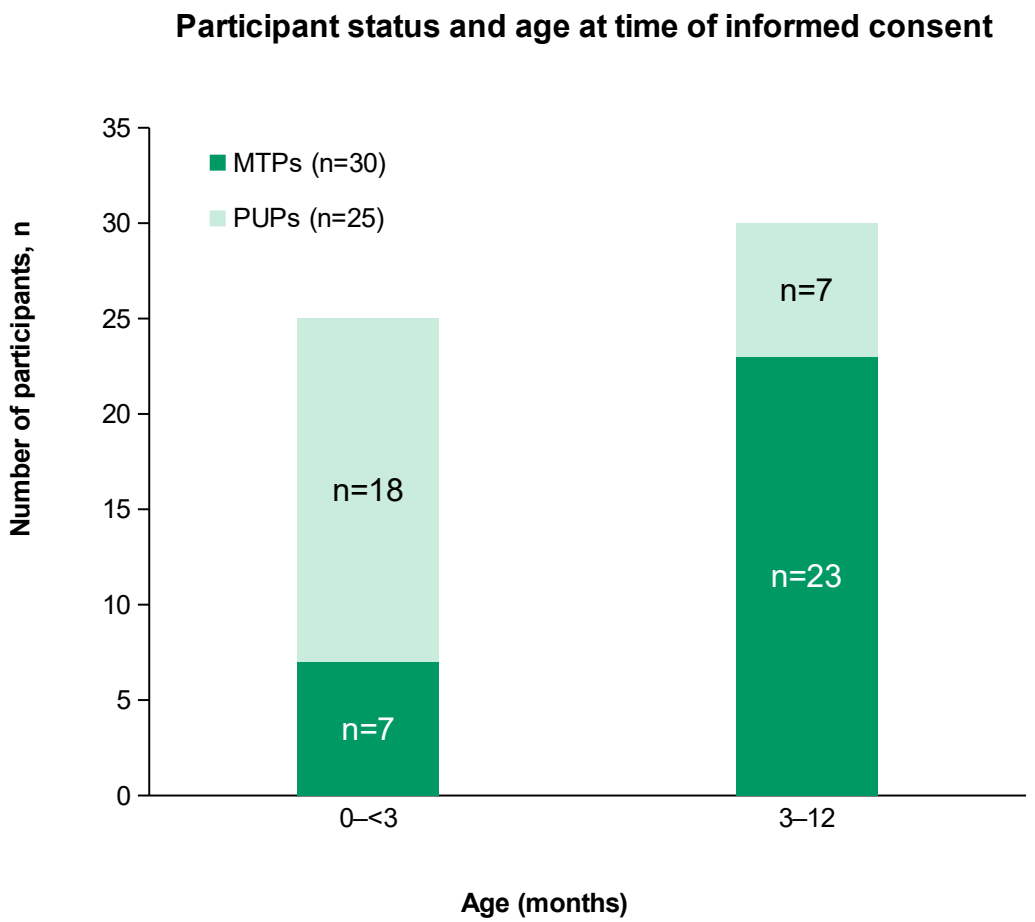
- Primary analysis clinical cut-off date: May 22, 2023
- Future analyses over the 7-year long-term follow-up period will include, but will not be limited to, safety, and joint health outcomes assessed by MRI

*Treatment exposure is defined as the last dose of study medication minus the date of the first dose plus one day. †Defined as a participant with ≤5 exposure days to FVIII. Recruitment was completed on May 20, 2022, with 55 participants. ABR, annualized bleeding rate; ADAs, anti-drug antibodies; AE, adverse event; AESI, adverse event of special interest; F, factor; HA, hemophilia A; ICH, intracranial hemorrhage; MRI, magnetic resonance imaging; MTP, minimally treated participant; PD, pharmacodynamics; PK, pharmacokinetics; PUP, previously untreated participant; QW, every week; Q2W, every 2 weeks; Q4W, every 4 weeks; TE, thrombotic event; TMA, thrombotic microangiopathy.

Pipe S, et al. ASH 2023; ústní prezentace 505.

Baseline characteristics

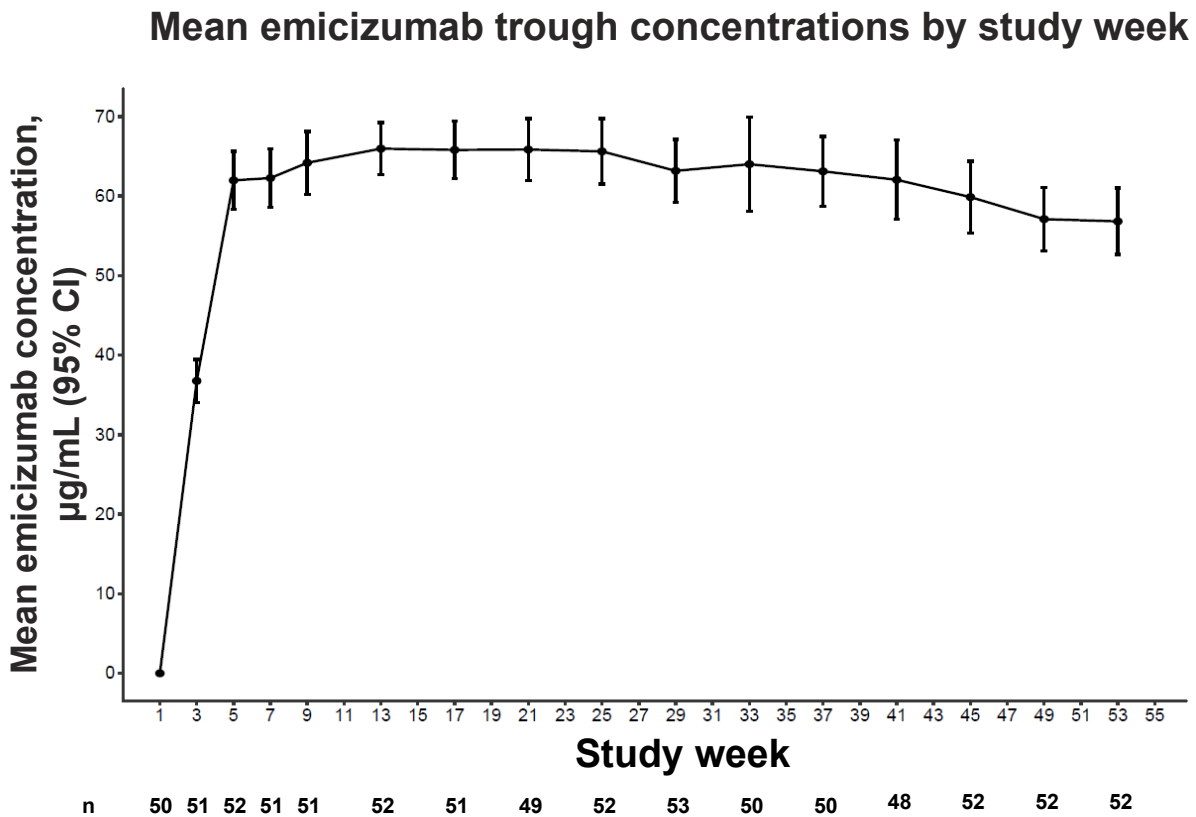
	Emicizumab (N=55)
Age at informed consent, months	
Mean (SD)	5.0 (3.9)
Median	4.0
Range	9 days–11 months 30 days
Age group, n (%)	
0–<3 months	25 (45.5)
3–12 months	30 (54.5)
Prior treatment status, n (%)	
MTP*	30 (54.5)
PUP	25 (45.5)
Historical bleeding episodes prior to first dose of emicizumab†	
Participants with ≥1 bleed, n (%)	36 (65.5)
Total number of bleeds, n	77
Spontaneous, n (%)	25 (32.5)
Traumatic, n (%)	19 (24.7)
Procedural/surgical, n (%)	33 (42.9)
Family history of HA, n (%)	41 (74.5)
Family history of FVIII inhibitors	7 (12.7)



*Defined as a participant with ≤5 exposure days to FVIII. †The reporting period was variable across the 36 participants who had ≥1 bleed prior to receiving emicizumab, with the median (min, max) age at time of first historical treated or untreated bleed being 1 (0, 49) week(s).
HA, hemophilia A; F, factor; MTP; minimally treated participant; PUP, previously untreated participant; SD, standard deviation.

Pipe S, et al. ASH 2023; ústní prezentace 505.

Effective emicizumab trough concentrations were achieved and sustained in infants



Emicizumab trough concentrations by study week

- Following loading doses, mean (95% CI) trough concentrations were **62.0 (58.3–65.6) µg/mL** at Week 5
- Steady-state trough concentrations of **~57–66µg/mL** were higher than those in older people with HA on the same dosing regimen in the HAVEN 1–4 studies (46.7µg/mL)
  - Injection site may have played a role, as 80% of loading dose administrations were in the thigh, which has been associated with a trend for higher exposure than abdomen or upper arm administrations

Emicizumab trough concentrations by age

- Mean steady-state trough concentrations **increased slightly with age** until approximately 6 months of age, whereupon trough concentrations were maintained at ≥60µg/mL
- Mean FIX and FX concentrations were **not impacted by emicizumab treatment**

For the participant whose dose was up-titrated, only data before up-titration are included.
CI, confidence interval; F, factor; HA, hemophilia A.

Pipe S, et al. ASH 2023; ústní prezentace 505.

No new safety signals were identified at primary analysis

	Emicizumab (N=55)
Total number of AEs, n	631
Participants with ≥1 AE, n (%)	55 (100)
AE with fatal outcome	0 (0)
AE leading to withdrawal from treatment	0 (0)
AE leading to dose modification/interruption	0 (0)
AE of Grade ≥3	17 (30.9)
AE related to treatment	9 (16.4)*
SAEs	16 (29.1)†
AEs of special interest, n (%)	
Systemic hypersensitivity reactions and anaphylactic / anaphylactoid reactions	1 (1.8)‡
Thromboembolic event	0 (0)
Thrombotic microangiopathy	0 (0)

No ICHs were reported

No AEs led to withdrawal or dose modification or interruption

All treatment-related AEs were **Grade 1 ISRs**

No SAEs were considered treatment-related; most were infant specific (respiratory-related and head-injury events) and considered serious due to required or prolonged hospitalization†

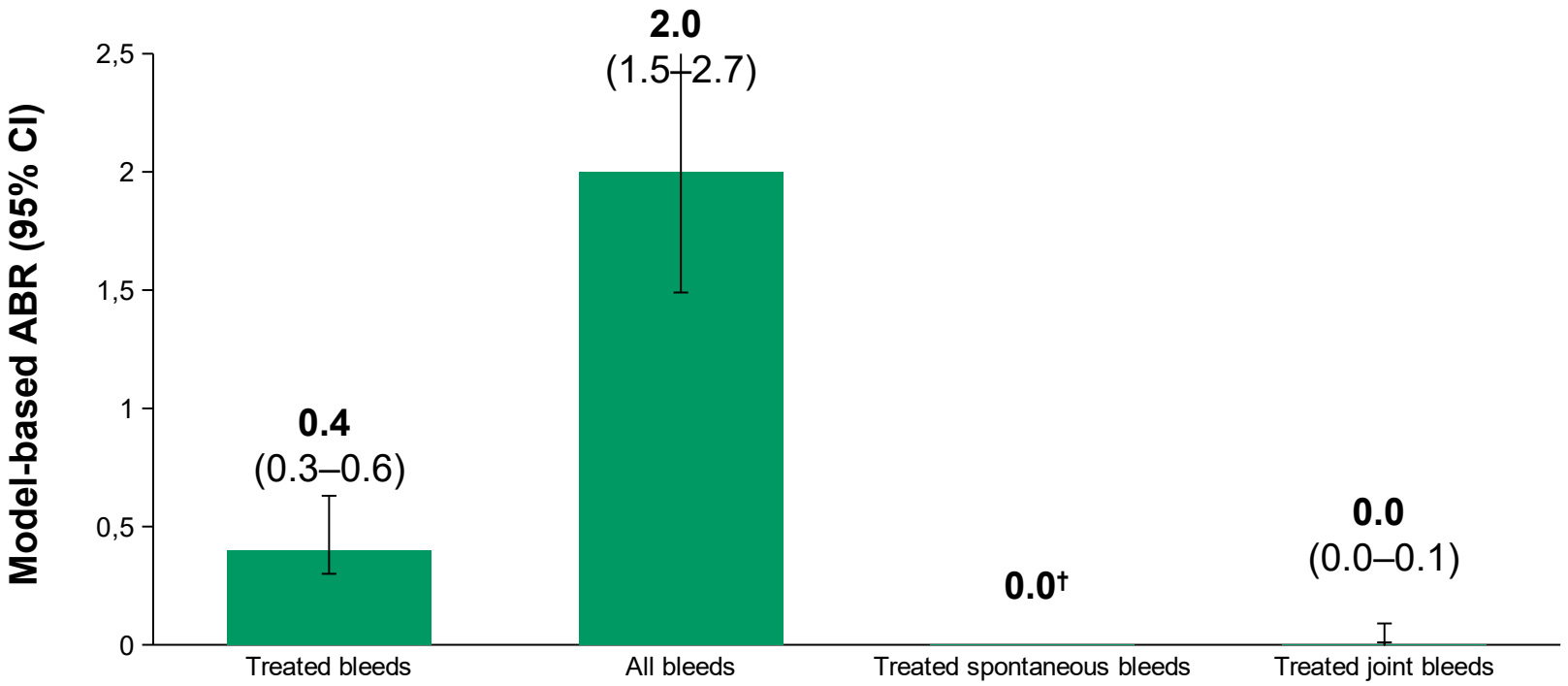
There was one anaphylactic reaction, confirmed to be due to egg allergy and deemed **unrelated to emicizumab**‡

*All treatment-related AEs were Grade 1 local injection-site reactions. †Sixteen participants reported 30 SAEs; none were considered emicizumab related and all considered serious due to hospitalization. SAEs included: fall (n=4); head injury (n=4); bronchiolitis, bronchitis, pneumonia, tonsillitis, mouth hemorrhage, tongue hemorrhage (n=2 for each); ear infection, laryngitis, upper respiratory tract infection, urinary tract infection, viral infection, eyelid contusion, post-procedural fever (liver biopsy), post-procedural hemorrhage (tonsillectomy), skin laceration, tongue injury (n=1 for each). ‡One Grade 2 anaphylactic reaction due to an egg allergy was reported in one participant; this event resolved and was considered not related to emicizumab. AE, adverse event; ICH, intracranial hemorrhage; ISR, injection-site reaction; SAE, serious adverse event.

Pipe S, et al. ASH 2023; ústní prezentace 505.

Emicizumab demonstrated consistent efficacy across bleeding endpoints

Model-based* ABRs across bleed categories



Median (range) follow-up: 101.9 (52.6–119.7) weeks (N=55)

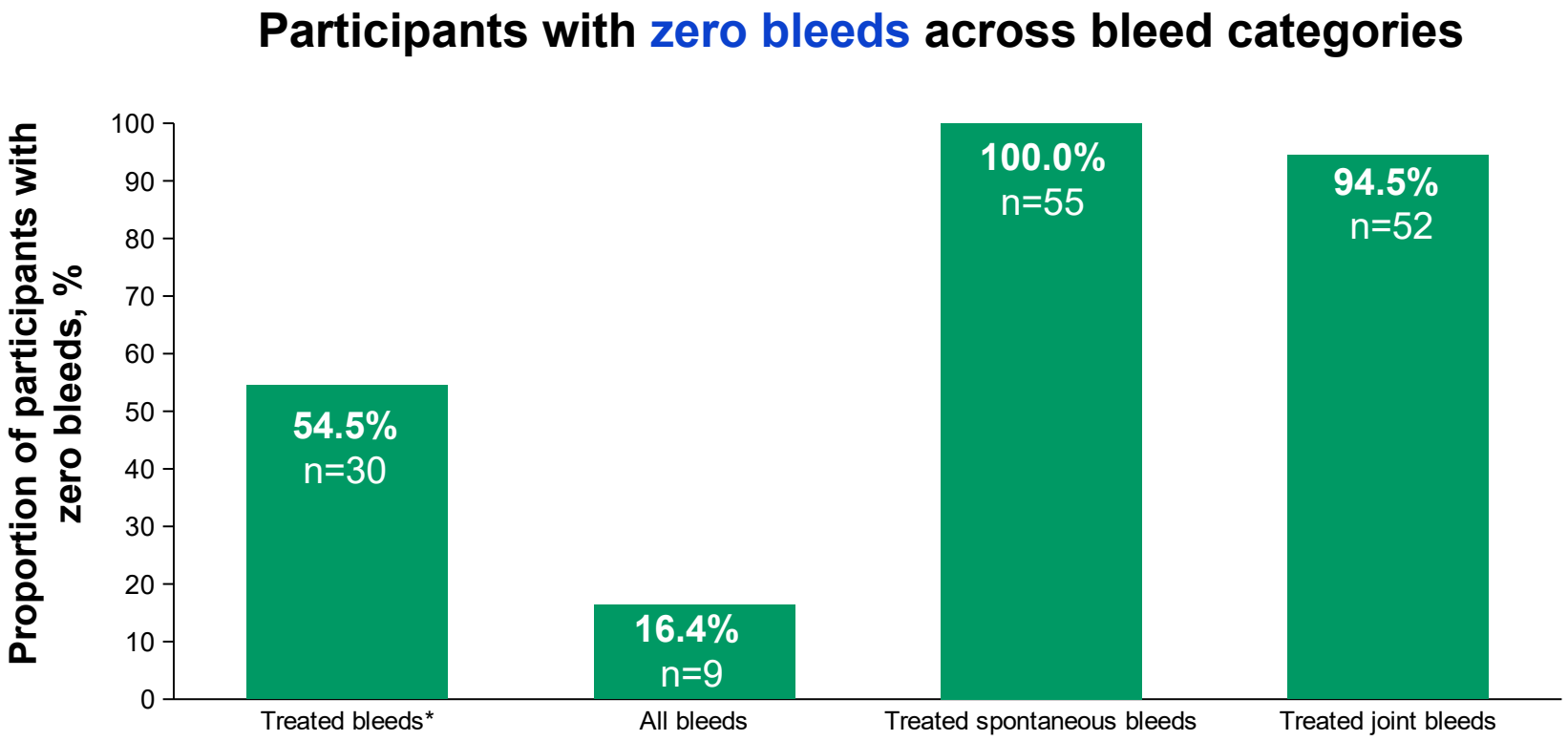
Median (range) age at analysis: 29 (12–39) months (N=55)

All treated bleeds were categorized as **traumatic**‡

*Model-based ABRs were assessed with aid of a negative binomial regression model. †ABR could not be estimated via the negative binomial regression model as no treated spontaneous bleeds were observed in the study; as a result, a value of 0.0 is reported instead. ‡Bleeds were categorized as traumatic if parents/caregivers recorded a bleed with a known or believed reason for the bleed. ABR, annualized bleeding rate; CI, confidence interval.

Pipe S, et al. ASH 2023; ústní prezentace 505.

Emicizumab demonstrated consistent efficacy across bleeding endpoints



No participant had >3 treated bleeds

Thirty-seven participants (67.3%) had **0–3 all bleeds**

Emicizumab dose was **up-titrated** to 3mg/kg QW in **one participant,** per investigator request based on decreasing emicizumab levels (locally assessed)†

Median (range) age at analysis: 29 (12–39) months and median (range) follow-up: 101.9 (52.6–119.7) weeks (N=55). *All 42 treated bleeds in 25 participants were traumatic. †Emicizumab level was confirmed retrospectively by central assessment to be 6.6 µg/mL at the lowest. The participant experienced three treated bleeds before up-titration (Day 374) and two untreated bleeds after up-titration until clinical cut-off date (328 days later); all bleeds were traumatic. Emicizumab level in this participant one week after up-titration was 22.7 µg/mL, and ranged from 46.6–62.4 µg/mL in samples collected between Weeks 3 and 13 post up-titration. The participant tested negative for ADAs at all timepoints before and after up-titration (baseline, Week 5, 17, 29, 41, and 53, as well as up-titration Week 1 and 5). ADA, anti-drug antibody; QW, every week

Pipe S, et al. ASH 2023; ústní prezentace 505.

Immunogenicity to emicizumab and FVIII

All 55 participants were evaluable for immunogenicity; **none tested positive for ADAs to emicizumab***

On study, 27 participants did not have any FVIII EDs. In the **28 participants with ≥1 FVIII ED(s)**

- Median (min, max) on-study FVIII ED(s) was 1 (0, 10), with a mean (SD) of 1.8 (3.3) doses
- On-study FVIII EDs were similar between PUPs (median [min, max]: 1 [0, 10], n=14) and MTPs (median [min, max]: 0 [0, 10], n=14)

Following FVIII exposure, 24 participants were tested for **FVIII inhibitors**,† with **two testing positive**; both were PUPs aged 0–3 months at enrollment

- **Low FVIII inhibitor rate** in HAVEN 7 (3.6%) may be a consequence of **reduced FVIII usage** in participants treated with emicizumab; however, many participants are still within the FVIII exposure risk period for inhibitors

Participant 1‡

- **No family history of FVIII inhibitors**
- Confirmed for FVIII inhibitors on **Day 603 (6.9CBU/mL)** and **Day 681 (1.5CBU/mL)**
- Experienced **three non-consecutive EDs with standard half-life FVIII** for traumatic bleed management

Participant 2§

- **Family history of FVIII inhibitors**
- Tested positive for FVIII inhibitors on **Day 428 (28.4 CBU/mL)** and confirmed post CCOD on **Day 532 (9.0 CBU/mL)**
- Experienced **10 non-consecutive EDs with extended half-life FVIII** for bleed treatment and surgical procedures

*ADAs were measured at weeks 1, 5, 17, 29, 41, and 53; and during long-term follow-up in the case of clinical suspicion. †Participants were tested for FVIII inhibitors following ≥3 EDs, or two consecutive doses, of FVIII. ‡A PUP (<1 month old) with large F8 deletion receiving five doses of standard half-life FVIII (500 IU; two doses on Day 333 and 404, one dose on Day 405) for treatment of two traumatic mouth bleeds. §A PUP (1 month old) with intron 22 inversion with a traumatic mouth bleed (Day 279) treated with 350 IU extended half-life FVIII and negative for inhibitors. On Days 414–422, seven non-consecutive EDs of preventative extended half-life FVIII were provided for adenotonsillectomy, ranging from 500 IU to 2550 IU. Tonsillectomy resumed (Day 425), accompanied by a post-procedural bleed treated with extended half-life FVIII (Day 425: 500 IU, 1200 IU, 250 IU; Day 426: 250 IU) and rFVIIa (Days 427–434).
ADA, anti-drug antibody; CBU, chromogenic Bethesda unit; CCOD, clinical cut-off date; ED, exposure day; F, factor; PUP, previously untreated participant; rFVIIa, recombinant activated factor VII.

Pipe S, et al. ASH 2023; ústní prezentace 505.

Conclusions

- Effective mean trough concentrations of emicizumab were **achieved and maintained**
- In line with the safety profile of emicizumab in clinical trials, **no new safety signals** were observed, and **no ICH** occurred
- Model-based ABRs were consistently low, all participants had **zero treated spontaneous bleeds**
- Up to CCOD, **no participant** developed **ADAs**, and **FVIII EDs were low**, resulting in 3.6% of participants developing *de novo* FVIII inhibitors

This primary analysis of HAVEN 7 indicates that emicizumab is **efficacious and well tolerated in infants with severe HA** without FVIII inhibitors; future analyses over the 7-year follow-up period will describe the **natural history** of children with HA initiating emicizumab soon after birth, including **joint health outcomes**

ABR, annualized bleeding rate; ADA, anti-drug antibody; CCOD, clinical cut-off date; ED, exposure day; F, factor; HA, hemophilia A; PD, pharmacodynamics; ICH, intracranial hemorrhage.

Pipe S, et al. ASH 2023; ústní prezentace 505.

Pharmacodynamic biomarkers in infants with hemophilia A receiving emicizumab in HAVEN 7

Upraveno podle posteru P1238 předneseného na kongresu Americké hematologické společnosti (ASH), 9. – 12. prosince 2023
Abstrakt je dostupný na: https://ash.confex.com/ash/2023/webprogram/Paper173015.html

Background

- Emicizumab, a bispecific antibody that mimics the cofactor function of activated FVIII, demonstrated a favorable safety and efficacy profile in infants with severe HA without FVIII inhibitors in HAVEN 7 (NCT04431726)

- 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 PD of emicizumab prophylaxis in infants with HA enrolled to HAVEN 7 from birth to ≤12 months of age

F, factor; HA, hemophilia A; PD, pharmacodynamics

Kiialainen A, et al. ASH 2023; prezentace posteru P1238.

Methods

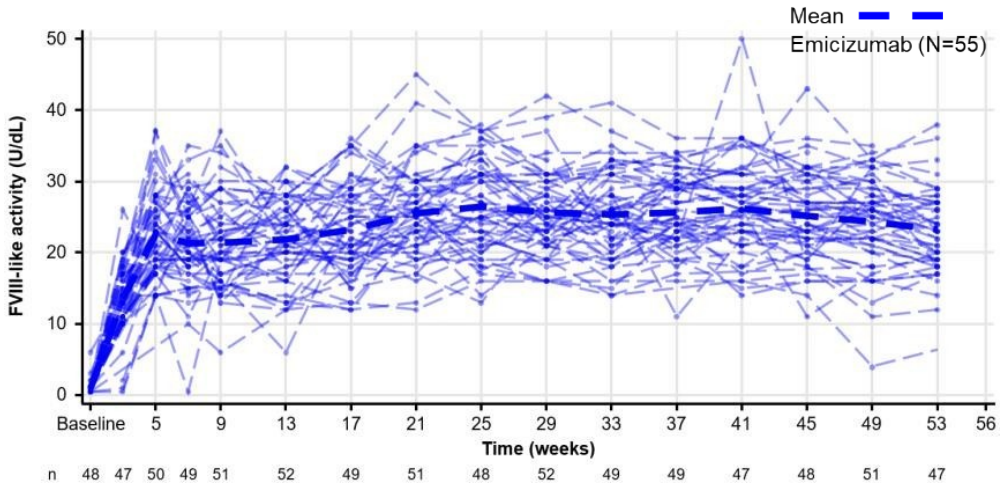
- Informed consent from the parents/legally authorized representative and ethics approval were obtained
- Trough plasma concentrations of emicizumab were measured by validated enzyme-linked immunosorbent assay
- PD was assessed by aPTT, FVIII activity using a chromogenic assay containing human FIX and FX (considered FVIII-like activity), and by FXIa-triggered 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

F, factor; TG, thrombin generation; PD, pharmacodynamics; aPTT, activated partial thromboplastin time;

Kiialainen A, et al. ASH 2023; prezentace posteru P1238.

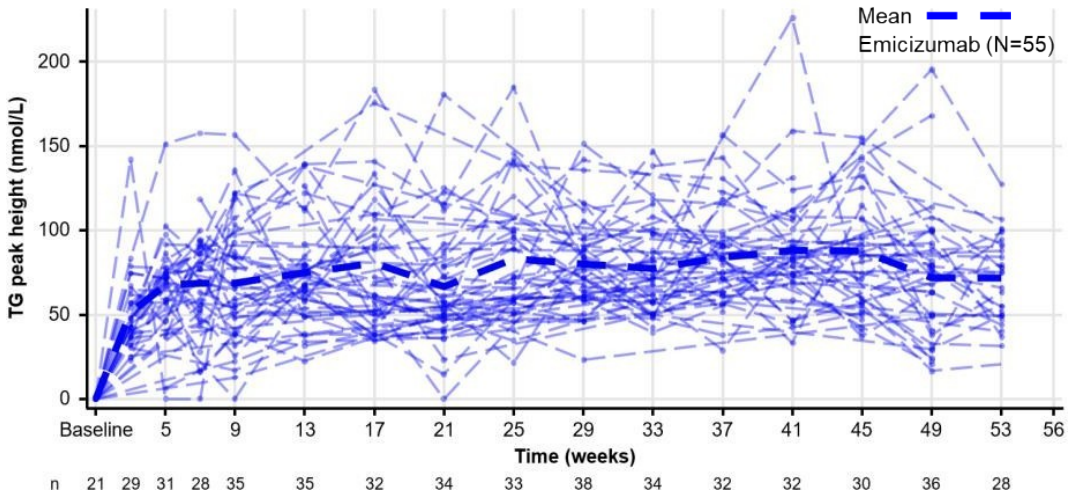
PD biomarkers, and FIX and FX plasma levels, were assessed in 55 participants during the first 52 weeks of emicizumab treatment (data cut-off: May 22, 2023)

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).

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.

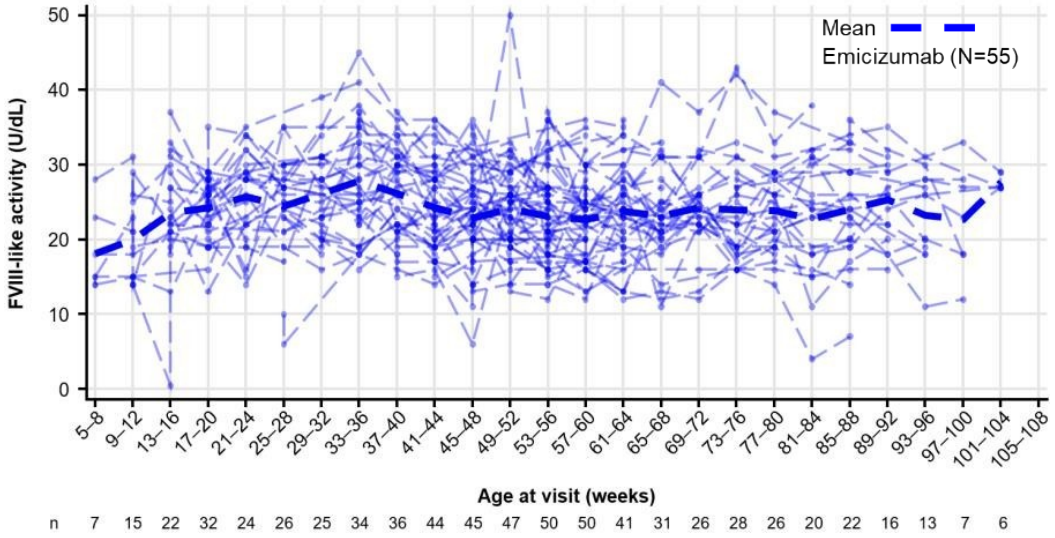
- By the first post-baseline visit (Week 3), aPTT was shortened to the age-matched reference range in most participants and was then generally maintained in the normal range throughout the treatment period
- Mean (SD) FVIII-like activity increased to 22.5 (6.1) U/dL at Week 5 after the emicizumab loading 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

F, factor; SD, standard deviation; PD, pharmacodynamics; aPTT, activated partial thromboplastin time; TG, thrombin generation.

Kiialainen A, et al. ASH 2023; prezentace posteru P1238.

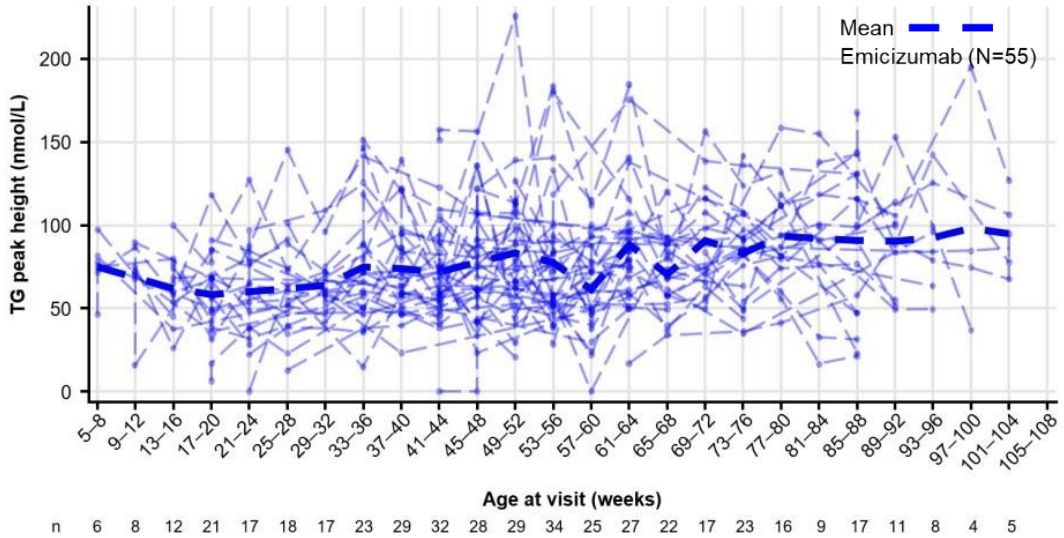
PD biomarkers as a function of age group

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.

- 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

F, factor; SD, standard deviation; PD, pharmacodynamics; TG, thrombin generation; aPTT, activated partial thromboplastin time.

Kiialainen A, et al. ASH 2023; prezentace posteru P1238.

FIX and FX plasma levels as a function of age group

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

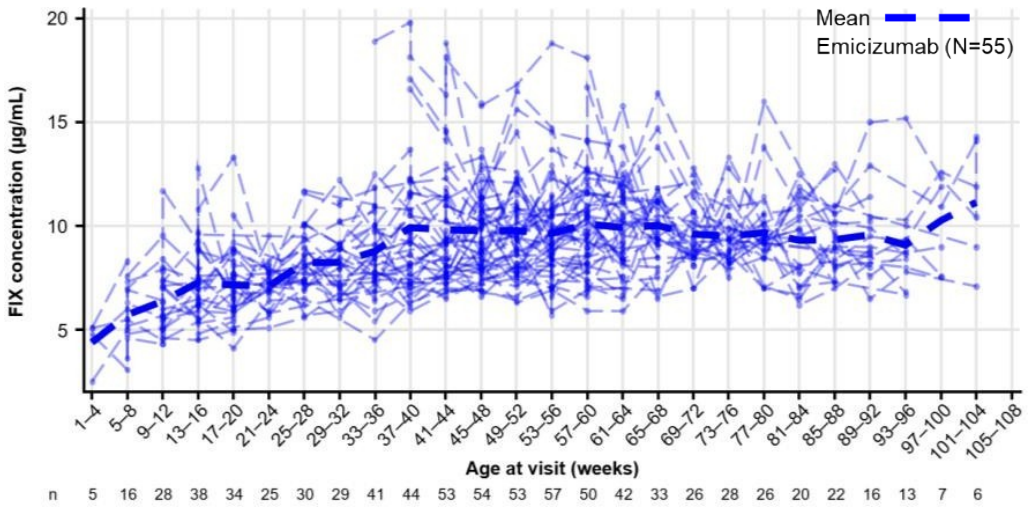
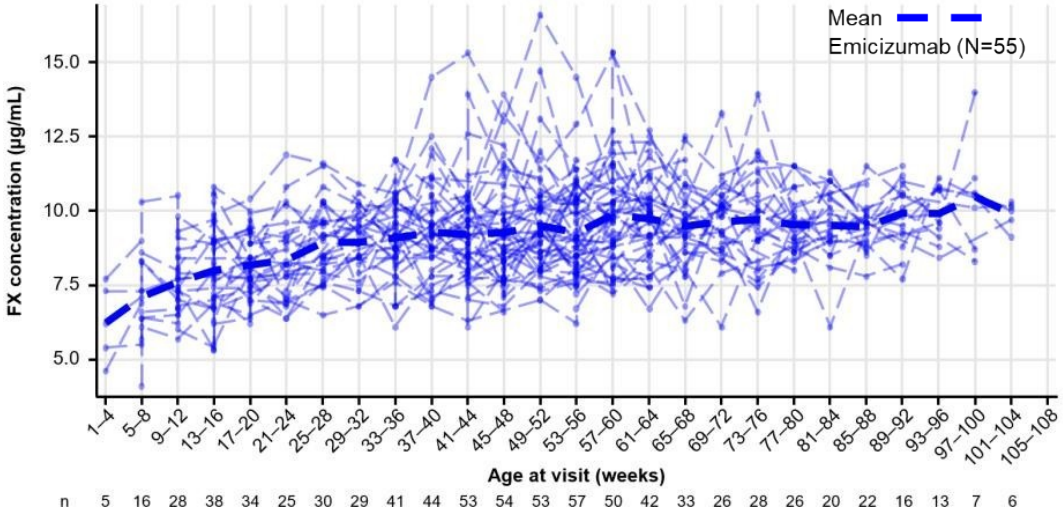


Figure 6. Mean and individual FX concentration by age at visit



- 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

F, factor; SD, standard deviation.

Kiialainen A, et al. ASH 2023; prezentace posteru P1238.

Biomarkers in age-matched 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.

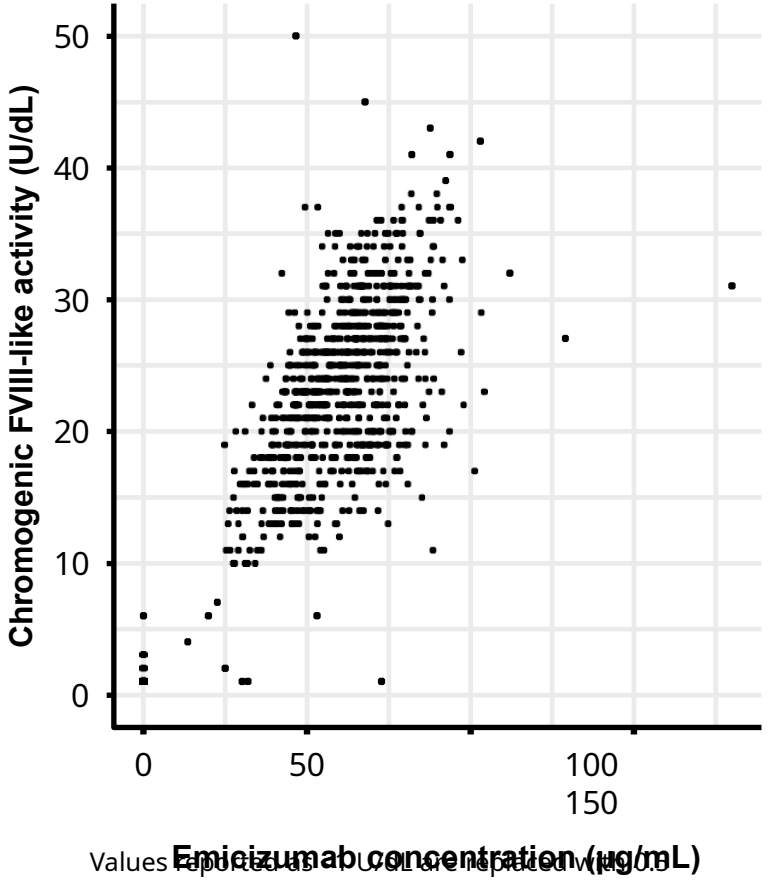
- Plasma samples from 110 healthy infants (0–3 months old, n=42; >3–24 months old, n=68) were collected separately to generate age-matched reference ranges.
- Lower plasma levels of FIX and FX, as well as FVIII activity, were observed in the healthy infants ≤3 months versus >3 months of age (**Table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

F, factor; TG, thrombin generation; aPTT, activated partial thromboplastin time;

Kiialainen A, et al. ASH 2023; prezentace posteru P1238.

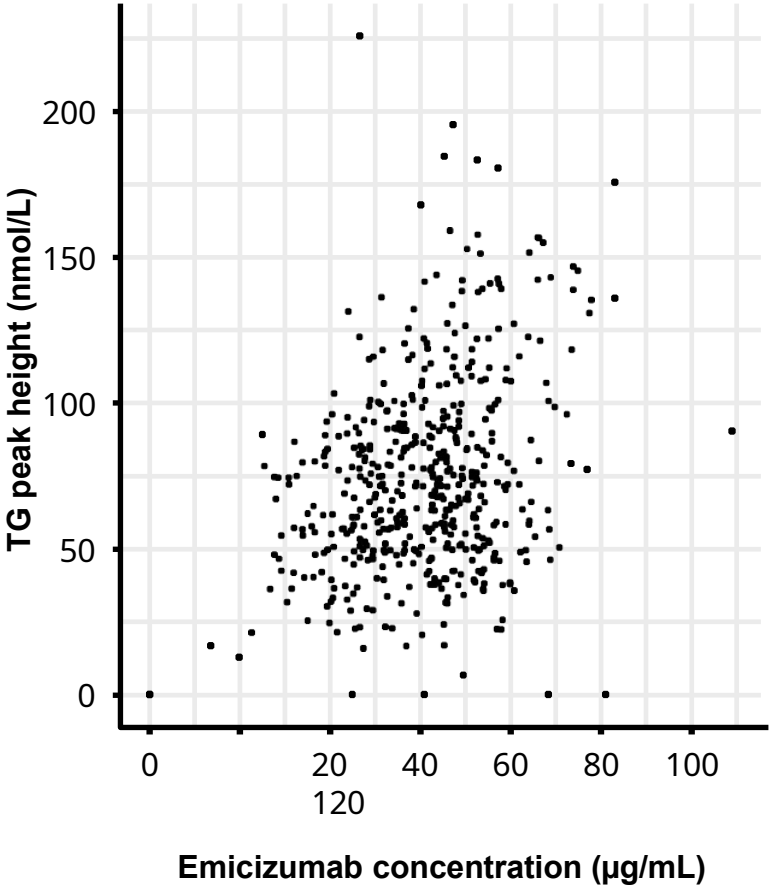
Pharmacokinetic/PD relationships

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



Values reported as 1 U/dL are replaced with 0.5 (lower limit of quantification)

Figure 8. Individual TG peak height by emicizumab concentration.



- 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**)
- 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.

F, factor; SD, standard deviation; PD, pharmacodynamics; aPTT, activated partial thromboplastin time;

Kiialainen A, et al. ASH 2023; prezentace posteru P1238.

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
- Hence, even with lower levels of FIX and FX observed in the youngest participants, emicizumab showed the expected PD response

F, factor; PD, pharmacodynamics; aPTT, activated partial thromboplastin time,

Kiialainen A, et al. ASH 2023; prezentace posteru P1238.

Physical activity, bleedings and quality of life in patients with haemophilia a without inhibitors - a multicenter, observational Italian study with a wearable device

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Upraveno podle ústní prezentace 663 přednesené na kongresu *Americké hematologické společnosti (ASH)*,
9. – 12. prosince 2023
Abstrakt je dostupný na: https://ash.confex.com/ash/2023/webprogram/Paper179089.html

Background and Objectives

- HA is characterized by spontaneous or traumatic recurrent bleedings, especially in joints and muscles, which can cause haemophilic arthropathy, impaired function, and in turn, reduce physical and social activities and negatively impact the quality of life

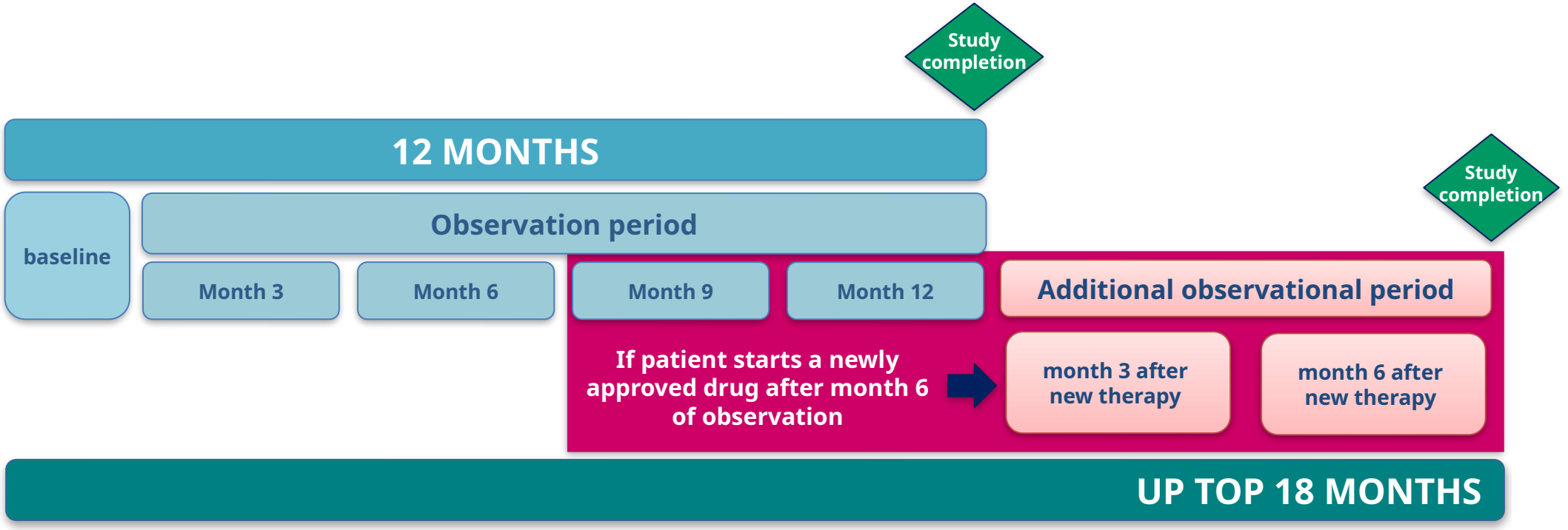
- Despite regular PA being strongly recommended by guidelines as a key element to improve well-being and mental health, the perception of an associated increased risk of bleeding and bleed-related issues discourage PWHA

This study (NCT04165135 – POWER) aimed to gather data on PA status, bleeding, HR-QoL, and health status, through the use of a **Wearable Device** and an **electronic Patient-Reported Outcome (ePRO) app**, in individuals with moderate or severe HA without inhibitors receiving treatment according to the clinical practice

- F, factor; HA, hemophilia A; PA, physical activity; PWHA, people with hemophilia A; HR-QoL, health-related quality of life.

Mancuso ME, et al. ASH 2023; ústní prezentace 663.

Study Design



A non-interventional, prospective, multicenter study conducted in 18 investigational Italian sites

The population was observed for 12 months or up to 18 months if the therapy with a newly approved product was initiated during the study

The study started in January 2020 and was completed in April 2022 with the last data collection

Mancuso ME, et al. ASH 2023; ústní prezentace 663.

Methods

- Data related to bleeding, bleeding treatment, HRQoL and VAS pain was collected through a dedicated ePRO application downloaded and run on the patient's own devices

- Participants were asked to wear the Fitbit Versa Health & Fitness Smartwatch (fitness tracker) in order to collect data about physical activity

All data were transferred to eCRF after evaluation by investigators

Criteria for defining study populations

Enrolled Subjects (N=103)

Intention-To-Treat Population – ITT (N=103)

All enrolled patients who received the ePRO application and the fitness tracker.

Evaluable population – EVL (N=54)

All enrolled patients with at least 6 valid months of physical activity evaluations during the study. The patients with 6 valid months of physical activity will be defined by an Extent of Exposure to the fitness tracker of at least 6 months (180 days) and a compliance to the use of the fitness tracker of at least 50% in the period define by the exposure.

The results related to the PA outcome have been described only for the EVL population, while all the other outcomes have been described for the ITT population.

- HR-QoL, health-related quality of life; VAS, visual analog score.

Mancuso ME, et al. ASH 2023; ústní prezentace 663.

Demographic and clinical characteristics at baseline

- The mean age in the overall ITT population was **28.3 years** (median 27.0 years, range 12-50 years)
- The overall **ITT population (103 patients)** included:
  - ✔ 17 patients aged 12-17 years
  - ✔ 46 patients aged 18-30 years
  - ✔ 40 patients aged 31-50 years
- More than 90% of patients overall (97 patients, **94.2%**) **had severe hemophilia** and the remaining (6 patients, 5.0%) had moderate hemophilia
- Approximately 10% of patients overall had a history of positive inhibitors against FVIII (eradicated since at least 3 years)

- F, factor; ITT, Intention-To-Treat Population.

Mancuso ME, et al. ASH 2023; ústní prezentace 663.

Treatment Regimens

- Over the ITT population, 102 subjects received at last 1 prophylaxis therapy while 1 subject received an on-demand therapy

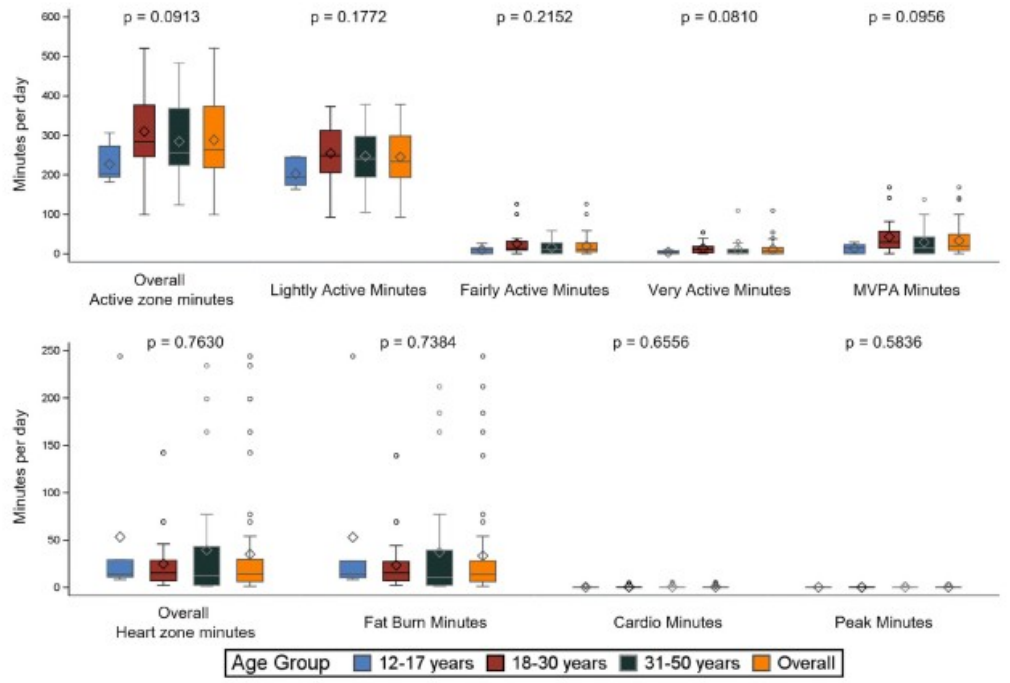
PROPHYLAXIS FOR HAEMOPHILIA	
BLOOD COAGULATION FACTORS	(84,3%)
OCTOCOG ALFA	(32.4%)
EFMOROCTOCOG ALFA	(21.6%)
RURIOCTOCOG ALFA PEGOL	(4.9%)
MOROCTOCOG ALFA	(5.9%)
TUROCTOCOG ALFA	(7.8%)
TUROCTOCOG ALFA PEGOL	(2,0%)
DAMOCTOCOG ALFA PEGOL	(2.9%)
LONOCTOCOG ALFA	(3.9%)
SIMOCTOCOG ALFA	(2,0%)
FACTOR VIII NO BETTER SPECIFIED	(1,0%)
OTHER SYSTEMIC HEMOSTATICS	(15.7%)
EMICIZUMAB	(15.7%)

- F, factor; ITT, Intention-To-Treat Population.

Mancuso ME, et al. ASH 2023; ústní prezentace 663.

Results – Primary Endpoint

Physical Activity data collected by the fitness tracker (active minutes, metabolic equivalents for tasks, and step counts)



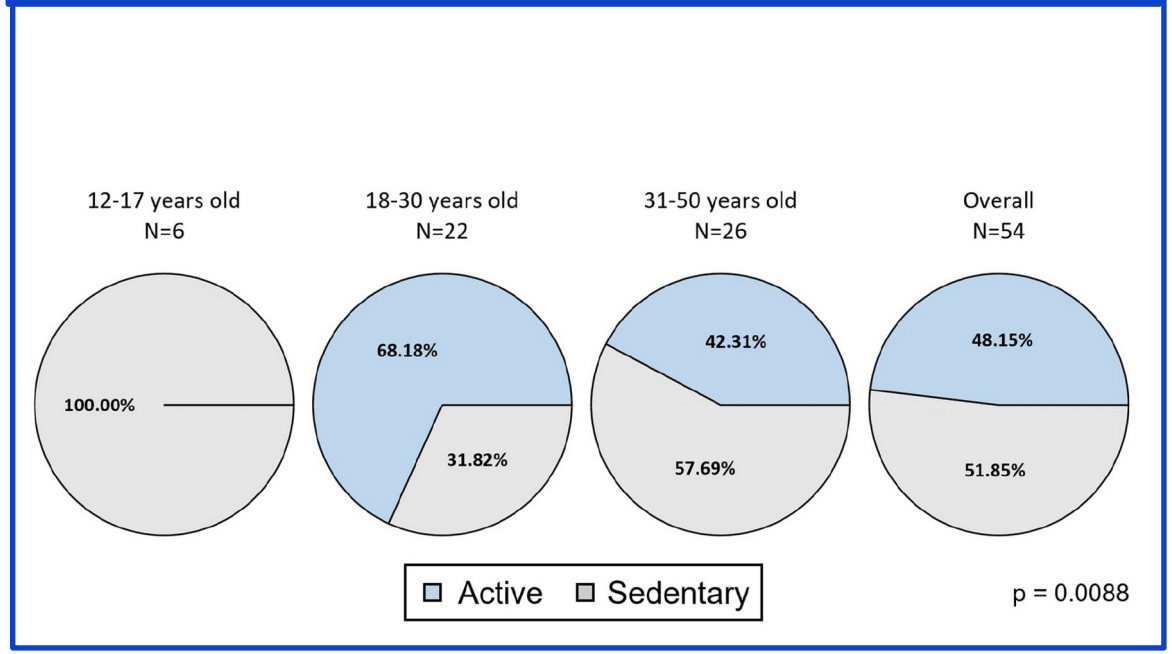
- Most of the active minutes were light (**high-intensity physical activities were poorly** represented in all the subgroups). The adolescents were in the active zone for a median of 203.0 minutes per day (of with only 9.7 very active minutes);
- **Low weekly rates for all activities** (no differences based on type of physical activity);
- The mean **METs** per day were lower in adults (adolescents kcal/kg/hour, young adults 5.3 kcal/kg/hour, adults 4.6 kcal/kg/hour);
- The number of **steps** per day resulted similar between the various age groups

- MVPA, Moderate to Vigorous Physical Activity; METs, metabolic equivalent of task.

Mancuso ME, et al. ASH 2023; ústní prezentace 663.

Results – Secondary Endpoints

Adherence to the WHO Guidelines for Physical Activity



- Approximately **51% of the subjects had sedentary behavior**
- **All the adolescents** included in **the EVL showed sedentary behavior** while the frequency of active subjects was higher in young adults of the EVL population (15/22, 68.2%) than in adults (11/26, 42.3%)
- Similar results can be observed in the ITT population

A patient will be defined "adherent" to WHO guidelines if:
- 12-17 years old:
  - MVPA minutes per day ≥ 60 minutes
- 18-50 years old:
  - Fairly active (moderate) minutes per week ≥ 150 minutes OR
  - Very active (vigorous) minutes per week ≥ 75 minutes OR
  - An equivalent combination of fairly and very active minutes (i.e. considering 1 fairly active minute as 0.5 very active minutes)

- EVL, Evaluable population; MVPA, Moderate to Vigorous Physical Activity; ITT, Intention-To-Treat Population

Mancuso ME, et al. ASH 2023; ústní prezentace 663.

Results – Secondary Endpoints

Number and types of bleeds

	12-17 years (N=17)	18-30 years (N=46)	31-50 years (N=40)	Overall (N=103)
Total number of bleeds per patient				
Number (%) of subjects with bleeding	6 (35.3%)	21 (45.7%)	18 (45.0%)	45 (43.7%)
Median number of bleeding Q1 ; Q3	1.5 1 ; 2	2.0 1 ; 3	2.5 2 ; 5	2.0 1 ; 3
• **Spontaneous bleeds**				
Number (%) of subjects with bleeding	2 (11.8%)	10 (21.7%)	7 (17.5%)	19 (18.4%)
Median number of bleeding Q1 ; Q3	1.5 1 ; 2	1.0 1 ; 2	2.0 2 ; 5	2.0 1 ; 2
• **Traumatic bleeds**				
Number (%) of subjects with bleeding	3 (17.6%)	18 (39.1%)	14 (35.0%)	35 (34.0%)
Median number of bleeding Q1 ; Q3	1.0 1 ; 4	2.0 1 ; 3	2.0 1 ; 4	2.0 1 ; 3
• **Bleeds related to procedures/surgeries**				
Number (%) of subjects with bleeding	0	0	1 (2.5%)	1 (1.0%)
Median number of bleeding Q1 ; Q3	0	0	1.0 1 ; 1	1.0 1 ; 1

- At least one bleeding (**mean 2.9; median 2.0**) was reported in **43.7% of the subjects**
- A total of 129 episodes, were observed, mainly at **joints** (N=84) and having **traumatic origin** (N=82);
- The most common symptom associated with the bleed reported by subjects was **pain**.
- The rate of bleeding in the **EVL population** was **numerically lower in subjects with active behavior** (1.384 [0.974; 1.907] bleeding/year) than in subjects with sedentary behavior (1.945 [1.481; 2.509] bleeding/year). **The physical activity in the 2 days preceding the bleeding was comparable to the one observed in the overall observational period**

- EVL, Evaluable population;

Mancuso ME, et al. ASH 2023; ústní prezentace 663.

Results – Other Secondary Endpoints

The mean EQ-5D VAS progressively worsened, indicating a situation of discomfort and pain during the study. The results of HRQoL showed that a sedentary condition was associated with a worse pain status, a higher risk of hospitalization, and a worse joint status compared to active patients

In the EVL population the rate of patients that had at least one hospitalization during the observational period was higher in subjects with sedentary behavior (5 patients, 17.9%) than in subjects with active behavior (1 patient, 3.8%)

The mean HJHS total score score increased (i.e., worsened) from baseline to month 6 and month 12 in both subjects with sedentary and active behavior, with more marked mean increases in subjects with sedentary behavior at both time points

In general, adherence to the treatment regimen was quite poor overall (mean 55%) and only 26.2% of the subjects had an adherence ≥ 80%

- EVL, Evaluable population; HJHS, Hemophilia Joint Health Score; HRQoL, health-related quality of life.

Mancuso ME, et al. ASH 2023; ústní prezentace 663.

Conclusions

- The use of a fitness tracker and an ePRO app allows the systematic recording of data on the daily activity, QoL, bleeding, and adherence to therapy in subjects with HA without inhibitors in their daily life.
- Patients with HA without inhibitors have a lower-than-expected physical activity based on adherence to WHO Guidelines.
- Despite the poor PA, about half of the subjects reported bleeds, especially in the sedentary population, suggesting that other causes than PA, such as treatment adherence and type of treatment, might affect number, frequency, and severity of bleedings.
- These outcomes might be particularly relevant considering the stringent monitoring of bleeding and PA being more accurate than in other studies and belonging to data systematically collected for 12 months in the real-world environment.
- Further research on a larger sample of patients is needed to confirm the relationship between bleeding and physical activity.

HA, hemophilia A; PA, physical activity; QoL, quality of life.

Mancuso ME, et al. ASH 2023; ústní prezentace 663.

Bone health of hemophilia A patients using emicizumab

Upraveno podle posteru P2620 předneseného na kongresu Americké hematologické společnosti (ASH), 9. – 12. prosince 2023
Abstrakt je dostupný na: https://ash.confex.com/ash/2023/webprogram/Paper174200.html

Background

- Hemophilia patients exhibit a higher prevalence of osteoporosis compared to age-matched general population

- Mechanism are still uknown, and there´re some hypothesis
  - FVIII may possess additional physiological functions contributing to bone health
  - Overall coagulation function or thrombin generation may be pivotal in maintaining optimal bone health

F, factor.

Lyu T, et al. ASH 2023; prezentace posteru P2620.

Aim

- Evaluate Emicizumab´s impact on Bone Health:
  - Emicizumab mimics the coagulation function of FVIII but possesses a structurally distinct composition
  - Compare the bone health in emicizumab users vs. emicizumab-naive patients
  - Provide information to explain the possible osteoporosis mechanism in hemophilia

F, factor.

Lyu T, et al. ASH 2023; prezentace posteru P2620.

Method

- Assessing Bone Health in Hemophilia Patients (June 2019 - June 2023) in National Taiwan University Hospital Hemophilia Center

- Examinations Conducted:
  - Routine annual joint health evaluations for PwHA and PwHB - DEXA to measure BMD in the lumbar spine, hip, and femur
  - Serum levels of P1NP and CTX were measured as reference markers for bone formation and bone resorption

- Statistical Analysis:
  - Utilized the Kruskal-Wallis test to statistically evaluate the observations among the three groups

PwHA, people with hemophilia A; PwHB, people with hemophilia B, DEXA, dual-energy X-ray absorptiometry scan; BMD, bone mineral density; P1NP, procollagen type 1 N-terminal propeptide; CTX, C-terminal telopeptide.

Lyu T, et al. ASH 2023; prezentace posteru P2620.

Results

- Study population:
  - PwHA utilizing emicizumab for more than one year (n=8),
  - PwHA receiving regular FVIII treatment (n=16),
  - PwHB (n=10),
- Characteristics:
  - Similarities in age, ABR, and joint conditions observed among the three groups
- Data Analysis:
  - No statistically significant differences detected in BMDs and biomarkers
  - Potential trend toward higher levels of P1NP in the PwHB group

Characters of different patient groups

	Hemophilia A emicizumab user (n=8)	Hemophilia A, emicizumab naïve (n=16)	Hemophilia B (n=10)	P valve
Age	37.5 (16-53)	46 (20-70)	42 (24-66)	0.804
ABR	1.5 (0-23)	2.5 (0-97)	4 (0-25)	0.638
BMD Lumbar spine	0.10 (-2.5-3.4)	-0.25 (-2.9- 1.2)	-0.3 (-2.0-3)	0.385
BMD femur	-0.7 (-2.2-1.5)	-1.0 (-3.6-1.9)	-1.0 (-2.4-0.5)	0.978
BMD hip	-1.15 (-2.0-1.5)	-1.0 (-3.2-1.8)	-1.0 (-2.0-0.7)	0.978
P1NP (ng/mL)	47.03 (26.78-105.5)	45.19 (24.05-124.00)	67.295 (38.88-96.30)	0.050
CTX (ng/mL)	0.536 (0.326-.875)	0.398 (0.159-0.767)	0.458 (0.329-0.919)	0.820
HJHS	14.50 (2-36)	17 (1-50)	10 (2-27)	0.868
HEAD-US	22 (5-41)	24 (1-42)	14.5 (6-31)	0.309

Data (median, range); ABR: annual bleeding rate; BMD: bone mineral density; P1NP: procollagen type 1 N-terminal propeptide; CTX: C-terminal telopeptide; HJHS: hemophilia joint health score; HEAD-US: hemophilia early arthropathy detection–ultrasound

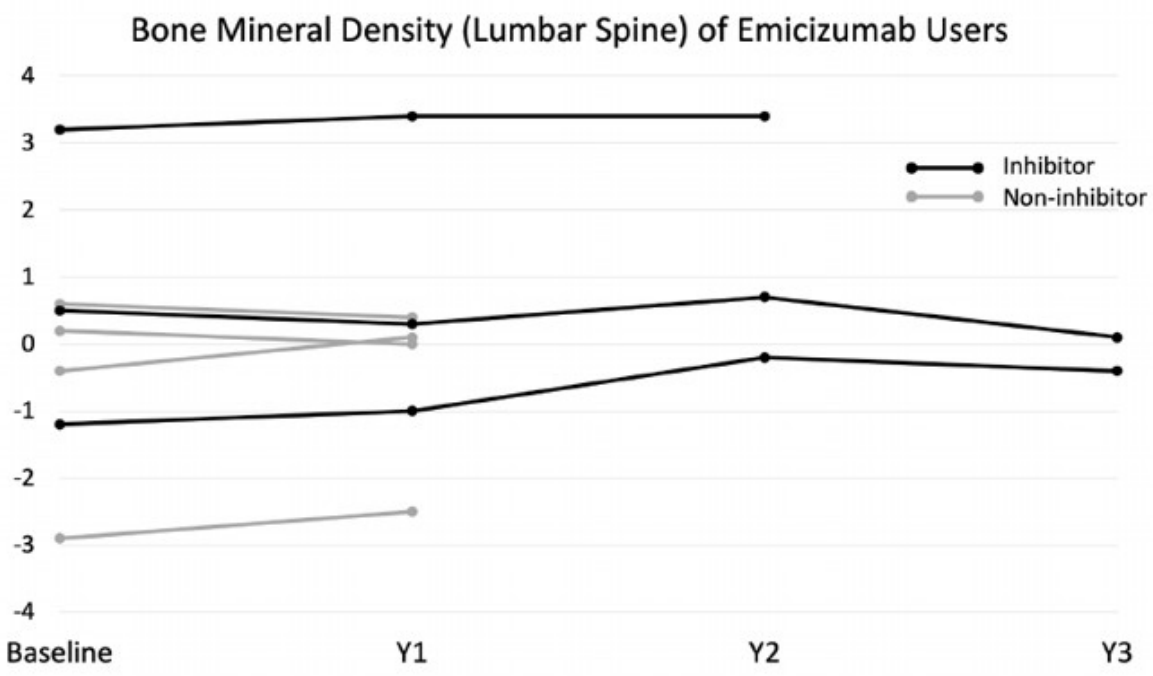
Reference range: P1NP: 15.13-58.59 ng/mL; CTX: ≤ 0.704 ng/ml

F, factor; PwHA, people with hemophilia A; PwHB, people with hemophilia B; ABR, annual bleeding rate; BMDs, bone mineral densities, P1NP, procollagen type 1 N-terminal propeptide; CTX, C-terminal telopeptide; HJHS, Hemophilia Joint Health Score; HEAD-US, Haemophilia Early Arthropathy Detection with UltraSound.

Lyu T, et al. ASH 2023; prezentace posteru P2620.

Results

- Longitudinal Analysis for PwHA using emicizumab:
  - Examined changes in T-score of BMD over time
  - Three PwHA patients with baseline T-scores below zero demonstrated improvements in their T-scores after one year of emicizumab treatment



PwHA, people with hemophilia A; BMD, bone mineral density.

Lyu T, et al. ASH 2023; prezentace posteru P2620.

Conclusions

- The results of this study indicate a lack of significant disparities in bone health between individuals utilizing emicizumab and those who are not

- Furthermore, our findings suggest that emicizumab usage does not lead to a decline in bone health over the observed period

Lyu T, et al. ASH 2023; prezentace posteru P2620.

Experience with emicizumab among people with hemophilia A in the Canadian hemophilia bleeding disorders registry

Upraveno podle posteru P1240 předneseného na kongresu Americké hematologické společnosti (ASH), 9. – 12. prosince 2023

Abstrakt je dostupný na: https://ash.confex.com/ash/2023/webprogram/Paper174057.html

Background

- The use of emicizumab as prophylaxis to prevent bleeding or reduce the frequency of bleeding episodes in congenital HA was approved by Health Canada for the treatment of PwHA with FVIII inhibitors in 2018, and without FVIII inhibitors in 2019
- Here, we present the results of a non-interventional cohort study, using data routinely collected by the CBDR to evaluate treatment patterns of emicizumab in Canada and the associated safety and effectiveness outcomes, including quality of life; this presentation summarizes the cumulative experience with emicizumab of PwHA registered in the CBDR up to December 31, 2022

F, factor; HA, hemophilia A; PwHA, people with hemophilia A; CBDR, Canadian Bleeding Disorders Registry.

Poon MC, et al. ASH 2023; prezentace posteru P1240.

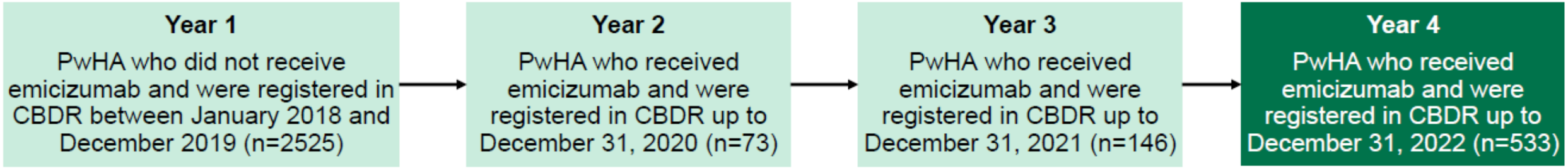
Methods

- De-identified data were extracted from the CBDR database for all registered PwHA who had received emicizumab at least once prior to December 31, 2022
- Effectiveness outcomes were measured by the proportion of PwHA with zero, traumatic, spontaneous, or joint bleeds as well as ABRs for all bleeds. Intra-patient comparisons of bleeding were performed, using a negative binomial regression model, for all PwHA and for those with ≥6 months of follow-up in both pre-and post-emicizumab periods as a sensitivity analysis
- Effectiveness outcomes also included participants' HJHS, PROBE, and EQ-5D index and VAS scores. We performed a complete data analysis, without imputation
- This study was approved by the research ethics board of McMaster University and other participating centers and abides by the guiding principles of the Declaration of Helsinki

F, factor; HA, hemophilia A; PwHA, people with hemophilia A; CBDR, Canadian Bleeding Disorders Registry; ABRs, annualized bleeding rates; HJHS, Hemophilia Joint Health Score; PROBE, Patient Reported Outcomes, Burdens and Experiences ; EQ-5D, standardised measure of health-related quality of life; VAS, visual analog score.

Poon MC, et al. ASH 2023; prezentace posteru P1240.

Overview of the study cohort using data collected by the CBDR



CBDR, Canadian Bleeding Disorders Registry; PwHA, people with hemophilia A.

Poon MC, et al. ASH 2023; prezentace posteru P1240.

Demographic characteristics

- Baseline demographic characteristics were stratified by disease severity (defined by the level of endogenous FVIII activity) and age
- Overall, 498 (93.4%) PwHAE (including two females) had severe disease, 28 (5.3%) had moderate disease, and 7 (1.3%) had mild disease
- At the start of emicizumab exposure: 220 (41.3%) PwHAEwere <18 years old, 78 (14.6%) PwHAEhad current FVIII inhibitors, 82 (15.4%) had a history of FVIII inhibitors, and 373 (70.0%) had no history of FVIII inhibitors

Characteristic	Overall	Severity of Hemophilia A*			Age	
		Severe	Moderate	Mild	<18 years	≥18 years
N (%)	533	498 (93.4)	28 (5.3)	7 (1.3)	220 (41.3)	313 (58.7)
Age, years						
Mean ± SD, n	25.2 ± 18.0, 533	24.8 ± 17.5, 498	32.4 ± 23.6, 28	27.8 ± 24.1, 7	8.9 ± 5.1, 220	36.7 ± 14.6 313
Median (Q1, Q3)	21.1 (10.6, 37.0)	21.2 (10.5, 36.8)	26.9 (13.0, 47.9)	17.0 (10.4, 48.0)	9.1 (4.5, 13.1)	34.3 (24.7, 46.0)
Male, n (%)	531/533 (99.6)	496/498 (99.6)	28/28 (100.0)	7/7 (100.0)	219/220 (99.5)	312/313 (99.7)
Mean BMI (kg/m^2) ± SD, n	23.8 ± 9.5, 424	23.8 ± 9.3, 393	25.9 ± 12.4, 27	17.3 ± 4.5, 4	19.7 ± 10.0, 191	27.3 ± 7.5, 233
FVIII inhibitor status†, n (%)						
Current	78/533 (14.6)	67/498 (13.5)	5/28 (17.9)	6/7 (85.7)	38/220 (17.3)	40/313 (12.8)
Low titer	44/533 (8.3)	38/498 (7.6)	3/28 (10.7)	3/7 (42.9)	22/220 (10.0)	22/313 (7.0)
High titer	34/533 (6.4)	29/498 (5.8)	2/28 (7.1)	3/7 (42.9)	16/220 (7.3)	18/313 (5.8)
Inhibitor history	82/533 (15.4)	77/498 (15.5)	4/28 (14.3)	1/7 (14.3)	25/220 (11.4)	57/313 (18.2)
No inhibitor	373/533 (70.0)	354/498 (71.1)	19/28 (67.9)	0/7 (0.0)	157/220 (71.4)	216/313 (69.0)
Emicizumab regimen, n (%)						
Weekly	260/533 (48.8)	241/498 (48.4)	15/28 (53.6)	4/7 (57.1)	76/220 (34.5)	184/313 (58.8)
Biweekly	229/533 (43.0)	216/498 (43.4)	10/28 (35.7)	3/7 (42.9)	121/220 (55.0)	108/313 (34.5)
Other‡	44/533 (8.3)	41/498 (8.2)	3/28 (10.7)	0/7 (0.0)	23/220 (10.5)	21/313 (6.7)
ITI while on emicizumab, n (%)	6/533 (1.1)	6/498 (1.2)	0/28 (0.0)	0/7 (0.0)	5/220 (2.3)	1/313 (0.3)

*Severe HA (FVIII <0.01IU/mL), moderate HA (0.01 ≤ FVIII ≤0.05IU/mL) and mild HA (0.05 < FVIII ≤0.40IU/mL). †Current (inhibitor at the time of receipt of the first dose of emicizumab), low titer (<5 BU), high titer (≥5 BU), history of FVIII inhibitors (inhibitor detected prior to emicizumab but no current inhibitors), no inhibitor (inhibitors not detected or observed). ‡Emicizumab regimen "Other" category includes every 5th, 8th, 9th, 11th, 12th, 15th, 16th, 19th, 28th, 30th days and bimonthly.

F, factor; HA, hemophilia A; PwHA, people with hemophilia A; BMI, body mass index; ITI, immune tolerance induction; Q1, first quartile; Q3, third quartile; SD, standard; PwHAE, patient with hemophilia A who received at least one dose of emicizumab.

Poon MC, et al. ASH 2023; prezentace posteru P1240.

The safety profile of emicizumab is consistent with previous reports

- A total of 22 AEs were reported during the entire observation period, nine of which were cases of COVID-19
- The other 13 AEs comprised an event of thrombosis (occurring in one person with COVID-19), seven allergic reactions, two incidences of FVIII inhibitor development, two neurological events (headache; headache, nausea, and vomiting) and one case of a large hematoma that developed at an operative site following removal of a port-a-cath
  - The event of thrombosis was considered by the clinician to be possibly related to the use of emicizumab; it was judged to be device-associated and occurred in a patient who had undergone surgery within three months prior to the event
- There were no discontinuations or dose modifications due to AEs

F, factor; AEs, adverse events; COVID-19, coronavirus disease 2019.

Poon MC, et al. ASH 2023; prezentace posteru P1240.

PwHA reported favorable effectiveness outcomes for emicizumab

- Over a median (Q1, Q3) follow-up time of 249 (136, 395) days, 388 (72.8%) PwHAE had no recorded bleeds

Effectiveness outcomes	Overall	Severity of hemophilia A*			Inhibitor status†		
		Severe	Moderate	Mild	Current	History	No inhibitor
N	533	498	28	7	78	82	373
Zero bleeds, n (%)	388 (72.8)	363 (72.9)	19 (67.9)	6 (85.7)	49 (62.8)	64 (78.0)	275 (73.7)
Traumatic bleeds, n (%)	87 (16.3)	83 (16.7)	3 (10.7)	1 (14.3)	16 (20.5)	7 (8.5)	64 (17.2)
Spontaneous bleed, n (%)	69 (12.9)	63 (12.7)	5 (17.9)	1 (14.3)	15 (19.2)	8 (9.8)	46 (12.3)
Joint bleeds, n (%)	106 (19.9)	100 (20.1)	5 (17.9)	1 (14.3)	21 (26.9)	12 (14.6)	73 (19.6)
ABR‡, median (Q1, Q3), n all PwHA	0.0 (0.0, 0.4), 533	0.0 (0.0, 0.4), 498	0.0 (0.0, 0.5), 28	0.0 (0.0, 0.0), 7	0.0 (0.0, 0.5), 78	0.0 (0.0, 0.0), 82	0.0 (0.0, 0.7), 373
Follow-up days for all PwHA, median (Q1, Q3), n	249 (136, 395), 533	248 (141, 393), 498	246 (67, 682), 28	681 (264, 906), 7	1067 (408, 1268), 78	238 (129, 396), 82	221 (128, 312), 373
ABR‡, median (Q1, Q3), n PwHA with bleeds	2.1 (1.1, 4.8), 145	2.1 (1.1, 4.7), 135	1.9 (0.6, 9.4), 9	6.0 (6.0, 6.0), 1	1.0 (0.4, 1.6), 29	1.7 (0.9, 4.3), 18	3.0 (1.5, 6.2), 98
Follow-up days for PwHA with bleeds, median (Q1, Q3), n	302 (218, 425), 145	298 (220, 410), 135	571 (47, 1079), 9	906 (906, 906), 1	1072 (571, 1254), 29	322 (236, 425), 18	264 (184, 354), 98
HJHS§ mean ± SD, n	9.4 ± 13.3, 76	9.6 ± 13.7, 69	5.8 ± 7.8, 5	12.4 ± 16.1, 2	17.8 ± 17.5, 22	7.6 ± 12.4, 16	5.3 ± 7.9, 38
PROBE score§, mean ± SD, n	0.8 ± 0.2, 59	0.8 ± 0.2, 53	0.6 ± 0.1, 4	0.9 ± 0.0, 2	0.7 ± 0.2, 14	0.8 ± 0.1, 8	0.8 ± 0.2, 37
EQ-5D index score§, mean ± SD, n	0.8 ± 0.2, 59	0.8 ± 0.2, 53	0.8 ± 0.1, 4	0.9 ± 0.0, 2	0.8 ± 0.2, 14	0.8 ± 0.1, 8	0.8 ± 0.2, 37
EQ-5D VAS score§, mean ± SD, n	77.0 ± 16.3, 59	77.7 ± 16.4, 53	64.1 ± 13.4, 4	85.0 ± 7.1, 2	75.6 ± 19.4, 14	71.8 ± 9.6, 8	78.7 ± 16.3, 37

*Severe HA (FVIII <0.01IU/mL), moderate HA (0.01 ≤ FVIII ≤0.05IU/mL) and mild HA (0.05 < FVIII ≤0.40IU/mL). †Current (inhibitor at the time of receipt of the first dose of emicizumab), history of FVIII inhibitors (inhibitors detected prior to emicizumab but no current inhibitors), no inhibitor (no inhibitors detected or observed yet). ‡Calculated as: (total number of bleeds/duration of follow-up [days])×365.25 for PwHA who received emicizumab prior to December 31, 2022. §The HJHS can range from 0 (normal) to 124 (worst joint status). The PROBE score can range from 0 (worst health status) to 1 (best health status). The EQ-5D utility index can range from −0.28 (worst health status) to 1 (best health status). The EQ-5D VAS can range from 0 (worst health status) to 100 (best health status).

ABR, annualized bleeding rate; F, factor; HA, hemophilia A; HJHS, Hemophilia Joint Health Score; PROBE, Patient Reported Outcomes Burdens and Experiences; PwHA, people with hemophilia A; Q1, quartile 1; Q3, quartile 3; SD, standard deviation; VAS, visual analog scale; PwHAE, patient with hemophilia A who received at least one dose of emicizumab.

Poon MC, et al. ASH 2023; prezentace posteru P1240.

Effectiveness outcomes after switching to emicizumab

- Using a negative binomial regression model, an intra-patient comparison in all PwHAE (n=533) showed a decrease in mean (95% CI) ABR from 1.22 (1.06–1.42), pre-emicizumab (2018, prior to first dose) to 0.50 (0.41–0.60) post-emicizumab (rate ratio [95% CI] 0.41 [0.33–0.50], p<0.001)
- The intra-patient comparison in PwHAE without current FVIII inhibitors (n=455) showed a decrease in mean ABR (95% CI) from 1.02 (0.87–1.19) to 0.54 (0.44–0.66) (rate ratio [95% CI] 0.53 [0.43–0.65], p<0.001)
- The intra-patient comparison in PwHAE with current FVIII inhibitors (n=78) showed a decrease in mean ABR (95% CI) from 5.03(3.30–7.66) to 0.41 (0.26–0.65) (rate ratio [95% CI] 0.08 [0.04–0.15], p<0.001)

PwHAE, patient with hemophilia A who received at least one dose of emicizumab; CI, confidence interval; F, factor; ABR, annualized bleeding rate.

Poon MC, et al. ASH 2023; prezentace posteru P1240.

Conclusions

- This analysis describes the baseline characteristics, safety and effectiveness outcomes of Canadian PwHA treated with emicizumab before December 31, 2022; a total of 387 new PwHA were included in this analysis compared with the previous analysis (data cut-off: December 31, 2022, n=146)

- The data show that 72.8% of PwHAE had no recorded bleeds since they started emicizumab, and that there was a substantial decrease in bleeds post-emicizumab in both PwHA with and without current FVIII inhibitors

- The safety profile of emicizumab was consistent with previous reports. The CBDR allows for a longitudinal follow-up of the Canadian HA population, which can inform healthcare practitioners and regulatory authorities of the safety and efficacy outcomes of treatments in routine clinical practice

PwHA, people with hemophilia A; HA, hemophilia A; CBDR, Canadian Bleeding Disorders Registry; PwHAE, patient with hemophilia A who received at least one dose of emicizumab.

Poon MC, et al. ASH 2023; prezentace posteru P1240.

Quality of life in emicizumab-treated people with hemophilia A in the ATHN 7 hemophilia natural history study – An assessment of baseline PROMIS®-29 Scores

Upraveno podle posteru P3998 předneseného na kongresu Americké hematologické společnosti (ASH), 9. – 12. prosince 2023

Abstrakt je dostupný na: https://ash.confex.com/ash/2023/webprogram/Paper174092.html

Background

- PwHA experience frequent bleeding into joints, muscles, and soft tissues due to a deficiency of FVIII, which has a substantial negative impact on their HRQoL
- Emicizumab is a bispecific antibody approved for prophylactic treatment of HA
- ATHN: A Natural History Cohort Study of the Safety, Effectiveness and Practice of Treatment for People with Hemophilia (NCT03619863) prospectively monitors safety and effectiveness of contemporary HA and B therapies, including emicizumab, in the US
- We describe baseline scores for a subset of adults with HA enrolled in ATHN 7 who were receiving emicizumab and completed the Patient-Reported Outcomes Measurement Information System (PROMIS®)-29 Profile measure at the time of study entry, with the aim of contributing to the literature on disease burden in PwHA

PwHA, people with hemophilia A; F, factor; HA, hemophilia A; HRQoL, health-related quality of life; ATHN, American Thrombosis and Hemostasis Network; US, United States.

Buckner TW, et al. ASH 2023; prezentace posteru P3998.

ATHN 7 is a longitudinal, prospective observational cohort study conducted at 26 ATHN-affiliated sites in the US

- Clinical and demographic information is collected at baseline
- PwHA not receiving emicizumab at baseline were excluded from this analysis
- The PROMIS-29 is a disease-agnostic measure capturing data across the following physical, mental, and social health domains: physical function, fatigue, sleep disturbance, pain intensity, pain interference, depressive symptoms, anxiety, and ability to participate in social roles/activities
- The PROMIS measures are scored using a standardized T-score metric with a reference population mean of 50 and a SD of 10, based on the US general population. Higher scores indicate the participant is experiencing more of the concept being measured (positive or negative). The limits for 'normal' function for each PROMIS assessment score varied between domains

PwHA, people with hemophilia A; F, factor; HA, hemophilia A; SD, standard deviation; HRQoL, health-related quality of life; ATHN, American Thrombosis and Hemostasis Network; US, United States.

Buckner TW, et al. ASH 2023; prezentace posteru P3998.

Participant demographics and baseline characteristics

	N=67
Age at study entry, years*	
Mean (SD)	34.8 (14.5)
Median (min, max)	30.0 (18.0, 75.0)
Age (at study entry) group, n (%)	
≤24 years	17 (25.4)
25–49 years	39 (58.2)
≥50 years	11 (16.4)
Sex, n (%)	
Male	67 (100.0)
Female	0 (0.0)
Primary HA diagnosis severity, n (%)	
Severe	53 (79.1)
Mild or moderate	14 (20.9)
FVIII inhibitors, n (%)	
Yes	12 (17.9)
No	55 (82.1)
Family history of HA, n (%)	
Yes	36 (53.7)
No	29 (43.3)
Unknown	2 (3.0)

Overall, 67 participants in ATHN 7 receiving emicizumab at study entry completed PROMIS-29 at baseline

- Participants had a median (min, max)
  age of 30.0 (18.0, 75.0) years
- Disease severity at diagnosis was severe for 53 (79.1%) participants and mild or moderate for 14 (20.9%) participants
- There were 12 (17.9%) PwHA with FVIII inhibitors

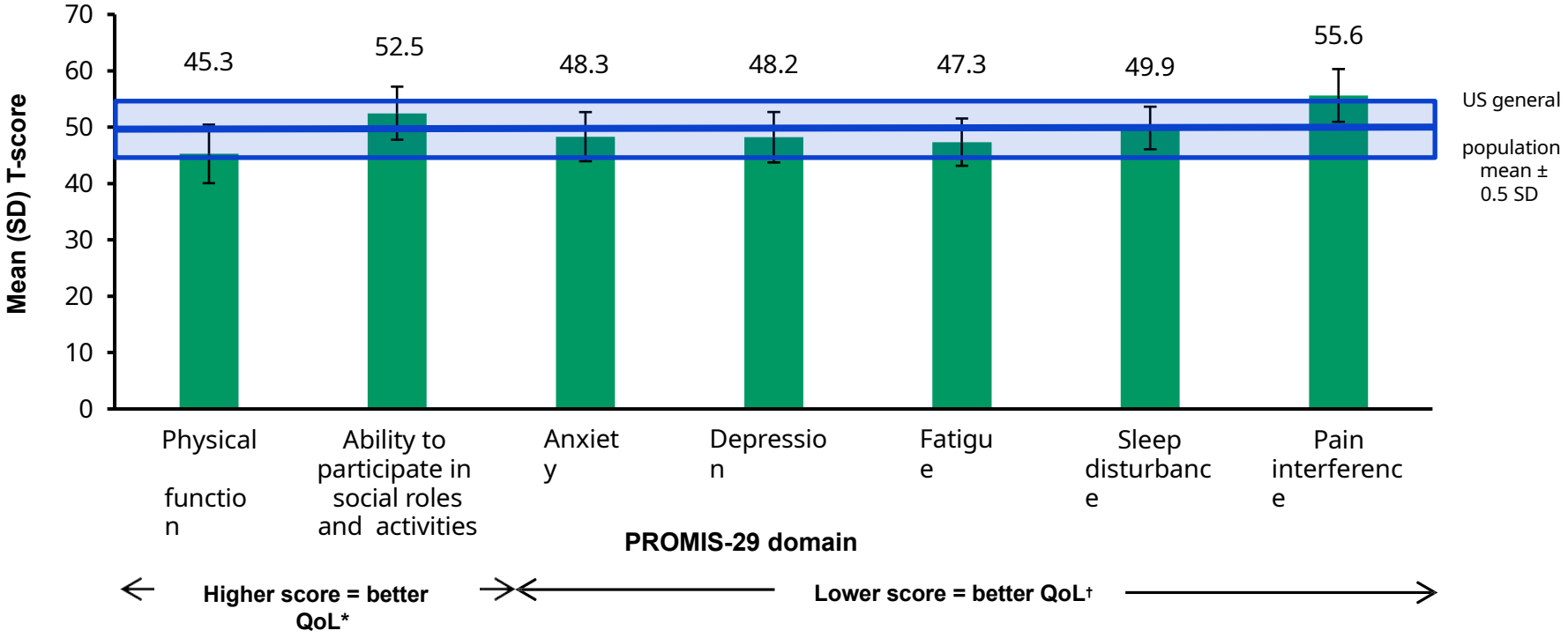
*Data on pediatric PwHA are being collected in ATHN 7 but are not reported here

PwHA, people with hemophilia A; F, factor; HA, hemophilia A; SD, standard deviation; ATHN, American Thrombosis and Hemostasis Network.

Buckner TW, et al. ASH 2023; prezentace posteru P3998.

PROMIS-29 domain T-scores at baseline aligned with the US reference population

Figure 1. Baseline PROMIS-29 T-scores for the overall population of participants treated with emicizumab in ATHN 7 (N=67)



- Mean PROMIS-29 domain T- scores for ability to participate in social roles and activities, symptoms of anxiety, sleep disturbance, depression, and fatigue at baseline all fell within 0.5 SD of the reference population mean (**Figure 1**)
- However, PwHA did demonstrate mild symptoms of pain interference (mean baseline T-score: 55.62; [normal: <55])

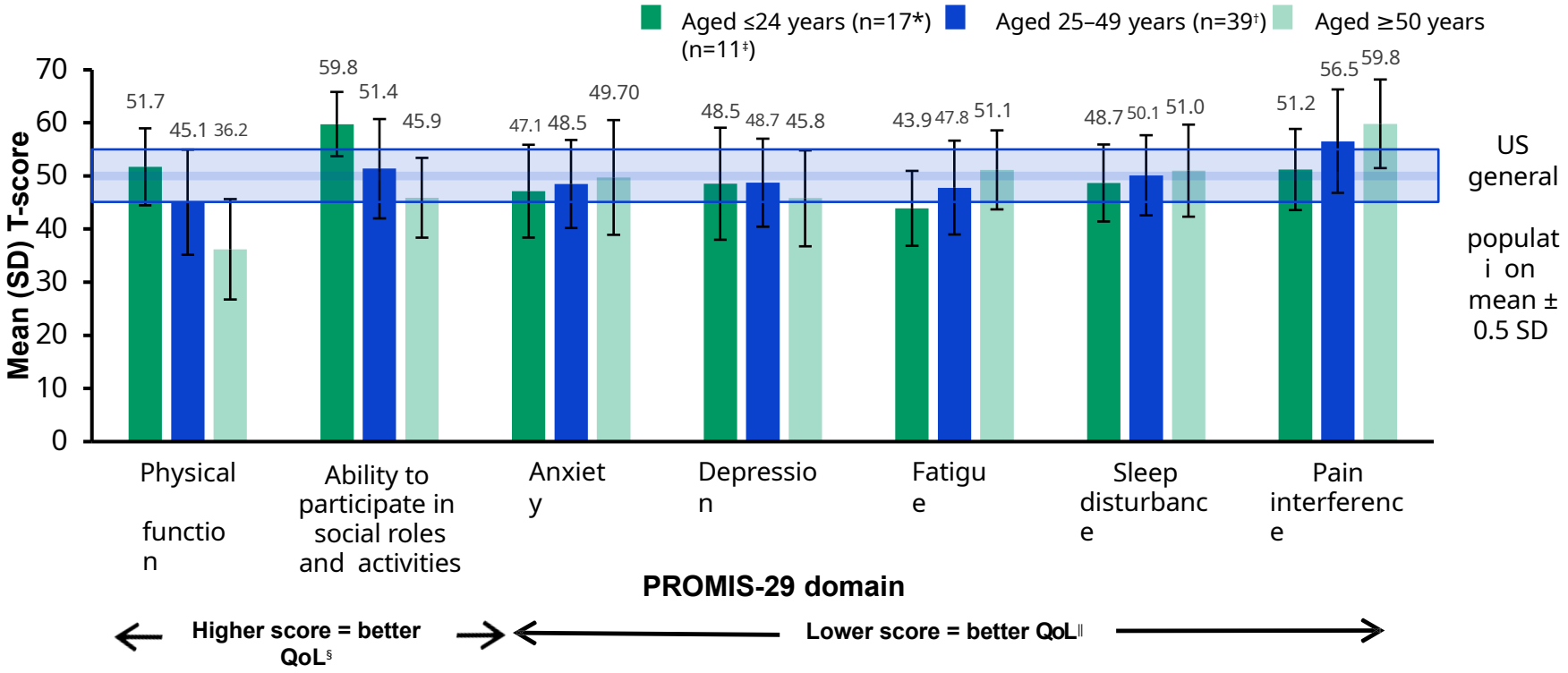
*Normal: >45; mild impairment: 40–45; moderate impairment: 30–40; severe impairment: <30; †Normal: <55; mild symptoms: 55–60; moderate symptoms: 60–70; severe symptoms: >70

ATHN, American Thrombosis and Hemostasis Network; PROMIS, Patient-Reported Outcomes Measurement Information System; QoL, quality of life; SD, standard deviation; US, United States.

Buckner TW, et al. ASH 2023; prezentace posteru P3998.

PROMIS-29 domain T-scores at baseline aligned with the US refere population

Figure 2. Baseline PROMIS-29 T-scores by age group for participants treated with emicizumab in ATHN 7 (N=67)



*n=16 for ability to participate in social roles and activities; †n=38 for pain interference; ‡n=10 for anxiety, depression, pain interference; §Normal: >45; ‖Normal: <55.

ATHN, American Thrombosis and Hemostasis Network; PROMIS, Patient-Reported Outcomes Measurement Information System; QoL, quality of life; SD, standard deviation; US, United States.

- PwHA with FVIII inhibitors had mild impairment of physical function (42.17) and mild symptoms of pain interference (58.64). People without inhibitors had physical function (45.96) and pain interference (55.00) within 0.5 SD of the reference population
- People with severe HA without FVIII inhibitors had mild impairment of physical function (44.76) and mild symptoms of pain interference (55.49), while people with mild/moderate HA without inhibitors had physical function (49.85) and pain interference (53.46) within 0.5 SD of the reference population
- Physical function decreased with age, from 51.71 in the group aged ≤24 years to 36.18 in the group aged ≥50 years, while pain interference increased with age, from 51.18 in the group aged ≤24 years to 59.80 in the group aged ≥50 years. There was no relationship between age group and anxiety, depression, and sleep disturbance (**Figure 2**)

Buckner TW, et al. ASH 2023; prezentace posteru P3998.

Limitations

- Results should be interpreted with caution as subgroup numbers are small, therefore no statistical tests were performed
- The exact duration of emicizumab exposure prior to study entry could not be extracted, meaning duration of treatment at the time of completing the PROMIS questionnaire could not be determined
- The disability paradox, in which people with persistent disabilities report better quality of life outcomes than perceived by those without disabilities, should also be considered

PROMIS, Patient-Reported Outcomes Measurement Information System;

Buckner TW, et al. ASH 2023; prezentace posteru P3998.

Conclusions

- In this analysis, we observed that HRQoL in PwHA receiving emicizumab, as measured by PROMIS-29 domain T-scores, generally did not differ from that of the US reference population
- PwHA did report mild symptoms of pain interference
- Physical function, ability to participate in social roles/function, and pain varied between age groups

PwHA, people with hemophilia A; HRQoL, health-related quality of life; PROMIS, Patient-Reported Outcomes Measurement Information System;

Buckner TW, et al. ASH 2023; prezentace posteru P3998.

HEMLIBRA 30 mg/ml injekční roztok, HEMLIBRA 150 mg/ml injekční roztok
– Zkrácená informace o přípravku

Účinná látka: emicizumab. **Držitel rozhodnutí o registraci:** Roche Registration GmbH, Grenzach - Wyhlen, Německo. **Registrační číslo:** EU/1/18/1271/001-004. **Indikace:** Přípravek Hemlibra je indikován k rutinní profylaxi krvácivých epizod u pacientů s hemofilií A s inhibitorem faktoru VIII, u pacientů s těžkou hemofilií A (vrozený deficit koagulačního faktoru VIII, FVIII < 1 %) bez inhibitoru faktoru VIII a u pacientů se středně těžkou hemofilií A (vrozený deficit koagulačního faktoru VIII, FVIII ≥ 1 % a ≤ 5 %) se závažným krvácivým fenotypem bez inhibitoru faktoru VIII. Přípravek Hemlibra mohou používat všechny věkové kategorie. **Dávkování a způsob podání:** Léčba musí být zahájena pod dohledem lékaře se zkušeností s léčbou hemofilie a/nebo krvácivých poruch. Den před zahájením léčby přípravkem Hemlibra musí být ukončena léčba (včetně rutinní profylaxe) bypassovými přípravky. Profylaxe faktorem VIII (FVIII) může pokračovat během prvních 7 dnů léčby přípravkem Hemlibra. Doporučená dávka je 3 mg/kg jednou týdně během prvních 4 týdnů (nasycovací dávka), po kterých následuje od týdne 5 udržovací dávka buď 1,5 mg/kg jednou týdně, nebo 3 mg/kg každé dva týdny nebo 6 mg/kg každé čtyři týdny, všechny dávky podávané formou subkutánní injekce. Režim nasycovací dávky je vždy stejný bez ohledu na režim udržovací dávky. Při sestavování celkového objemu dávky pro podání nesměšujte různé koncentrace roztoku Hemlibra (30 mg/ml a 150 mg/ml) v jedné injekční stříkačce. Nepodávejte objem větší než 2 ml na injekci. Přípravek Hemlibra je určen k dlouhodobé profylaktické léčbě. Nejsou doporučeny žádné úpravy dávkování přípravku Hemlibra. Přípravek Hemlibra je určen pouze k subkutánnímu použití a musí být aplikován pomocí vhodné aseptické techniky. Během léčby přípravkem Hemlibra mají být jiné léčivé přípravky k subkutánní aplikaci aplikovány přednostně v jiných místech. Přípravek Hemlibra je určen k používání pod vedením zdravotnického pracovníka. Po důkladném zaškolení v aplikaci subkutánní injekce jej může aplikovat pacient nebo pečovatel, uzná-li to lékař za vhodné. **Kontraindikace:** Hypersenzitivita na léčivou látku nebo na kteroukoli pomocnou látku. **Imunogenita:** U pacientů s klinickými projevy ztráty účinnosti (např. nárůst počtu průlomových krvácivých příhod) je třeba okamžitě zhodnotit etiologii a při podezření, že příčinou jsou neutralizující protilátky proti emicizumabu, je třeba zvážit jiné možnosti léčby. **Významné interakce:** S emicizumabem nebyly provedeny žádné adekvátní ani dostatečně kontrolované studie interakcí. Klinické zkušenosti naznačují, že emicizumab interaguje s aPCC. Emicizumab zvyšuje koagulační potenciál; dávka FVIIa nebo FVIII potřebná k zajištění hemostázy může být proto nižší než bez profylaxe přípravkem Hemlibra. Zkušenosti se souběžným podáváním antifibrinolytik s aPCC nebo rFVIIa u pacientů léčených emicizumabem jsou omezené. Při podávání systémových antifibrinolytik v kombinaci s aPCC nebo rFVIIa u pacientů léčených emicizumabem je však třeba vzít v úvahu možnost trombotických příhod. **Hlavní klinicky významné nežádoucí účinky:** Nejzávažnějšími nežádoucími účinky hlášenými v klinických studiích s přípravkem Hemlibra byly trombotická mikroangiopatie (TMA) a trombotické příhody včetně trombózy kavernózního splavu (CST) a trombóza povrchových žil s kožní nekrózou. Nejčastějšími nežádoucími účinky u pacientů léčených přípravkem Hemlibra byly reakce v místě vpichu, bolest kloubů a bolest hlavy. Celkem tři pacienti na profylaxi přípravkem Hemlibra v klinických studiích ukončili léčbu kvůli nežádoucím účinkům, ke kterým patřila TMA, kožní nekróza současně s povrchovou tromboflebitidou a bolest hlavy. **Druh obalu a dostupná balení:** Injekční lahvička 3 ml, Hemlibra s koncentrací 30 mg/ml obsahuje 12 mg emicizumabu v 0,4 ml injekčního roztoku, nebo obsahuje 30 mg emicizumabu v 1ml injekčního roztoku. Injekční lahvička 3ml, Hemlibra s koncentrací 150 mg/ml obsahuje 60 mg emicizumabu v 0,4 ml injekčního roztoku, nebo obsahuje 105 mg emicizumabu v 0,7 ml injekčního roztoku, nebo obsahuje 150 mg emicizumabu v 1 ml injekčního roztoku, nebo obsahuje 300 mg emicizumabu ve 2 ml injekčního roztoku. Balení obsahuje vždy jednu injekční lahvičku.
Podmínky uchovávání: Uchovávejte v chladničce (2–8 ºC). Neotevřené injekční lahvičky lze po vyjmutí z chladničky uchovávat při pokojové teplotě (do 30 °C) až po dobu 7 dnů kumulativně. Chraňte před mrazem a před světlem.

Datum registrace: 23.2.2018 **Datum poslední úpravy textu Zkrácené informace o přípravku:** 9.11.2023. **Aktuální verze Souhrnu údajů o přípravku je dostupná na** https://www.sukl.cz, **resp.** https://www.roche.cz/cs/produkty-vpois/produkty-lekari.html

Výdej léčivého přípravku je vázán na lékařský předpis. Léčivý přípravek Hemlibra je v indikaci rutinní profylaxe krvácivých epizod u pacientů s hemofilií A (vrozený deficit koagulačního faktoru VIII) s inhibitorem faktoru VIII a v indikaci rutinní profylaxe krvácivých epizod u pacientů s těžkou hemofilií A (vrozený deficit koagulačního faktoru VIII, FVIII < 1 %) bez inhibitoru faktoru VIII hrazen z prostředků veřejného zdravotního pojištění. Léčivý přípravek zatím není hrazen u pacientů se středně těžkou hemofilií A (vrozený deficit koagulačního faktoru VIII, FVIII ≥ 1 % a ≤ 5 %) se závažným krvácivým fenotypem bez inhibitoru faktoru VIII. Podmínky úhrady viz www.sukl.cz. Další informace o přípravku získáte z platného Souhrnu údajů o přípravku Hemlibra, nebo na adrese Roche s.r.o., Sokolovská 685/136f, 18600

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