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AOZORA: safety and joint health outcomes over 6 years in children with hemophilia A – preliminary report from an early cohort

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Summary

This 6-year analysis of the AOZORA study is evaluating long-term safety and joint health in children with severe hemophilia A, without FVIII inhibitors, receiving emicizumab who transferred from the HOHOEMI study

After 6 years, the safety profile was favorable, with no thromboembolic events, fatal adverse events or treatment discontinuations due to adverse events

Overall, results suggest that emicizumab is effective in maintaining and improving joint health in children with hemophilia A

Despite increased physical activity, bleeding rates remained low and joint health was preserved or improved in most participants following emicizumab

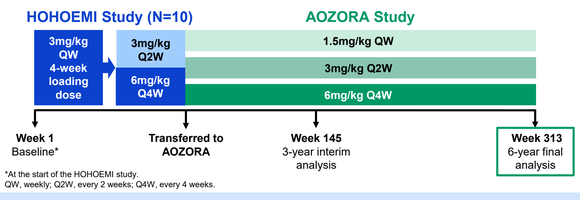
Background

- In people with hemophilia A (PwHA), recurrent joint bleeds from a young age can lead to hemophilic arthropathy, resulting in limited movement and chronic pain.[1,2]
- Early prophylaxis reduces joint damage risk in PwHA; however, limitations in long-term joint health preservation have been reported with factor (F)VIII prophylaxis.[3]
- Emicizumab maintains stable trough levels, offering continued protection against bleeding;[4] however, long-term safety and joint health data are limited, particularly in children with HA.
- We report preliminary 6-year safety and joint health outcomes in 10 children (<12 years) with HA without FVIII inhibitors receiving emicizumab in the Phase 4 AOZORA study (jRCT1080224629),[5] who had transferred from the Phase 3 HOHOEMI study (JapicCTI-173710).[6]

Methods

- Thirty children (<12 years) with HA were enrolled into the AOZORA study, including 10 PwHA transitioning from the HOHOEMI study; this analysis focuses on these 10 participants, who were emicizumab-naïve before enrollment in HOHOEMI (**Figure 1**).[6]
- Primary endpoints included long-term safety and joint health/function, evaluated using the International Prophylaxis Study Group (IPSG) MRI scale and Hemophilia Joint Health Score (HJHS) version 2.1[5]
  - Exploratory endpoints included physical activity levels and activity-related bleeding events.

Figure 1. Study design.



*At the start of the HOHOEMI study.
QW, weekly; Q2W, every 2 weeks; Q4W, every 4 weeks.

Nine of 10 participants completed the 6-year observation period

- The median observation period was 2185 days (approximately 6 years; **Table 1**).
  - One participant discontinued the study to undergo immune tolerance induction (ITI) therapy.

Table 1. Baseline characteristics.

	Participants from HOHOEMI (N=10)
Median (range) age, years	5.9 (1.5–10.7)
Age group, n (%)	
0 to <2 years	2 (20.0)
2 to <6 years	3 (30.0)
6 to <12 years	5 (50.0)
Male, n (%)	10 (100)
Median (range) weight, kg	19.4 (9.5–35.6)
Treatment regimen prior to enrollment, n (%)	
Episodic FVIII	0 (0)
Prophylactic FVIII*	10 (100)
History of ITI therapy, n (%)	2 (20.0)
Median (range) duration of ITI, years	0.8 (0.5–1.2)
Median (range) period from end of ITI to emicizumab initiation, years	3.9 (0.4–7.4)
Dosing regimen, n (%)	
Q2W	4 (40.0)
Q4W	6 (60.0)†
Presence of target joints,‡ n (%)	1 (10.0)
Median (range) observation period, days	2185 (1385–2192)

*For prophylactic FVIII administration, 8 participants used standard half-life, and 2 participants used extended half-life products;
†One participant switched to QW; ‡One participant had a target joint (left knee) at baseline.
FVIII, factor VIII; ITI, immune tolerance induction; QW, weekly; Q2W, every 2 weeks; Q4W, every 4 weeks.

No thromboembolic events, thrombotic microangiopathy or new safety concerns were observed

- A total of 337 adverse events (AEs) were reported in 10 participants, of which 4 AEs from a total of 4 participants were considered to be related to emicizumab
  - Emicizumab-related AEs: injection-site reaction (n=1), anemia (n=2), delayed callus formation (n=1).
- Six serious AEs were reported by a total of 5 participants (none considered emicizumab-related); all 6 were caused by falls or accidents.
- No thromboembolic events, including thrombotic microangiopathy, fatal AEs, or AEs leading to discontinuation of emicizumab were observed.
- During the study period, for 1 of the 2 participants with a history of ITI, FVIII inhibitors reappeared
  - The participant had received prior extended half-life FVIII prophylaxis, with inhibitors (0.8 BU/mL) detected at Week 169, which followed 1 FVIII infusion for a joint bleed at Week 157
  - He withdrew from AOZORA at Week 198 to undergo ITI.
- No inhibitors occurred in the 8 participants with no history of ITI (all with estimated ≥50 FVIII exposure days prior to emicizumab initiation).

After 6 years of follow-up, 78% of participants had a HJHS of zero

- A trend towards improvement was observed in HJHS total score up to Week 313 (**Table 2**)
  - At Week 313, 7 of 9 participants (78%) had a HJHS of 0
  - In 4 participants, HJHS score was maintained at 0 from Week 1 through Week 313.

Table 2. Changes in HJHS total score.*

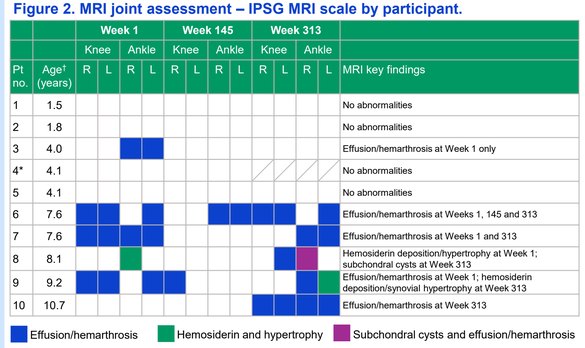
	Week 1 (N=10)	Week 49 (n=10)	Week 97 (n=10)	Week 145 (n=10)	Week 193 (n=10)	Week 241 (n=9)	Week 313 (n=9)
Mean (SD)	1.7 (2.7)	1.4 (3.2)	1.5 (3.2)	0.6 (1.4)	0.2 (0.6)	0.3 (0.7)	0.3 (0.7)
Median	0.0	0.0	0.0	0.0	0.0	0.0	0.0
Min–Max	0–8	0–10	0–9	0–4	0–2	0–2	0–2

*Lower HJHS indicates better joint health; maximum score possible is 124.
HJHS, Hemophilia Joint Health Score v2.1; SD, standard deviation.

Three participants showed no MRI abnormalities throughout the 6-year follow-up

- At Week 313, 4 participants showed no abnormalities, all of whom initiated emicizumab aged ≤4.1 years; 3 participants had no findings throughout the 6-year period (**Figure 2**).
- Among the remaining participants, 3 showed effusion/hemarthrosis only; 1 developed hemosiderin deposition and synovial hypertrophy, and 1 showed progression to subchondral cysts.
- Although the MRI IPSG scale cannot distinguish between effusion and hemarthrosis:
  - Few participants showed progression to synovial hypertrophy or hemosiderin deposition, suggesting minimal joint impact even if hemarthrosis occurred
  - Findings may also reflect joint effusion associated with increased physical activity with age (**Figure 3**).

Figure 2. MRI joint assessment – IPSG MRI scale by participant.



*Participant 4 discontinued the study following MRI assessment at Week 198; †At Week 1.
IPSG, International Prophylaxis Study Group; L, left; Pt, participant; R, right.

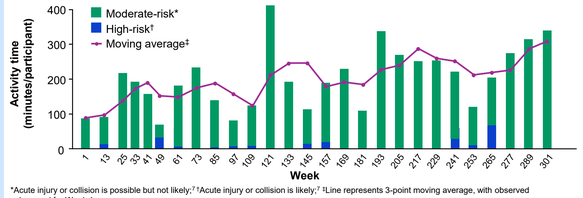
In two participants, despite new MRI findings, joint function was well preserved throughout 6 years

- There were two notable cases with soft tissue/osteochondral changes:
- Participant 8 (aged 8 years at Week 1; **Figure 2**)
  - Synovial hypertrophy/hemosiderin deposition at Week 1, which resolved by Week 145
  - New osteochondral changes in the right ankle at Week 313; with no reported joint bleeds over 6 years and a HJHS of 0
  - The participant was highly active, experiencing 3 right ankle sprains in the year prior to the Week 313 analysis; imaging findings were assessed as inconsistent with hemophilic arthropathy.
- Participant 9 (aged 9 years at Week 1; **Figure 2**)
  - The participant had a history of ITI and a high pre-enrollment annual joint bleeding rate of 8.69. Despite this background, only one joint bleed in the left ankle was reported over 6 years after enrollment (at Day 37).
  - Although new synovial hypertrophy and/or hemosiderin deposition was observed in the left ankle at Week 313, the HJHS improved from 2 at Week 1 to 0 from Week 49 through Week 313, indicating that joint function was preserved.

Time spent engaging in moderate–high-risk activity showed an increasing trend

- The proportion of participants who engaged in moderate-risk exercise remained at a high level after Week 1.
- High-risk exercise was seen being performed throughout the study period, with an increasing trend in minutes per participant spent doing moderate–high-risk activity (**Figure 3**).

Figure 3. Change in average time spent on moderate- and high-risk exercise.



*Acute injury or collision is possible but not likely; †Acute injury or collision is likely; ‡Line represents 3-point moving average, with observed value used for Week 1.

Emicizumab provided sustained bleed protection over 6 years, irrespective of Q2W or Q4W dosing regimen

- The annualized bleeding rate for treated bleeds was reduced following treatment with emicizumab (**Table 3**).
- A total of 50 treated bleeds were reported from 8 participants (42 traumatic, 8 spontaneous); 2 participants had no reports of treated bleeds over the 6-year period.

Table 3. Calculated mean ABR for treated bleeds pre and post emicizumab initiation.

Mean (95% CI) ABR	Timing*	Cohort Q2W (n=4)	Cohort Q4W (n=6)	Cohort All (N=10)
Treated bleeds	**Pre**	10.3 (5.02–18.81)	4.0 (1.08–10.22)	**6.5 (2.52–13.77)**
	Post	1.4 (0.09–6.29)	0.5 (0.00–4.69)	**0.9 (0.01–5.35)**
Treated joint bleeds	**Pre**	2.7 (0.50–8.34)	0.4 (0.00–4.41)	**1.3 (0.07–6.09)**
	Post	0.3 (0.00–4.20)	0.2 (0.00–4.04)	**0.2 (0.00–4.10)**
Treated spontaneous joint bleeds	**Pre**	1.1 (0.04–5.72)	0.4 (0.00–4.41)	**0.7 (0.00–4.95)**
	Post	0.1 (0.00–3.86)	0.1 (0.00–3.86)	**0.1 (0.00–3.86)**

*Pre-emicizumab ABR was based on the 24 weeks prior to study enrollment. ABR, annualized bleeding rate; CI, confidence interval; Q2W, every 2 weeks; Q4W, every 4 weeks.

Conclusions

- This 6-year analysis of the AOZORA study is the longest follow-up for children with HA treated with emicizumab to date.
- In these 10 participants receiving emicizumab prophylaxis (Q2W or Q4W) who transferred from the HOHOEMI study, a favorable safety profile and low bleed rates were observed throughout the 6 years.
- Preserved or improved joint function was also demonstrated, with early prophylaxis specifically associated with no detectable structural MRI progression.
- These findings suggest that initiating emicizumab treatment early, before the onset of joint changes, is important for preserving joint health.
- Data from the final analysis of all 30 participants from AOZORA are anticipated.

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