PB0950

Long-term safety and efficacy of emicizumab for up to >5 years in a phase 1/2 study in patients with severe hemophilia A

Midori Shima[1], Azusa Nagao[2], Masashi Taki[3], Tadashi Matsushita[4], Koichi Oshida[5], Kagehiro Amano[6], Sayaka Nagami[7], Norihiro Okada[7], Keiji Nogami[1]

[1]Department of Pediatrics, Nara Medical University, Kashihara, Japan; [2]Department of Blood Coagulation, Ogikubo Hospital, Tokyo, Japan; [3]Department of Pediatrics, St Marianna University School of Medicine, Kawasaki, Japan; [4]Department of Transfusion Medicine, Nagoya University, Nagoya, Japan; [5]Department of Pediatrics, University of Occupational and Environmental Health, Kitakyushu, Japan; [6]Department of Laboratory Medicine, Tokyo Medical University, Tokyo, Japan; [7]Chugai Pharmaceutical Co., Ltd, Tokyo, Japan.

Objective of Research

To evaluate further long-term safety and efficacy of emicizumab.

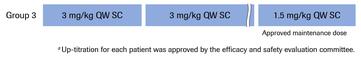
Introduction

- Emicizumab (HEMLIBRA®; Chugai Pharmaceutical Co., Ltd, Tokyo, Japan) is a bispecific antibody mimicking the cofactor function of activated FVIII [1].
- Clinically meaningful efficacy for bleeding prevention was demonstrated with subcutaneous maintenance doses of 1.5 mg/kg every week (QW), 3 mg/kg every 2 weeks (Q2W), and 6 mg/kg every 4 weeks (Q4W) in patients with haemophilia A with or without inhibitors regardless of age [2-6].

Methods

- Eighteen Japanese patients with severe haemophilia A with or without inhibitors aged ≥12 years were enrolled.
- Emicizumab was administered QW at maintenance doses of 0.3, 1, or 3 mg/kg with potential up-titration [Figure 1].
- Finally, all patients were switched to the approved maintenance dose of 1.5 mg/kg QW after Japanese regulatory approval.
- Bleeding episodes that occurred after dose modification were summarized according to the modified dose when calculating annualized bleeding rates (ABRs).

Figure 1. Study design schema of the phase 1 study and phase 1/2 extension study



[a]Up-titration for each patient was approved by the efficacy and safety evaluation committee.

Reference

1. Kitazawa T, Esaki K, Tachibana T, et al. Factor VIIIa-mimetic cofactor activity of a bispecific antibody to factors IX/IXa and X/Xa, emicizumab, depends on its ability to bridge the antigens. Thromb Haemost. 2017;117:1348–1357.
2. Oldenburg J, Mahlangu JN, Kim B, et al. Emicizumab prophylaxis in hemophilia A with inhibitors. N Engl J Med. 2017;377:809–818.
3. Mahlangu J, Oldenburg J, Paz-Priel I, et al. Emicizumab prophylaxis in patients who have hemophilia A without inhibitors. N Engl J Med. 2018;379:811–822.
4. Pipe SW, Shima M, Lehle M, et al. Efficacy, safety, and pharmacokinetics of emicizumab prophylaxis given every 4 weeks in people with haemophilia A (HAVEN 4): a multicentre, open-label, non-randomised phase 3 study. Lancet Haematol. 2019;6:e295–e305.
5. Young G, Liesner R, Chang T, et al. A multicenter, open-label phase 3 study of emicizumab prophylaxis in children with hemophilia A with inhibitors. Blood. 2019;134:2127–2138.
6. Shima M, Nogami K, Nagami S, et al. A multicentre, open-label study of emicizumab given every 2 or 4 weeks in children with severe haemophilia A without inhibitors. Haemophilia. 2019;25:979–987.
7. Shima M, Hanabusa H, Taki M, et al. Factor VIII-mimetic function of humanized bispecific antibody in hemophilia A. N Engl J Med. 2016;374:2044–2053.
8. Callaghan M, Negrier C, Paz-Priel I, et al. Emicizumab treatment is efficacious and well tolerated long term in persons with haemophilia A (PwHA) with or without FVIII inhibitors: Pooled data from four HAVEN studies. Res Pract Thromb Haemost. 2019;3(Suppl 1):116.
9. Gomperts ED. FEIBA safety and tolerability profile. Haemophilia. 2006;12(Suppl 5):14–19.

Abbreviations

FVIII, factor VIII; SC, subcutaneous; AE, adverse event; BPA, bypassing agent; aPCC, activated prothrombin complex concentrate; rFVIIa, recombinant activated factor FVII

Results

Study population

- In the 12-week phase 1 study, 18 patients (11 patients with inhibitors and 7 patients without inhibitors) aged 12–58 years were enrolled in 3 dose groups (6 patients for each).
- Of the 18 patients, 1 patient in the 1 mg/kg QW group discontinued emicizumab administration on Day 29 due to injection site erythema; all the other 17 patients completed the phase 1 study.
- Of those 17 patients, 16 patients were enrolled in the phase 1/2 study (6, 5, and 5 patients in the 0.3, 1, and 3 mg/kg QW groups, respectively).
- Demographics and baseline characteristics of patients have been reported previously [7].
- The medians (ranges) of total treatment duration through the phase 1 study plus its extension phase 1/2 study were 5.2 years (5.2–5.8 years), 4.8 years (29 days–5.3 years), and 4.3 years (85 days–4.8 years) in the 0.3, 1, and 3 mg/kg QW groups, respectively.

Table 1. Adverse events reported in at least 3 patients

- All patients experienced at least 1 AE, and a total of 226 AEs were reported.
- Most AEs (89.4%) were mild and unrelated to emicizumab.
- No thrombotic events including thrombotic microangiopathy or deaths were reported.

	Total (N = 18)	1st year (N = 18)	2nd year (N = 16)	3rd year (N = 16)	4th year (N = 16)	5th year (N = 16)	6th year (N = 8)
Number of patients with ≥1 adverse event, n (%)	18 (100.0)	17 (94.4)	15 (93.8)	15 (93.8)	15 (93.8)	13 (81.3)	3 (37.5)
Number of patients with adverse events (MedDRA preferred term) reported in ≥3 patients, n (%)							
Nasopharyngitis	12 (66.7)	7 (38.9)	3 (18.8)	7 (43.8)	4 (25.0)	5 (31.3)	0 (0.0)
Contusion	9 (50.0)	4 (22.2)	5 (31.3)	5 (31.3)	5 (31.3)	3 (18.8)	1 (12.5)
Dental caries	7 (38.9)	4 (22.2)	3 (18.8)	1 (6.3)	1 (6.3)	0 (0.0)	0 (0.0)
Pharyngitis	5 (27.8)	5 (27.8)	3 (18.8)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Upper respiratory tract infection	5 (27.8)	2 (11.1)	1 (6.3)	2 (12.5)	1 (6.3)	2 (12.5)	0 (0.0)
Excoriation	5 (27.8)	4 (22.2)	0 (0.0)	0 (0.0)	1 (6.3)	1 (6.3)	1 (12.5)
Headache	5 (27.8)	3 (16.7)	2 (12.5)	1 (6.3)	0 (0.0)	0 (0.0)	0 (0.0)
Gastroenteritis	3 (16.7)	0 (0.0)	1 (6.3)	1 (6.3)	1 (6.3)	0 (0.0)	0 (0.0)
Influenza	3 (16.7)	1 (5.6)	0 (0.0)	1 (6.3)	1 (6.3)	0 (0.0)	0 (0.0)
Ligament sprain	3 (16.7)	1 (5.6)	0 (0.0)	1 (6.3)	2 (12.5)	0 (0.0)	1 (12.5)
Tongue injury	3 (16.7)	3 (16.7)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Wound	3 (16.7)	3 (16.7)	0 (0.0)	0 (0.0)	0 (0.0)	1 (6.3)	0 (0.0)
Diarrhoea	3 (16.7)	2 (11.1)	1 (6.3)	1 (6.3)	1 (6.3)	0 (0.0)	0 (0.0)
Haemorrhoids	3 (16.7)	1 (5.6)	0 (0.0)	0 (0.0)	1 (6.3)	1 (6.3)	0 (0.0)
Injection site erythema	3 (16.7)	3 (16.7)	1 (6.3)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Injection site haematoma	3 (16.7)	2 (11.1)	1 (6.3)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Injection site pruritus	3 (16.7)	1 (5.6)	2 (12.5)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Pyrexia	3 (16.7)	0 (0.0)	1 (6.3)	0 (0.0)	1 (6.3)	1 (6.3)	0 (0.0)
Erythema	3 (16.7)	3 (16.7)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Myalgia	3 (16.7)	3 (16.7)	2 (12.5)	0 (0.0)	1 (6.3)	0 (0.0)	0 (0.0)
Rhinitis allergic	3 (16.7)	0 (0.0)	1 (6.3)	1 (6.3)	0 (0.0)	1 (6.3)	0 (0.0)

If the same adverse event was reported more than once in the same patient during each period, it was counted as one.

Figure 2. Individual time courses of factor VIII inhibitor titre

- FVIII inhibitor titres declined in the majority of the 11 patients with inhibitors even without immune tolerance induction therapy.
- A transient spike in inhibitor titres was observed on Day 672 in 1 patient with inhibitors after repeated administrations of aPCC (Days 624–635).
- Two patients without inhibitors at baseline tested positive for inhibitors during emicizumab prophylaxis.
  - One patient tested positive (0.6 BU/mL) at only 1 time point (Day 253) transiently, and the other patient tested positive with low titre values (0.6–1.1 BU/mL) at all time points but 1 from Day 16 until the end of the study on Day 1932 (a negative test result was observed on Day 442).
  - Titre values for this patient never reached the level of a high responder (≥5 BU/mL), and the values did not show any increasing trend throughout the treatment period.

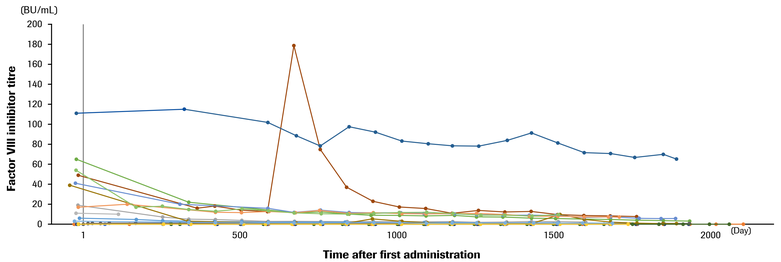


Table 2. Coagulation factor products required for treatment of breakthrough bleeds under emicizumab prophylaxis before and after issuance of guidance

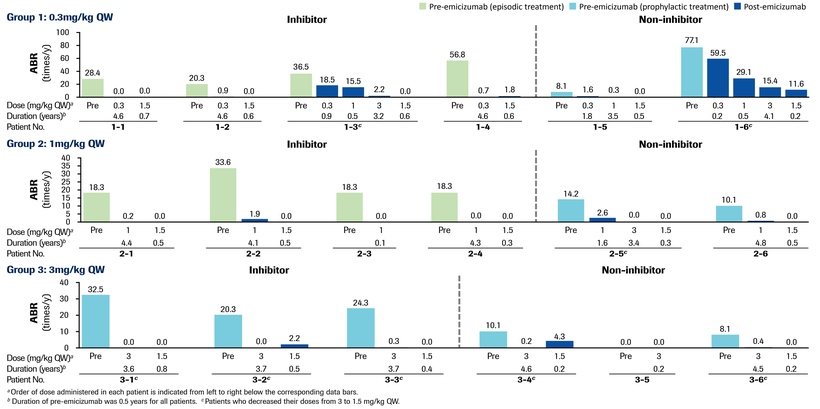
- In November 2016, following the occurrence of thromboembolic events and thrombotic microangiopathy in the HAVEN 1 study [2], the sponsor issued a guidance recommending patients with inhibitors to BPAs, preferably rFVIIa, at the lowest dose expected to achieve haemostasis for breakthrough bleeds.
- Breakthrough bleeds during emicizumab prophylaxis were successfully managed by episodic treatment with either FVIII or BPAs without any related safety events reported.
- FVIII dose per administration did not change after the guidance was issued.
- aPCC and rFVIIa doses per administration decreased.

	Pre-guidance	Post-guidance
FVIII		
Number of patients administered more than once	5	3
Number of administrations	230	218
Dose per administration [IU/kg]	28.9 (12.3–41.6)	27.8 (16.3–41.6)
Number of administrations per bleed	3 (1–41)	2 (1–40)
Cumulative dose per bleed [IU/kg]	73.5 (12.3–1184.2)	65.4 (20.8–1111.1)
aPCC		
Number of patients administered more than once	4	2
Number of administrations	22	6
Dose per administration [U/kg]	84.0 (72.5–101.4)	43.5 (38.5–43.5)
Number of administrations per bleed	1 (1–4)	3 (1–5)
Cumulative dose per bleed [U/kg]	84.0 (72.5–405.8)	1279 (38.5–2174)
rFVIIa		
Number of patients administered more than once	4	3
Number of administrations	54	57
Dose per administration [μg/kg]	252.1 (85.7–252.1)	870 (49.0–975)
Number of administrations per bleed	1 (1–4)	2 (1–54)
Cumulative dose per bleed [μg/kg]	252.1 (85.7–1008.4)	194.9 (49.0–4695.7)

Only treatment for bleeding is included. Data are reported as median (min-max).

Figure 3. Individual annualized bleeding rates for treated bleeds in the periods before and during emicizumab prophylaxis

- In all patients, ABRs for bleeds treated with coagulation factors during emicizumab prophylaxis decreased from pre-emicizumab rates or remained zero, regardless of inhibitor status or usage of prior prophylactic treatment.
- Of the 8 patients who decreased their doses from 3 to 1.5 mg/kg QW, ABRs for treated bleeds decreased in 4, remained at zero in 2, and increased in 2. The 2 patients with increased ABRs each had 1 traumatic treated bleed in the 1.5 mg/kg dosing period.



[a]Order of dose administered in each patient is indicated from left to right below the corresponding data bars.
[b] Duration of pre-emicizumab was 0.5 years for all patients. [c]Patients who decreased their doses from 3 to 1.5 mg/kg QW.

Table 3. Median annualized bleeding rates for treated bleeds by bleeding site

Bleeding site	All sites		Joint		Muscle		Subcutaneous		Others	
Dosing regimen	Before emicizumab	During emicizumab	Before emicizumab	During emicizumab	Before emicizumab	During emicizumab	Before emicizumab	During emicizumab	Before emicizumab	During emicizumab
0.3 mg/kg QW SC (N=6)	32.46 (8.1–77.1)	1.25 (0.0–59.5)	27.39 (8.1–69.0)	0.87 (0.0–59.5)	1.01 (0.0–6.1)	0.00 (0.0–9.2)	0.00 (0.0–4.1)	0.00 (0.0–0.0)	3.04 (0.0–8.1)	0.44 (0.0–2.3)
1 mg/kg QW SC (N=9)	18.26 (8.1–77.1)	0.83 (0.0–29.1)	16.23 (8.1–69.0)	0.41 (0.0–27.0)	2.03 (0.0–20.3)	0.00 (0.0–5.8)	0.00 (0.0–4.1)	0.00 (0.0–0.6)	2.03 (0.0–8.1)	0.00 (0.0–7.7)
3 mg/kg QW SC (N=9)	20.29 (0.0–77.1)	0.22 (0.0–15.4)	12.17 (0.0–69.0)	0.00 (0.0–14.4)	2.03 (0.0–12.2)	0.00 (0.0–3.2)	0.00 (0.0–10.1)	0.00 (0.0–0.3)	0.00 (0.0–8.1)	0.00 (0.0–0.4)
1.5 mg/kg QW SC (N=16)	20.29 (8.1–77.1)	0.00 (0.0–11.6)	17.25 (2.0–69.0)	0.00 (0.0–11.6)	1.01 (0.0–20.3)	0.00 (0.0–0.0)	0.00 (0.0–10.1)	0.00 (0.0–0.0)	1.01 (0.0–8.1)	0.00 (0.0–2.2)

The values in the table show the median and range. Bleeds that occurred after dose modification were summarized according to the modified dose.

Conclusion

Favourable safety and efficacy of emicizumab was maintained for up to >5 years in patients with severe haemophilia A.

- In the phase 1 study and phase 1/2 extension study, no clinically relevant safety concerns were indicated; most AEs were mild and unrelated to emicizumab.
- ABRs for treated bleeds decreased from rates in the pre-emicizumab period or remained zero in all patients.
  - ✓ After doses were changed from 3 to 1.5 mg/kg, ABRs decreased or remained zero in most patients.
  - ✓ Robust evaluation of the long-term effect on ABRs is difficult since ABRs can be affected by dose modification.
  - ✓ However, a gradual downward trend on ABRs over about 2 years was reported in phase 3 studies [8], which supported the validity of our finding of the long-term effect.
- The decreasing trend seen in FVIII inhibitor titres over time may be due to reduced use of aPCC involving trace amounts of FVIII [9] for breakthrough bleeds.
  - ✓ The inhibitor titres in the patient with sustained low titres were considered not clinically relevant, since breakthrough bleeds were successfully managed with FVIII, the dose of which was lower than that used in the pre-emicizumab period.

Acknowledgements

Editorial assistance for this poster was provided by Tomomi Niino of Chugai Pharmaceutical Co., Ltd. and Asahi C&I Co., Ltd., and was funded by Chugai Pharmaceutical Co., Ltd.

Disclosures

This work was supported by Chugai Pharmaceutical Co., Ltd (research funding [M.S., M.T., K.O., K.A., K.N.]; honoraria [M.S., A.N., M.T., T.M., K.O., K.A., K.N.], advisory committee/consultancy [M.S., M.T., T.M., K.A., K.N.]; employment [S.N., N.O., S.M.]). M.S. and K.N. are advisory committee members for F. Hoffmann-La Roche Ltd.; M.S. and K.N. are listed on patents for anti-FIXa/X bispecific antibodies.