Accepted Manuscript

Submission Date: 2024-02-21
Accepted Date: 2024-08-04
Accepted Manuscript online: 2024-08-12

Thrombosis and Haemostasis

Final Analysis Results from the AGEHA Study: Emicizumab Prophylaxis for Acquired Hemophilia A with or without Immunosuppressive Therapy

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DOI: 10.1055/a-2384-3585

Please cite this article as: Shima M, Suzuki N, Nishikii H et al. Final Analysis Results from the AGEHA Study: Emicizumab Prophylaxis for Acquired Hemophilia A with or without Immunosuppressive Therapy. Thromb Haemost 2024. doi: 10.1055/a-2384-3585

Conflict of Interest: M. Shima has received research funding from Chugai Pharmaceutical Co., Ltd., CSL Behring, and Takeda; has received honoraria from Bayer, Chugai Pharmaceutical Co., Ltd., CSL Behring, Fujimoto Seiyaku, Sanofi, Novo Nordisk, Pfizer, and Takeda; holds patents with Chugai Pharmaceutical Co., Ltd.; and has participated on a data safety monitoring board or advisory board for Chugai Pharmaceutical Co., Ltd., Fujimoto Seiyaku, KYORIN Pharmaceutical Co., Ltd., Novo Nordisk, and Pfizer. N.S. has received honoraria from Bayer, Chugai Pharmaceutical Co., Ltd., CSL Behring, Japan Blood Products Organization, KM Biologics, Novo Nordisk, Pfizer, Sanofi, and Takeda. K.A. has received research funding from KM Biologics; has received consulting fees from Chugai Pharmaceutical Co., Ltd.; has received honoraria from Bayer, Chugai Pharmaceutical Co., Ltd., CSL Behring, Fujimoto Pharmaceutical Corporation, Japan Blood Products Organization, KM Biologics, Novo Nordisk, Pfizer, Sanofi, and Takeda; has participated on a data safety monitoring board or advisory board for Chugai Pharmaceutical Co., Ltd.; and is belong to endowed chair for CSL Behring. Y.O. has received consulting fees and honoraria from Chugai Pharmaceutical Co., Ltd. R.K. and R.O. are employees of Chugai Pharmaceutical Co., Ltd. K.Y. is an employee of Chugai Pharmaceutical Co., Ltd. and an inventor of patents related to anti-activated FIX/FX bispecific antibodies. N.M. is an employee of Chugai Pharmaceutical Co., Ltd. and has stocks of Chugai Pharmaceutical Co., Ltd. E.S. has received research funding from Eisai; has received honoraria from Janssen, Novartis, Pfizer, Sanofi and Takeda and has leadership or fiduciary role in other board, society, committee or advocacy group (unpaid) for Japan Adult Leukemia Study Group and Japanese Society of Myeloma. S.H. has received research funding from Chugai Pharmaceutical Co., Ltd. and has received honoraria from Bayer, Chugai Pharmaceutical Co., Ltd., CSL Behring, Novo Nordisk, Sanofi, and Takeda. K.N. has received research funding from Bayer, Chugai Pharmaceutical Co., Ltd., CSL Behring, KM Biologics, Novo Nordisk, Sanofi, and Takeda; has received consulting fees from Chugai Pharmaceutical Co., Ltd.; and has received honoraria from Bayer, Chugai Pharmaceutical Co., Ltd., CSL Behring, KM Biologics, Novo Nordisk, Sanofi, and Takeda. The remaining authors have no conflicts of interest to declare.

This study was supported by Chugai Pharmaceutical (http://dx.doi.org/10.13039/100010795)

Trial registration: jRCT2080225056, Japan Primary Registries Network (http://rctportal.niph.go.jp), Prospective, Multicenter, Open-label, Non-randomized, Phase III Study

Abstract:
Background: Primary analysis of the phase III AGEHA study suggested a favorable benefit-risk profile for emicizumab prophylaxis in patients with acquired hemophilia A (PwAHA); however, only patients undergoing immunosuppressive therapy (IST) (Cohort 1) were included.
Objectives: To present final analysis results of AGEHA, including data on IST-ineligible patients (Cohort 2) and on long-term prophylaxis with emicizumab.
Methods: For patients in both Cohorts 1 and 2, emicizumab was administered subcutaneously at 6 mg/kg on Day 1, 3

mg/kg on Day 2, and 1.5 mg/kg once weekly from Day 8 onward.
Results: Twelve patients (Cohort 1) and 2 patients (Cohort 2) were enrolled. Duration of emicizumab treatment was 8–639 days (median: 44.5 days) in Cohort 1 and 64 and 450 days in Cohort 2. In both cohorts, no major bleeds were observed after initial emicizumab administration. Six patients started their first rehabilitation sessions during emicizumab treatment and no rehabilitation-related bleeds occurred. Twenty-three surgeries were performed under emicizumab prophylaxis and there were no bleeds related to surgeries. Although asymptomatic deep vein thrombosis was reported in 1 patient in the primary analysis, no other thrombotic events occurred thereafter. Two patients developed anti-emicizumab antibodies, 1 of whom showed accelerated emicizumab clearance. Tailored IST approaches (delayed initiation, no use, or reduced dose) were successfully executed in 3 patients undergoing emicizumab prophylaxis.
Conclusions: These results suggest that emicizumab prophylaxis has a favorable benefit–risk profile in PwAHA regardless of eligibility for IST.

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SUPPORTING INFORMATION

Supplemental Method S1. Study design and patients

This study was conducted at 17 hospitals in Japan.

PwAHA who were aged ≥18 years, had FVIII activity of <50 IU/dL and FVIII inhibitor titer of ≥0.6 BU/mL (or ≥1.0 BU/mL if the detection limit was 1.0 BU/mL) measured at the study site within 7 days before enrollment, and had a history of bleeds and/or bleeding symptoms related to AHA with or without hemostatic treatment were eligible to be enrolled in this study. A documented history of bleeding episodes and treatment with coagulation factor products within 24 weeks before enrollment had to be available. Patients who had bleeding disorders other than AHA, had received nonprophylactic treatment for thromboembolic disease within 12 months before enrollment, were at a high risk of thrombotic microangiopathy, or were pregnant or breastfeeding were excluded.

IST was to be administered according to the available treatment guidelines for AHA, in which prednisolone monotherapy or combination therapy with prednisolone plus cyclophosphamide is positioned as the first-line treatment option. Patients who were ineligible for IST at enrollment in Cohort 2 were allowed to start IST during the study. No prophylactic use of coagulation factor products was allowed. For hemostasis, rFVIIa was recommended, with instructions to administer no more than 90 μg/kg as an initial dose to minimize the risk of thromboembolic events and thrombotic microangiopathy. If aPCC and pd-FVIIa/FX were the only available bypass agents, treatment was permitted to start with them at the lowest dose expected to achieve hemostasis (eg, initial dose of no more than 50 units/kg in the case of aPCC and that of 60 μg/kg in the case of pd-FVIIa/FX).

Supplemental Method S2. Endpoints

AGEHA was designed as a descriptive study with no primary or secondary endpoints defined formally. To comprehensively explore potential benefits from emicizumab, a variety of efficacy endpoints, including the number of bleeds, usage of coagulation factor products and transfusion, hospitalization period, and time to the first rehabilitation session, were investigated. Eastern Cooperative Oncology Group Performance Status[S1] was also investigated because a poor performance status has been suggested to be a prognostic factor in AHA[3].

Any bleeding event that occurred during a predefined evaluation period, regardless of the severity or necessity of treatment, was recorded as an “all bleed.” Among them, with reference to a previous report[S2], a bleed satisfying any of the following conditions was judged as a “major bleed” by an investigator: (1) life-threatening, (2) symptomatic in an important region or major organ (eg, intracranial, intraspinal, intraocular, retroperitoneal, intraarticular, or pericardiac bleeds, or muscle bleeds associated with compartment syndrome), or (3) associated with a decrease of ≥2 g/dL in hemoglobin level or necessitating transfusion of ≥2 units of whole blood or packed red cells.

In PwAHA, it was considered difficult to determine how multiple bleeding symptoms should be counted as a “treated bleed”; therefore, we employed the standardized definition used in previous studies in PwCHA[6, S3-7]. Regardless of the bleeding severity, a bleed was counted as a “treated bleed” if it was directly followed by the use of a coagulation factor product indicated for “treatment for bleed” without an

intervening bleed. Even a major bleed could be classified as a “nontreated bleed” if it did not meet this definition.

The safety endpoints included the incidence of AEs, serious AEs, thromboembolic events, thrombotic microangiopathy, injection site reactions, and abnormal laboratory values. D-dimer and prothrombin fragment 1+2 were measured as hypercoagulation-related markers. ADAs were measured using an enzyme-linked immunosorbent assay, and the *in vitro* neutralizing capacity of ADAs was measured using a chromogenic substrate assay[19].

The plasma emicizumab concentrations were measured using an enzyme-linked immunosorbent assay[S8]. FVIII activity was measured by a one-stage clotting assay with emicizumab in plasma samples neutralized by adding 2 anti-emicizumab idiotype monoclonal antibodies *ex vivo* (OSAwEN)[S9]. OSAwEN was employed to guide the completion of emicizumab dosing given the real-world setting in Japan where this study was conducted and no chromogenic substrate assay using bovine coagulation factors is commercially available. In this article, FVIII activity refers to the results derived by OSAwEN unless otherwise stated. FVIII inhibitors were measured by a clotting time–based Bethesda assay with *ex vivo* emicizumab neutralization (OSAwEN-based Bethesda assay) [S9]. Determination of FVIII inhibitor titers was standardized by employing a minimum dilution ratio to provide residual FVIII activity of >50% to <75% of control in the assay without identifying the inhibitor type.

Supplemental Method S3. Definition of the Evaluation Periods

Pre-treatment period: The start of the period was defined as the date of AHA diagnosis or the beginning date of first bleed before first emicizumab administration,

whichever was earlier. In the case that the selected date was earlier than 24 weeks prior to the date of first emicizumab administration, the start date was defined as 24 weeks prior to the date of first emicizumab administration. The end of the period was defined as the date of first emicizumab administration.

On-treatment period: The start of the period was defined as the date of first emicizumab administration. The end of the period was defined as the cutoff date or the date of completion or discontinuation of emicizumab administration, whichever was earlier.

Safety follow-up period: The start of the period was defined as the day following the date of completion or discontinuation of emicizumab administration. The end of the period was defined as the cutoff date, 24 weeks after the date of completion or discontinuation of emicizumab administration, or the date of discontinuation of the study, whichever was earlier.

Supplemental Method S4. Derivation of Annualized Bleeding Rates

ABRs were calculated to correct for the differences in the lengths of an evaluation period among patients. Calculated ABRs were derived as 365.25 times the number of bleeding events that occurred in an evaluation period divided by the number of days in the corresponding evaluation period for each patient and each bleed definition. Model-based ABRs were also estimated using a negative binomial regression model with an offset for the annualized length of an evaluation period, as in previous studies in PwCHA[6, S3-7].

Supplemental Result S1. Case presentations

Delayed IST: Patient 13, who became able to undergo IST after the start of emicizumab

Patient 13 was an 82-year-old woman with mild level of liver impairment (ULN < total bilirubin ≤ 1.5*ULN and aspartate aminotransferase > ULN) and renal impairment (60 ≤ CLCr < 90 mL/min). The patient diagnosed with AHA 6 days before enrollment (**Table 1**). The patient was judged ineligible for intensive corticosteroid therapy owing to her uncontrolled diabetes at enrollment. After her diabetes was effectively managed by adjustment of the insulin preparation, IST was able to be initiated 4 days after her initial emicizumab administration. Owing to the effect of the IST, FVIII activity was restored to more than 50 IU/dL, and emicizumab treatment was completed on Day 64. During the safety follow-up period, FVIII inhibitors were detected and FVIII activity decreased again in association with IST tapering, and therefore intravenous cyclophosphamide administration was started. After the last visit of the study, the patient received rituximab and her AHA resolved. Two active major bleeds at the time of initial emicizumab administration stopped within the following 3 days, which was before the start of IST. No new major or new treated bleeds occurred after initial emicizumab administration.

No IST: Patient 14, who did not tolerate IST

Patient 14 was a 59-year-old woman with moderate level of renal impairment (30 ≤ CLCr < 60 mL/min) and had Hashimoto's disease and multiple myeloma as underlying diseases for AHA. The patient diagnosed with AHA 1009 days before enrollment and had been receiving a prophylactic regimen of aPCC (3000 units every 2 or 3 days) for the last 24 weeks prior to enrollment (**Table 1**). This patient

was judged ineligible for IST because past ISTs had not been effective for AHA for a long time. Additionally, IST was almost contraindicated due to a complication of infections associated with osteonecrosis of the jaw. Therefore, no IST for AHA was introduced during the study except for transient prednisolone use for the treatment of urticaria. At the time of initial emicizumab administration, there was 1 active non-major bleed that had started on Day −3 and stopped on Day 15 (the end day of the bleed was missing due to the nature of the subcutaneous bleed, and the date was imputed by using the last day of the recorded month). After initial emicizumab administration, no major or treated bleeds occurred for 450 days, and efficacious bleeding control was sustained after switching from aPCC prophylaxis to emicizumab prophylaxis.

Low-dose IST: Patient 04, for whom the goal of AHA remission was given up owing to insufficient IST response and in whom the dose of IST was reduced to avoid side effects of IST

Patient 04 was an 88-year-old woman diagnosed with AHA 419 days before enrollment. Although this patient had been receiving IST for more than 1 year before enrollment, remission of AHA had not been achieved. Since efficacious bleeding control was obtained under emicizumab prophylaxis, the dose of prednisolone was reduced from 20 to 6 mg/day to minimize side effects. During the pre-treatment period, 12 non-major bleeds were reported, 11 of which were spontaneous bleeds. After starting emicizumab, 27 non-major bleeds developed, but 26 of those were traumatic. Throughout the pre- and on-treatment periods, the patient used only a single dose of rFVIIa for a traumatic bleed from a cat bite wound requiring suturing

that occurred on Day 587. Despite an increase in FVIII inhibitor levels while tapering prednisolone, bleeding was well controlled by emicizumab and the frequency of bleeding gradually decreased during the latter half of the emicizumab treatment period. Consequently, the patient continued emicizumab until the end of this study, a total of 639 days.

These case presentations of Patient 13, Patient 14, and Patient 04 are also shown in **Supplemental Figure S2**.

Supplemental Table S1. Summary of patient disposition at the primary and final analyses

	At primary analysis		At final analysis	
	Cohort 1	Cohort 2	Cohort 1	Cohort 2
No. of patients treated with emicizumab	12	0	12	2
Duration of treatment period (days)	44.5 (8-208) median (range)	—	44.5 (8-639) median (range)	64, 450
No. of patients who met the completion criteria	11	—	11	1
No. of patients who completed the safety follow-up period	2	—	9[a]	1
Duration of the safety follow-up period (days)	116.0 (14–170)	—	168 (14-171)	174

	median (range)		median (range)	

[a] Excluded 2 patients who were withdrawn from the study after completing emicizumab administration because of death (exacerbation of chronic kidney disease) and patient's withdrawal of consent.

Supplemental Table S2. Endoscopic procedures with high bleeding risk

Patient ID	Type of surgery	Major/ Minor	Date of surgery (Study day)	FVIII activity (IU/dL) (Study day[a])	Emicizumab completion status at the time of surgery	Using coagulation factor product at the time of surgery	Bleeding related to surgery
03	Clipping hemostasis surgery of large intestine	Minor	17	< 1.0 (Day 15)	Ongoing	Yes[b]	No
03	Clipping hemostasis surgery of large intestine	Minor	29	11.6 (Day 29)	Ongoing	Yes[b]	No
10	Endoscopic papillotomy	Major	29	8.6 (Day 29)	Ongoing	No	No
10	Endoscopic biliary	Minor	29	8.6 (Day	Ongoing	No	No

	dilation			29)			
10	Cauterization	Minor	36	14.9 (Day 36)	Ongoing	Yes[b]	No
11	Cold snare polypectomy	Minor	22	20.5 (Day 22)	Ongoing	No	No

[a]Same day as the day of surgery or nearest sampling point.

[b]Coagulation factor products were administered for managing bleeds that occurred before surgery and were unrelated to surgery.

FVIII, factor VIII; IU, international units.

Supplemental Table S3. Coagulation monitoring under IST

Monitoring	On-treatment period	24-week safety follow-up period
FVIII activity	Once weekly	Once weekly (Safety follow-up Week 1-5)
FVIII inhibitor		Once every 4 weeks (Safety follow-up Week 5-25)

FVIII, factor VIII.

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Supplemental Figure S1. Study scheme. The study was completed when the 2 patients who were still on emicizumab treatment were switched to a commercial emicizumab product. BU, Bethesda units; FVIII, factor VIII; IST, immunosuppressive therapy; IU, international units; LPLV, last patient last visit; PwAHA, patients with acquired hemophilia A.

Supplemental Figure S2. Case presentations. These figures show 1) Status of immunosuppressive therapy, 2) Duration of bleeds (each bleeding event), 3) Administration of coagulation factor products or transfusions, and 4) Time courses of FVIII activity and FVIII inhibitor. aPCC, activated prothrombin complex concentrate; BU, Bethesda Units; FFP, fresh frozen plasma; FVIII, factor VIII; IU, international units; PRC, packed red cells; rFVIIa, recombinant activated factor VII.

A) Patient 13

B) Patient 14

C) Patient 04

Final Analysis Results from the AGEHA Study: Emicizumab Prophylaxis for Acquired Hemophilia A with or without Immunosuppressive Therapy

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Abstract

Background: Primary analysis of the phase III AGEHA study suggested a favorable benefit-risk profile for emicizumab prophylaxis in patients with acquired hemophilia A (PwAHA); however, only patients undergoing immunosuppressive therapy (IST) (Cohort 1) were included.

Objectives: To present final analysis results of AGEHA, including data on IST-ineligible patients (Cohort 2) and on long-term prophylaxis with emicizumab.

Methods: For patients in both Cohorts 1 and 2, emicizumab was administered subcutaneously at 6 mg/kg on Day 1, 3 mg/kg on Day 2, and 1.5 mg/kg once weekly from Day 8 onward.

Results: Twelve patients (Cohort 1) and 2 patients (Cohort 2) were enrolled. Duration of emicizumab treatment was 8–639 days (median: 44.5 days) in Cohort 1 and 64 and 450 days in Cohort 2. In both cohorts, no major bleeds were observed after initial emicizumab administration. Six patients started their first rehabilitation sessions during emicizumab treatment and no rehabilitation-related bleeds occurred. Twenty-three surgeries were performed under emicizumab prophylaxis and there

were no bleeds related to surgeries. Although asymptomatic deep vein thrombosis was reported in 1 patient in the primary analysis, no other thrombotic events occurred thereafter. Two patients developed anti-emicizumab antibodies, 1 of whom showed accelerated emicizumab clearance. Tailored IST approaches (delayed initiation, no use, or reduced dose) were successfully executed in 3 patients undergoing emicizumab prophylaxis.

Conclusions: These results suggest that emicizumab prophylaxis has a favorable benefit–risk profile in PwAHA regardless of eligibility for IST.

KEYWORDS

Factor VIII deficiency, acquired; Long-Term Care; Immunosuppressive therapy; Rehabilitation; Surgery.

INTRODUCTION

Acquired hemophilia A (AHA) is a disorder involving sudden onset of serious bleeding episodes caused by the development of autoantibodies (called “inhibitors”) against coagulation factor VIII (FVIII). Patients with acquired hemophilia A (PwAHA) remain at a high risk of bleeding until remission of AHA is achieved.[1]

For hemostatic treatment, bypassing agents (e.g., recombinant activated factor VII [rFVIIa] or activated prothrombin complex concentrate [aPCC]) or recombinant porcine FVIII (rpFVIII) are used episodically.[2] However, although bypassing agents can be effective, there are cases where sufficient hemostatic effect cannot be

achieved, necessitating multiple intravenous administrations at short intervals because of the short half-life of these agents. And although rpFVIII can also be an effective treatment option if the patient's FVIII inhibitor does not cross-react with rpFVIII, *de novo* anti-rpFVIII antibodies are often induced, which can render rpFVIII treatment ineffective. Prophylactic treatment with bypassing agents has not been established as a standard of care for PwAHA,[2] but prophylactic treatment would be an optimal treatment option in some cases because serious bleeding often occurs even in the post-acute phase, and patients at risk of such bleeding may require bed rest, with prolonged bed rest potentially increasing the risk of poor prognosis. Effective prophylaxis may also allow an earlier start to rehabilitation, improving the QoL and prognosis of PwAHA.

For the treatment of AHA, it is recommended to initiate immunosuppressive therapy (IST) immediately after diagnosis to eliminate the FVIII inhibitors.[2] In general, as the standard of care for AHA, IST is started as prednisolone 1 mg/kg/day or as a combination of prednisolone plus cyclophosphamide. Although most patients achieve remission of AHA by IST, there are a certain number of patients who remain persistently refractory to IST. In addition, fatal or severe infections that occur due to IST are among the primary causes of death in PwAHA (4.2-16%).[3,4] Furthermore, patients at particularly high risk of infection (e.g., patients with autoimmune disease already receiving long-term IST, bedridden elderly patients, and diabetic patients) are not able to tolerate high doses of IST. Therefore, if bleeding risks can be appropriately controlled by effective prophylactic treatment, then tailored IST approaches such as dose reduction, no use, or delayed initiation of IST based on each patient’s specific condition could be considered.

Emicizumab is a recombinant, humanized, bispecific monoclonal antibody designed to bridge activated factor IX and factor X (FX), and exerts cofactor activity substituting for activated FVIII regardless of FVIII inhibitor status.[5] Phase III studies of emicizumab in patients with congenital hemophilia A (PwCHA) showed a clinically meaningful prophylactic effect of emicizumab irrespective of FVIII inhibitors,[6] and real-world experience with usage of emicizumab in PwCHA is accumulating.[7] Given that the pathogenesis of AHA is the emergence of FVIII inhibitors, evidence from non-clinical studies[8,9] suggested that emicizumab could be expected to become a treatment option for AHA.

To evaluate the benefit–risk profile of emicizumab prophylaxis with a new dosing regimen and completion criteria in PwAHA, we conducted a first prospective, multicenter, open-label phase III study (AGEHA). The previously reported primary analysis results from AGEHA suggested that emicizumab prophylaxis had a favorable benefit-risk profile in PwAHA; however, that analysis included only patients who had already started IST.[10] Results of a recent prospective clinical trial investigating the prophylactic effect of emicizumab without IST in 47 PwAHA regardless of their eligibility for IST suggested the efficacy of emicizumab prophylaxis for 12 weeks with delayed initiation of IST.[11] The final analysis of AGEHA reported here includes an additional 2 patients who were ineligible for IST to obtain data from a sub-population for whom a tailored IST approach would be the most desired in clinical practice. In addition, at the primary analysis, most patients who had met the completion criteria had not completed the 24-weeks safety follow-up period during which emicizumab is remaining in plasma after partial remission of AHA (i.e. FVIII activity >50 IU/dL). We report herein pharmacokinetics, efficacy and safety data of emicizumab prophylaxis from the 14 patients in total from the entire

study period including full data on the 24-week safety follow-up period as well as long-term emicizumab prophylaxis data exceeding 1 year. Furthermore, results of rehabilitation, performance status, and perioperative bleeding management are also reported.

METHODS

Study design and patients

AGEHA was a prospective, multicenter, open-label, non-randomized, phase III study investigating the safety, efficacy, and pharmacokinetics of emicizumab in PwAHA. AGEHA consisted of Cohort 1 (patients already undergoing or scheduled to immediately undergo IST) and Cohort 2 (patients for whom it was considered difficult to undergo IST) (**Supplemental Figure S1**). Patients are numbered consecutively from Cohort 1 into Cohort 2. The eligibility criteria, requirement for concomitant therapies, and study location are described in **Supplemental Method S1**.

This study was conducted from June 2020 (first patient first dose) to August 2022 (last patient last visit) in accordance with the International Conference on Harmonisation Guideline for Good Clinical Practice. The study protocol was approved by the institutional review board at each study site, and all patients and/or their legally authorized representatives provided written informed consent. This study is registered at https://jrct.niph.go.jp/ (JapicCTI-205151/jRCT2080225056).

Emicizumab was administered subcutaneously at 6 mg/kg on Day 1, 3 mg/kg on Day 2, and 1.5 mg/kg once weekly from Day 8 onward (AGEHA protocol), and the study protocol required weekly coagulation monitoring (FVIII activity and FVIII inhibitors). After the investigator confirmed that both of following criteria for completion of

emicizumab administration had been met: (1) FVIII activity measured in the absence of interference of emicizumab and coagulation factor products had been confirmed to exceed 50 IU/dL and (2) more than 72 hours had passed since the last use of coagulation factor products for the last bleed requiring treatment, patients transitioned to a 24-week safety follow-up period.

Endpoints

In addition to the endpoints described in **Supplemental Method S2**, we also conducted an analysis of bleeding management on surgery (including procedures unless otherwise noted). Surgery data, perioperative use of coagulation factor products, and bleeding data were reported by the investigators. Surgery performed during the emicizumab treatment period and the safety follow-up period was included in our analysis. Surgery was classified as “major” or “minor” based on invasiveness: surgery that involved entering a body cavity, opening a fascial surface, or removing an organ was classified as major; other surgery was classified as minor.[12] Endoscopic procedures were classified according to the risk of bleeding referring to the guidelines for the management of antithrombotic agents for endoscopic procedures.[13] In the analysis of safety upon restoration of endogenous FVIII activity, the cutoff level defining FVIII activity overshoot was set as 150 IU/dL as previously reported.[14]

Statistical analysis

AGEHA was ended when all patients completed the safety follow-up period, were withdrawn from the study, were lost to follow-up, or switched to a commercial

emicizumab product (only for patients still on emicizumab), whichever was later. After the last visit of the last patient on August 9, 2022 (end of study), the final analysis was performed (**Supplemental Figure S1**).

Detailed definitions of the three evaluation periods (the pre-treatment period [observation period before initial emicizumab administration], the on-treatment period [observation period during emicizumab treatment], and the safety follow-up period [follow-up period after completing emicizumab administration]) and derivation of calculated annualized bleeding rate (ABR) are described in **Supplemental Method S3 and S4**, respectively.

The start of a bleed was defined as the date/time of the initial appearance of the bleed regardless of bleed type. The end of a bleed was defined as the time of disappearance of symptoms or 72 hours after the last use of coagulation factor products for the bleeding event, whichever was later.

SAS software version 9.4 (SAS Institute Inc., Cary, NC, USA) was used for the analyses.

RESULTS

Patient demographics

Fourteen patients were included in the final analysis: 12 patients in Cohort 1 and 2 patients in Cohort 2. No patient was excluded from any of the analyses. Patient demographics are provided in **Table 1**.

Patient disposition and emicizumab treatment

At the time of the primary analysis, 11 of the 12 patients in Cohort 1 had met the emicizumab completion criteria, 8 of the 11 were still under observation in the 24-week safety follow-up period. In this final analysis, 7 of those 8 patients had completed the safety follow-up period and the 1 remaining patient withdrew consent on Day 246 during the safety follow-up period. Among the 2 patients in Cohort 2, 1 had completed emicizumab administration and the safety follow-up period. Patient 04 in Cohort 1 and Patient 14 in Cohort 2 had not met the emicizumab completion criteria by the end of the study and continued on long-term emicizumab prophylaxis for the maximum duration of treatment in each cohort. Both patients were transitioned to a commercial emicizumab product after the end of the study (**Supplemental Figure S1**).

Overall, the duration of emicizumab treatment in the study ranged from 8 to 639 days (median: 44.5 days) in Cohort 1, and was 64 and 450 days in the 2 patients in Cohort 2. The patient disposition summary at the primary analysis and at the final analysis is shown in **Supplemental Table S1**.

Immunosuppressive therapies

All 12 patients in Cohort 1 were receiving prednisolone at around 1 mg/kg or less on Day 1 (**Table 2**). In addition, 3 received cyclophosphamide and 1 received cyclosporin during the study. In 9 of the 11 patients in Cohort 1 who had met the emicizumab completion criteria, the intensity of IST was decreased from Day 1 until the end of the safety follow-up period or the date of study discontinuation. The dosage of prednisolone in Patient 04 in Cohort 1 who did not meet the emicizumab

completion criteria was also tapered throughout the study to avoid serious side effects of IST.

Patient 13 in Cohort 2 started IST 4 days after initial emicizumab administration and finally met the emicizumab completion criteria. For this patient, it was deemed challenging to commence IST at enrollment owing to poor control of diabetes; however, once insulin treatment had improved glycemic control, it was subsequently determined that initiating IST was feasible after initiation of emicizumab treatment. Patient 14 in Cohort 2 have not been received any ISTs for AHA throughout the study.

Pharmacokinetics

In an overall assessment through Cohorts 1 and 2, the mean plasma emicizumab concentration exceeded 30 μg/mL by 4 days after starting emicizumab treatment and was maintained at steady-state trough thereafter, ranging from 38.2 to 40.9 μg/mL during 1 to 4 weeks after starting emicizumab treatment (n = 11 to 14). There was no clear difference between Cohorts 1 and 2 in the time course of plasma emicizumab concentration. The mean (standard deviation) half-life after completing emicizumab administration was 34.2 (14.3) days (n = 11).

Prophylactic effect for bleeds

No major bleeds occurred in either cohort after starting emicizumab treatment. Nine of 12 patients (75%) in Cohort 1 and both patients (100%) in Cohort 2 had no treated bleeds during the on-treatment period, and no patient in either cohort had any

treated bleeds during the safety follow-up period (**Table 3**). For Cohort 1, only 1 patient experienced a treated bleed after the cutoff date of the primary analysis; it occurred on Day 587 (on-treatment period), and hemostasis was confirmed on Day 618. This was a traumatic bleed caused by a cat bite; it was treated by suturing and a single dose of rFVIIa but judged as non-major by the investigator. Among 5 of 14 patients in the two cohorts who did not experience any major or treated bleeds during the pre-treatment period, the number of all bleeds was zero or ABR of all bleeds decreased after starting emicizumab treatment.

Comparing the bleeding rates on a population level, the mean calculated annualized bleeding rates of major bleeds, treated bleeds, and all bleeds for the on-treatment period were, respectively, 0.0, 3.2, and 5.3 in Cohort 1 and 0.0, 0.0, and 3.7 in Cohort 2, while those for the pre-treatment period were 66.4, 35.6, and 77.0 in Cohort 1 and 15.9, 17.0, and 26.0 in Cohort 2 (**Figure 1**).

Rehabilitation

Of the 14 patients in the two cohorts, 6 patients (42.9%) could start their first rehabilitation sessions 11 days (median) after starting emicizumab treatment, all of which were conducted during hospitalization and before the emicizumab completion criteria had been met (**Table 4**). The rehabilitation sessions for 5 of these 6 patients comprised disuse syndrome rehabilitation, prevention of disuse syndrome, occupational therapy, physical therapy, or range of motion, all of which were not limited to rehabilitation to improve contractures at bleeding sites. The remaining patient conducted stretching and relaxation of left calf where bleeding had occurred. The median (range) FVIII activity on the day of first rehabilitation session or nearest

sampling point before it was 2.0 IU/dL (<1.0-11.9). In 4 out of the 6 patients, rehabilitation sessions were started after hemostasis of all active bleeds had been confirmed. There was no clear relationship between the timing of starting rehabilitation and restoration of endogenous FVIII activity levels. Regardless of the FVIII activity level when the rehabilitation sessions began, no rehabilitation-related bleeds occurred in any patient.

Eastern Cooperative Oncology Group Performance Status

In Cohort 1, 2 patients had Eastern Cooperative Oncology Group Performance Status (ECOG-PS) scores 0 (fully active) at baseline, at the date of emicizumab completion, and at the last observation (**Table 5**). Among the other 10 patients, ECOG-PS scores for 4 patients (40.0%) improved by 1 from baseline to the date of emicizumab completion and ECOG-PS scores for 7 patients (70.0%) improved by 1 from baseline to the last observation. In Cohort 2, the ECOG-PS score for 1 patient improved by 2 from baseline to the date of emicizumab completion. For the remaining 3 patients in Cohort 1 (baseline scores: 1, 2, and 4) and 1 patient in Cohort 2 (baseline score: 1), ECOG-PS scores remained almost unchanged throughout the study.

In both cohorts, there was no clear association between improvement in ECOG-PS and duration from the diagnosis of AHA to the start of emicizumab. Among 7 patients with high ECOG-PS (≥ 3) at baseline, emicizumab treatment was started within 1 week of diagnosis of AHA in 3 patients and within 1 month of diagnosis in the remaining 4 patients. All 3 patients who started emicizumab within 1 week of diagnosis showed ECOG-PS improvement at the date of emicizumab completion,

but none of the patients with longer duration from diagnosis showed improvement or worsening at the date of emicizumab completion. Among 5 patients with low ECOG-PS (1 or 2) at baseline, emicizumab treatment was started more than 1 year after diagnosis of AHA in 3 patients and within 1 or 3 weeks of diagnosis in the remaining 2 patients. Although ECOG-PS improvement was observed in 2 of the 5 patients at the date of emicizumab completion, both patients had more than 1-week interval between AHA diagnosis and emicizumab initiation.

Hemostatic management on surgery and procedure

From the start of emicizumab treatment, 32 surgeries/procedures were performed; 1 procedure (endoscopic papillotomy) was classified as major, and the others were classified as minor (13 endoscopic procedures, 7 dental treatments, 1 peripherally inserted central catheter, and 10 others). Twenty-three of the 32 surgeries/procedures, including 6 endoscopic procedures with high risk for bleeding (**Supplemental Table S2**), were performed during the on-treatment period, and there were no bleeds related to surgeries/procedures.

At the time of the primary analysis, 1 patient had been administered a single prophylactic dose of rFVIIa (80 μg/kg) for endoscopic retrograde cholangiopancreatography, but no other perioperative prophylactic coagulation factor products were specifically provided throughout the study in either cohort. On the other hand, during on-treatment period, there were 6 minor surgeries where bypass agents (rFVIIa in all cases) were administered on the same day, but all were administered for existing bleeds unrelated to the surgeries.

Adverse events

Adverse events are summarized in **Table 6**. At the time of the primary analysis, 1 thromboembolic event (deep vein thrombosis; DVT) considered related to emicizumab and 1 death due to exacerbation of chronic kidney disease were reported in 1 patient each, but no other thromboembolic events or deaths were reported thereafter. No thrombotic microangiopathy or local injection-site reactions were reported throughout the study.

After the cutoff date of the primary analysis, 2 treatment-related adverse events (Basedow's disease and rash) were reported in 1 patient each in Cohort 2. Basedow's disease was a serious adverse event of Grade 4 severity which occurred during the on-treatment period. This patient originally had a complication of Hashimoto's disease, but a causal relationship between emicizumab and Basedow's disease was not completely ruled out by the investigator considering the temporal relationship with emicizumab initiation. The event was brought to remission by medication without modification or discontinuation of emicizumab treatment. Rash of Grade 2 severity occurred on Day 4 and resolved in 3 days by medication without modification or discontinuation of emicizumab treatment. The event was not classified as an injection-site reaction or systemic hypersensitivity by the investigator.

Safety of concomitant use of coagulation factor products

Two patients, who had been using aPCC or plasma-derived factor VIIa and X mixture (pd-FVIIa/FX) until 3 days prior to the start of emicizumab treatment, each had a relatively high FX level at baseline (10.9 and 14.4 μg/mL, respectively; median

[range] FX level of the other patients: 4.89 [2.89-6.57] μg/mL), but no laboratory findings indicating hypercoagulability were observed after starting emicizumab treatment.

Five patients used rFVIIa with doses ranging from 80 μg/kg to 110 μg/kg, 2 used fresh frozen plasma, and 1 used coagulation factor XIII (FXIII) during the on-treatment period; 1 patient used fresh frozen plasma during the safety follow-up period. No thrombotic events were observed during or within 72 hours after the use of coagulation factor products. Of note, the patient who had DVT had had low FVIII activity and had been using FXIII from 11 to 9 days before diagnosis of the DVT.

Restoration of endogenous FVIII activity

Of the 12 patients who met the emicizumab completion criteria, 7 patients (58.3%) experienced FVIII activity exceeding 150 IU/dL (range: 150.4-284.7 IU/dL) at least once after completing emicizumab administration. One of them had a peak FVIII activity of 284.7 IU/dL, which was the value at the date of death. For the other 6 patients, the range of FVIII activity exceeding 150 IU/dL was 150.4 to 200.0 IU/dL. No thrombotic events were observed after restoration of endogenous FVIII activity.

On the other hand, 9 patients (75.0%) had FVIII activity decreasing to below 50 IU/dL (range: 1.1-45.7 IU/dL) at least once after meeting the emicizumab completion criteria, but none had any treated bleeds during the safety follow-up period (**Table 3**).

Immunogenicity

Two of the 14 patients (14.3%) developed anti-emicizumab (drug) antibodies (ADAs) (**Table 6**); 1 patient showed accelerated emicizumab clearance (half-life: 9.77 days) that was considered attributable to the ADAs. The ADAs were first detected at safety follow-up Week 13 or Week 25 after completing emicizumab administration, while not detected before completing emicizumab administration. The ADAs did not exhibit *in vitro* neutralizing activity.

Tailored IST approaches

For 2 cases in Cohort 2 (Patients 13 and 14) and 1 case in Cohort 1 (Patient 04), tailored IST approaches were adopted comprising delayed IST, no IST, and low-dose IST, respectively. Details of these 3 cases are described in **Supplemental Result S1**.

DISCUSSION

This final analysis included a total of 14 patients judged eligible or ineligible for IST at enrollment, with results suggesting that emicizumab exerts a prophylactic effect in both types of patients. In addition, long-term emicizumab prophylaxis of up to 1.75 years showed sustained bleed prevention and a favorable safety profile. In the primary analysis, 1 patient experienced DVT, but no additional thrombotic events occurred thereafter throughout the study, including during concomitant use with coagulation factor products and after emicizumab completion following restoration of endogenous FVIII activity. Rehabilitation and minor surgeries were found to have been performed safely under emicizumab prophylaxis. Moreover, the clinical courses of three patients suggest that the introduction of emicizumab prophylaxis allows

individualized IST approaches tailored to each patient's specific condition. Thus, emicizumab prophylaxis was suggested to be of consistent efficacy and safety, regardless of the patient's tolerance of IST. Furthermore, the results of this final analysis also suggest the usefulness of emicizumab prophylaxis during the course of AHA treatment involving concomitant use of coagulation factor products, AHA remission, rehabilitation, and surgery.

This final analysis indicated that the 1-week loading regimen adopted in this study achieved maximum prophylactic effect of emicizumab (plasma emicizumab concentration >30 μg/mL) by 4 days after starting emicizumab treatment. Potentially owing to this rapid increase of emicizumab cofactor activity, the hemostatic effect of emicizumab, which was suggested in the primary analysis,[10] was re-confirmed in Patient 13 in whom 2 active major bleeds stopped within 3 days after initial emicizumab administration without influence of IST. There is accumulating evidence on the use of emicizumab to achieve hemostasis for acute bleeding and a subsequent sustained preventive effect.[15] Further accumulation of data on the 1-week loading regimen of emicizumab as a second-line hemostatic treatment for acute bleeding is needed.

In one retrospective study, overshoot of FVIII activity (i.e., ≥150 IU/dL) was observed in 64.7% of PwAHA after AHA remission.[14] Although it is unknown to what extent this supranormal elevation of FVIII activity actually contributes to the risk of thrombosis in PwAHA, FVIII is generally considered a major and dose-dependent risk factor for venous thrombosis.[16] In AGEHA, 58.3% of patients experienced FVIII activity exceeding 150 IU/dL at least once after completing emicizumab administration along with AHA remission; nonetheless, no thrombotic events related to restoration or supranormal level of endogenous FVIII activity occurred. These results support the

appropriateness of the emicizumab completion criteria and the regular coagulation monitoring mandated in this study (**Supplemental Table S3**).

To the best of our knowledge, there are few case reports evaluating the effectiveness of rehabilitation in PwAHA.[17,18] In the case reported by Goto et al.,[17] rehabilitation during the period when FVIII inhibitors were detected was possible only immediately following prophylactic administration of rFVIIa, and was limited to low load rehabilitation for conditioning. Relatively stressful rehabilitation for muscle strengthening could not be started until after the FVIII inhibitor had disappeared. In AGEHA, the median FVIII activity at the time rehabilitation was started was 2 IU/dL (most rehabilitation was performed to prevent disuse syndrome aiming for early mobilization), and no haemorrhage associated with rehabilitation was reported, suggesting that rehabilitation can be started safely under emicizumab prophylaxis before restoration of FVIII activity. On the other hand, no firm conclusion on the impact of emicizumab prophylaxis on the timing of rehabilitation initiation can be reached from this study because the time from diagnosis of AHA to initiation of emicizumab varied widely from 2 to 2167 days and because 8 of the 14 patients had either already started their first rehabilitation before starting emicizumab or did not engage in any rehabilitation throughout the study. In addition, there is a possibility that the implementation of rehabilitation itself may become unnecessary as a result of early emicizumab initiation, and this is also an important future research question.

Regarding performance status, improvements in ECOG-PS were observed in most patients after starting emicizumab. Because this study included patients with various ECOG-PS scores at baseline and some patients had been diagnosed with AHA more than 1 year previously, it could not be confirmed whether starting of emicizumab treatment soon after the diagnosis of AHA contributed to improvement

in ECOG-PS. However, when analysis was limited to patients with high ECOG-PS (≥ 3), all patients who had started emicizumab within 1 week of diagnosis of AHA achieved improvement in ECOG-PS at the time of emicizumab completion. This result suggests that an early start of emicizumab prophylaxis to prevent bleeding may provide improvements in performance status in PwAHA with poor performance status already before partial remission of AHA.

Even minor invasive procedures can cause severe bleeds in PwAHA, and therefore, it is currently recommended that any surgery or procedures be delayed until FVIII inhibitors have been eradicated if possible and that prophylactic use of bypassing agents or rpFVIII be considered both for minor and major surgeries.[2] In this study, a total of 23 surgeries or procedures were conducted during on-treatment period. Remarkably, none of these surgeries or procedures resulted in treated bleeds, although bypass agents were used on the day of surgery in 7 of the 23 events, either for short-term prophylaxis or for treatment of existing bleeds unrelated to the surgeries. These findings suggest that minor surgeries can be safely undertaken under emicizumab prophylaxis.

The incidence of ADAs in this study was 14.3% (2 of 14 patients), which is numerically higher than that reported in PwCHA (5.1%)[19] but was based on a small sample size. Although it is reported that autoimmune diseases may increase the likelihood of ADAs developing,[20] it remains unclear whether the incidence of ADAs substantially differs between PwAHA and PwCHA. ADAs affecting pharmacokinetics have been observed in PwCHA,[19] and such ADAs were observed in 1 patient in this study. Although the ADAs in this patient had an impact on pharmacokinetics, the ADAs did not exhibit *in vitro* neutralizing activity, suggesting that they might accelerate the clearance of emicizumab without directly inhibiting its cofactor activity.

Of note, the ADAs in the 2 ADA-positive patients in this study were detected only in the safety follow-up period following completion of emicizumab administration. Further investigations are warranted to investigate whether there is any temporal association between the discontinuation of emicizumab treatment due to remission of AHA and the appearance of ADAs.

Controlling bleeds is especially challenging in PwAHA who cannot use IST due to high risk of infection or who are refractory to IST. A recent study has suggested that IST can be safely postponed while patients are receiving emicizumab prophylaxis, but patients were enrolled regardless of whether or not it was necessary to delay IST.[11] In AGEHA, we did not restrict the type or dosage of IST during the study, and we set up a sub-cohort for patients who were ineligible for IST. As a result, we have been able to present 3 cases highlighting different tailored IST approaches: not only delayed IST, but also no IST and low-dose IST. These results indicate that emicizumab prophylaxis may enable a variety of IST approaches tailored to the specific circumstances of individual patients.

AGEHA was the first prospective interventional clinical study of emicizumab prophylaxis with the new dosing regimen, pre-defined treatment completion criteria, and 2 cohorts according to the patients' tolerance to IST. This study was designed based on the standard treatment algorithm,[2] which is to start IST as early as possible after the diagnosis of AHA, and we prospectively collected data encountered in actual clinical practice such as concomitant use of coagulation factor products, remission of AHA, rehabilitation, and surgery. However, it had several limitations: it was a single-arm study, included only 2 patients in Cohort 2 (patients deemed ineligible for IST), and it was performed in a single country.

In conclusion, the final analysis results of AGEHA suggest that emicizumab prophylaxis has a favorable benefit–risk profile in PwAHA regardless of their IST eligibility. The data in this study have the potential to change the standard of care for AHA, including the establishment of hemostatic prophylaxis and more tailored IST approaches, and to contribute to increasing the available treatment options and improving the prognosis for PwAHA.

Summary Table

What is known on this topic?
· Severe bleeding and infections that occur due to immunosuppressive therapy (IST) are major causes of death in patients with acquired hemophilia A (PwAHA). · The previously published primary analysis of this prospective phase III study of emicizumab prophylaxis (AGEHA) suggested its favorable benefit-risk profile in PwAHAs under IST.
What does this paper add?
· Tailored IST approaches (delayed initiation, no use, or reduced dose) were successfully executed in 3 patients under emicizumab prophylaxis. · Long-term emicizumab prophylaxis for up to 1.75 years provided sustained bleed prevention. · Rehabilitation and minor surgeries were safely conducted under emicizumab prophylaxis.

AUTHOR CONTRIBUTIONS

M. Shima, R.K., and N.M. wrote and edited the manuscript. M. Shima, K.A., Y.O., R.K., R.O., K.Y., and K.N. designed the study. N.S., H.N., K.A., Y.O., E.S., M. Saito, T.O., T.I., N.H., S.H., and Y.S. acquired the data. K.Y. and R.O. analyzed the data. All authors interpreted the data, critically reviewed the manuscript, approved the final version, and supported the publication.

ACKNOWLEDGEMENTS

The authors thank all the patients and their families who participated in the clinical study; investigators and staff of the study sites; and colleagues at Chugai Pharmaceutical Co., Ltd., especially Sayaka Nagami (formerly), Kayo Haraguchi, Tomomi Niino, and Hiroki Oki for their support in the study design, study conduct, and data analysis.

DATA SHARING STATEMENT

Chugai's clinical trial data sharing policy is available at www.chugai-pharm.co.jp/english/profile/rd/ctds_request.html.

FUNDING

This study was funded by Chugai Pharmaceutical Co., Ltd.

CONFLICT-OF-INTEREST STATEMENT

M. Shima has received research funding from Chugai Pharmaceutical Co., Ltd., CSL Behring, and Takeda; has received honoraria from Bayer, Chugai Pharmaceutical Co., Ltd., CSL Behring, Fujimoto Seiyaku, Sanofi, Novo Nordisk, Pfizer, and Takeda; holds patents with Chugai Pharmaceutical Co., Ltd.; and has participated on a data safety monitoring board or advisory board for Chugai Pharmaceutical Co., Ltd., Fujimoto Seiyaku, KYORIN Pharmaceutical Co., Ltd., Novo Nordisk, and Pfizer. N.S. has received honoraria from Bayer, Chugai Pharmaceutical Co., Ltd., CSL Behring, Japan Blood Products Organization, KM Biologics, Novo Nordisk, Pfizer, Sanofi, and Takeda. K.A. has received research funding from KM Biologics; has received consulting fees from Chugai Pharmaceutical Co., Ltd.; has received honoraria from Bayer, Chugai Pharmaceutical Co., Ltd., CSL Behring, Fujimoto Pharmaceutical Corporation, Japan Blood Products Organization, KM Biologics, Novo Nordisk, Pfizer, Sanofi, and Takeda; has participated on a data safety monitoring board or advisory board for Chugai Pharmaceutical Co., Ltd.; and is belong to endowed chair for CSL Behring. Y.O. has received consulting fees and honoraria from Chugai Pharmaceutical Co., Ltd. R.K. and R.O. are employees of Chugai Pharmaceutical Co., Ltd. K.Y. is an employee of Chugai Pharmaceutical Co., Ltd. and an inventor of patents related to anti-activated FIX/FX bispecific antibodies. N.M. is an employee of Chugai Pharmaceutical Co., Ltd. and has stocks of Chugai Pharmaceutical Co., Ltd. E.S. has received research funding from Eisai; has received honoraria from Janssen, Novartis, Pfizer, Sanofi and Takeda and has leadership or fiduciary role in other board, society, committee or advocacy group (unpaid) for Japan Adult Leukemia Study Group and Japanese Society of Myeloma. S.H. has received research funding from Chugai Pharmaceutical Co., Ltd. and has received honoraria from Bayer,

Chugai Pharmaceutical Co., Ltd., CSL Behring, Novo Nordisk, Sanofi, and Takeda. K.N. has received research funding from Bayer, Chugai Pharmaceutical Co., Ltd., CSL Behring, KM Biologics, Novo Nordisk, Sanofi, and Takeda; has received consulting fees from Chugai Pharmaceutical Co., Ltd.; and has received honoraria from Bayer, Chugai Pharmaceutical Co., Ltd., CSL Behring, KM Biologics, Novo Nordisk, Sanofi, and Takeda. The remaining authors have no conflicts of interest to declare.

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Figure 1. Bleeding rate. Calculated ABRs were derived as 365.25 times the number of bleeding events that occurred in an evaluation period divided by the number of days in the corresponding evaluation period for each patient and each bleed definition. ABR, annualized bleeding rate.

Table 1. Patient demographics

	Cohort 1	Cohort 2	
	N=12	Patient 13	Patient 14
Age, years	76 (50-92) [a]	82	59
Sex	Male n=6 Female n=6	Female	Female
Body mass index, kg/m^2	21.08 (16.3-30.2) [a]	24.5	21.9
Duration from AHA diagnosis to enrollment, days	17.5 (2-2167) [a]	6	1009
FVIII activity at diagnosis, IU/dL	1.0 (<0.8 to 36.6) [a]	<1	<1
FVIII inhibitor titer at diagnosis, BU/mL	40.5 (1-149) [a]	58	33
Prior or current use of coagulation factor products or transfusion	Yes: n=8 No: n=4	Yes	Yes
Regimen of coagulation factor products	Episodic: n=8 Prophylactic: n=0	Episodic (rFVIIa & FFP)	Prophylactic and Episodic (aPCC)

[a]The value is median (range).

AHA, acquired hemophilia A; aPCC, activated prothrombin complex concentrate; BU, Bethesda units; ECOG-PS, Eastern Cooperative Oncology Group Performance Status; FFP, fresh frozen plasma; FVIII, factor VIII; IU, international units; rFVIIa, recombinant activated factor VII.

Table 2. Emicizumab treatment period and status of immunosuppressive therapy

Patient ID	Emicizumab treatment period (days)	On Day1				At last observation			
		Medication[a]	Route	Dose/day (mg)	Body weight (kg)	Status	Medication[a]	Route	Dose/day (mg)
Cohort 1									
01	47	PSL CPA	IV Oral	30 50	52.1	Withdrawn from study	None	—	—
02	36	PSL	Oral	40	40.2	Completed	None	—	—
03	50	PSL	Oral	40	61.7	Completed	PSL	Oral	7
04	639	PSL	Oral	20	51.6	Ongoing emicizumab[b]	PSL	Oral	6
05	29	PSL	Oral	50	54.4	Completed	PSL	Oral	12
06	106	PSL	Oral	30	51.3	Withdrawn from study	PSL	Oral	9
07	29	PSL	Oral	60	85.2	Completed	PSL CPA	Oral Oral	12.5 50
08	8	PSL	Oral	7.5	46.1	Completed	PSL	Oral	5

		CYA	Oral	100			CYA	Oral	100
09	42	PSL	Oral	40	38.4	Completed	PSL	Oral	15
10	64	PSL CPA	IV Oral	50 50	49.3	Completed	PSL CPA	Oral Oral	3 50
11	57	PSL	Oral	60	56.5	Completed	None	—	—
12	15	PSL	Oral	5	50.2	Completed	PSL	Oral	5
Cohort 2									
13	64	None	—	—	52.2	Completed	PSL CPA	Oral IV	2.5 500
14	450	None	—	—	54.2	Ongoing emicizumab[b]	None	—	—

[a]Immunosuppressive therapies indicated for acquired hemophilia A are included.

[b]Patients 04 and 14 did not meet the emicizumab completion criteria during the study and were transitioned to a commercial emicizumab product

CPA, Cyclophosphamide; CYA, Cyclosporin; IV, Intravenous; PSL, prednisolone.

Table 3. Bleeding events in each cohort

	Observation period, median (range), days	No. of patients with ≥ 1 **treated bleeds** (total no. of events), n	No. of patients with ≥ 1 **major bleeds** (total no. of events), n	No. of patients with ≥ 1 **all bleeds** (total no. of events), n
Pre-treatment Period Cohort 1 (N=12), Cohort 2 (N=2)				
Cohort 1	68.0 (17-168)	6 (30)	7 (77)	11 (110)
Cohort 2	95.5 (23-168)	2 (3)	1 (2)	2 (5)
On-treatment Period Cohort 1 (N=12), Cohort 2 (N=2)				
Cohort 1	44.5 (8-639)	3 (6)	0 (0)	5 (34)
Cohort 2	257.0 (64-450)	0 (0)	0 (0)	2 (3)
Safety Follow-up Period Cohort 1 (N=11), Cohort 2 (N=1)				
Cohort 1	168.0 (14-171)	0 (0)	0 (0)	7 (12)
Cohort 2	174(174)	0 (0)	0 (0)	1 (1)

A major bleed was reported by the investigator if any of the following conditions were met: (1) life-threatening, (2) symptomatic in an important region or major organ (e.g., intracranial, intraspinal, intraocular, retroperitoneal, intraarticular, or pericardiac bleeds, or muscle bleeds associated with compartment syndrome), or (3) associated with a decrease of ≥2 g/dL in hemoglobin or necessitating transfusion of ≥2 units of whole blood or packed red cells. A treated bleed was defined as a bleed directly followed by use of a coagulation factor product without an intervening bleed. Bleeds due to surgery/procedures were excluded.

Table.4. Rehabilitation sessions started after initial emicizumab dose

	Patient ID	Type of rehabilitation session	Start day of first rehabilitation session (Study day)	FVIII activity (IU/dL) (Study day[a])
Cohort 1	03	Prevention of disuse syndrome	14	< 1.0 (Day 8)
	04	Disuse syndrome rehabilitation	4	11.9 (Day 1)
	06	Prevention of disuse syndrome	15	2.4 (Day 15)
	09	Occupational therapy Physical therapy	8	1.5 (Day 8)
	11	Stretching and relaxation of left calf	17	8.7 (Day 16)
Cohort 2	13	Range of motion	6	< 1.0 (Day 1)

[a]Same day as the start day of first rehabilitation session or nearest sampling point before it.

FVIII, factor VIII; IU, international units.

Table 5. Duration from the date of AHA diagnosis to Day 1 (the date of starting emicizumab) and ECOG Performance Status at Baseline, Follow-up Week 1 (the date of emicizumab completion), and last observation

	Patient ID	Duration from the date of AHA diagnosis to Day1 (days)	ECOG-PS		
			Baseline	Follow-up Week 1	Last observation
Cohort 1	01	11	4	4	4
	02	6	2	2	2
	03	2	3	2	2
	04	419	2	1[a]	1[a]
	05	57	0	0	0
	06	14	3	3	2
	07	14	4	4	3
	08	2167	1	1	1
	09	2	4	3	3
	10	29	4	4	3
	11	21	1	0	0
	12	36	0	0	0
Cohort 2	13	6	3	1	1
	14	1009	1	1[a]	1[a]

[a]For patients who did not meet the emicizumab completion criteria, the day of last observation was deemed the same day as Follow-up Week 1.

AHA, acquired hemophilia A; ECOG-PS, Eastern Cooperative Oncology Group Performance Status

Table 6. Safety summary

	Both cohorts (N=14)
Total number of AEs	120
Total number of patients with ≥ 1 AE, n (%)	
Any AE	14 (100)
Fatal AE	1 (7.1)[a]
Serious AE	6 (42.9)[b]
AE leading to treatment/study discontinuation	0
AE leading to dose modification/interruption	1 (7.1)[c]
Study treatment-related AE	5 (35.7)[d]
Study treatment-related AE with Grade ≥ 3 severity	2 (14.3)[e]
Study treatment-related serious AE	1 (7.1)[b]
Total number of patients with AEs of interest, n (%)	
Thromboembolic event	1 (7.1)[c]
Thrombotic microangiopathy	0
Systemic injection reaction	0
Local injection site reaction	0
Total number of patients with anti-emicizumab antibodies, n (%)	0

Baseline prevalence Postbaseline incidence	2 (14.3)

[a]One patient died owing to exacerbation of chronic kidney disease that was considered unrelated to emicizumab.

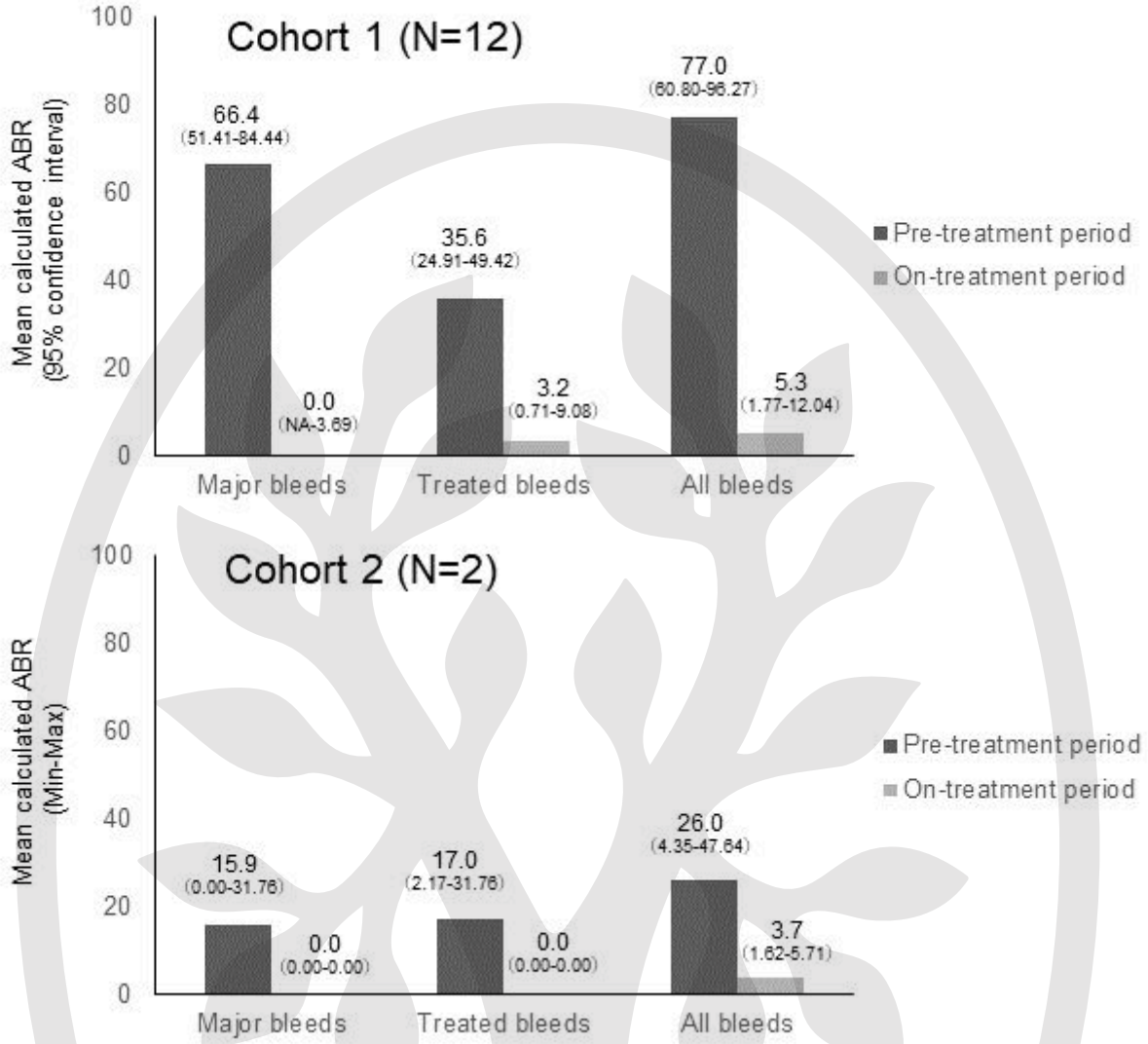
[b]Cholangitis acute and cholangitis chronic (1 patient), cholelithiasis and shock haemorrhagic (1 patient), pneumonia, chronic kidney disease, and orthostatic hypotension (1 patient each), all of which were considered unrelated to emicizumab. Basedow's disease (1 patient), considered related to emicizumab.

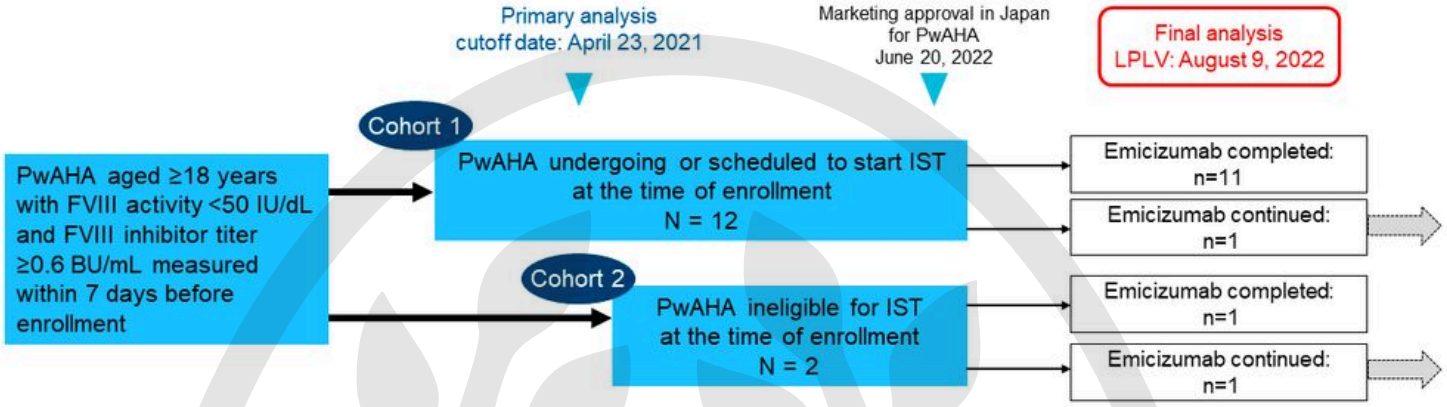
[c]Deep vein thrombosis necessitating interruption of emicizumab treatment (1 patient).

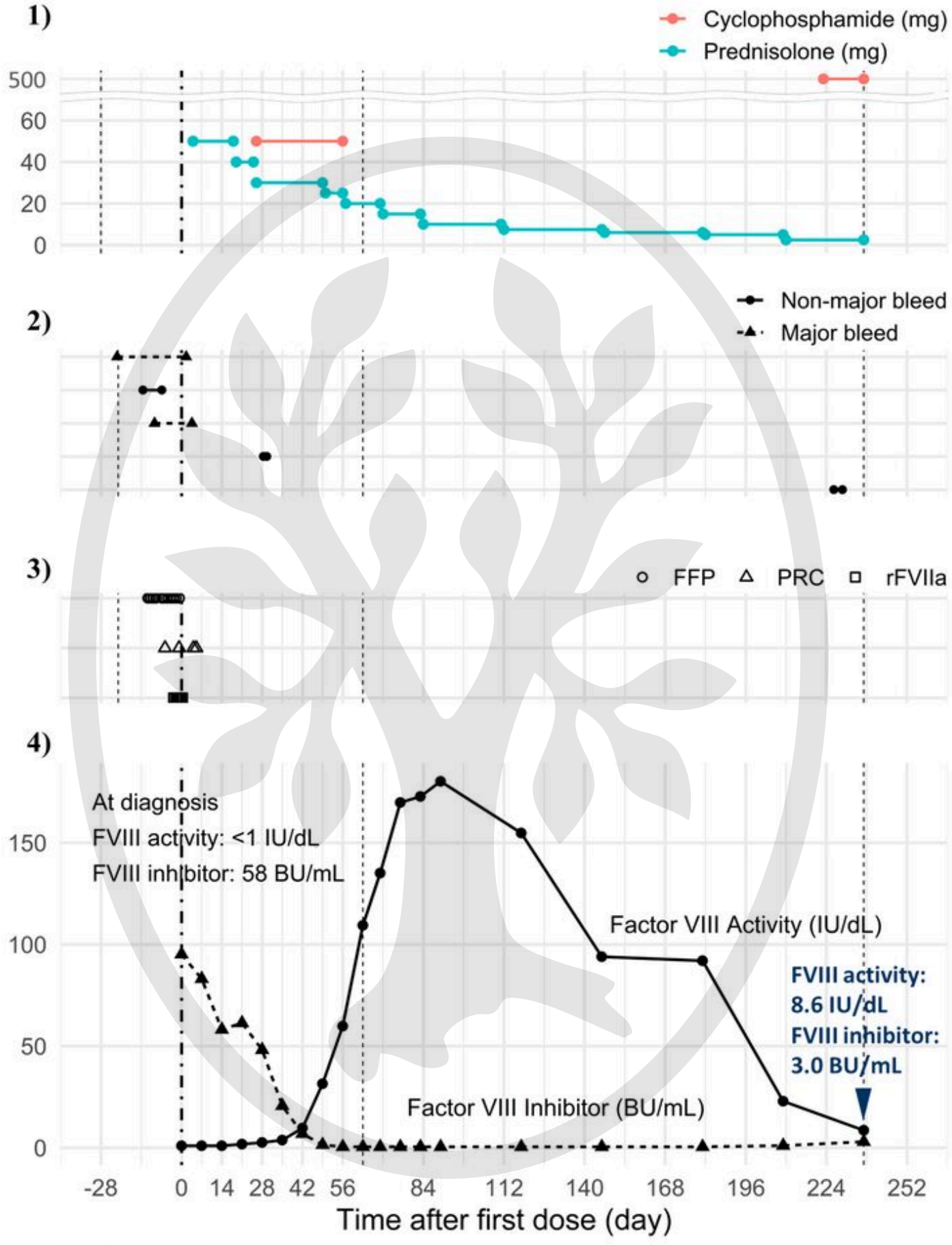
[d]Thrombocytopenia, prothrombin fragment 1.2 increased, deep vein thrombosis, Basedow's disease, and rash (1 patient each).

[e]Thrombocytopenia and Basedow's disease (1 patient each).

AE, adverse event.







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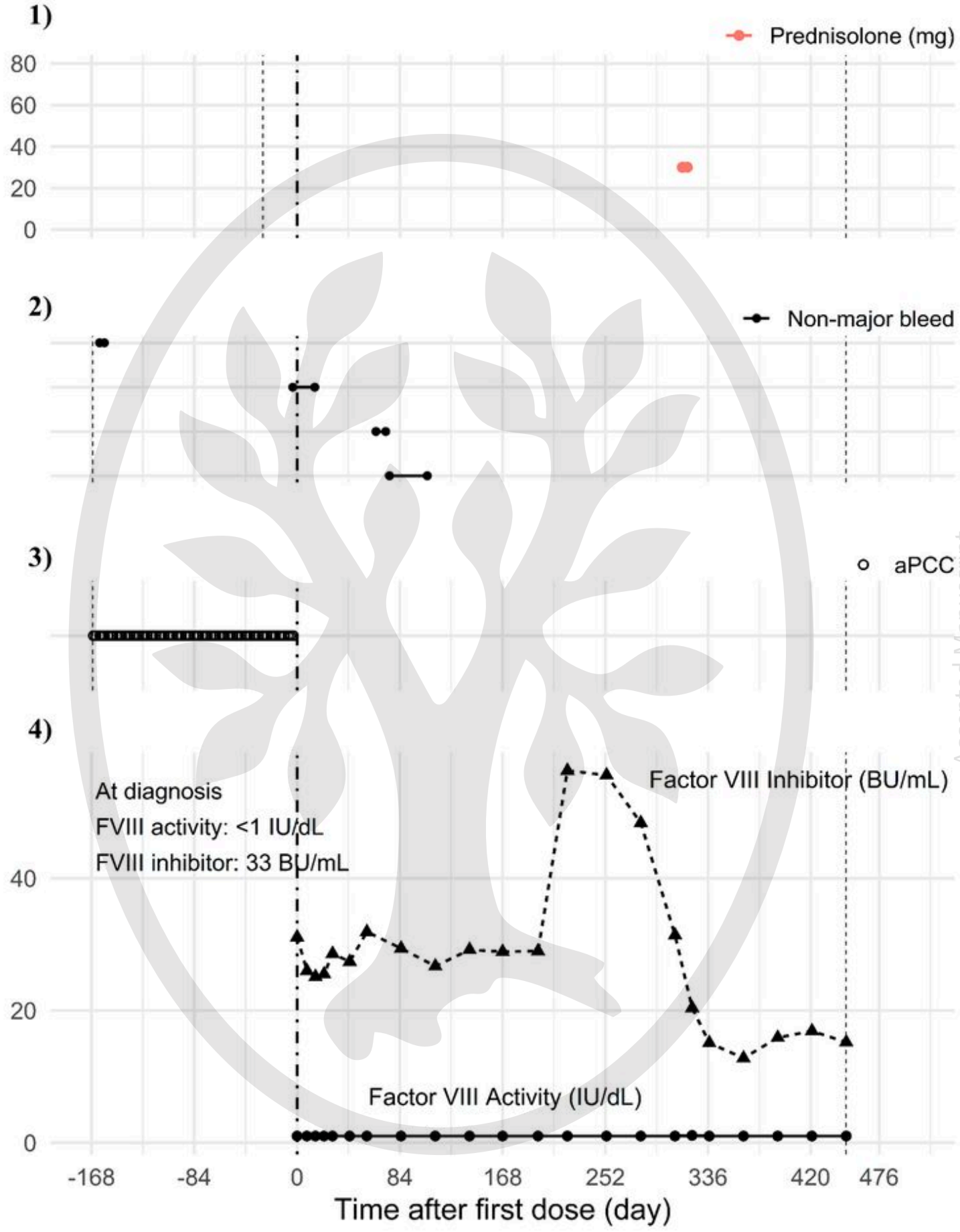

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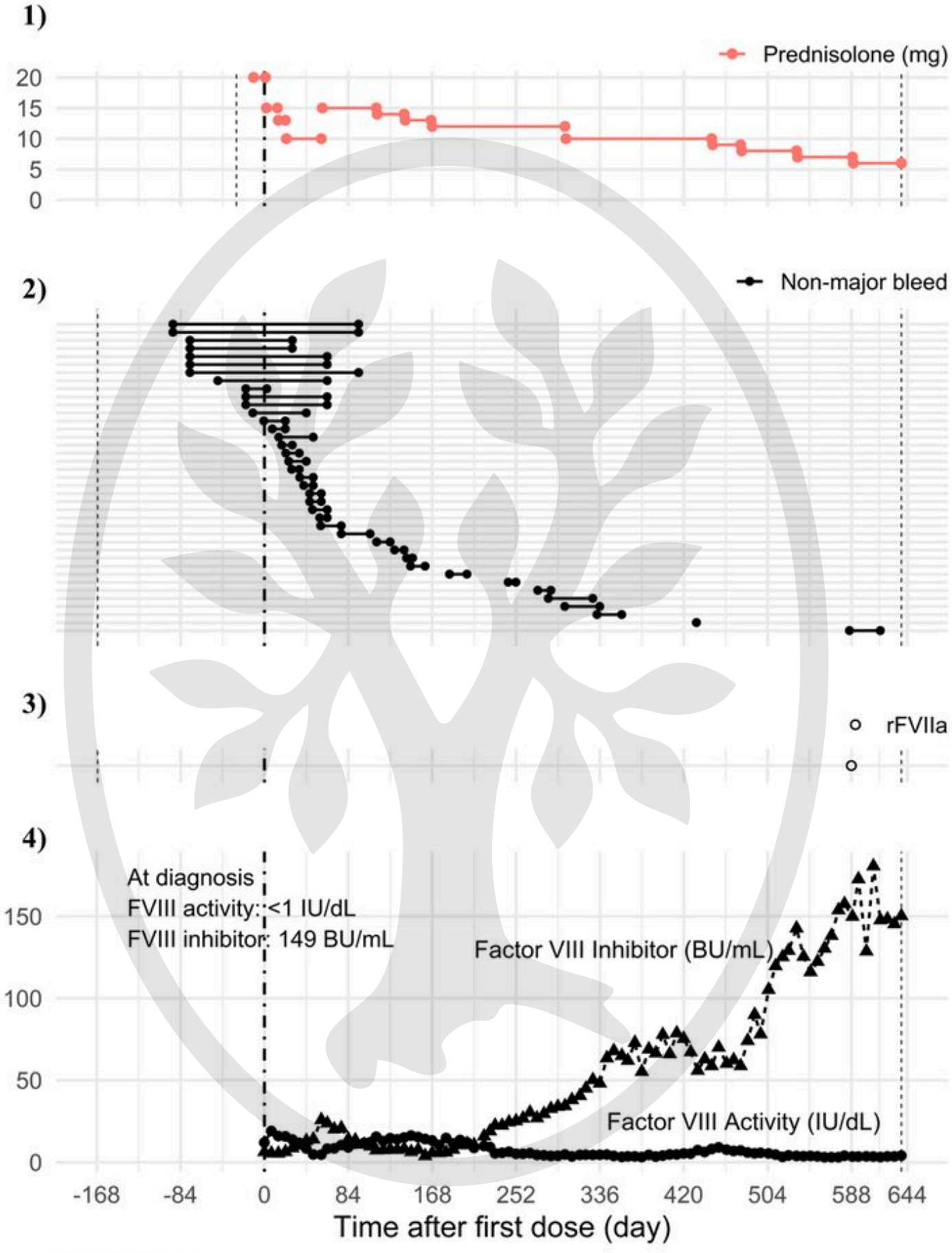

Patient ID: 04