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AOZORA: long-term safety and joint health in paediatric persons with haemophilia A without factor VIII inhibitors receiving emicizumab – protocol for a multicentre, open-label, phase IV clinical study

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ABSTRACT

Introduction Persons with haemophilia A (PwHA) commonly experience regular bleeding into joints, which may result in joint damage and complications such as degenerative arthritis. Emicizumab has previously demonstrated efficacy in reducing the occurrence of joint bleeds and target joints, along with having a favourable safety profile; however, data on the long-term effects on joint health are lacking. The AOZORA study will evaluate the long-term safety and joint health of paediatric PwHA without factor (F)VIII inhibitors taking emicizumab; here, we report the details of the study protocol and baseline data.

Methods and analysis AOZORA is a multicentre, open-label, phase IV clinical study in Japan that aims to enrol approximately 30 PwHA aged <12 years without FVIII inhibitors. The primary endpoints include a long-term safety evaluation of adverse events, laboratory test abnormalities and FVIII inhibitor development; and a long-term joint health assessment using MRI and the Hemophilia Joint Health Score. Exploratory endpoints include characterising participants' physical activities and the number of activity-related bleeds requiring coagulation factor treatment. Currently, 30 participants have been enrolled, including 20 emicizumab-naïve participants and 10 who transferred from HOHOEMI, a previous study in paediatric PwHA.

Ethics and dissemination The AOZORA study was approved by the Institutional Review Boards of Nara Medical University and the St Marianna University Group. The study will be conducted in compliance with the Declaration of Helsinki, the standards stipulated in paragraph 3 of Article 14 and Article 80-2 of the Pharmaceuticals, Medical Devices and Other Therapeutic Products Act, the Ministerial Ordinance on Good Clinical Practice and the Ministerial Ordinance on Good Post-marketing Study Practice. Data will be published in peer-reviewed journals and presented at Global congresses.

Trial registration number JapicCTI-194701.

STRENGTHS AND LIMITATIONS OF THIS STUDY

⇒ AOZORA is a multicentre, open-label, phase IV clinical study with a planned long-term follow-up period of 6 years.
⇒ A sample size of 30 participants was selected based on feasibility and the minimum number of persons with haemophilia A required to assess the long-term effects of emicizumab on joints.
⇒ Although MRI for children can be difficult due to the need for sedation, this mode of imaging is known to be effective for early detection of arthropathy and both reversible and irreversible changes can be evaluated.
⇒ A limitation of AOZORA is that it is a single-arm study, which makes it difficult to evaluate the isolated effect of the study treatment compared with the effect of the disorder's natural history.

INTRODUCTION

Haemophilia A (HA) is caused by a deficiency in factor (F)VIII; persons with HA (PwHA) experience regular bleeding, most commonly into joints and muscles.[1 2] Frequent bleeding into joints may result in joint damage and complications such as degenerative arthritis.[2 3] Treatment for HA traditionally consists of intravenous infusions of FVIII multiple times per week.[4 5] FVIII prophylaxis has demonstrated significant reductions in joint bleed rates compared with on-demand FVIII treatment; however, even with regular FVIII prophylaxis, bleeding can still occur.[6–9]

Emicizumab is a bispecific monoclonal antibody that bridges activated FIX(a) and FX, restoring haemostasis.[10] Emicizumab is administered subcutaneously, once every week, every 2 weeks or every 4 weeks (QW,

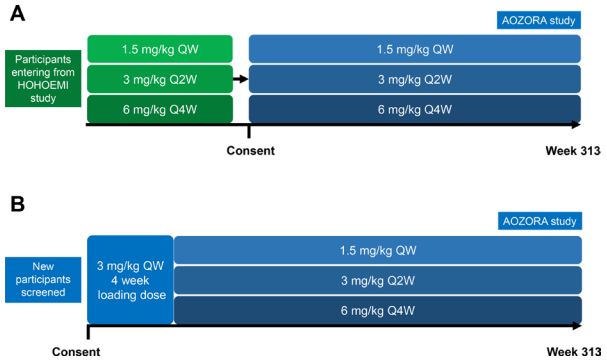

Figure 1 Summary of the AOZORA study design. (A) participants entering AOZORA from the HOHOEMI study will remain on emicizumab at one of the three permitted doses for a total of 313 weeks from the date of the first injection after HOHOEMI enrolment; this treatment period is inclusive of the emicizumab administered within HOHOEMI. (B) The treatment period for emicizumab-naïve participants newly entering AOZORA will incorporate a 4 week loading dose, followed by either of the three dose regimens until week 313. The emicizumab treatment regimen may be modified from among the approved dosage regimens. QW, Weekly; Q2W, every 2 weeks; Q4W, every 4 weeks

Q2W or Q4W).[1] Emicizumab has demonstrated efficacy and tolerability in children and adults, regardless of FVIII inhibitor status, through the phase III HAVEN clinical programme[9 11–13] and studies performed in Japan.[1 14 15] In the HAVEN 2 study, emicizumab resulted in a low annualised bleeding rate for treated bleeds (0.3, 95% CI 0.17 to 0.50) in 65 paediatric PwHA with FVIII inhibitors, with 76.9% of participants having no treated bleeding events. In the 23 participants who had received emicizumab for ≥52 weeks, and who had target joints at baseline, all 45 evaluable target joints resolved during the study period.[12] Furthermore, twenty of the 23 participants (87.0%) had no target joint bleeds while receiving emicizumab, including two participants who had three and five target joints at baseline, respectively.[12] In the phase III HOHOEMI study of emicizumab in paediatric PwHA without FVIII inhibitors, 53.8% of 13 participants had no bleeding events. No thrombotic microangiopathies (TMAs), thromboembolic events (TEs) or fatalities were reported in either study. Overall, emicizumab had a favourable safety profile.[1 12]

Despite extensive evidence on the efficacy and safety of emicizumab, there is a lack of data regarding the long-term joint health effects in PwHA. MRI is currently considered to be the most suitable method for early detection of joint disease. The Hemophilia Joint Health Score (HJHS) was developed for joint evaluation in paediatric PwHA and is increasingly being used in this population.

Building on previous paediatric studies, AOZORA (JapicCTI-194701, www.clinicaltrials.jp) was designed to investigate the long-term safety and joint health effects of emicizumab in PwHA aged <12 years without FVIII inhibitors. This manuscript outlines the protocol for the AOZORA study, providing baseline demographic and disease characteristics for enrolled participants.

METHODS AND ANALYSIS

Objectives

The primary objectives of this study are to evaluate the long-term safety and joint health effects of emicizumab in PwHA <12 years of age without FVIII inhibitors. As an exploratory objective, activities (type and duration) performed by participants receiving emicizumab will be documented, and their association with bleeding events will be assessed.

Study design and participants

AOZORA is a multicentre, open-label, phase IV clinical study performed in paediatric PwHA without FVIII inhibitors. Approximately 30 PwHA aged <12 years, without FVIII inhibitors, will be enrolled from 10 centres in Japan. Participants will enter AOZORA either as an emicizumab-naïve participant, or following on from the HOHOEMI phase III study (figure 1).[1] Participants from HOHOEMI will continue their emicizumab regimen at one of the three permitted doses.

The study period will be from the date of informed consent, or start of screening of the first participant, to the date of study completion by all participants. The first participant was enrolled on 13 May 2019 and the study is expected to extend to July 2027.

Eligibility criteria

Eligibility criteria have been designed to exclude PwHA at higher risk for toxicities. Emicizumab-associated risks include injection-site reactions; acute systemic hypersensitivity reactions, including anaphylaxis and anaphylactoid reactions; TEs and TMAs.

To be included in this study, participants will be aged <12 years, weigh >3 kg, have a diagnosis of severe (endogenous FVIII level <1%) congenital HA and have negative results for FVIII inhibitors within 8 weeks prior to enrolment. All participants must have written consent provided by their legal representative and be able to comply with the scheduled study visits, treatment plans, laboratory tests and other procedures.

Key exclusion criteria include: an inherited or acquired bleeding disorder other than HA, currently undergoing immune tolerance induction therapy, previous or current treatment for/signs of thromboembolic disease, prior receipt of emicizumab (participants transferring from HOHOEMI were exempt from this criterion), or currently receiving an investigational drug to treat HA. A full list of eligibility criteria is provided in table 1.

Patient and public involvement

There was no patient or public involvement in the design and conduct of this study.

Interventions and study procedures

Emicizumab will be administered subcutaneously as one of three approved regimens: 1.5 mg/kg QW, 3.0 mg/kg Q2W or 6.0 mg/kg emicizumab Q4W. Dose selection is to be made at the discretion of the treating physician and will not be influenced by study participation.

Table 1 AOZORA study inclusion and exclusion criteria

Inclusion	Exclusion
► Written informed consent for study participation from the PwHA's legally acceptable representative; where possible, written informed consent from the participant ► Aged <12 years at the time of informed consent ► Body weight of >3 kg ► Ability to comply with scheduled study visits, treatment plans, laboratory tests and other procedures ► Caregiver ability to comply with all procedures (eg, completion of questionnaires on bleeds and drugs used) ► Diagnosis of severe (endogenous FVIII level <1%) congenital HA ► Negative results for FVIII inhibitors (<0.6 BU/mL) in the most recent assay within 8 weeks prior to enrolment ► Adequate haematological function at the time of screening (WCC ≥100×10^9 cells/L, haemoglobin ≥8 g/dL (4.97 mmol/L)) ► Adequate hepatic function at the time of screening (total bilirubin ≤1.5 × age-specific ULN (excluding patients with Gilbert's syndrome), AST and ALT≤3 × age-specific ULN) ► Adequate renal function at the time of screening (serum creatinine ≤1.5 × age-specific ULN). Creatinine clearance >70 mL/min/1.73 m^2 (as calculated by the bedside Schwartz formula) if the serum creatinine is ≥1.5 × ULN ► Female patients of childbearing potential must have a negative result on a serum pregnancy test at the time of screening. Female patients of childbearing potential must also agree to remain abstinent (refrain from heterosexual intercourse) or use contraceptive methods that result in a failure rate of <1% per year during the emicizumab treatment period and for at least 24 weeks (five elimination half-lives) after the last emicizumab dose	► Inherited or acquired bleeding disorder other than HA ► Current receipt of ITI therapy ► Previous (within the past 12 months) or current treatment for thromboembolic disease ► History of clinically significant hypersensitivity associated with monoclonal antibody therapies ► Prior receipt of emicizumab* ► Currently receiving an investigational drug; receipt of an investigational drug to treat or reduce the risk of haemophilic bleeds within five half-lives of last drug administration; or receipt of a non-HA-related investigational drug within the last 30 days or five half-lives ► Any other reason that, in the judgement of the investigator, would render the participant unsuitable for inclusion

*Participants entering AOZORA from the HOHOEMI study will be exempt from this exclusion criterion.
ALT, alanine transaminase; AST, aspartate transaminase; BU, bethesda units; F, factor; HA, haemophilia A; ITI, immune tolerance induction; PwHA, person with haemophilia A; ULN, upper limit of normal; WCC, white cell count.

Emicizumab-naïve participants will be initiated on a 3 mg/kg loading dose QW for 4 weeks, then will commence with one of the approved regimens. Participants transferring from HOHOEMI will continue on their current dosing regimen; however, the dose can be adjusted from among the approved maintenance regimens. Modifications to emicizumab dosing can be made only by Investigators at the site. Participants will receive emicizumab for 313 weeks from the time of their first injection (for those who transfer from HOHOEMI, this is the first injection during HOHOEMI).

In those participants previously receiving FVIII prophylaxis, administration may continue, to reduce the risk of bleeding, until the day before the second dose of emicizumab. Participants may receive short-term FVIII prophylaxis in anticipation of a surgery-related bleed, or when an unexpected event occurs. FVIII products may be used episodically to treat bleeds that require treatment. The decision to administer FVIII products concomitantly with study treatment, and the dose used, will be at the discretion of the treating physician, as emicizumab will increase the clotting ability. Additional authorised concomitant medications include drugs used to manage adverse events (AEs); topical and local drugs that do not result in systemic exposure, such as topical antiseptics, local anaesthetic and eye-drops; topical anaesthetic creams used collectively with emicizumab injections; sedatives used with MRI scans; and vaccinations. Prohibited concomitant treatments include other investigational drugs, regular FVIII prophylaxis (except the aforementioned) and situational prophylaxis (such as for bleeding prevention before sports and rehabilitation activities).

Baseline measurements will include body weight, physical examination, concomitant medication(s), survey of activities, MRI of the ankles and knees, and HJHS V.2.1 joint assessment.[16] MRI joint assessments will be performed at the following time points: for emicizumab-naïve participants, weeks 1, 145 and 313 (or early termination); and for HOHOEMI participants, week 1 of the HOHOEMI study, then weeks 145 and 313. HJHS joint assessments will occur at weeks 1, 25, 49, 98 and every 48 weeks thereafter (except week 289), week 145 and week 313 for emicizumab-naïve participants; and weeks 1, 49, 97 and every 48 weeks thereafter (except week 289), week 145 and week 313 for participants from HOHOEMI.

Safety assessments will be performed from week 1 to week 313 for all participants. A safety follow-up visit will be performed 24 weeks after the final dose in participants who discontinue emicizumab; this visit will not be performed for participants who continue emicizumab after the end of the study.

Activities will be assessed in treatment-naïve participants only on weeks 1, 5 and 13; and for both groups, weeks 25, 37, 49, 61 (and every 12 weeks thereafter), and week 145. Caregivers will be asked to record the types and durations of physical activities of participants at the scheduled time points (see online supplemental file 1 for the Activities Questionnaire).

The full schedules of assessments for all participants are shown in online supplemental tables 1 and 2.

Endpoints

Primary endpoint

The primary endpoint of assessing the long-term safety of emicizumab in paediatric PwHA will include: AEs, AEs leading to discontinuation of emicizumab, AEs of special interest, physical examination findings, laboratory test abnormalities, and development of FVIII inhibitors. The primary endpoint of evaluating joint health effects of emicizumab will be evaluated by MRI-determined knee and ankle scores, and a total score for elbows, knees, ankles and gait, as determined using HJHS V.2.1.

MRI evaluation will be performed using the International Prophylaxis Study Group (IPSG) MRI scale.[17] Both the left and right elbows, knees and ankles will be assessed using the HJHS. Joint assessments will consider swelling, swelling duration, muscle atrophy, crepitus on motion, flexion loss, extension loss, joint pain and strength.[16 18]

Exploratory endpoints

Exploratory endpoints will include the number, duration and type of activities and the associated number of activity-related bleeds during emicizumab prophylaxis that require coagulation factor treatment. An event is considered a treated bleed if coagulation factors are administered after the development of signs and symptoms of bleeding (eg, pain and swelling). A single bleeding episode will begin with the first sign of a bleed and end 72 hours after the last coagulation factor infusion. Any injection given to treat the bleed >72 hours after the previous infusion will be considered the first infusion to treat a new bleed at the same location.[19]

Bleeds will be categorised as any of the following three types: spontaneous, defined as a bleed without an identifiable cause; traumatic, when a participant reports a known or believed reason for the bleed (eg, undertaking strenuous exercise, despite the presence or lack of obvious injury); and procedural/surgical, including haematomas resulting from any surgeries or invasive procedures (eg, tooth extraction, venipuncture, or subcutaneous drug administration) or invasive diagnostic procedures (eg, lumbar puncture, arterial blood gas determination or endoscopy with biopsy). Bleeds from procedures or surgeries will not be counted, but will be recorded in the Bleeding Episode Log. Bleed sites will be categorised as: target joints, defined as a major joint (eg, hip, elbow, wrist, shoulder, knee or ankle) in which at least three bleeds have occurred within the last 24 weeks prior to emicizumab initiation, joints, intramuscular or other.

Data analysis

Statistical hypothesis testing was not used to determine the required sample size of this study. A sample size of 30 participants was selected based on feasibility and the minimum number of PwHA required to assess the long-term effects of emicizumab on joints; the 30 participants include those transferring from HOHOEMI.

Data will be collected via electronic data capture (EDC) through use of electronic case report forms (eCRFs). Study sites will be responsible for data entry into the EDC system, Medidata Classic Rave. Participant-reported and caregiver-reported outcome data (bleeds/drugs used, activities) will be collected using paper questionnaires; the data will be entered into the EDC system by study site staff.

All AEs occurring through to the last observation, the completion of the safety follow-up visit performed 24 weeks after discontinuation of emicizumab, the withdrawal of informed consent, or loss to follow-up, regardless of relationship with emicizumab, should be recorded on the eCRF. A consistent methodology of non-directive questioning will be adopted to prevent prompted answers from participants. The WHO toxicity grading scale will be implemented to assess AE severity. Alternatively, reported AEs that are not specifically listed in the WHO scale will be assessed against the AE severity grading scale (online supplemental table 3). All TE and TMA events should be reported as AEs of special interest, as well as serious AEs if they fulfil the seriousness criteria (online supplemental table 4). Serious AEs are required to be reported by the investigator to the sponsor ≤24 hours after learning of the event.

All deaths that occur during the protocol-specified AE reporting period, regardless of relationship to emicizumab, must be recorded on the AE eCRF page and immediately reported to the sponsor. Death will be considered an outcome and not a distinct event. The event or condition that caused or contributed to the fatal outcome should be recorded as the single medical concept on the eCRF.

No confirmatory hypothesis is proposed. Demographic and baseline characteristics will be summarised using means, SD, medians and ranges for continuous variables and incidences and proportions for categorical variables. The safety analysis set will consist of all participants who receive emicizumab at least once during the study. Safety will be assessed through AEs, laboratory test data, and narrative summaries of the development of FVIII inhibitors. The joint assessment analysis set will consist of all participants who receive emicizumab at least once and have at least one MRI measurement and/or HJHS. Joint assessments will be analysed at week 313 or at study withdrawal, whichever occurs first. The change from baseline will be described for each participant. An independent evaluation committee will assess the MRI images.

The exploratory analyses will include all participants who receive emicizumab at least once. Information on activities (type, duration, number of bleeds), and the number of bleeds requiring treatment with coagulation factors will be summarised. An interim analysis will be

performed to evaluate HJHS and MRI scores when all participants have completed week 145.

Ethics and dissemination

The AOZORA study was approved by the Institutional Review Boards of Nara Medical University and the St Marianna University Group. The study will be conducted in compliance with the Declaration of Helsinki, the study protocol, the standards stipulated in Paragraph 3 of Article 14 and Article 80-2 of the Pharmaceuticals, Medical Devices and Other Therapeutic Products Act, the Ministerial Ordinance on Good Clinical Practice and the Ministerial Ordinance on Good Post-marketing Study Practice. Data will be published in peer-reviewed journals and presented at Global congresses.

Written informed consent for participation will be obtained by study staff prior to performing any study-related procedures. Written informed consent from the legal representative and, where possible, assent from paediatric PwHA ≥3 years old will be obtained. Each participant will be assigned a unique identification number to maintain patient confidentiality.

DISCUSSION

The AOZORA study will evaluate the long-term joint health of paediatric PwHA without FVIII inhibitors receiving emicizumab prophylaxis, an area that requires further research. Currently, 30 participants have been enrolled, including 20 emicizumab-naïve participants and 10 who transferred from HOHOEMI (online supplemental figure 1 and online supplemental table 5).

Previous trials in adolescent and adult PwHA without FVIII inhibitors have demonstrated the safety and efficacy of emicizumab. The HOHOEMI study evaluated the rate of joint bleeds in a paediatric population of PwHA without FVIII inhibitors; however, the long-term effects of bleeding on joint health were not assessed.[1]

In PwHA, haemarthrosis typically occurs before 2 years of age.[20] If inadequately treated, these individuals will develop haemophilic arthropathy by 20 years of age.[21] At baseline in this study, 12 (41.4%) of the 29 participants with evaluable MRI data displayed pathological changes of knee and/or ankle joints at baseline (positive IPSG score), including two of the six participants aged <2 years (online supplemental figure 2). Although MRI for children can be difficult due to the need for sedation, this mode of imaging is known to be effective for early detection of arthropathy and both reversible and irreversible changes can be evaluated.[17]

The baseline MRI data demonstrated effusion/haemarthrosis in 18.1% of evaluable joints, while synovial hypertrophy and haemosiderin were each identified in 8.6% of joints (online supplemental table 6). In a recent study, synovial MRI changes, including synovial hypertrophy and haemosiderin deposits, were a strong predictor of joint bleeding and progression of arthropathy in persons with haemophilia, although effusion was not.[22] This highlights the importance of identifying early changes to joints.

Use of MRI at multiple time points in AOZORA will enable assessment of how IPSG scores change over time. There are a number of studies evaluating joint health in paediatric PwHA receiving FVIII prophylaxis.[23–25] Since the half-life of emicizumab is longer than that of FVIII concentrates,[5 14] microbleeding may be suppressed and joint health retained. Emicizumab prophylaxis, therefore, might maintain or improve MRI IPSG scores. No association between treated bleeding and pathological changes were evident in these baseline data. While only two participants reported a treated joint bleed in the 24 weeks prior to enrolment, 12 demonstrated pathological changes at baseline, suggesting that asymptomatic bleeding may affect joint health. As bleeds are treated according to subjective assessment of symptoms by the PwHA or their caregiver, a more objective assessment would be required to fully evaluate the association between bleeding and joint health.

A limitation of AOZORA is that it is a single-arm study, which makes it difficult to evaluate the isolated effect of the study treatment compared with the effect of the disorder's natural history.[26] The study will also not include any significance testing for comparison with previous treatment, and will solely evaluate emicizumab. A further limitation of this study is the small sample size, which is planned to be 30 participants; however, this is similar to the number of participants in other HA clinical trials.[27] Furthermore, recruitment of paediatric participants to clinical trials is difficult due to the requirement for consent from a parent or legal representative, assent from the child, and school attendance and parental availability.[28]

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SUPPLEMENTARY MATERIAL

Supplementary Table 1. Schedule of assessments for treatment-naïve participants

	Screening	Wk1	Wk2	Wk3	Wk4	Wk5	Wk13	Wk25	Wk37	Wk49	Wk61 and every 12 weeks thereafter	Wk73 and every 24 weeks thereafter	Wk98 and every 48 weeks thereafter (except Wk289)	Wk145	Wk313/early termination†	Safety F/U visit†
Informed consent	x															
Inclusion/exclusion criteria	x															
Medical history and demographic data	x															
Height	x									x			x	x	x	
Body weight	x	x				x	x	x	x	x	x			x	x	x
Physical examination‡	x	x				x	x	x	x	x	x			x	x	x
Vital signs	x															
Concomitant medications§		x	x	x	x	x	x	x	x	x	x			x	x	x
Electrocardiogram	x															
Haematology/blood chemistry¶	x							x		x		x		x	x	x
FVIII inhibitors‡‡	x		x					x		x		x		x	x	x
Questionnaires on bleeds and drugs used††		←											→	x	x	x
Activities survey		x				x	x	x	x	x	x			x		
Adverse events§§		←											→	x	x	x
MRI joint assessment¶¶		x												x	x	
HJHS joint¶¶ assessment		x						x		x			x	x	x	
Pregnancy test	x															

Permissible time windows: The permissible length of time between screening and enrolment is ≤28 days. Patients who are not enrolled within 28 days after screening must be rescreened. Emicizumab may be injected within a window of 3 days before the scheduled treatment date (scheduled date –3 days). If the participant forgets or is unable to inject emicizumab within the permitted dosing window, the injection should be given as soon as possible within 3 days after the scheduled treatment date in participants receiving QW dosing, within 7 days after the scheduled treatment date in participants receiving Q2W dosing, and within 14 days after the scheduled treatment date in participants receiving Q4W dosing. To monitor treatment compliance when emicizumab is administered at home by the patient or caregiver, the patient/caregiver will be asked about emicizumab usage at each scheduled study visit.

BU, Bethesda unit; eCRF, electronic case report form; FVIII, factor VIII; F/U, follow-up; HJHS, Hemophilia Joint Health Score; MRI, magnetic resonance imaging; QW, weekly; Q2W, every 2 weeks; Q4W, every 4 weeks; Wk, week.

†The early termination visit is conducted when a participant is discontinued from emicizumab after having received emicizumab treatment. The safety follow-up visit is conducted 24 weeks after emicizumab is discontinued. This visit will not be performed for participants who continue emicizumab treatment after the end of the study.

‡A complete physical examination should be performed at screening. Subsequent physical examinations will evaluate joints (bleeds, arthropathy findings) and skin (contusions, haematomas, injection site reactions, lipodystrophy), as well as other organs if clinically necessary and/or new or worsened adverse events are observed.

§Treatment for bleeds requiring treatment with coagulation factors will be entered on the eCRF at the study site based on the information provided in the questionnaires on coagulation factors used.

¶Haematological laboratory tests included haemoglobin, haematocrit, platelet count, red blood cell count, white blood cell count, differential white blood cell count (neutrophils, eosinophils, lymphocytes, monocytes, basophils), mean cell volume, mean cell haemoglobin concentration, and red cell distribution width. Blood chemistry tests included sodium, potassium, chloride, calcium, phosphorus, magnesium, glucose, blood urea nitrogen, creatinine, total bilirubin, total protein, albumin, alanine aminotransferase, aspartate aminotransferase, lactate dehydrogenase, creatine phosphokinase, and uric acid.

††The participant must have a negative result (<0.6 BU/mL) on an FVIII inhibitor assay conducted at screening or within 8 weeks prior to enrolment.

‡‡The bleeds/drugs used logs should be completed by the caregiver. The caregiver will complete the Emicizumab Injection Log each time emicizumab is injected, the Bleeding Episode Log each time a bleed requiring treatment with coagulation factors occurs, and the Coagulation Factors Log each time coagulation factors are used. When

a participant is discontinued from emicizumab treatment, the caregiver will continue to update the Bleeding Episode Log and Coagulation Factors Log until completion of the safety follow-up visit.

§§The participant will inform the investigator about adverse events at each study visit. Adverse events will be reported on the eCRF by the investigator.

¶¶The MRI and HJHS joint assessments will be performed within ±28 days of the scheduled time point at Week 1. The Week 145 and Week 313 MRI joint assessments may be performed within ±84 days of the scheduled time point. The HJHS joint assessment may be performed within ±28 days of the scheduled time point at Weeks 25 and 49 and within ±84 days of the scheduled time point thereafter.

Supplementary Table 2. Schedule of assessments for participants entering from HOHOEMI

	Screening	Wk25†	Wk37	Wk49	Wk61 and every 12 weeks thereafter	Wk73 and every 24 weeks thereafter	Wk97 and every 48 weeks thereafter (except Wk289)	Wk145	Week313/ Early termination‡	Safety F/U visit‡
Informed consent	x									
Inclusion/exclusion criteria	x									
Medical history and demographic data	x									
Height				x			x	x	x	
Body weight		x	x	x	x			x	x	x
Physical examination§		x	x	x	x			x	x	x
Concomitant medications¶		x	x	x	x			x	x	x
Haematology/blood chemistry††		x		x		x		x	x	x
FVIII inhibitors		x		x		x		x	x	x
Questionnaires on bleeds and drugs used‡‡		←	—	—	—	—	→	x	x	x
Activities survey		x	x	x	x			x		
Adverse events§§		←	—	—	—	—	→	x	x	x
MRI joint assessment¶¶								x	x	
HJHS joint assessment¶¶				x			x	x	x	

Emicizumab may be injected within a window of 3 days before the scheduled treatment date. If the participant forgets or is unable to inject emicizumab within the permitted dosing window, the injection should be given as soon as possible within 3 days after the scheduled treatment date in participants receiving QW dosing, within 7 days after the scheduled treatment date in participants receiving Q2W dosing, and within 14 days after the scheduled treatment date in participants receiving Q4W dosing. To monitor

treatment compliance when emicizumab is administered at home by the patient or caregiver, the patient/caregiver will be asked about emicizumab usage at each scheduled study visit.

BU, Bethesda unit; eCRF, electronic case report form; FVIII, factor VIII; F/U, follow-up; HJHS, Hemophilia Joint Health Score; MRI, magnetic resonance imaging; QW, weekly; Q2W, every 2 weeks; Q4W, every 4 weeks; Wk, week.

†Day 1 (Wk 1) is defined as the day of administration of the first dose of emicizumab in HOHOEMI. Week numbers of visits are ongoing from HOHOEMI in participants entering from HOHOEMI.

‡The early termination visit is conducted when a participant is discontinued from emicizumab after having received emicizumab treatment. The safety follow-up visit is conducted 24 weeks after emicizumab is discontinued. This visit will not be performed for participants who continue emicizumab treatment after the end of the study.

§Physical examinations will evaluate joints (bleeds, arthropathy findings) and skin (contusions, haematomas, injection site reactions, lipodystrophy), as well as other organs if clinically necessary and/or new or worsened adverse events are observed.

¶Treatment for bleeds requiring treatment with coagulation factors will be entered on the eCRF at the study site based on the information provided in the questionnaires on factors used.

††Haematological laboratory tests included haemoglobin, haematocrit, platelet count, red blood cell count, white blood cell count, differential white blood cell count (neutrophils, eosinophils, lymphocytes, monocytes, basophils), mean cell volume, mean cell haemoglobin concentration, and red cell distribution width. Blood chemistry tests included sodium, potassium, chloride, calcium, phosphorus, magnesium, glucose, blood urea nitrogen, creatinine, total bilirubin, total protein, albumin, alanine aminotransferase, aspartate aminotransferase, lactate dehydrogenase, creatine phosphokinase, and uric acid.

‡‡The bleeds/drugs used logs should be completed by the caregiver. The caregiver will complete the Emicizumab Injection Log each time emicizumab is injected, the Bleeding Episode Log each time a bleed requiring treatment with coagulation factors occurs, and the Coagulation Factors Log each time coagulation factors are used. When a participant is discontinued from emicizumab treatment, the caregiver will continue to update the Bleeding Episode Log and Coagulation Factors Log until completion of the safety follow-up visit.

§§The participant will inform the investigator about adverse events at each study visit. Adverse events will be reported on the eCRF by the investigator.

¶¶MRI and HJHS joint assessments will be performed within –84 to 0 days of the scheduled time point. If an assessment cannot be performed within –84 to 0 days of the scheduled time point, the assessment may be performed up to 84 days after the scheduled time point.

Supplementary Table 3. Adverse event severity grading scale for events excluded from World Health Organization toxicity grading scale

Grade	Severity
1	**Mild**: Transient or mild discomfort (<48 hours); no medical intervention or therapy required
2	**Moderate**: Mild to moderate limitation in activity; some assistance may be needed; no or minimal medical intervention or therapy required
3	**Severe**[†]: Marked limitation in activity; some assistance usually required; medical intervention or therapy required; hospitalization possible
4	**Life-threatening**: Extreme limitation in activity; significant assistance required; significant medical intervention or therapy required; hospitalization or hospice care possible

Developed by the Division of Microbiology and Infectious Diseases.

[†]Regardless of severity, some events may also meet seriousness criteria; the terms “serious” and “severe” are not synonymous, both need to be independently assessed.

Supplementary Table 4. Seriousness criteria of adverse events

Number	Criteria
1	Is fatal (i.e., the adverse event causes or leads to death)
2	Is life threatening† (i.e., the adverse event, in the view of the investigator, places the participant at immediate risk of death)
3	Requires or prolongs inpatient hospitalization
4	Results in persistent or significant disability/incapacity (i.e., the adverse event results in substantial disruption of the participant's ability to conduct normal life functions)
5	Is any serious adverse event associated with the pregnancy of a female participant (e.g., an event in the foetus, an event in the mother during or after pregnancy, or a congenital anomaly/birth defect in the child)
6	Is a significant medical event in the investigator's judgment (e.g., may jeopardize the participant or may require medical/surgical intervention to prevent one of the outcomes listed above)

†This does not include any adverse event that, had it occurred in a more severe form or could continue, might have caused death. The terms "severe" and "serious" are not synonymous; severity refers to the intensity of an adverse event.

Supplementary Table 5. Baseline characteristics of participants enrolled in AOZORA

	Participants entering from HOHOEMI N = 10	New participants N = 20	Total participants N = 30
Age (years), median (range)	5.8 (1.5–10.7)	3.7 (0.7–11.0)	4.1 (0.7–11.0)
Age category, n (%)			
0 to <2 years	2 (20.0)	4 (20.0)	6 (20.0)
2 to <6 years	3 (30.0)	9 (45.0)	12 (40.0)
6 to <12 years	5 (50.0)	7 (35.0)	12 (40.0)
Male, n (%)	10 (100)	20 (100)	30 (100)
Weight (kg), median (range)	19.4 (9.5–35.6)	15.9 (7.3–63.1)	16.3 (7.3–63.1)
Treatment regimen with coagulation factor products prior to enrolment, n (%)			
Episodic FVIII	0 (0)	2 (10.0)	2 (6.7)
Prophylactic FVIII	10 (100)	17 (85.0)	27 (90.0)
Previously untreated participants	0 (0)	1 (5.0)	1 (3.3)
Participants previously treated with ITI therapy, n (%)	2 (20.0)	3 (15.0)	5 (16.7)
Duration of ITI (years), median (range)	0.8 (0.4–1.1)	2.3 (0.6–5.3)	1.1 (0.4–5.3)
Period from end of ITI to emicizumab initiation (years), median (range)	3.9 (0.3–7.4)	3.2 (1.1–5.0)	3.2 (0.3–7.4)
Participants with target joints, n (%)	1 (10.0)	0 (0)	1 (3.3)

FVIII, factor VIII; ITI, immune tolerance induction.

Supplementary Table 6. Baseline participant IPSG MRI Scale; the number of joints with a positive score (≥1 point) according to each item

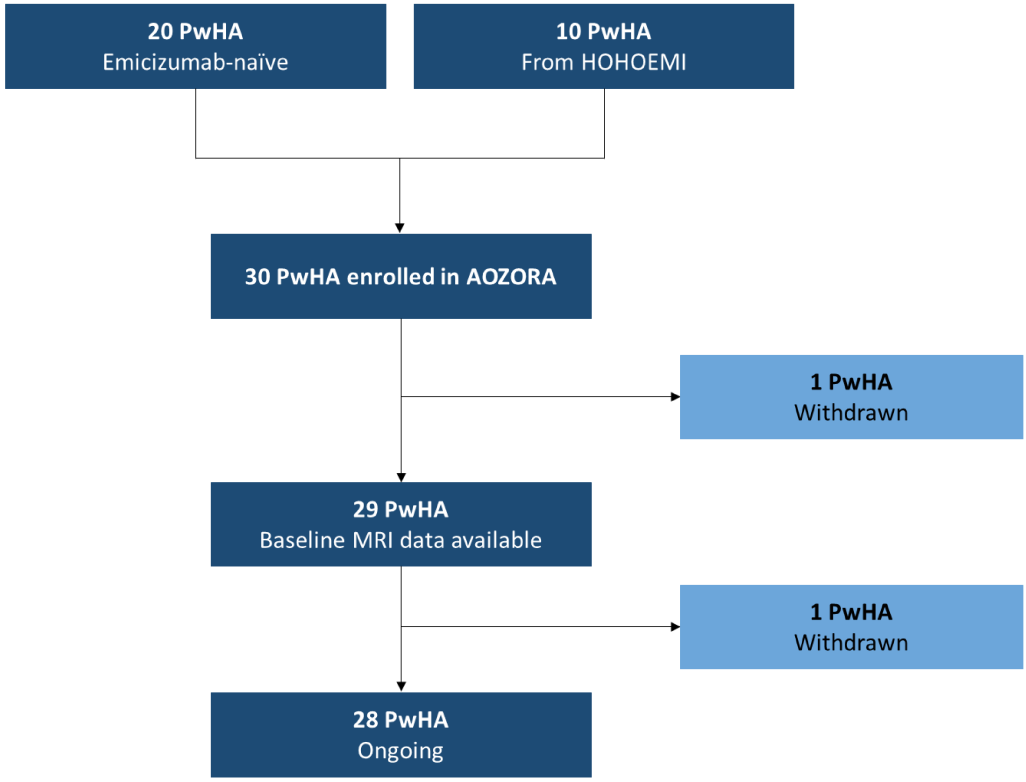
	Knee (N = 58)	Ankle (N = 58)	Total (N = 116)
Soft tissue changes, n (%)†	12 (20.7)	16 (27.6)	28 (24.1)
Effusion/haemarthrosis, n (%)	11 (19.0)	10 (17.2)	21 (18.1)
Small, n (%)	11 (19.0)	10 (17.2)	21 (18.1)
Moderate, n (%)	0	0	0
Large, n (%)	0	0	0
Synovial hypertrophy, n (%)	1 (1.7)	9 (15.5)	10 (8.6)
Small, n (%)	1 (1.7)	7 (12.1)	8 (6.9)
Moderate, n (%)	0	2 (3.4)	2 (1.7)
Large, n (%)	0	0	0
Haemosiderin, n (%)	1 (1.7)	9 (15.5)	10 (8.6)
Small, n (%)	1 (1.7)	7 (12.1)	8 (6.9)
Moderate, n (%)	0	2 (3.4)	2 (1.7)
Large, n (%)	0	0	0
Osteochondral changes, n (%)	0	1 (1.7)	1 (0.9)
Surface erosions involving subchondral cortex or joint margins, n (%)	0	1 (1.7)	1 (0.9)
Subchondral cysts, n (%)	0	0	0
Cartilage degradation, n (%)	0	0	0

IPSG, International Prophylaxis Study Group; n, number of joints; MRI, magnetic resonance imaging.

†Effusion/haemarthrosis, synovial hypertrophy and haemosiderin may be scored more than once in the same joint.

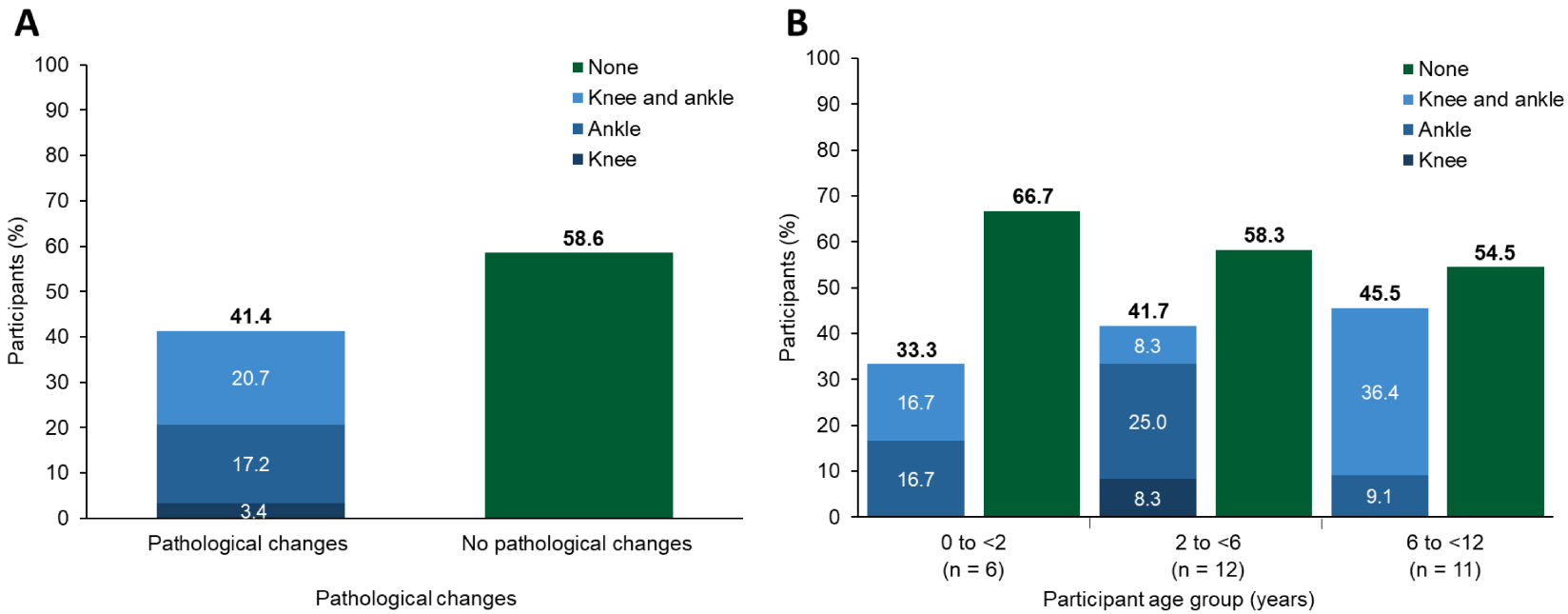
Bilateral ankles and knees were centrally scored using the additive MRI scale of the IPSG.

Supplementary Figure 1. Participant disposition



MRI, magnetic resonance imaging; PwHA, persons with haemophilia A

Supplementary Figure 2. Participants with pathological changes in the knee and ankle joints at baseline



A) Proportions of participants with and without pathological changes at baseline. **B**) Proportions of participants in different age groups with pathological changes in joints at baseline.

Participants with a positive score (>1) of the additive IPSG MRI scale on at least one joint are defined as having pathological change (soft tissues changes and osteochondral changes). MRI evaluation was performed on 29 participants.

IPSG, International Prophylaxis Study Group; MRI, magnetic resonance imaging

Activities questionnaire

After carefully reading the following instructions, enter the activities of your child during the week.

Instructions

(1) Use a ballpoint pen, felt-tip pen, or other writing utensil with permanent ink.
(2) Submit the completed questionnaire to the physician or study collaborator at the next study visit.
(3) If you make a mistake, do not use the correction fluid. Revise the text so that the changes are apparent, by, for example, drawing a strikethrough line through the mistaken text.
(4) If you misplace the questionnaire, contact the study site.

Patient No.:

Period covered: 20 / / ～ 20 / / (Wk)

■ Record the duration of activities in the following week, using the Table of Activity Categories provided below as reference.

- For activities performed for at least 15 minutes in one day, select the type of activity from the Table of Activity Categories provided below and record the appropriate category number and the duration of the activity. (If you have trouble determining which category is appropriate, select the category with the highest number.). If you have more than one activity in the same category during a day, enter the total time.
- If activities belonging to different categories are performed in the same day, enter the additional activities in the Activities 2, 3, and 4 columns. If an activity causes bleeding, check the box in the "activity-related bleeding" field and enter the number of bleeds in the parentheses. If you have more than one site of bleeding, count each as one time (e.g., If you have bleeding in two sites after falling, please enter "2").

	Item	M: D: 20:	M: D: 20:	M: D: 20:	M: D: 20:	M: D: 20:	M: D: 20:	M: D: 20:
Activity 1	Category No.							
	Activity duration	min	min	min	min	min	min	min
	Activity-related bleeds	□ (bleed(s))	□ (bleed(s))	□ (bleed(s))	□ (bleed(s))	□ (bleed(s))	□ (bleed(s))	□ (bleed(s))
Activity 2	Category No.							
	Activity duration	min	min	min	min	min	min	min
	Activity-related bleeds	□ (bleed(s))	□ (bleed(s))	□ (bleed(s))	□ (bleed(s))	□ (bleed(s))	□ (bleed(s))	□ (bleed(s))
Activity 3	Category No.							
	Activity duration	min	min	min	min	min	min	min
	Activity-related bleeds	□ (bleed(s))	□ (bleed(s))	□ (bleed(s))	□ (bleed(s))	□ (bleed(s))	□ (bleed(s))	□ (bleed(s))
Activity 4	Category No.							
	Activity duration	min	min	min	min	min	min	min
	Activity-related bleeds	□ (bleed(s))	□ (bleed(s))	□ (bleed(s))	□ (bleed(s))	□ (bleed(s))	□ (bleed(s))	□ (bleed(s))
Activity 5	Category No.							
	Activity duration	min	min	min	min	min	min	min
	Activity-related bleeds	□ (bleed(s))	□ (bleed(s))	□ (bleed(s))	□ (bleed(s))	□ (bleed(s))	□ (bleed(s))	□ (bleed(s))

	Item	M: D: 20:	M: D: 20:	M: D: 20:	M: D: 20:	M: D: 20:	M: D: 20:	M: D: 20:
Activity 6	Category No.							
	Activity duration	min	min	min	min	min	min	min
	Activity-related bleeds	□ (bleed(s))	□ (bleed(s))	□ (bleed(s))	□ (bleed(s))	□ (bleed(s))	□ (bleed(s))	□ (bleed(s))
Activity7	Category No.							
	Activity duration	min	min	min	min	min	min	min
	Activity-related bleeds	□ (bleed(s))	□ (bleed(s))	□ (bleed(s))	□ (bleed(s))	□ (bleed(s))	□ (bleed(s))	□ (bleed(s))
Activity 8	Category No.							
	Activity duration	min	min	min	min	min	min	min
	Activity-related bleeds	□ (bleed(s))	□ (bleed(s))	□ (bleed(s))	□ (bleed(s))	□ (bleed(s))	□ (bleed(s))	□ (bleed(s))
Activity 9	Category No.							
	Activity duration	min	min	min	min	min	min	min
	Activity-related bleeds	□ (bleed(s))	□ (bleed(s))	□ (bleed(s))	□ (bleed(s))	□ (bleed(s))	□ (bleed(s))	□ (bleed(s))
Activity 10	Category No.							
	Activity duration	min	min	min	min	min	min	min
	Activity-related bleeds	□ (bleed(s))	□ (bleed(s))	□ (bleed(s))	□ (bleed(s))	□ (bleed(s))	□ (bleed(s))	□ (bleed(s))

Physician Signature:_____ Confirmation date:_____

■ Table of Activity Categories

Category	Activity type	Examples
1	Home duties	Vacuuming, cleaning, dusting (e.g., with mop), sweeping, cooking, painting, gardening, lawn mowing, shopping, picking up rubbish
2	Jogging/walking/sprinting	Transport, recreation, jogging, sprint races, long distance running, marching, athletics, hiking, cross country running
3	Swimming	Freestyle, breaststroke, butterfly, backstroke, kickboard, treading water
4	Light play	Playing with friends, playing with dog, playing with blocks, drumming, Wii fit or Wii sports, jumping, slide, see-saw, frisbee, skipping, hula hoop, swing, card games, theme parks
5	Non-contact sports	Archery, darts, bowling, golf, fishing, tai chi, pool, table tennis, marbles, badminton
6	Dancing	Hip hop, jazz, ballroom dancing, contemporary dance, folk dancing
7	Light gym activities	Lifting weights, exercise using gym equipment, cardio, stretching, physiotherapy, gym class exercises
8	PE	School PE lessons
9	Low-contact ball games	Handball, playing catch
10	Throwing	Shot put, javelin, discus
11	Water play	Wind surfing, snorkeling, scuba diving, rowing, canoeing, lifesaving
12	Water activities	Surfing, waterskiing, diving, water slides, rafting, sailing
13	Unstructured park/open space activities	Jumping castle, trampolining, climbing, tug-o-war, climbing trees, swinging from ropes, playing on play equipment
14	Gymnastics	Artistic, rhythmic, acrobatics, competitive trampolining
15	Low-risk riding activities	Bike riding, riding scooter, riding horse, rollerblading, roller-skating
16	Wilderness	Rock climbing, abseiling, chopping wood

Category	Activity type	Examples
17	Hard ball games/training	Baseball, softball, cricket
18	Running games/jumping	Chasings, running long jump, running high jump, hurdles
19	Racquet sports	Tennis, squash
20	Low-contact sports	Soccer, basketball, volleyball, field hockey, football umpire, school sport (club activities)
21	Winter sports	Skiing, ice-skating, sledding, snowboarding
22	Martial arts	Karate, Kung Fu, Tae Kwon Do, Judo, boxercise, boxing drill
23	Contact/collision sports	Rugby, American football, ice hockey, wrestling, boxing
24	Motor sports	Motocross
25	High-risk riding activities	Skateboarding, rip-stick
26	Rough play	Wrestling, dodge ball