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AKATSUKI study: a prospective, multicentre, phase IV study evaluating the safety of emicizumab under and immediately after immune tolerance induction therapy in persons with congenital haemophilia A with factor VIII inhibitors

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ABSTRACT

Introduction For persons with haemophilia A with factor (F) VIII inhibitors (PwHAwI), immune tolerance induction (ITI) therapy is indicated for inhibitor eradication; however, since PwHAwI on ITI were excluded from the emicizumab clinical development programme, there are limited safety data for emicizumab treatment under/immediately after ITI in PwHAwI. Accordingly, there is a need to collect safety and efficacy data on this concomitant treatment strategy. The AKATSUKI study aims to evaluate the safety of emicizumab under/immediately after ITI in PwHAwI; here we report details of the study protocol.

Methods and analysis AKATSUKI is an open-label, non-randomised, interventional, multicentre study. Twenty participants with congenital HA with FVIII inhibitors will be enrolled from 17 sites across Japan. Emicizumab will be administered subcutaneously, with an initial loading dose of 3 mg/kg once per week (QW) for the first 4 weeks, followed by a maintenance dose of 1.5 mg/kg QW, 3 mg/kg once every 2 weeks or 6 mg/kg once every 4 weeks. For ITI therapy, 50 IU/kg FVIII will be administered three times per week. For extended half-life FVIII, a dosing frequency of twice per week will be permitted. The primary endpoint is a comprehensive safety evaluation of adverse events (mainly thromboembolic events) and abnormal laboratory values over time. Secondary endpoints are the number of bleeds requiring coagulation factor treatment, the number of participants achieving a partially successful ITI response, FVIII inhibitor titres under/immediately after ITI, quality of life and time to achieve a negative FVIII inhibitor result (<0.6 BU/mL) and partial success in PwHAwI starting ITI after study enrolment.

Conclusions AKATSUKI will evaluate the safety of emicizumab administered under/immediately after ITI, providing reference data to inform treatment strategies in PwHAwI.

Ethics and dissemination The results of this study will be published in a peer-reviewed international journal and presented at national and/or international medical scientific conferences; the major findings of this study will be published on the jRCT registry website (https://jrct.niph.go.jp).

Trial registration number jRCTs041200037.

Strengths and limitations of this study

- The prospective, interventional AKATSUKI study will address the knowledge gap on the safety of emicizumab prophylaxis administered under or immediately after immune tolerance induction (ITI) in persons with haemophilia A (PwHA) with factor (F) VIII (FVIII) inhibitors.
- Secondary outcomes will provide data on efficacy and quality of life for PwHA with FVIII inhibitors receiving emicizumab under or immediately after ITI.
- The study aims to enrol 20 participants and results obtained from small sample sizes should be interpreted with caution.
- Participant backgrounds are not unified; individuals already receiving ITI and/or emicizumab prior to enrolment are eligible for inclusion alongside those initiating ITI and emicizumab at study entry.
- The lack of a control group means that no direct comparison to standard treatment can be made.

INTRODUCTION

Haemophilia A (HA) is a bleeding disorder associated with spontaneous/traumatic bleeding caused by a deficiency in coagulation factor (F) VIII[1]; furthermore, up to 30% of persons with HA (PwHA) treated with FVIII products develop antibodies to FVIII, neutralising the function of infused FVIII products, further complicating management[2]

and increasing disease burden, for both PwHA and their caregivers.[3–5]

Historically, bleeding in PwHA with FVIII inhibitors (PwHAwI) was managed with the use of bypassing agents (BPAs), consisting of recombinant activated FVII or activated prothrombin complex concentrate (aPCC). However, neither agent is as effective as FVIII for achieving haemostasis; therefore, eradication of FVIII inhibitors via immune tolerance induction (ITI) is usually attempted.[2 6 7] With ITI, FVIII concentrates are administered frequently to downregulate the established antibody response and, thus, induce immune tolerance to FVIII.[8] ITI has a 60%–80% success rate in adult and paediatric PwHAwI.[9–11]

Emicizumab is a humanised, bispecific, monoclonal antibody that bridges activated FIX and FX to restore the function of missing activated FVIII and haemostasis in PwHA.[12] The pharmacokinetic properties of emicizumab[13] allow for a marked extension of the dosing interval, compared with FVIII, to only once every week (QW), once every 2 weeks (Q2W) or once every 4 weeks (Q4W), which, coupled with a subcutaneous route of administration,[14] offers PwHA with or without FVIII inhibitors a less burdensome treatment relative to traditional products. The efficacy and favourable safety profile of emicizumab prophylaxis in PwHA with or without FVIII inhibitors were demonstrated during the global HAVEN 1–4 clinical development programme,[15–19] as well as in studies conducted in Japan.[20–22] Such efficacy may suggest that eradication of FVIII inhibitors is not required for PwHAwI receiving emicizumab prophylaxis; however, there remain situations where additional factor concentrate may be required, including for treatment of breakthrough bleeds and for management of bleeds due to trauma or surgery.[23] While BPAs can provide additional coverage in such cases, they are not as effective as FVIII and use of high doses of aPCC (>100 U/kg/24 hours for 24 hours or more) in combination with emicizumab is advised against, as it has been associated with increased risk of thrombotic events (TEs) and thrombotic microangiopathies (TMAs).[15] Eradication of FVIII inhibitors using ITI has therefore been advocated for PwHAwI being treated with emicizumab prophylaxis.[23]

As PwHAwI receiving ITI therapy were excluded from the emicizumab clinical development programme, there are currently limited data on the safety and efficacy of emicizumab administered in combination with ITI therapy. Emicizumab administered immediately post-ITI or alongside ITI is, therefore, a current area of interest for clinicians.

Guidance published by the Japanese Society on Thrombosis and Haemostasis recommends that therapeutic decision-making on combining emicizumab prophylaxis with ITI should be done under specialist advisement.[24] Accordingly, there is a need for the medical community to collect data on the safety and efficacy of emicizumab when administered under or immediately after ITI therapy. The AKATSUKI study was planned for this purpose; here we report the study objectives, design, outcomes and assessments.

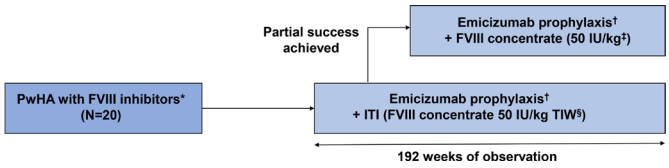

Figure 1 AKATSUKI study design. *PwHA receiving ITI therapy and/or emicizumab at study enrolment are eligible for participation. †Emicizumab prophylaxis will be administered according to the dosing regimen approved in Japan. ‡The dosing regimen is as follows: 50 IU/kg QW for the first 24 weeks and then 50 IU/kg Q2W for the next 24 weeks, after which the FVIII concentrate may be discontinued at the investigator's discretion. The dose of FVIII concentrate may be adjusted by ±20%. §A dosing frequency of twice per week is permitted when using extended half-life FVIII concentrates. The dose of FVIII concentrate may be adjusted by ±20%. FVIII, factor VIII; ITI, immune tolerance induction; PwHA, persons with haemophilia A; QW, once per week; Q2W, once every 2 weeks; TIW, three times per week.

MATERIALS AND METHODS

Additional details of the AKATSUKI study are provided in online supplemental material.

Objectives

The primary objective of the study is to evaluate the safety of emicizumab prophylaxis administered under and immediately after ITI with FVIII concentrates in PwHAwI.

Study design and setting

The AKATSUKI study is an open-label, non-randomised, interventional, multicentre phase IV study of emicizumab administered under and immediately after ITI therapy with FVIII concentrates in PwHAwI for 192 weeks (figure 1). Participants will be enrolled from 17 sites across Japan. The first participant was enrolled on 6 November 2020 and the enrolment period was planned to continue for 48 weeks from this date. The total duration of the study is estimated to be 320 weeks, with completion expected in 2027.

The AKATSUKI study is registered in the Japan Registry of Clinical Trials (available online at: https://jrct.niph.go.jp/en-latest-detail/jRCTS041200037).

Interventions

Emicizumab prophylaxis is administered subcutaneously, with an initial loading dose of 3 mg/kg QW for the first 4 weeks, followed by a maintenance dose of 1.5 mg/kg QW, 3 mg/kg Q2W or 6 mg/kg Q4W.[25] For ITI therapy, 50 IU/kg FVIII will be administered three times per week (TIW). This dosing frequency was selected based on a previous study that demonstrated similar ITI success for dosing regimens of 50 IU/kg TIW and 200 IU/kg daily.[11] Although there was a higher rate of bleeding in the group of participants who received the lower dose, it is expected

that the emicizumab administered in the present study will provide more effective bleed control. In addition, Japanese guidelines state that the burden on PwHA and their families resulting from frequent injections should be considered when selecting an ITI regimen.[26] For extended half-life (EHL) FVIII, a dosing frequency of two times per week will be permitted. There will be no restrictions on the type of FVIII concentrates used. A central venous access device can be employed if deemed necessary. The dose of FVIII will be allowed to adjust by ±20% for ITI and post-ITI maintenance therapy. ITI therapy will be used for as long as necessary and can be continued after the end of the study if deemed appropriate by the treating physician.

Participants with an ITI response identified as partially successful by the investigator will receive emicizumab and FVIII starting from the date of their next scheduled study visit. Post-ITI maintenance therapy will consist of any FVIII concentrate administered at 50 IU/kg QW for 24 weeks followed by 50 IU/kg Q2W for 24 weeks, after which the use of FVIII may be discontinued at the investigator's discretion. This maintenance regimen was selected by the investigators based on the proposal by the Future of Immunotolerance Treatment (FIT) group.[27]

Eligibility

Inclusion criteria

Eligible participants must have a diagnosis of congenital HA and fulfil one of the two following criteria: (1) will start ITI therapy after study enrolment and have a positive FVIII inhibitor titre (≥0.6 BU/mL) as evidenced by the most recent laboratory test result within the 8 weeks prior to enrolment, or (2) is currently undergoing ITI, and has not met the criteria for ITI partial success, as evidenced by the most recent laboratory test result within the 8 weeks prior to study enrolment. Individuals with long-standing FVIII inhibitors and those with a history of failed ITI can be included. Participants (or their legally recognised representative) are required to provide written informed consent and be willing/able to complete all study procedures and study questionnaires.

Exclusion criteria

Participants will be excluded if they satisfy any of the following criteria: have an inherited or acquired bleeding disorder other than HA, have previous (≤12 months prior to study enrolment) or current treatment for, or high risk of, TEs (with the exception of previous catheter-associated TEs for which anti-TE treatments are not currently ongoing), are at high risk for TMA based on familial history of TMAs, are participating in or planning to participate in another interventional study, or are otherwise considered unsuitable for study participation by the investigator.

Outcome measures

For a discussion of the endpoint rationale, see online supplemental material.

Primary outcome

The primary outcome of the AKATSUKI study will be to comprehensively evaluate adverse events (AEs; mainly TEs) and abnormal laboratory values reported over time following administration of emicizumab in combination with and immediately after ITI therapy. Over time is defined as: (1) from first emicizumab dose post-enrolment until a negative FVIII inhibitor titre (<0.6 BU/mL); (2) from the time to achieve a negative FVIII inhibitor titre until normal FVIII recovery (FVIII recovery ≥66% of predicted value on two consecutive occasions at least 2 weeks apart); and (3) from normal FVIII recovery until last observation at week 192.

After initiation of emicizumab, all AEs occurring through the date of the last observation, completion of the safety follow-up visit performed 24 weeks after emicizumab discontinuation, withdrawal of informed consent, or loss to follow-up, will be recorded in the electronic case report form (eCRF), regardless of relationship to emicizumab. Severity will be assessed using the WHO toxicity grading scale (grade 1=mild; grade 2=moderate; grade 3=severe; grade 4=life-threatening).

Data will also be summarised by timing of treatment and use of concomitant medications, such as when using BPAs.

Secondary outcomes

Secondary outcome measures include: (1) number of bleeds over time requiring treatment with coagulation factors; (2) number of participants achieving an ITI response defined as partial success; (3) time to achieve negative FVIII inhibitor titre and partial success in participants starting ITI after study enrolment; (4) FVIII inhibitor titres under and immediately after ITI; and (5) paediatric and adolescent participant-reported haemophilia-related quality of life (QoL) as measured by the Haemophilia-specific Quality of Life Short Form (Haemo-QoL-SF) and patient health-related QoL according to caregivers as measured by the adapted Inhibitor-specific Quality of Life with Aspects of Caregiver Burden (INHIB-QoL) questionnaire scores.

ITI response will be defined based on the definitions used in the International Immune Tolerance Study (table 1).[11] An ITI response is defined as a partial success if the participant has a negative FVIII inhibitor result plus normal FVIII recovery. Partial success is achieved on the date that the participant's blood sample shows normal FVIII recovery. For a successful ITI response, the participant must meet the criteria for partial success plus demonstrate a normal FVIII half-life; however, due to potential burden on the participant, half-life assessment based on full pharmacokinetic analysis is not mandatory. Whereas the International ITI study defined ITI success as having achieved all three criteria of negative FVIII inhibitor result, normal FVIII recovery and normal FVIII half-life,[11] the AKATSUKI study defines that participants achieving partial success will proceed to post-ITI treatment. This decision was based on a thorough review of the nature/

Table 1 Assessment criteria for partial and complete success

	Assessment criteria
Negative FVIII inhibitor titre*†	FVIII inhibitor titre <0.6 BU on two consecutive occasions at least 2 weeks apart
Normal FVIII recovery*†	FVIII recovery ≥66% of predicted value on two consecutive occasions at least 2 weeks apart
Normal FVIII half-life†	FVIII half-life ≥6 hours for standard half-life FVIII concentrates or ≥7 hours for extended half-life FVIII concentrates

*Criteria for partial success.
†Criteria for complete success; however, due to the participants' burden, FVIII half-life assessment based on full pharmacokinetic analysis is not mandatory.
BU, Bethesda Unit; FVIII, factor VIII.

extent of assessments performed under ITI as advised by haemophilia specialists in Japan.

Assessments

The schedule of assessments is shown in online supplemental table 1 (emicizumab under ITI) and online supplemental table 2 (emicizumab immediately after ITI).

Safety

At each study visit, participants will be required to report any AEs; the investigator will then record these AEs in the eCRF. Laboratory tests will be performed at the study site if aPCC or activated human blood coagulation FVII concentrate containing FX (Byclot) are administered, and will include the following variables: prothrombin time, activated partial thromboplastin time, D-dimer, fibrin and fibrinogen degradation products, lactate dehydrogenase, platelets and creatinine. Tests can also be performed at unscheduled timepoints during the study at the investigator's discretion.

ITI response

For participants receiving emicizumab prophylaxis under ITI therapy, FVIII inhibitor titre and FVIII activity assays will be performed Q4W after *ex vivo* spiking of sample solutions with anti-idiotypic antibodies to emicizumab.[28] Blood samples will be collected following a 48-hour or 72-hour washout period after the last dose of standard or EHL FVIII concentrate, respectively. Following two consecutive negative FVIII inhibitor results at an interval of at least 2 weeks, FVIII recovery will be assayed until normal. Blood samples will be collected 15–30 min before and after administration of FVIII following a 48-hour or 72-hour washout period after the last dose of standard or EHL FVIII, respectively.

If FVIII half-life is being assessed, and FVIII recovery has normalised, the assay will be performed until the results show that FVIII half-life has normalised; however, this step is not mandatory. Blood samples will be collected every 15–30 min, and 1, 2, 4, 6, 24 and 48 hours before and after administration of the FVIII following a 48-hour or 72-hour washout period after the last dose of standard or EHL FVIII, respectively. For participants receiving EHL FVIII, sampling will also occur at 72-hour and 96-hour postdose.

For participants receiving emicizumab immediately after ITI therapy, FVIII inhibitor titre and FVIII activity assays will be performed once every 12 weeks; samples will be collected after the 48-hour or 72-hour washout period following the last dose of standard or EHL FVIII, respectively. FVIII inhibitor titre, FVIII recovery and half-life are tested via one-stage clotting assay.

Participant-reported and caregiver-reported outcomes

Participant-reported outcomes will be recorded on a mobile device by the participant/caregiver, and subsequently collected via an electronic participant-reported outcomes (ePRO) system, including bleeds requiring treatment with coagulation factors and all doses of emicizumab and other factor concentrates. Procedure-related/surgery-related bleeds will be captured in the eCRF or ePRO system. Haemophilia-related QoL will be measured in participants aged 8–17 years using the Haemo-QoL-SF questionnaire, and in caregivers of participants aged <18 years using the adapted INHIB-QoL questionnaire at prespecified timepoints (online supplemental tables 1 and 2).

Data analysis

Sample size

The target study sample size was selected based on the feasibility of recruitment and was decided following consultation with specialists in the treatment of HA in Japan. The decision was based on the number of PwHAwI expected to be eligible to participate, taking into account factors including age distribution, prevalence of congenital haemophilia, percentage of PwHA expected to develop FVIII inhibitors, predicted rate of informed consent and study enrolment period. The sample size was, therefore, set at 20 participants. Owing to the characteristics of Japanese medical practice, with centres each responsible for a small number of patients, a total of 17 institutions were required to achieve the desired sample size.

Data collection and management

All participant information and data will be maintained as confidential; data entry in eCRFs will be performed by the investigator or relevant study personnel with authorised access at each participating site and collated via the electronic data capture system (Viedoc). Participant-reported

and caregiver-reported outcomes will be captured using an ePRO system (ViedocMe).

Statistical analyses

Due to the exploratory nature of the AKATSUKI study, no confirmatory hypothesis was proposed. Continuous data will be described using arithmetic and geometric means, median, range, SD and coefficient of variation, and categorical data will be described as frequencies and contingency tables.

Safety will be evaluated in the Safety Analysis Set, which will comprise all participants who receive at least one dose of emicizumab and FVIII for ITI therapy during the study period. AEs and changes from baseline in laboratory values will be reported. Summary statistics will be provided for AEs; specifically, the number and percentage of participants reporting AEs. AEs will be summarised by event, classified by System Organ Class and preferred term.

The number of bleeds over time requiring treatment with coagulation factors, number of participants achieving an ITI response defined as partial success, FVIII inhibitor titres under and immediately after ITI (change over time in FVIII inhibitor titres) and participant haemophilia-related QoL (using descriptive statistics and changes from baseline) will each be assessed in participants who received FVIII concentrate for ITI and emicizumab at least once during the study. Emicizumab efficacy will be reported as bleed rate (ie, the number of bleeds requiring coagulation factor treatment over time). Participants will be stratified according to whether they started emicizumab prestudy or poststudy enrolment.

Time to achieve a negative FVIII inhibitor result and partial success in participants starting ITI therapy after study enrolment will be evaluated for those who received emicizumab and FVIII concentrate at least once during the study period. Results will be reported as time from the start of FVIII concentrate administration until a negative FVIII inhibitor result is achieved, and time from a negative FVIII inhibitor result until partial success is achieved. The proportion of participants in each category will be presented.

Interim analyses evaluating the safety of emicizumab prophylaxis administered in combination with ITI will be performed at weeks 25 and 49, and safety and efficacy will be evaluated at weeks 97 and 145.

Safety, efficacy and haemophilia-related QoL data will be analysed using Stata Statistical Software: Release 15 and SAS software, V.9.4 of the SAS System.

Ethics and dissemination

The study will be conducted in compliance with the principles of the Declaration of Helsinki and the Clinical Trials Act in Japan (Act No. 16 of 14 April 2017). Participating sites will obtain approval to conduct the study from the Certified Review Board (CRB): Nagoya University CRB; following which, investigators will obtain permission from their Study Site Director. Written informed consent will be obtained from all participants by the investigator. Informed consent will be obtained from adolescents aged ≥16 years whom the investigator deems capable of voluntarily agreeing to participate in the study. For adolescents aged <16 years who are willing and able to participate in the study, an informed assent form will be completed instead. For those aged <20 years at the time of consent, written informed consent will be provided by the participant's legally authorised representative.

The results of this study will be published in a peer-reviewed international journal and presented at national and/or international medical scientific conferences; the major findings of this study will be published on the jRCT registry website (https://jrct.niph.go.jp).

Patient and public involvement

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

DISCUSSION

Owing to the burden of FVIII inhibitor development, there remains a need for improved treatment strategies in PwHAwI. Previous demonstration of the efficacy and safety of emicizumab in PwHAwI[19] will naturally be followed by case reports of concomitant use of emicizumab and ITI therapy; establishment of an evidence base on ITI in the setting of emicizumab prophylaxis is an important step in developing improved treatment strategies.

To our knowledge, there is only one report evaluating the concomitant use of emicizumab and ITI therapy. In this case series, seven paediatric PwHAwI received emicizumab and ITI therapy with 50–100 IU/kg FVIII (TIW); four participants reported nine bleeds and there were no TEs.[29] The AKATSUKI study will primarily focus on the safety of emicizumab administered with FVIII ITI therapy, providing much needed evidence on the use of this treatment approach for PwHAwI. The data generated will complement the findings of two other planned studies.[30 31] The first of these will evaluate inhibitor eradication in PwHA of any age treated with emicizumab in combination with recombinant anti-haemophilic factor, Fc fusion protein.[30] The second will assess the safety and efficacy of emicizumab in combination with low-dose recombinant FVIII in PwHA aged <3 years.[31]

ITI therapy has been used for more than 30 years to eradicate FVIII inhibitors in PwHA, and data from several registries have been used to determine ITI regimens.[32] Since the success of FVIII inhibitor eradication is influenced by a variety of factors, evidence-based recommendations for PwHAwI are well established.[33] These were used as a basis for the ITI regimen selected for the AKATSUKI study; however, alternative dosing regimens and schedules are possible and may enable further optimisation in the setting of emicizumab prophylaxis. Additionally, since emicizumab is effective in preventing bleeding, FVIII can be administered solely for the purpose of inducing

tolerance, and at a lower dose/frequency than is typically used when undertaking ITI.[27]

There is currently no consensus on whether to continue maintenance of tolerisation following successful ITI; however, to maintain immune tolerance against FVIII inhibitors, the AKATSUKI study investigators selected emicizumab and low-dose FVIII combination therapy, based on the proposal by the FIT group.[27]

There are some limitations in the AKATSUKI study. Results obtained from small sample sizes should be interpreted with caution, particularly those evaluating ITI success. Participant backgrounds are not unified (participants who have already been administered emicizumab or ITI can register for study participation, regardless of their administration period). The lack of a control group means that no direct comparison to standard treatment can be made. Additionally, as participant safety is always the priority, interventional studies can be confounded by concomitant treatments. A further point to note is that activated FVII in combination with FX (Byclot) is a product available only in Japan, which may obscure the evaluation of treatment for bleeding in PwHA while on emicizumab. Despite these limitations, administration of emicizumab and ITI is a promising option, offering PwHA the potential for reduced bleeding plus FVIII inhibitor eradication.

CONCLUSION

For PwHAwI, treatment options are limited and can be suboptimal. While emicizumab has previously demonstrated good efficacy and tolerability in PwHAwI, there are currently limited data on its efficacy and safety profile when administered with ITI therapy.

The AKATSUKI study is designed to evaluate the safety and efficacy of emicizumab administered under/immediately after ITI therapy in PwHAwI. Data collected during this study will allow evaluation of this regimen and generate reference data to inform treatment strategies in PwHAwI.

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Contributors TM, NS, AN, CN, HY-S, YK, AI and KN designed and conducted the study. TM, NS, AN, CN and KN were responsible for participant recruitment and follow-up. TM, NS, AN, CN and KN collected, analysed and interpreted the data. All authors revised the manuscript critically and provided final approval of the version to be published. All authors agree to be accountable for all aspects of the work.

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SUPPLEMENTAL MATERIAL

METHODS

Interventions

Participants initially meeting the criteria required for partial success, but later found not to meet the negative factor (F)VIII inhibitor titre or normal FVIII recovery criterion, will have their treatment plan determined by the investigator.

Outcome measures

The rationale for the primary endpoint of the AKATSUKI study is as follows: Studies have hypothesised that persons with haemophilia A (PwHA) taking emicizumab prophylaxis typically have increased coagulation function and a milder haemophilia phenotype relative to baseline.[1 2] In PwHA with FVIII inhibitors, the activity of infused FVIII concentrates used in immune tolerance induction (ITI) therapy is neutralised or rapidly cleared; however, this activity could theoretically be partially restored when the FVIII inhibitor titre decreased.[3] Therefore, when concomitantly administering emicizumab and FVIII concentrates for ITI, potentially in addition to bypassing agents, the safety of the treatment regimen especially after eradication of FVIII inhibitors should be assessed for the risk of thromboembolic events, particularly given the potential for hypercoagulation.

Secondary outcomes

The definition of a bleeding event is as follows: An event will be considered a bleed if coagulation factors are administered to treat signs or symptoms of bleeding. A single bleeding episode starts with the first sign of a bleed and ends 72 h post-last injection; recurrent symptoms of bleeding at the same location, or repeated injections <72 h apart, will be considered related to the same bleed. Injections received >72 h after the preceding injection will be considered the first injection and, subsequently, a new bleed at the same location.

Matsushita T, *et al. BMJ Open* 2022; 12:e057018. doi: 10.1136/bmjopen-2021-057018

Bleed data will be categorised by spontaneous bleeds (defined as a bleed without an identifiable cause), traumatic bleeds (defined as a haemorrhage occurring secondary to an event such as trauma, strenuous activity, or overuse), joint bleeds and target joint bleeds (defined as a bleed in which ≥3 bleeds have occurred within 24 weeks prior to study enrolment). As per International Society on Thrombosis and Haemostasis definition, target joints will be defined as major joints in which ≥3 bleeding events occur over a 24-week period.[4] Documentation of bleeding episodes for 24 weeks prior to study enrolment will be required for the identification of target joints in participants aged <2 years.

Assessments

Sample preparation for measuring ITI response

Samples for central laboratory assay will be prepared by drawing a 4.5 mL blood sample into a blood collection tube containing 0.5 mL of 3.2% sodium citrate solution, mixing by inverting 5–6 times and then immediately centrifuging the sample in a cooling centrifuge for 15 min at 4 °C and 1700 G. The supernatant will then be pipetted into a designated container and cryostored. When drawing blood samples via a catheter or central venous access device (CVAD), a disposable tube must be used prior to sample collection to avoid potential contamination of the catheter/CVAD with isotonic sodium chloride solution used for cleaning or anticoagulant drug.

Ethics and dissemination

The study will be conducted in compliance with the principles of the Declaration of Helsinki, the Clinical Trials Act in Japan (Act No. 16 of 14 April 2017), the Enforcement Regulations of the Clinical Trials Act (MHLW Ordinance 17, 2018), the Ethical Guidelines for Medical and Health Research Involving Human Subjects (2017 Notification No. 1 of the Ministry of Education, Culture, Sports, Science and Technology and MHLW, 2017), other relevant guidelines and the approved study protocol.

Protocol amendments will be submitted by the Co-ordinating Principal Investigator for approval by the Certified Review Board (CRB). These changes will be implemented in the registered trial information and a notice of change submitted to the MHLW. The CRB and investigators will be notified of these changes.

Monitoring

To ensure the study is being conducted safely and in accordance with the approved protocol, independent monitoring will be performed biannually; the Periodic Monitoring Reports generated will contain information on recruitment status, participant eligibility, status of/reasons for treatment discontinuations, site-specific non-compliance and serious adverse events, adverse drug reactions and adverse events, and other study-/safety-related issues. For quality control and assurance purposes, periodic monitoring will be performed based on aggregated data entries in the electronic case report forms to ensure data are being collected appropriately. All study-related material will also be made available to independent quality assurance auditors, as required.

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SUPPLEMENTAL TABLE 1 Assessment schedule for PwHA with FVIII inhibitors receiving emicizumab prophylaxis under ITI therapy*

	Screening†	Week 1 (enrolment to first emicizumab study dose, +7 days)	Week 5 (±7 days)	Week 9 (±7 days)	Week 13 (±7 days)	Week 17 and every 4 weeks thereafter (±7 days)	Week 25 and every 12 weeks thereafter (±28 days)	Week 49 and every 48 weeks thereafter (±28 days)	Week 193‡ (±28 days)	Safety follow-up visit‡ (±28 days)
Informed consent	X									
Inclusion and exclusion criteria	X									
Medical history and demographic data	X									
Weight	X				X		X		X	X
FVIII inhibitor titre§	X	X	X	X	X	X			X	X
FVIII activity‖	X	X	X	X	X	X			X	X
FVIII recovery¥	X	X	X	X	X	X	X	X	X	X
FVIII half-life**		X	X	X	X	X	X	X	X	X
Laboratory tests††		←	—	—	—	—	—	—	—	→
Emicizumab plasma concentration‡‡		X	X	X	X	X	X	X	X	X

Haemo-QoL-SF and adapted INHIB-QoL questionnaires[§§]	X						X	X	
Bleeds and drugs used[‖‖]	X	X	X	X	X	X	X	X	X
AEs[¥¥]	X	X	X	X	X	X	X	X	X

The permissible time window for assessments between screening and enrolment is ≤28 days.

*For assessments scheduled on, or after, the date of the next study visit following investigator confirmation of ITI partial success, see Table 2.

[†]Screening results obtained prior to acquisition of informed consent can be used in lieu of retesting provided that they are considered medically appropriate by the investigator.

[‡]Participants who discontinue FVIII concentrates for ITI therapy will be requested to undergo early termination assessments at the next scheduled study visit following their last treatment. Participants who discontinue emicizumab will be requested to attend a follow-up assessment scheduled at 24 weeks after the last emicizumab dose.

[§]FVIII inhibitors will be centrally measured using anti-idiotypic antibodies to emicizumab. However, results measured by the study site after spiking the sample solution with anti-idiotypic antibodies to emicizumab can be used at screening provided they were obtained within 8 weeks before enrolment. Results of screening assays can also be used as the Week 1 results, provided the interval between screening and Week 1 does not exceed 7 days. Blood samples for central laboratory analysis can also be collected at unscheduled timepoints during the study at the investigator's discretion. FVIII inhibitor assay samples will be collected after the 48-h washout period following the last dose of FVIII concentrate (or after 72 h when using extended half-life FVIII concentrates).

[‖]FVIII activity will be centrally measured using anti-idiotypic antibodies to emicizumab. Results of screening assays can also be used as the Week 1 results provided the interval between screening and Week 1 does not exceed 7 days. Blood samples for central laboratory analysis can also be collected at unscheduled timepoints during the study at the clinical discretion of the investigator. FVIII activity assay samples will be collected after the 48-h washout period following the last dose of FVIII concentrate (or after 72 h when using extended half-life FVIII concentrate).

[¥]In the event of two consecutive negative FVIII inhibitor assay results (<0.6 BU/mL) at screening and at the next study site visit with an interval of ≥2 weeks, FVIII recovery will be assayed until it is confirmed to be normal (ie, two consecutive assays at an interval of ≥2 weeks showing ≥66% of predicted value). Samples for FVIII recovery assay will be collected 15–30 min pre-/post-FVIII concentrate administration and after a washout period of 48 h from the last dose of 50 IU/kg FVIII concentrate (or 72 h when

using extended half-life FVIII concentrates). However, FVIII recovery is not a mandatory screening test if the result of screening FVIII inhibitor titre testing is confirmed to be ≥0.6 BU/mL; moreover, results measured by the study site can be used at screening provided that they were obtained within 8 weeks before enrolment. Blood samples for central laboratory analysis can also be collected at unscheduled timepoints during the study at the investigator's discretion.

**In the event of two consecutive negative FVIII inhibitor assay results (<0.6 BU/mL) at an interval of ≥2 weeks, FVIII recovery will be assayed until it is confirmed to be normal (ie, two consecutive assays at an interval of ≥2 weeks showing ≥66% of predicted value). Samples for FVIII half-life measurements will be collected 15–30 min and at 1, 2, 4, 6, 24 and 48 h pre-/post-FVIII concentrate administration and after a washout period of 48 h from the last dose of 50 IU/kg FVIII concentrate (or 72 h when using extended half-life FVIII concentrates). Additional sampling timepoints will be established at 72 and 96 h after administration for patients receiving extended half-life FVIII concentrates. Blood samples for central laboratory analysis can also be collected at unscheduled timepoints during the study at the investigator's discretion.

††Laboratory tests will be performed if aPCC or FVIII concentrates were administered, and will include the following variables: PT, APTT, D-dimer, fibrin, FDP, LDH, platelets and creatinine. Tests can also be performed at unscheduled timepoints during the study at the investigator's discretion.

‡‡Plasma emicizumab concentrations measured using a post-authorisation assay program will be reported in the eCRF if the investigator makes a clinical assessment that the participant may have developed antibodies to emicizumab after exhibiting signs of reduced therapeutic response.

§§Participants aged 8–17 years at study enrolment will be instructed to complete the Haemo-QoL-SF questionnaire and all caregivers will be instructed to complete the adapted INHIB-QoL questionnaire using a web application programme. If a participant has difficulty inputting responses to the questionnaires into the device, the caregiver may enter the response as given by the participant.

‖‖The participant or caregiver will record any bleeds requiring treatment with coagulation factors and all doses of emicizumab and other blood coagulation factor concentrates using the web application programme. Information on procedure-/surgery-related bleeds will be recorded in the eCRF or ePRO device.

¥¥Participants will be required to inform the investigator about any AEs at each study visit; AEs will be reported in the eCRF by the investigator.

AE, adverse event; aPCC, activated prothrombin complex concentrate; APTT, activated partial thromboplastin time; BU, Bethesda unit; eCRF, electronic case report form; ePRO, electronic participant-reported outcome; FDP, fibrin and fibrinogen degradation products; FVIII, factor VIII; Haemo-QoL-SF, haemophilia-specific Quality of Life Short Form; INHIB-QoL, Inhibitor-specific Quality of Life with Aspects of Caregiver Burden; ITI, immune tolerance induction; LDH, lactate dehydrogenase; PT, prothrombin time; PwHA, person with haemophilia A.

SUPPLEMENTAL TABLE 2 Assessment schedule for PwHA with FVIII inhibitors receiving emicizumab prophylaxis immediately after ITI therapy

	Immediately after ITI		**Every 48 weeks after first emicizumab dose (±28 days)**	**Week 193 after first emicizumab dose (±28 days)**	**Discontinuation (±28 days)**	**Safety follow-up visit† (±28 days)**
	Week 1* (±28 days)	**Week 13 and every 12 weeks thereafter (±28 days)**				
Weight	X	X		X	X	
FVIII inhibitor titre‡	X	X		X	X	
FVIII activity§	X	X		X	X	X
FVIII recovery‖	X	X	X	X	X	X
FVIII half-life¥	X	X	X	X	X	X
Laboratory tests**	◄	———	———	———	———	►
Plasma emicizumab concentration††	X	X	X	X	X	X
Haemo-QoL-SF and adapted INHIB-QoL questionnaires‡‡			X	X	X	
Bleeds and drugs used§§	X	X	X	X	X	X
AEs‖‖	X	X	X	X	X	X

The permissible time window for assessments between screening and enrolment is ≤28 days.

*Assessments to be performed on the date of the next scheduled study visit following investigator confirmation of partial success. If body weight was measured ≤28 days before transition to post-ITI prophylaxis, this measurement can be used as the Week 1 measurement.

†Participants who discontinue from emicizumab prophylaxis will be requested to attend a follow-up assessment 24 weeks after the last dose of emicizumab.

‡FVIII inhibitors will be centrally measured using anti-idiotypic antibodies to emicizumab. Blood samples for central laboratory analysis can also be collected at unscheduled timepoints during the study at the investigator's discretion. FVIII inhibitor assay samples will be collected after the 48-h washout period following the last dose of FVIII concentrate (or after 72 h when using extended half-life FVIII concentrates).

§FVIII activity will be centrally measured using anti-idiotypic antibodies to emicizumab. Blood samples for central laboratory analysis can also be collected at unscheduled timepoints during the study at the investigator's discretion. FVIII activity assay samples will be collected after the 48-h washout period following the last dose of FVIII concentrate (or after 72 h when using extended half-life FVIII concentrates).

‖Blood samples for FVIII recovery measured during the study at the investigator's discretion. Samples for FVIII recovery assay will be collected 15–30 min pre-/post-FVIII concentrate administration and after a washout period of 48 h from the last dose of FVIII concentrate (or 72 h when using extended half-life FVIII concentrates).

¥Blood samples for FVIII half-life measurement will be drawn during the study at the investigator's discretion, and will be collected 15–30 min and at 1, 2, 4, 6, 24 and 48 h pre-/post-FVIII concentrate administration and after a washout period of 48 h from the last dose of FVIII concentrate (or 72 h when using extended half-life FVIII concentrates). Additional sampling timepoints will be established at 72 and 96 h after administration for participants receiving extended half-life FVIII concentrates.

**Laboratory tests will be performed at the investigator's discretion, and will include the following variables: PT, APTT, D-dimer, FDP, LDH, platelets and creatinine.

††Plasma emicizumab concentrations measured using a post-authorisation assay program will be reported in the eCRF if the investigator makes a clinical assessment that the participant may have developed antibodies to emicizumab after exhibiting signs of reduced therapeutic response.

‡‡Participants aged 8–17 years at study enrolment will be instructed to complete the Haemo-QoL-SF questionnaire and all caregivers will be instructed to complete the adapted INHIB-QoL questionnaire using a web application programme. If a participant has difficulty inputting responses to the questionnaires into the device, the caregiver may enter the response as given by the participant. The questionnaire scheduled at Week 193 may be omitted if no more than 28 days has elapsed from the questionnaires performed in Weeks 1 or 49, or every 48 weeks thereafter following ITI.

§§The participant or caregiver will record any bleeds requiring treatment with coagulation factors and all doses of emicizumab and other blood coagulation factor concentrates using the web application programme. Information on procedure-/surgery-related bleeds will be recorded in the eCRF or ePRO device.

‖‖Participants will be required to inform the investigator about any AEs at each study visit; AEs will be reported in the eCRF by the investigator.

AE, adverse event; APTT, activated partial thromboplastin time; eCRF, electronic case report form; ePRO, electronic participant-reported outcome; FVIII, factor VIII; FDP, fibrin and fibrinogen degradation products; Haemo-QoL-SF, haemophilia-specific Quality of Life Short Form; INHIB-QoL, Inhibitor-specific Quality of Life with Aspects of Caregiver Burden; ITI, immune tolerance induction; LDH, lactate dehydrogenase; PT, prothrombin time; PwHA, person with haemophilia A.