







BMJ Open 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,

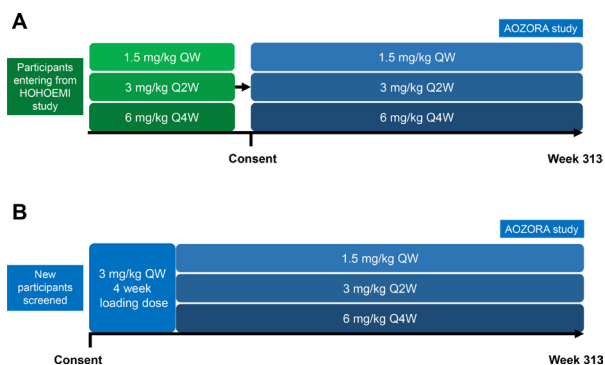


Figure 1 Summary of the AOZORA study design. (A) participants entering AOZORA from the HOHOEMI study will remain on emicizumab at one of the three permitted doses for a total of 313 weeks from the date of the first injection after HOHOEMI enrolment; this treatment period is inclusive of the emicizumab 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
<ul style="list-style-type: none"> ▶ 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 $\geq 100 \times 10^9$ cells/L, haemoglobin ≥ 8 g/dL (4.97 mmol/L)) ▶ Adequate hepatic function at the time of screening (total bilirubin $\leq 1.5 \times$ age-specific ULN (excluding patients with Gilbert's syndrome), AST and ALT $\leq 3 \times$ age-specific ULN) ▶ Adequate renal function at the time of screening (serum creatinine $\leq 1.5 \times$ age-specific ULN). Creatinine clearance >70 mL/min/1.73m² (as calculated by the bedside Schwartz formula) if the serum creatinine is $\geq 1.5 \times$ 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 	<ul style="list-style-type: none"> ▶ 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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REFERENCES

- Shima M, Nogami K, Nagami S, *et al*. A multicentre, open-label study of emicizumab given every 2 or 4 weeks in children with severe haemophilia A without inhibitors. *Haemophilia* 2019;25:979–87.
- Srivastava A, Santagostino E, Dougall A, *et al*. WFH guidelines for the management of hemophilia, 3rd edition. *Haemophilia* 2020;26 Suppl 6:1–158.
- Knobe K, Berntorp E. Haemophilia and joint disease: pathophysiology, evaluation, and management. *J Comorb* 2011;1:51–9.
- Pipe SW. New therapies for hemophilia. *Hematology Am Soc Hematol Educ Program* 2016;2016:650–6.
- Aledort L, Mannucci PM, Schramm W, *et al*. Factor VIII replacement is still the standard of care in haemophilia a. *Blood Transfus* 2019;17:479–86.
- Valentino LA, Mamonov V, Hellmann A, *et al*. A randomized comparison of two prophylaxis regimens and a paired comparison of on-demand and prophylaxis treatments in hemophilia a management. *J Thromb Haemost* 2012;10:359–67.
- Manco-Johnson MJ, Soucie JM, Gill JC, *et al*. Effect of late prophylaxis in hemophilia on joint status: a randomized trial. *J Thromb Haemost* 2017;15:2115–24.
- Manco-Johnson MJ, Soucie JM, Gill JC, *et al*. Prophylaxis usage, bleeding rates, and joint outcomes of hemophilia, 1999 to 2010: a surveillance project. *Blood* 2017;129:2368–74.
- Mahlangu J, Oldenburg J, Paz-Priel I, *et al*. Efficacy of emicizumab prophylaxis in patients who have hemophilia A without inhibitors. *N Engl J Med* 2018;379:811–22.
- Kitazawa T, Esaki K, Tachibana T, *et al*. Factor VIIIa-mimetic cofactor activity of a bispecific antibody to factors IX/IXa and X/Xa, emicizumab, depends on its ability to bridge the antigens. *Thromb Haemost* 2017;117:1348–57.
- Oldenburg J, Mahlangu JN, Kim B, *et al*. Efficacy of emicizumab prophylaxis in hemophilia A with inhibitors. *N Engl J Med* 2017;377:809–18.
- Young G, Liesner R, Chang T, *et al*. A multicenter, open-label phase 3 study of emicizumab prophylaxis in children with hemophilia A with inhibitors. *Blood* 2019;134:2127–38.
- Pipe SW, Shima M, Lehle M, *et al*. Efficacy, safety, and pharmacokinetics of emicizumab prophylaxis given every 4 weeks in people with haemophilia A (Haven 4): a multicentre, open-label, non-randomised phase 3 study. *Lancet Haematol* 2019;6:e295–305.
- Uchida N, Sambe T, Yoneyama K, *et al*. A first-in-human phase 1 study of ACE910, a novel factor VIII-mimetic bispecific antibody, in healthy subjects. *Blood* 2016;127:1633–41.
- Shima M, Hanabusa H, Taki M, *et al*. Long-Term safety and efficacy of emicizumab in a phase 1/2 study in patients with hemophilia A with or without inhibitors. *Blood Adv* 2017;1:1891–9.
- Feldman BM, Funk SM, Bergstrom Britt-Marie, *et al*. Validation of a new pediatric joint scoring system from the International hemophilia prophylaxis Study group: validity of the hemophilia joint health score. *Arthritis Care Res* 2011;63:223–30.
- Lundin B, Manco-Johnson ML, Ignas DM, *et al*. An MRI scale for assessment of haemophilic arthropathy from the International prophylaxis Study Group. *Haemophilia* 2012;18:962–70.
- Feldman BM, Funk S, Lundin B, *et al*. Musculoskeletal measurement tools from the International prophylaxis Study Group (IPSG). *Haemophilia* 2008;14 Suppl (3):162–9.
- Blanchette VS, Key NS, Ljung LR, *et al*. Definitions in hemophilia: communication from the SSC of the ISTH. *J Thromb Haemost* 2014;12:1935–9.
- Srivastava A, Brewer AK, Mauser-Bunschoten EP, *et al*. Guidelines for the management of hemophilia. *Haemophilia* 2013;19:e1–47.
- Blanchette P, Rivard G, Israels S, *et al*. A survey of factor prophylaxis in the Canadian haemophilia a population. *Haemophilia* 2004;10:679–83.
- Foppen W, van der Schaaf IC, Beek FJA, *et al*. MRI predicts 5-year joint bleeding and development of arthropathy on radiographs in hemophilia. *Blood Adv* 2020;4:113–21.
- Manco-Johnson MJ, Abshire TC, Shapiro AD, *et al*. Prophylaxis versus episodic treatment to prevent joint disease in boys with severe hemophilia. *N Engl J Med* 2007;357:535–44.
- Feldman BM, Pai M, Rivard GE, *et al*. Tailored prophylaxis in severe hemophilia A: interim results from the first 5 years of the Canadian hemophilia primary prophylaxis study. *J Thromb Haemost* 2006;4:1228–36.
- Chozie NA, Primacakti F, Gatot D, *et al*. Comparison of the efficacy and safety of 12-month low-dose factor VIII tertiary prophylaxis vs on-demand treatment in severe haemophilia a children. *Haemophilia* 2019;25:633–9.
- Evans SR. Clinical trial structures. *J Exp Stroke Transl Med* 2010;3:8–18.
- Gringeri A, Lundin B, von Mackensen S, *et al*. A randomized clinical trial of prophylaxis in children with hemophilia A (the ESPRIT study). *J Thromb Haemost* 2011;9:700–10.
- Denhoff ER, Milliren CE, de Ferranti SD, *et al*. Factors Associated with Clinical Research Recruitment in a Pediatric Academic Medical Center—A Web-Based Survey. *PLoS One* 2015;10:e0140768.