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Rationale for a randomized controlled trial comparing two prophylaxis regimens in adults with severe hemophilia A: the Hemophilia Adult Prophylaxis Trial

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Abstract

A major goal of comprehensive hemophilia care is to prevent occurrence of bleeds by prophylaxis or regular preventive factor, one or more times weekly. Although prophylaxis is effective in reducing bleeding and joint damage in children, whether it is necessary to continue into adulthood is not known. The purpose of this article is to describe a Phase III randomized controlled trial to evaluate prophylaxis comparing two dose regimens in adults with severe hemophilia A. I hypothesize that adults with mature cartilage and joints are less susceptible to joint bleeds and joint damage, and that once-weekly recombinant factor VIII prophylaxis, with up to two rescue doses per week, is as effective as thrice-weekly prophylaxis in reducing bleeding frequency, but less costly and more acceptable, with higher quality of life. The ultimate goal of this project is to determine whether once-weekly prophylaxis is any worse than thrice-weekly prophylaxis in reducing joint bleeding frequency, while potentially utilizing less factor, at lower cost, leading to a better quality of life. This is an innovative concept, as it challenges the current paradigm of thrice-weekly prophylaxis in adults, which is based on dosing in children. Furthermore, this trial will assess interdose thrombin generation, a novel tissue factor-based assay of hemostasis, to determine if individualized thrombin generation can predict more individualized prophylaxis dosing, which would be practice changing.

Keywords

factor VIII; hemophilia; joint bleeds; prophylaxis; thrombin generation

Hemophilia A is an X-linked bleeding disorder resulting from deficiency of factor VIII (FVIII) and characterized by bleeding into joints (hemarthroses) and muscles (hematomas). Over 65% of sufferers have severe disease, defined as FVIII <0.01 international unit (IU)/ml, which is associated with recurrent spontaneous bleeding into joints, leading to synovial inflammation and degenerative arthritis over time. Pathologically, hemophilic arthropathy involves cartilage degeneration, caused by iron-catalyzed destructive oxygen metabolites and synovial inflammation, caused by hemosiderin deposition and catabolism [1]. Clinically, hemophilic arthropathy leads to pain, disability and orthopedic surgery, contributing to high morbidity and high healthcare costs. Thus, a major goal of hemophilia treatment is to

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prevent hemorrhages by frequent prophylactic factor infusion one or more times weekly, termed ‘prophylaxis.’

The concept of regular infusion of factor concentrate to prevent bleeding in hemophilia was first introduced in 1958 by Nilsson *et al.* (discussed in [2]). Her pioneering work demonstrated that prophylaxis, when introduced early, could prevent or delay the onset of joint damage (hemophilic arthropathy). Subsequently, prophylaxis was adopted at other hemophilia treatment centers [3], and, following the 2007 landmark trial demonstrating fewer joint bleeds and less joint damage in children with severe hemophilia A receiving prophylactic treatment every other day, than those on ‘on-demand’ therapy [4], prophylaxis became the standard of care for children with severe hemophilia [101].

For how long prophylaxis should be continued remains an unanswered question. The optimal prophylactic dose in adults also is not known [5]: specifically, whether adults require the same intensity of prophylaxis, that is, three-to-four-times weekly, as currently recommended in children, or whether once-weekly dosing is sufficiently effective to prevent joint bleeding and joint damage, remains unknown. As many adolescents who have received prophylaxis since childhood are now reaching adulthood with excellent musculoskeletal status, it is critical to generate data to guide the future management of adults with hemophilia. Children have less mature cartilage and joints and greater susceptibility to joint damage than adults, and as prophylaxis is weight-based, it is less expensive than in adults. Furthermore, adults with hemophilia generally use factor less frequently but still have fewer joint bleeds than children [6,7]. Finally, there are no predictors of bleeding frequency that can be applied to the debate on optimal prophylaxis in adults.

Thus, the trial we propose, the Hemophilia Adult Prophylaxis Trial, is a Phase III randomized controlled trial comparing two doses of prophylaxis in adults with severe hemophilia A. This trial concept was the top-rated randomized clinical trial concept proposed for hemophilia by the National Heart, Lung, and Blood Institute (NHLBI)-sponsored State of the Science Symposium for Hemostasis & Thrombosis [102]. If safe and effective, this new approach to hemophilia prophylaxis will have a significant public health impact on joint damage, cost of care and quality of life, while enhancing our understanding of thrombin generation and joint bleeding. The purpose of this article is to present the background and justification for this trial, and to describe the Phase III randomized controlled trial and the pilot feasibility study, which includes a pilot feasibility trial and establishment of a hemophilia treatment center (HTC) network.

Background

Adult prophylaxis in hemophilia: is it practiced or necessary?

Despite the effectiveness of prophylaxis in reducing bleeds and hospitalizations and improving the number of days at work and quality of life in adults [8,9], significant barriers to prophylaxis exist: it is invasive, inconvenient and very costly [10]. A 70 kg male with severe hemophilia A requires 40–50 IU/kg three-times weekly, at an estimated cost of US \$0.80 per unit, meaning that the yearly cost approaches US\$400,000–500,000 or even higher if there is surgery or trauma. For many, these exorbitant costs threaten lifetime insurance caps. According to the CDC Universal Data Collection (UDC) database [103] – which collects data on over 12,000 individuals with hemophilia in the USA, representing 60% of the total hemophilia population – prophylaxis is practiced by only half of sufferers overall and 57.5% of those with severe hemophilia A. Among adults, the figure is lower: a recent survey of 145 adults from ten HTCs with severe hemophilia A found that only 33% of adults continue on prophylaxis [11]. Despite the reduction in bleeds, days lost at work, need for orthopedic surgery and improved quality of life, the most common barriers identified by

adults to prophylaxis were interference with lifestyle and cost [11]. A 2007 European survey of prophylaxis reported that 92 out of 218 men (42%) between the ages of 16 and 24 years with severe hemophilia A, who were previously on prophylaxis, had stopped prophylaxis. Of the latter, however, only 28% required reintroduction of prophylaxis for bleeding and only 20% who reduced prophylaxis intensity required a future more intense regimen [7].

These data suggest that while a significant proportion of young adults reduce or discontinue prophylaxis, once-weekly or twice-weekly prophylaxis regimens may be sufficient to prevent joint bleeding and damage in some patients. How to predict response to reduction in prophylaxis frequency and how to determine in whom it may be safely reduced is not known, but is an important clinical management issue. It is also an economic issue, as dose is based on weight and therefore adults require larger doses and at greater cost than children. This is also a timely issue, as the first cohorts of children on prophylaxis throughout childhood are now reaching adulthood with minimal or no joint disease, yet no objective data to support choice of a prophylaxis regimen exist. Furthermore, there are no comparator data with which to judge relative safety and efficacy of these new long-acting products.

Joint bleeding risk, FVIII & thrombin generation

Studies of prophylaxis in hemophilia have primarily been carried out in children [4,11]. Little is known about these parameters in adults. While it is generally recognized that bleeding frequency is higher on less intensive prophylaxis regimens in children, it is still lower than on no prophylaxis at all – that is, on-demand therapy. On-demand therapy means reactive treatment is given after a bleed has occurred. The number of children experiencing a bleed during a 6-month period of prophylaxis every other day, four out of 32 (12.5%) participating in the US primary prophylaxis study [4; Shearer R, Pers. Comm.], was lower than that in children on once-weekly prophylaxis (11 out of 56 [19.6%]) enrolled in the Canadian Hemophilia Prophylaxis Trial [11; McLimont M, Pers. Comm.], yet the latter was still lower than that in children on no prophylaxis (15 out of 33 [45.4%]) [4; Shearer R, Pers. Comm.].

Whether once-weekly prophylaxis, even with rescue doses, in adults whose mature cartilage and joints may make them less sensitive to joint damage than children, is sufficiently effective in reducing joint bleeds, but not at the expense of loss of motion, remains to be proven. Moreover, little is known about prophylaxis that is begun after there has been some degree of hemophilic arthropathy, termed ‘secondary prophylaxis’, which is commonly used in adults. In a recent clinical trial of 20 adults with severe hemophilia A previously receiving on-demand therapy, the initiation of standard prophylaxis at a FVIII dose of 20–40 IU/kg significantly reduced joint bleeding frequency and improved joint scores (median 0 vs 20; $p < 0.001$), with persistently detectable FVIII trough levels up to 48–72 h after infusion [12]. Notably, these prophylaxis regimens appeared to be safe, with no inhibitor formation in any subject, consistent with a number of studies suggesting inhibitor formation is unlikely to occur in an adult after multiple exposures to FVIII [13]. These data further suggest that, even in adults with arthropathy from past bleeds, prophylaxis may safely reduce bleeding frequency and joint damage. As age, race and BMI are strongly associated with joint range of motion (ROM) [14], it is critical to consider these variables in the interpretation of studies of hemophilic arthropathy.

Joint bleeding frequency in hemophilia is related to the severity of FVIII deficiency. Those with severe FVIII <0.01 IU/ml have frequent, spontaneous and traumatic bleeding, while those with moderate 0.01 – 0.05 IU/ml and mild disease >0.06 IU/ml suffer less frequent and primarily traumatic bleeding. In patients receiving prophylaxis, it has been suggested that the time spent at nadir FVIII levels may be more predictive of bleeding risk than random FVIII levels, and it is generally agreed that spontaneous bleeding may be averted by

maintaining FVIII levels of >0.01 IU/ml. Thus, prophylaxis at 25 IU/kg every-other-day dosing generally maintains FVIII >0.01 IU/ml and reduces joint bleeding and MRI evidence of joint damage in children with severe hemophilia A [4]. By contrast, 25 IU/kg thrice-weekly dosing, results in somewhat more bleeds, while 50 IU/kg every-other-day dosing results in fewer bleeds than 25 IU/kg every-other-day dosing [4,11]. However, as FVIII half-life varies from 6–25 h depending on dose and frequency [15], it is unlikely that FVIII levels during prophylaxis regimens given less often than every otherday, would be helpful in predicting bleeding, as the nadir level would probably be $<1\%$.

It is important to recognize that the relationship between joint bleeding frequency and FVIII activity is further limited by the known variability and error in FVIII assays, with significant inter-patient variability in half-life and dose frequency required to sustain a desired trough level [15]. Thus, optimal prophylaxis dosing to prevent bleeding remains a critical question in adults who may have greater baseline joint pathology than children. Moreover, now that long-acting FVIII is in early-phase clinical trials, data generated from the proposed pilot feasibility study and Phase III multicenter trial may provide critical comparative information on the relationship between interdose FVIII levels and prevention of joint bleeding.

As the capacity to generate thrombin at sites of vascular injury, or thrombin generation and the enzymatic potential of thrombin, or endogenous thrombin potential (ETP), determine coagulability [16–18], interest has increased in the application of the thrombin generation assay (TGA) to assess clinical bleeding [18,19]. In the classical view of coagulation, coagulation is initiated when tissue factor (TF) from damaged endothelium generates small amounts of thrombin, which primes the VIIa–TF extrinsic pathway to produce a thrombin burst, a pathway dependent on IXa and Xa formation (intrinsic tenase) [20], and a pathway rapidly shut down by TF pathway inhibitor [21]. In fact, clot formation, based on conversion of fibrinogen to fibrin, measured by prothrombin time- and activated partial thromboplastin time-based assays, occurs with less than 5% of total thrombin generation in a sample [20]. By contrast, in a whole-blood TGA after TF initiation, there is a 4-min lag time with an exponential rise to the thrombin burst [17], dependent not only on clot formation (the standard clot-based assay end point), but also on other proteins in the ‘hemostatic network’ [20].

Recent studies suggest that thromboplastin generation test (TGT) and ETP, which measure propagation of TF-induced thrombin formation, may provide a more precise measure of bleeding risk in hemophilia A than FVIII levels [19]. In fact, in a study of hemophilia patients, Brummel-Ziedins *et al.* demonstrated that the maximum thrombin generated in the TGA was strongly correlated with clinical severity of bleeding [22]. The TGA also provides individualized thrombin generation curves, for the same TF challenge, among those with the same FVIII level, suggesting the possibility of individualized assessment of patient bleeding severity [22]. The TGA may be modified for plasma samples, commonly drawn in the clinic, by using corn trypsin inhibitor to block the contact pathway and subsequently recalcify the sample prior to initiation with a tissue factor stimulus in the TGA [23]. Whether the TGA is sensitive to differences in bleeding severity and frequency during prophylaxis, specifically between factor doses when FVIII levels may fall to undetectable levels, is not known, but will be examined prospectively in the proposed pilot study and Phase III randomized trial of adult prophylaxis in hemophilia. Such information could have clinical utility in predicting bleeding frequency and potentially determine an individualized minimal effective prophylaxis dose to reduce bleeding.

FVIII, aging & cardiovascular risk

As individuals with hemophilia age, the safety of prophylaxis is an important consideration. Although population-based studies suggest that mortality from coronary disease is 60%

lower among those with hemophilia than the general population [24], the effect of durable, persistent FVIII levels in individuals with hemophilia, who are now aging with the general population [103], is a focus of some concern. Elevated FVIII is considered a risk factor for cardiovascular disease [25] and, thus, there is concern regarding potential cardiovascular disease risks in adults with hemophilia as they age, with persistent FVIII levels generated during prophylaxis. We have recently shown that individuals with hemophilia can develop diabetes, hyperlipidemia, hypertension, obesity and coronary symptoms (angina) at the same frequency as the general population [26]. Furthermore, the frequency and extent of pathologic coronary atherosclerosis in adult males with hemophilia is similar to that in the general population [26]. Thus, the results of an adult prophylaxis study will not only answer questions of joint health, but may also have significant impact on future cardiovascular health outcomes in adults with hemophilia.

Phase III randomized controlled trial

Research question

Among the most important clinical management questions in hemophilia today is whether prophylaxis with recombinant FVIII (rFVIII), which effectively prevents joint bleeding and joint damage in children, should be continued into adulthood and at the same dose intensity. As many young teenage males with hemophilia are reaching adulthood with excellent musculoskeletal status, it is critical to generate data to guide future management of adults with hemophilia. The trial concept we propose was developed as the top-rated randomized clinical trial concept of four proposed for bleeding disorders for the next 5–10 years, by the NHLBI State of the Science Hemophilia & von Willebrand Disease Subcommittee [102]. We specifically propose a large Phase III randomized clinical trial of hemophilia adult prophylaxis, as it will have significant public health impact on joint damage, cost of care and quality of life for young adults with hemophilia, while enhancing our understanding of thrombin generation and joint bleeding. The goals of this study, to prevent complications in individuals with bleeding disorders and promote blood product safety, represent two of the major goals within Healthy People 2010, as noted on the government website [104].

Study design

The future Phase III trial is an outpatient 52-week Phase III randomized, noninferiority, crossover clinical trial comparing once-weekly versus thrice-weekly prophylaxis with rFVIII in which adults with severe hemophilia A will be enrolled at their local HTC (Figure 1). The aims of the pilot feasibility study, which will precede the Phase III trial, will be to conduct a pilot feasibility trial of 20 patients to assess and assure the feasibility of end point measures, and to set up an HTC infrastructure to assure consensus on trial design and assure a sufficient number of subjects are available and eligible for the large Phase III trial. For clarity, since the pilot feasibility trial and Phase III trial share the same overall design, the Phase III trial will be described in the next section, following which additional details of the feasibility trial and HTC infrastructure will be described.

Study population

Inclusion criteria will be adult males >18 years of age; severe hemophilia A; FVIII <0.01 IU/ml; at least 150 prior exposure days to FVIII, according to patient treatment records; no prior history of, or currently detectable, inhibitor (defined as >0.6 Bethesda units) by the local laboratory; no prior history of an allergic reaction or anaphylaxis to FVIII products; and willingness to comply with the crossover design – take once-weekly and thrice-weekly prophylaxis for 26 weeks each, keep a personal diary of bleeding frequency and factor treatment and undergo coagulation testing at weeks 8 and 34, study visits, and joint ROM annually for 5 years post-study during annual comprehensive HTC clinics.

Exclusion criteria will include: acquired hemophilia; bleeding disorder other than hemophilia A; presence of an inhibitor; historical platelet count $<100,000/\mu\text{l}$; use of experimental drug(s); surgery anticipated within 52 weeks; symptomatic hepatitis C infection with end-stage liver disease – that is, portal hypertension, splenomegaly, varices, gastrointestinal bleeding, ascites, edema or encephalopathy; symptomatic HIV infection or with $\text{CD4} <200/\mu\text{l}$, detectable HIV viral load >48 copies/ml or noncompliance with combined antiretroviral therapy; life expectancy <5 years; treatment with another study treatment or investigational agent within 4 weeks prior to study; or inability to comply with study requirements.

Study population estimates

Based on an estimated 20,000 patients with hemophilia in the USA, of whom 85% have hemophilia A, 50% are >18 years of age, 60% have severe disease and 80% have no inhibitors [27]. Therefore it is estimated that 4080 patients are potentially eligible for this study. If 3% participate, 124 adults would be potentially eligible for study. To verify these projections, we conducted an HTC survey (Table 1), including the six core HTCs: these HTCs have a total of 301 adults >18 years of age with severe hemophilia and no inhibitors [28]. If only 7% of the 301 patients agree to participate, this would meet the $n = 20$ subjects required for the pilot study. Extrapolated to a future Phase III trial, if only 9–10% from 47 HTCs agree to enroll, there would be 126–140 subjects, sufficient for a future Phase III trial. Additional subjects will be sought through affiliated pediatric HTCs, and, in addition, we will seek additional participating HTCs through focus groups held at national meetings with HTC physicians and meetings with foreign HTCs to encourage participation in the trial (see the section entitled ‘Pilot feasibility study’ later).

Intervention

Half of the subjects will be randomized to once-weekly prophylaxis on Monday with rFVIII 40 IU/kg and half will be randomized to thrice-weekly prophylaxis on Mondays, Wednesdays and Fridays with rFVIII 40 IU/kg (Figure 1). Dosing was based on the results of a US HTC survey of adult prophylaxis indicating that thrice-weekly is the most commonly prescribed regimen in adults [28], and it was agreed by consensus of HTC investigators that breakthrough bleeds during the 72-h dose-free interval was unlikely in adults. For those randomized to once-weekly prophylaxis, up to two additional ‘rescue’ doses will be allowed to treat up to two bleeds per week, with resumption of the assigned prophylaxis arm at the next scheduled dosing day. Although the primary end point is based on bleeding with two rescue doses per week, additional rescue doses will be allowed at the physicians discretion. At 26 weeks, following a 4-day washout period (a period of time with no factor and no bleeds requiring factor), subjects will crossover to the alternate arm (i.e., thrice- or once-weekly), beginning the first dose on Monday of week 27, to ensure seamless transition between arms. If a bleed occurs, crossover will be delayed until a 4-day washout can be completed. The weekly dosing day will remain Monday, to distinguish it from rescue dosing. Follow-up will be at weeks 13, 26, 39 and 52.

Recruitment & randomization

Eligible subjects will be recruited from HTCs indicating interest and with eligible subjects. Potential subjects will sign informed consent forms, will be screened and, once eligibility is verified by meeting all inclusion criteria and none of the exclusion criteria, subjects will be randomized within 24 h of screening. Following consent, screening and enrollment, subjects will be randomized to prophylactic rFVIII 40 IU/kg once weekly or 40 IU/kg thrice weekly. Up to two rescue doses weekly will be allowed for bleeding in the once-weekly arm. The study drug will be supplied by an NHLBI contracted distribution center and provided to study subjects at no charge. Randomization will be by permuted block randomization,

performed by a web-based entry system, and separate randomization schemes will be created for each HTC site to ensure that there are similar numbers of subjects in each treatment arm. Allocation to treatment arms will vary by baseline prognostic factors, including age, frequency of prophylaxis in the past year and presence of a target joint, to ensure balance between groups.

Study drug & crossover

Recombinant FVIII will be distributed overnight from the NIH contracted distribution center to the local HTC site pharmacist where labeling for subjects randomized to the once-weekly or thrice-weekly arm and crossover will occur. A form will be completed for each subject confirming that treatment was received. After 26 weeks, following a 4-day washout period, subjects will be crossed over to the alternate treatment arm until week 52. Follow-up visits will be at weeks 13, 26, 39 and 52, during which patient diaries will be reviewed for bleeding frequency, the primary end point, and factor use (Table 2).

Clinical trial end points

The primary end point is joint bleeding frequency captured by patient diary. We hypothesize that once-weekly prophylaxis is as effective as thrice-weekly in preventing joint bleeding in adults with severe hemophilia A. The secondary end points will include blood product usage by diary, joint ROM by goniometry measured on digital images of hips, knees, elbows and ankles; quality of life by Haemo-QoL-A questionnaire; and interdose hemostasis by thrombin generation and FVIII assays. We hypothesize that once-weekly prophylaxis reduces costly and invasive factor use, with no greater loss of joint ROM, and better quality of life than thrice-weekly prophylaxis. We also hypothesize that thrombin generation is a better measure of hemostasis and better correlate of bleeding frequency than FVIII.

Baseline joint bleeding frequency and prophylaxis dosing, if used, will be obtained from annual home treatment records and reviewed at study visits. Joint ROM and quality of life will be assessed at baseline and weeks 26 and 52. Safety will be assessed by allergic reaction, thrombosis and inhibitor formation by anti-FVIII Bethesda assay.

Thrombin generation assay and FVIII one-stage assay will be performed on samples from approximately ten subjects who volunteer, at weeks 8 and 34, immediately before and 10 min, 1, 2, 4, 6, 12, 24, 36 (± 2), 48, 72 and 96 h after rFVIII prophylaxis dose on each arm to assess hemostasis between doses and the relationship with joint bleeding frequency (Table 3).

Data collection & follow-up

Demographic data collected at baseline by HTC study nurse on study subjects will include age, race, height, weight, target joint(s), prophylaxis dosing in the past year (if used) and past orthopedic surgery – variables that are associated with joint bleeds and loss of motion [4,11,14]. Vital signs and concomitant medications will be collected. Subject weight will be obtained at each visit. Subject follow-up will be by in-person visits at the local HTC on weeks 13, 26, 39 and 52 to review study adherence, bleeding and factor usage and to complete study assessments. During the first month of each treatment arm, the HTC nurse will make weekly, then monthly, phone calls to study subjects to encourage compliance with treatment and visits, and to identify unexpected or unresponsive bleeding or adverse events, or need for in-person evaluation. Subject factor supply will be replenished at study visits. Joint assessment and quality-of-life assessment will be performed at baseline and weeks 26 and 52, with 5-year long-term ROM measure at annual HTC visits. Blood sampling of study subjects will be by venepuncture performed by the HTC study nurse for anti-FVIII inhibitor titer at baseline, weeks 26 and 52; and for FVIII and TGA at weeks 8 and 34, for a total of

75 cc (5 tbsp), or with additional sampling of 300 cc (20 tbsp). Data will be uploaded by HTC nurses for web-based data entry. Crossover will occur at week 26, following a 4-day washout period: study arm 1 will be completed on week 26, while study arm 2 will begin week 27 and be completed week 52. At the end-of-study visit at week 52, anti-FVIII inhibitor antibody will be drawn, joint images taken, and patient diaries and quality-of-life forms collected. The development of an allergic reaction, thrombosis, inhibitor formation, or bleeding unresponsive to or in addition to those prompting rescue doses, constitutes an adverse event, and must be reported within 24 h to HTCs and study principal investigator, and rated by the National Cancer Institute Common Terminology Criteria for Adverse Events [105].

Outcome measures

For each outcome measure, the specific test instrument to be employed, justification, methodology, anticipated findings and limitations are described. In addition, the feasibility end points for the pilot trial are also included for each end point.

Bleeding frequency—The primary outcome measure, joint bleeding frequency, will be by patient diary.

Methodology: Subjects will complete monthly patient diaries on a daily basis, in monthly calendar format, and include all joint bleeds, all other bleeding events and all factor usage, including rescue doses. Any time a bleed occurs, it must be recorded on the patient diary, including the day, date, site, side, trauma and duration. Factor use, including rescue doses, must include the day, date and dose. Diaries are standard tools used by patients and reviewed at HTC visits and with which patients and nurses have experience. HTC study nurses will review the diaries during follow-up visits for completeness and accuracy at study visits, transcribe them onto case report forms and upload for web-based entry. Bleeds may occur in other body cavities, for example, CNS, gastrointestinal or retroperitoneal, the latter are anticipated to be too rare to use as end points, but will be collected for completeness and safety assessment. To avoid end point contamination, a 4-day washout standard for studies of new recombinant FVIII products, will be required prior to crossover.

Anticipated findings: We anticipate no more than one bleed will occur in 26 weeks (6 months) in those on the thrice-weekly prophylaxis arm, based on pediatric experience [4,11; Shearer R, Pers. Comm.; McLimont M, Pers. Comm.] and by consensus experience in adults by the HTCs coinvestigators and HTC survey [28]. Furthermore, we anticipate bleeding frequency on once-weekly prophylaxis, with up to two rescue doses, will be no greater than thrice-weekly prophylaxis. It is possible that joint bleeding frequency in the thrice-weekly arm will be more frequent than anticipated, especially during the 72-h interval between Friday and Monday dosing, but this is a question to be answered in this trial. If patient diaries are incomplete, inaccurate, lost or not completed in a timely fashion, this could adversely affect interpretation of study results. This is unlikely as patients routinely complete treatment records as part of comprehensive hemophilia care. HTC nurses will call subjects weekly in the first month of study, in order to ensure compliance with diaries and review diaries at monitoring visits. If the number of bleeds in the once-weekly prophylaxis arm, even after two rescue doses for bleeds, exceeds the bleeding frequency in the thrice-weekly arm, then this would be an adverse event that would stop the study.

Factor usage—Factor usage will be measured by patient diary and expressed in units and units/kg.

Methodology: Subjects will complete monthly patient diaries for factor usage, by day, date, time and dose, and similarly, for rescue doses. HTC nurses will review diaries for accuracy and completeness at follow-up visits. Subject weights will be obtained at study visits to determine dose by IU/kg. Factor cost will be derived using a fixed price, based on average market cost (average wholesale price) of rFVIII during study.

Anticipated findings: We anticipate once-weekly prophylaxis, even with rescue doses, will result in lower factor usage than thrice-weekly dosing, and, applying average wholesale price, lower usage will result in lower cost. If the number of rescue doses in the once-weekly arm results in factor usage not significantly different from factor use on the thrice-weekly arm, this would suggest no clinical or economic advantage to once-weekly dosing. However, if bleeding frequency is no greater and joint ROM loss is not different, but quality of life is better, either treatment approach might be considered acceptable in practice. It is anticipated that the findings of this study will require a cost-effectiveness analysis to help with this assessment.

Joint assessment—Range of motion will be assessed by digital image goniometry of four joint groups.

Methodology: Digital cameras, supplied to each HTC, will be used by the HTC study nurse to take photographs (digital images) of four joint group (bilateral hips, knees, elbow and ankles) on study subjects in the nonbleeding state (or rescheduled 2 weeks later) by goniometry, at baseline and weeks 26 and 52 and uploaded for web-based entry and read in blinded fashion by the study physical therapist using the Universal Data Collection Joint Range of Motion Manual [29]. This highly reproducible tool has been validated for digital image joint measure and is used by HTC staff to assess patients during routine exams. ROM is performed by goniometry on four sets of joint groups (hips, knees, elbows and ankles) through a full arc of motion, in the side-lying position for hip extension, 30° and flexion, 120°; and the seated position for knee flexion, 135° and extension, 0°; elbow flexion, 150°, extension, 0°, pronation, 80°; supination, 80°; for ankle dorsiflexion, 20°; and plantarflexion, 50°. For each joint group, loss of ROM from normal range will be recorded. With start-up HTC nurse training in use of this tool, joint ROM measure will be standardized and interoperator differences minimized. Web-based images will be centrally reviewed by a qualified, certified physical therapist. Proportionate ROM loss will be compared by study arm in the first period prior to crossover, by joint group and summary measure [Soucie R, Pers. Comm.].

Anticipated findings: We anticipate little, if any, loss of joint ROM in subjects from baseline between treatment arms, in either order. This is based on a study showing high BMI, African-American race, and inhibitor formation but not prophylaxis predicted ROM loss [14], based on 10-year longitudinal findings in a CDC-UDC study of children on prophylaxis [Soucie R, Pers. Comm.]. Age, BMI and race will be collected at baseline for analysis. As few data exist on bleeds and ROM in adults on prophylaxis, ROM data will remain exploratory, and to avoid contamination, analysis will be before crossover only. Long-term 5-year ROM will be at annual HTC visits. Whether ROM reflects 6-month, 1-year or 5-year prophylaxis, and the effects of intervening treatment, are unknown. If minimal or no joint ROM change is detected on either study arm, then it may be less useful in assessing prophylaxis differences, but this will be new information, not previously reported. Although MRI is more sensitive to joint change than x-ray [30] and is used in clinical joint scoring assessment [31–33], it is costly (US\$1500), and unlikely to detect change in a 52-week trial.

Quality of life—Quality of life will be measured by a hemophilic-specific instrument, Haemo-QoL-A.

Methodology: Study subjects will complete Haemo-QoL-A at baseline and weeks 26 and 52, which will be reviewed by HTC study nurses for completeness and accuracy and uploaded to a web-based entry system. The tool is an adult- and hemophilia-specific health-related quality-of-life questionnaire, which is validated, reliable and sensitive to hemophilia-specific changes in disease severity and physical functioning [17], which is not possible with general tools, for example, the short form-36 [34]. Haemo-QoL-A contains 41 items covering six domains, including physical functioning, role functioning, worry, consequences of bleeding, emotional impact and treatment concerns. Internal consistency is good to excellent, and it discriminates between adults with hemophilia by severity and HIV status and between those receiving prophylaxis and on-demand therapy by physical functioning [19].

Anticipated findings: We anticipate study subjects on once-weekly prophylaxis, even with rescue dosing, will have significantly a better quality of life than those on thrice-weekly arm, as it is less invasive, more suitable to lifestyle and less costly, which are the major barriers to prophylaxis in adults [10]. Quality of life may be biased by the unblinded nature of the trial, either in the positive or negative direction, based on fewer treatments or bleeding difference between treatments. This bias is not measurable. However, quality of life will be interpreted only in the context of noninferiority results for bleeding, so we are aware of the impact of the two prophylaxis regimens on overall health. If once-weekly prophylaxis does not prevent bleeding or maintain joint health to the same degree as thrice-weekly prophylaxis, quality of life may not improve. If joint bleeding frequency is similar between arms, but long-term joint outcomes are worse in the once-weekly arm, then findings may not reflect long-term joint damage or quality of life. As joint bleeding is a surrogate for joint disability, we believe the latter is unlikely.

Hemostatic assays—Hemostasis will be assessed by one-stage FVIII assay and TGA. Safety will be assessed by anti-FVIII inhibitor Bethesda assay.

Methodology: Samples for the hemostatic assays will be drawn by the HTC coordinator on study subjects by venepuncture, just before and 10 min after prophylaxis dose on Monday of weeks 8 and 34, for example, week 8 of each study arm, in the nonbleeding state. Additional sampling on up to ten of the subjects that day will be at 1, 2, 4, 6, 12, 24, 36 (± 2), 48, 72 and 96 h after dosing. For ease, the 36 h sample will be 36 ± 2 h.

Factor VIII activity will be measured on citrated plasma samples by standard one-stage FVIII assay, using activated partial thromboplastin time reagent (Pathrombin SL, Dade-Behring/Siemens, Newark, DE, USA) and calcium chloride (0.025 mol/l). The coagulation time will be determined in an automated coagulation analyzer (Siemens BCS-XP) and FVIII activity read from a standard curve constructed from FVIII-deficient plasma. TGT and ETP and maximum thrombin level will be measured by thrombin TGA on corn trypsin inhibitor/citrate plasma samples, as previously described [23]. After thawing at 37°C, 80 μ l of plasma is added to an Immulon 96-well plate (Thermo Electron, MA, USA), and incubated with a 20 μ l HEPES Buffered Saline pH 7.4 solution containing Z-GGR-AMC (416 μ M) and CaCl_2 (15 mM final) for 3 min. The assay is initiated by the addition of 20 μ l HEPES Buffered Saline solution containing relipidated TF (1–243) (5 pM) and PCPS (2–20 μ M), and thrombin generation is monitored by the rate of substrate hydrolysis measured in a BioTek Synergy 4 fluorescence plate reader (Bio Tek, Winooski VT). Nadir and peak TGT, ETP and FVIII levels will be compared with joint bleeding frequency by study arm. Anti-FVIII inhibitor antibody formation will be drawn at baseline, and at weeks 26 and 52, and

performed in the Pittsburgh laboratory on citrated plasma samples by Bethesda assay, as previously described, in which residual FVIII is measured by one-stage FVIII activity, with one Bethesda unit/ml defined as the amount of inhibitory activity producing 50% inhibition of FVIII activity [35].

Anticipated findings: We anticipate that thrombin generation will better predict intradose bleeding risk than FVIII levels, and will be more readily detected than FVIII following rFVIII prophylaxis, as previously shown in nonprophylaxis settings [23]. We expect no anti-FVIII development, as it is rare in those with >150 exposure days [13]. If thrombin generation is no better than FVIII in detecting hemostasis during prophylaxis, does not correlate with clinical bleeding or is inaccurate in frozen samples, then its use in clinical practice may be limited.

Sample size & statistical power

We propose a randomized, crossover, noninferiority trial comparing thrice-weekly with once-weekly prophylaxis. The number of joint bleeds per 6 months per patient is the primary outcome of interest. We aim to determine if the rate of bleeds on once-weekly prophylaxis is no greater than 50% more than on thrice-weekly prophylaxis (noninferiority). The null hypothesis in this trial states the rate ratio of bleeds (once weekly/thrice weekly) exceeds $\delta = 1.5$ (inferiority). The alternative hypothesis being tested is that the rate ratio of bleeds (once weekly/thrice weekly) is less than 1.5 (noninferiority). The noninferiority margin of 50% was chosen based on trials demonstrating overwhelming efficacy of prophylactic over on-demand treatment for hemophilia. The rate of bleeding (P1) on prophylaxis is at least 80% less than the rate on on-demand treatment (P1/observed rate of bleeding [O1] = 20%). By allowing up to a 50% increase in bleeding rates (expected rate of bleeding [E1]/O1 = *150% P1/O1 = 20%*150% = 30%), we still preserve 88% of the original prophylaxis effect relative to on-demand therapy ($[1-E1/O1]/[1-P1/O1]$). In sample size calculations for a noninferiority trial with a negative binomial outcome, we must specify: the mean rate of bleeds in thrice weekly group (λ); the overdispersion parameter for variance (ϕ); and the noninferiority margin (δ). A recent study in adults showed an annual bleeding rate on prophylaxis of four per person and an overdispersion parameter of 0.6 [9]. This rate is a midrange value compared with other published studies in adults [2,36,37]. The overdispersion parameter estimates varied across studies from 0.3 to 3; thus, for sample size calculations, we used two bleeds per person per 6 months and a conservative overdispersion parameter of 1.5. Sample size analyses using NCSS/PASS 2008 determined that a sample size of 106 achieves 80% power to detect noninferiority ($E1 = 1.5*P1$, 1-sided $\alpha = 0.025$). To account for 15% attrition, we propose to recruit and enroll 124 individuals into the trial.

Data analysis

The treatment effect of once-weekly versus thrice-weekly prophylaxis will be estimated from a generalized linear model assuming a negative binomial distribution, while accounting for the crossover design via generalized estimating equations. The coefficient for the treatment effect is the log(bleeding rate ratio) and the one-sided 97.5% upper bound can be calculated for the estimate (β) using the normality assumption. Inverse log transformation will be used for the corresponding upper bound of the rate ratio; noninferiority for bleeding events will be declared if the upper bound is less than 1.5. Confidence interval estimation is more informative in noninferiority trials than p-values [38]. Despite limited power, carryover effects (treatment–period interaction) will be explored using this same model, and sensitivity analyses conducted using the first period to assess consistency in findings. The secondary outcome, joint ROM, will be analyzed using only the first period of the crossover trial (between subject comparisons) owing to concerns about loss of joint function that could not be reversed in the second period. Quality of life will be compared by treatment arm in

both periods and analyzed by linear models and generalized estimating equations to control for repeated measures within each subject.

Trial monitoring & interim analysis

The Data Safety Monitoring Board will meet halfway through the study (26 weeks after study initiation) to review study protocol, progress, enrollment, retention, safety, efficacy and protocol adherence. Early termination of the trial will be considered if one treatment group experiences significantly worse outcomes – that is, bleeding, inhibitor, thrombosis or allergic reaction. Database management and data entry systems to monitor accuracy, quality and completeness of data will be performed by a web-based system. Case report forms and digital joint assessment images will be developed for web-based application at HTC study sites. An operations manual to standardize all procedures will be developed.

Pilot feasibility study

The purpose of the pilot study is to determine the feasibility of the large Phase III randomized controlled trial. The specific aims and trial design of the pilot study, to be conducted before the Phase III randomized controlled trial, are to conduct a pilot trial in 20 adult men with severe hemophilia A, to assess the feasibility of end point measures; and to set up an HTC infrastructure of more than 47 HTC physicians to build consensus on, and assure a sufficient number of eligible subjects for, the large Phase III randomized controlled trial.

Pilot trial

The pilot trial will be conducted at six core HTCs and designed to compare once-weekly versus thrice-weekly rFVIII for 52 weeks in 20 adult men with severe hemophilia A, FVIII <0.01 IU/ml and age <18 years. The study schema is identical to the proposed large Phase III randomized trial (see the earlier section entitled ‘Phase III randomized controlled trial’), but will assess the feasibility, validity and acceptance of end point measures. Joint bleeding frequency, the primary efficacy end point, will be assessed by patient diary; factor usage and cost will be assessed by patient diary; joint assessment by digital range of motion images; quality of life by Haemo-QoL-A questionnaire; and hemostatic assays by one-stage FVIII assay, anti-VIII Bethesda assay and TGA. Assessment of each assay in the pilot trial is described in the following paragraphs.

Bleeding frequency—We will establish the proportion of time subjects have bleeds and the proportion of bleeds that are unresponsive to rescue doses or require additional healthcare utilization. Validity checking will be carried out on bleeding frequency relative to dose used. Subject adherence to the prescribed dosing will be measured by patient diary, including the frequency of missed doses, the proportion in whom rescue doses were missed and difficulty with venous access.

Factor usage—We will establish the factor usage, including rescue doses, comparing patients between both arms. Although exploratory, this will provide a comparative idea of the proportion of time rescue doses are required for the once-weekly prophylaxis arm, which could promote or shut down the trial.

Joint assessment—We will establish the proportion of digital joint images that are clear and correctly positioned in the seated and side-lying positions for accurate ROM measure of all joint groups based on central reading by the physical therapist. Data generated from the pilot will provide new baseline information on ROM loss on prophylaxis, which is currently unknown.

Quality of life—We will establish whether those who use thrice-weekly prophylaxis have better quality of life when they use once-weekly prophylaxis. We will also be able to determine if quality of life relates to frequency of rescue doses and the number of additional bleeds per week in the once-weekly prophylaxis arm, compared with thrice-weekly arm. Quality-of-life questionnaires will be tested for ease of completion and clarity. While there may be inherent bias in those agreeing to participate, whether for financial, insurance or other reasons, each subject will receive both doses in a randomized fashion, allowing for intrasubject comparisons and providing new data from a clinical trial of adults.

Hemostatic assays—The feasibility of the TGA will be assessed by performing the assay on frozen, shipped control samples, up to ten who volunteer (two to four per site). The results will be compared with those from fresh controls at the six core HTC sites. These data will also provide preliminary information regarding the relationship between thrombin generation, nadir FVIII activity and frequency of joint bleeding for each study arm, which will help determine the feasibility of these assays and allow for adjustment in sampling and processing for the Phase III clinical trial.

Adherence & compliance—Patient adherence and acceptability of the treatment intervention will be assessed by patient diary, weekly nurse phone calls, digital joint imaging, quality-of-life tools and TGAs. Drug compliance, the number of doses taken and the proportion of time the study drug was taken will be assessed by patient diary.

Limitations—If the pilot trial is unable to enroll 20 subjects, insufficient data will be available to determine feasibility of the large Phase III trial, leading to a ‘No-Go’ decision for the Phase III trial. In order to avoid this, should enrollment fall below projections, pediatric HTCs affiliated with adult HTCs participating in the pilot trial will be identified to identify potentially eligible subjects. If bleeding frequency is greater than anticipated on once-weekly prophylaxis, this poses a safety and a possible ‘No-Go’ decision for the Phase III trial. If factor usage on once-weekly prophylaxis, including rescue doses, is no different from that on thrice-weekly prophylaxis, this would suggest no economic or health advantage with once-weekly dosing, resulting in a ‘No-Go’ decision for the Phase III trial. Such results would suggest exploring twice-weekly prophylaxis as an alternate approach, but this would add cost and delay a future Phase III trial. If patient diaries are incomplete or inaccurate, or data capture is delayed, this could adversely affect interpretation of the primary end point of bleeding frequency, as well as factor use, and lead to a ‘No-Go’ decision for a Phase III trial. Meticulous review of diaries for accuracy and completeness, telephone calls and study visits with patients to encourage subjects in careful diary completion and stress the importance of diaries in the outcome of the trial should help to promote optimal data generation. If factor adherence is low, pilot results will be unhelpful, leading to a ‘No-Go’ decision for a future Phase III trial.

HTC infrastructure

To establish an HTC infrastructure of >47 HTC physicians will be accomplished through facilitated focus groups, telephone interview and in-person meetings to jointly build consensus on trial design, including dose and day flexibility, subject recruitment and trial participation to assure a sufficient number of eligible subjects to conduct the large Phase III trial. The HTC infrastructure will be operationalized by hiring a dedicated nurse coordinator to prepare Institutional Review Board (IRB) submission and contracts for participating HTCs. The six core HTC physicians will review and finalize case report forms and the manual of operations for the future Phase III trial. Exploratory meetings will be held with foreign HTC physicians to determine the potential for study participation and subject recruitment to ensure the feasibility of conducting a future Phase III randomized trial.

Focus groups—Up to ten focus groups and in-person meetings will be conducted with HTC physicians, 20 per group, selected from CDC and Hemophilia and Thrombosis Research Society membership lists. Meetings will last 1.5 h and be held at the annual National Hemophilia Foundation, The American Society of Hematology, and Hemophilia and Thrombosis Research Society meetings to gauge interest, discern barriers and discuss design for the large Phase III trial. To underscore the importance of the meeting, key NHLBI senior investigators and the six core HTC physicians will be invited to participate in discussions. Key critical issues for discussion will include the prophylaxis dose, rescue plan, competing trials, HTC staff needs and funding. Invitation flyers will be mailed 1 month before the meeting.

Nurse coordinator—To ensure timely and efficient enrollment for a future Phase III trial, a nurse will be hired to complete IRB submissions and contracts for all 47+ HTCs, an approach that has been used successfully to accomplish other multicenter studies. The study coordinator will communicate with HTC sites to determine if our approach is meeting HTC needs – that is, if participant earnings are sufficient to cover patient costs, if competing studies discourage enrollment and if refresher infusion training improves patient compliance on study. The coordinator will also post study flyers at annual meetings and on the National Hemophilia Foundation, The American Society of Hematology, Hemophilia and Thrombosis Research Society, and the International Society on Thrombosis and Haemostasis websites.

Operational procedures—Case report forms will be prepared and a manual of operations developed, including procedures for all aspects of the study from enrollment, randomization, monitoring, diary review and sample processing and shipping. Mid-course corrections will be based on interview of eligible subjects or investigators who do not participate in the pilot study. The randomization scheme will be assessed for timeliness and acceptability.

Exploratory meetings with foreign HTCs—To assure sufficient eligible subjects are available for timely conduct of the large Phase III trial, the feasibility of foreign HTC participation will be explored, including regulatory and funding issues through telephone and in-person meetings, for example at national meetings.

Limitations—Although enrollment of adults with hemophilia in an adult prophylaxis trial may be difficult, the question is compelling. Through focus groups and investigator meetings, HTC physicians can discuss trial design with key senior investigators and identify and resolve barriers to patient enrollment. Several scenarios could bring into serious question whether a future Phase III trial should be conducted: fewer than 47 HTCs or fewer than 124 patients would lead to a ‘No-Go’ decision for a future Phase III trial. If sufficient concerns remain regarding study design, or if regulatory issues prohibit foreign HTC participation, this could be a ‘No-Go’ decision for a future Phase III trial.

Conclusion

The findings will provide data for recommendations for management of young adults, previously on prophylaxis with minimal joint damage and with mature cartilage and joints, potentially less susceptible to joint damage than children. In addition, dose is based on weight and is thus higher in adults in whom prophylaxis is more costly, and contributes to higher healthcare costs. The pilot and future Phase III trials are innovative, as they challenge the current paradigm of thrice-weekly prophylaxis in adults based on children, and will provide interdose (between-prophylaxis dosing) thrombin generation, which may determine individualized prophylaxis dosing, a novel approach to therapy.

Expert commentary

To date, no randomized controlled trials of prophylaxis have been conducted in adults with severe hemophilia. Despite the difficulties that clinical trials in rare diseases entail, the optimal prophylaxis in adults is arguably among the most important questions among individuals with hemophilia. Available recommendations for prophylaxis pertain only to children, with less mature joints and for whom weight-based dosing is less expensive than in adults. With transition to adulthood, many young adults with severe hemophilia A have spent a lifetime on prophylaxis, but therapeutic guidelines are lacking though observational studies indicate lower bleeding frequency in the mature joints of adults, even with less frequent treatment. Predicting response to prophylaxis is important, as it is not only a management issue, but also an economic issue that will have a far-reaching impact on the standard of care for adults with hemophilia.

Five-year view

A speculative view for the next 5 years is that the optimal approach to prevention of bleeds in patients with severe hemophilia A will involve an individualized approach, based on genotype, bleeding phenotype, bleeding severity score and thrombin generation, for example estimated thrombin potential. Based on these variables, an optimal prophylaxis frequency will be determined for each patient, which will calculate a likelihood of bleeding based on prophylaxis frequency. Whether long-acting concentrates are optimal for certain ages or certain subsets of patients will hopefully be individualized to determine minimum effective prophylaxis dose frequency to prevent bleeds, while maintaining optimal joint scores.

Key issues

- Evidence-based recommendations for factor prophylaxis to prevent joint bleeding in adults with hemophilia do not exist.
- Current factor prophylaxis strategies in children may not apply to adults who have more mature joints and a lower frequency of joint bleeding.
- Measurement of thrombin generation and estimated thrombin potential can predict bleeding risk and hemostasis with more precision than standard factor levels, and may help to individualize prophylaxis.
- The proposed Phase III randomized controlled trial will determine if a once-weekly prophylaxis is a safe and effective approach in adults with hemophilia.
- Outcome measures will include bleeding frequency, inhibitor formation, joint range of motion, factor usage and cost, thrombin generation and quality of life.
- The role of a hemophilic center infrastructure to perform clinical trials, with central contracting and Institutional Review Board preparation, will inform future trials in rare disorders research.

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Figure 1. Clinical design of the Hemophilia Adult Prophylaxis trial
rfVIII: Recombinant factor VIII.

Table 1

2010 hemophilia treatment center survey potential participating subjects.

2010 HTC survey	Total number of hemophilia A patients >18 years of age without an inhibitor	Number eligible to participate				Number (%) HTCs agree to				Identified barriers			
		5%	10%	15%	20%	Trial	40 IU/kg	5-year FU	IRB prep	Staff	Costs		
University of Pittsburgh (PA, USA)	54	2.5	5	7.5	10	Yes	Yes	Yes	–	–	–		
University of Pennsylvania (PA, USA)	76	4	8	12	16	Yes	Yes	Yes	+	+	+		
University of Washington, Seattle (WA, USA)	73	5.5	7	10.5	14	Yes	Yes	Yes	–	+	–		
Georgetown (DC, USA)	50	2.5	5	7.5	10	Yes	Yes	Yes	–	+	+		
Vanderbilt, Nashville (TN, USA)	36	2	4	6	8	Yes	Yes	Yes	–	–	–		
Children's Hospital (PA, USA)	12		1	1.5	2	Yes	Yes	Yes	–	–	–		
Total: 6 HTCs	301	15	30	45	60	6 (100%)	6 (100%)	6 (100%)	1 (17%)	3 (50%)	2 (33%)		
Grand total of HTCs in survey: 47 HTCs	1401	70	140	210	280	43 (92%)	45 (96%)	46 (98%)	17 (36%)	25 (53%)	26 (55%)		

+: Barrier was identified in institution; –: Barrier was not identified in institution.

FU: Follow-up; HTC: Hemophilia treatment center; IRB: Institutional Review Board.

Table 2

Trial outcome measures.

Outcome measure	Test instrument
Bleeding frequency	Diary: to include day and date time of bleeds, and whether bleeds were traumatic or spontaneous
Factor usage	Diary: to include regular and rescue infusions, with projected cost
Joint range of motion	Goniometry: digital camera measurement of elbows, hips, knees and ankles
Hemostasis	Factor VIII one-stage, anti-factor VIII Bethesda, thrombin generation assays
Quality of life	Quality-of-life Tool: Haemo-QoL-A survey

Table 3

Schedule of events in the Phase III trial and pilot feasibility trial.

Schedule of events	Study arm: weeks 1–26										Study arm: weeks 27–52			
	Week -1	Week 1	Week 8	Week 13	Week 26	Week 27	Week 34	Week 39	Week 52					
Screening, consent	X													
Randomization		X												
Initiate study, subject diary		X												
Clinical monitoring														
Crossover (following 4-day washout)			X		X			X						
End-of-study visit														X
Subject diary		X			X			X					X	X
Digital joint imaging	X				X									X
Quality-of-life questionnaire	X				X									X
Coagulation assays														
Anti-FVIII Bethesda assay	X				X									X
Factor VIII one-stage assay			XX								XX			
– All subjects (pre-, post-dose)			XXXXXXXXXXXX								XXXXXXXXXXXX			
– Ten subjects intensively sampled (1, 2, 4, 6, 12, 24, 36, 48, 72 and 96 h)														
Thrombin generation assay			XX								XX			
– All subjects (pre-, post-dose)			XXXXXXXXXXXX								XXXXXXXXXXXX			
– Ten subjects intensively sampled (1, 2, 4, 6, 12, 24, 36, 48, 72 and 96 h)														