Trial Title:

A single centre, open label, pilot study evaluating the effect of intra-articular hyaluronic acid injection on pain and functionality when injected into the ankle (tibio-talar and sub-talar) joint in patients with haemophilic arthropathy.

Short title: Intra-articular Hyaluronic acid for haemophilic arthropathy of the ankle complex

Ethics Ref: Insert

Date and Version No: 04/06/2018 Version 0.16

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Sponsor: Oxford University Hospitals NHS Foundation Trust

Funder: TRB Chemedica (UK) Ltd

Chief Investigator Signature:

There are no conflicts of interest.

Confidentiality Statement

This document contains confidential information that must not be disclosed to anyone other than the Sponsor, the Investigator Team, HRA, host organisation, and members of the Research Ethics Committee, unless authorised to do so.

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1. KEY TRIAL CONTACTS

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2. SYNOPSIS

Trial Title	A single centre, open label, pilot study evaluating the effect of intra-articular hyaluronic acid injection on pain and functionality when injected into the ankle (tibio-talar and sub-talar) joint in patients with haemophilic arthropathy
Internal ref. no. (or short title)	Intra-articular Hyaluronic acid for haemophilic arthropathy of the ankle complex
Trial Design	Single centre, open label, pilot study
Trial Participants	***Inclusion criteria*:** Patients are eligible for this trial if: *1.* Adult males with any severity of haemophilia A and B, including those with inhibitors, age 18 and above 2. Written, informed consent has been obtained 3. The participant is confirmed to have haemophilic arthropathy, including synovitic and/or degenerative changes to one or both ankle joints, as determined by MRI ***Exclusion criteria:*** A patient will not be eligible for this study if he fulfils one or more of the following criteria: 1. Presence of infection including participants taking antibiotic therapy 2. Known inflammatory joint disease, including crystal disease 3. Intra-articular steroid injection within the preceding 6 months 4. Known allergy to the excipients of Ostenil Plus+
Planned Sample Size	20 patients This is a pilot feasibility study and therefore a formal sample size calculation is not required. A clinically meaningful reduction in VAS pain score would be achieved when the VAS score decreases from baseline by 30%. For this pilot study to be successful, we would expect that 80% of patients will achieve at least a 30% reduction in their VAS pain score. If the proportion of participants whose VAS scores decreases by 30% is 80%, a sample size of 20 will yield a 95% confidence interval for this estimate of between 62.5% and 97.5%.

Treatment duration	Two intra-articular injections	
Follow up duration	12 months	
Planned Trial Period	The recruitment phase will last 12 months. Follow-up will be for 12 months from the date of enrolment of the last participant. Recruitment and follow-up for the trial will last 24 months. All participants to this study will be known patients under the care of Oxford Haemophilia Centre or Basingstoke Haemophilia Centre. Loss to follow-up is likely to be minimal and the research team will make every effort to ensure that all outcome measures will be evaluated. If a participant drops out without collection of full outcome data we will replace that participant, where possible. Safety data will be collected in all participants to 52 weeks.	
	Objectives	Outcome Measures
Primary	To determine whether Ostenil Plus leads to a clinically significant reduction in pain in the affected ankle.	1. Change to the VAS pain score
Secondary	To determine whether Ostenil Plus leads to a change in joint function, quality of life and whether there are any safety concerns with using Ostenil Plus for haemophilia patients.	<u>Joint endpoints:</u> 1. Changes to ankle functionality as defined by changes to: o Ankle HJHS score o Foot and Ankle Ability Measure (FAAM) 2. Changes to global HJHS score (including gait) 3. Changes to the annualised bleeding rate <u>Quality of life endpoints:</u> 1. EQ-5D-5L score 2. Haemophilia Activity List (HAL) <u>Safety endpoints:</u> 1. Adverse events including increased pain, stiffness and swelling to the joint Outcomes will be measured at 3, 6, 9 and 12 months.
Device name	Ostenil Plus	
Device manufacturer	TRB Chemedica (UK) Ltd	

Device classification	Class III medical device

3. ABBREVIATIONS

ABR	Annualised bleeding rate
AE	Adverse event
AR	Adverse reaction
CI	Chief Investigator
CLRN	Comprehensive Local Research Network
COX-2	Cyclo-Oxygenase 2 Inhibitor
CRF	Case Report Form
CT	Clinical Trials
DCF	Data Clarification Form
DMC/DMSC	Data Monitoring Committee / Data Monitoring and Safety Committee
FAAM	Foot and Ankle Measure
GCP	Good Clinical Practice
GP	General Practitioner
HA	Hyaluronic Acid
HAL	Haemophilia Activities List
HJHS	Haemophilia Joint Health Score
HRA	Health Research Authority
IA	Intra Articular
ICF	Informed Consent Form
ICH	International Conference on Harmonisation
IRAS	Integrated Research Application System
IRB	Independent Review Board
ISRCTN	International Standard Randomised Controlled Trial Number
MHRA	Medicines and Healthcare products Regulatory Agency
NHS	National Health Service
NIHR	National Institute for Health Research
NRES	National Research Ethics Service
NSAID	Non-Steroidal Anti-Inflammatory Drug

OA	Osteoarthritis
OHTC	Oxford Haemophilia & Thrombosis Centre
PALS	Patient Advice and Liaison Service
PI	Principal Investigator
PIC	Participant Identification Centre
PIL	Participant/ Patient Information Leaflet
PwH	Person(s) with Haemophilia
QoL	Quality of Life
RCT	Randomised Controlled Trial
R&D	NHS Trust R&D Department
REC	Research Ethics Committee
SAE	Serious Adverse Event
SAR	Serious Adverse Reaction
SDV	Source Data Verification
SOP	Standard Operating Procedure
SUSAR	Suspected Unexpected Serious Adverse Reactions
TMF	Trial Master File
TMG	Trial Management Group
TSG	Oxford University Hospitals NHS Foundation Trust / University of Oxford Trials Safety Group
VAS	Visual Analogue Scale

4. BACKGROUND AND RATIONALE

Haemophilia, the most common inherited severe bleeding disorder, is an X-linked disorder affecting males of all ethnic groups.[1] A major morbidity experienced by patients with haemophilia is joint disease [2], as a result of repeated bleeding episodes into the joint spaces. Bleeding leads to changes within the joints, including synovial proliferation, and this in turn results in further bleeding and chronic synovitis. Blood in the joint can also directly damage the cartilage, and with repeated bleeding, there is progressive destruction of both cartilage and bone. The end result is known as haemophilic arthropathy. Common joints affected are the ankles, knees and elbows. In the recent era of prophylaxis - where clotting factor concentrate therapy is given regularly to persons with haemophilia (PwH) - the most common joint affected with haemophilic arthropathy is the ankle complex.[3] Both the tibiotalar and the subtalar joints may be affected within the ankle complex. Haemophilic arthropathy affects young men and this has a significant impact on their occupation and earning capacity and participation in normal family life.

Although prophylactic administration of factor concentrates has demonstrated a significant reduction in haemophilic joint disease burden[2], repeated bleeding episodes induce synovitis that is irreversible.[4] There are effective surgical and non-surgical treatments for haemophilic synovitis. Intra-articular steroid can reduce the pain from synovitis and arthropathy although duration of action is often short-lived;

radioactive synovectomy can be used to reduce synovial overgrowth that accompanies haemophilic synovitis thus reducing bleeding frequency and surgical synovectomy is effective for the same reasons.[4,5]

However, the MRI scans of many affected haemophilic joints do not show synovitis rather a severely damaged joint with loss of articular cartilage with a 'bone-on-bone' appearance. In these patients surgical fusion or joint replacement have been the only therapeutic options to date.[5,6,7] It is often the ankle and the sub-talar joints that are affected and fusion here may result in significant morbidity, operative risk, long periods away from work and a dysfunctional gait with concomitant biomechanical problems. Ankle replacements have a shorter longevity when compared with other large joint replacements. [8] This is particularly relevant in the haemophilia population where patients are typically young at the time of consideration for orthopaedic surgery.

Physiotherapy, [9] analgesia and intra-articular steroid are all helpful for management of haemophilic arthropathy but there is a need for an intervention for the damaged osteoarthritic joint where surgery is not appropriate. Intra-articular (IA) hyaluronic acid injections have been used for other patient groups with significant arthropathy i.e. osteoarthritis, and there are theoretical advantages of using hyaluronic acid over steroid in some haemophilic joints. The main potential advantage is that hyaluronic acid may substitute for the loss of cartilage in affected joints, providing cushioning between the bones making up the joint, and thereby potentially providing pain relief and increased functionality of the joint.

Routine options for pharmacological analgesic therapy for many patients with arthropathy include simple analgesics, non-steroidal anti-inflammatory drugs (NSAIDs), and cyclo-oxygenase type 2 (COX-2) inhibitors. Pain relief options are limited for patients with haemophilia. NSAIDs are relatively contraindicated due to the increased risk of bleeding [10] and COX-2 inhibitor therapy has associations in certain patient groups with increased cardiovascular risk. [10]

Ostenil Plus (Hyaluronic acid plus mannitol) has the potential to bridge the 'treatment gap' between simple analgesia and more complex orthopaedic solutions for haemophilic arthropathy. In particular in those patients with 'bone-on-bone' arthropathic changes, Ostenil Plus may provide cushioning to the damaged joint and in turn reduce pain and increase functionality of the joint. The potential benefits to patients may be great, and may also be more acceptable to patients when compared with an orthopaedic solution.

Hyaluronic acid (HA) is a long chain polysaccharide found in connective tissue, skin, the eye and synovial fluid. It is secreted continuously by the synovial membrane into the joint space and comprises a major part of the synovial fluid. It is highly concentrated at articular cartilage surfaces and acts as both a lubricant and a shock absorber [11] within a joint. In addition, it also acts as a semi-permeable barrier regulating metabolic exchanges between cartilage and the synovial fluid, and provides a viscoelastic shield around synoviocytes and adjacent nerve endings. [12] HA is a large molecule and its size reduces the free movement of lytic enzymes and inflammatory mediators thus enhancing chrondrocyte metabolism. [13] Ostenil Plus is non-animal derived, non-crosslinked HA with a molecular weight optimal for binding with CD44 receptors.

Hyaluronic acid has been tested previously in small cohorts of haemophilia patients in the setting of arthropathy to the knee [14,15], but no studies have reported the effects on ankle arthropathy in this patient population. When used in knee joints, an improvement was seen in function (longer walking distance, stair-climbing and reduced pain)[14,15] and in one study it was reported to reduce the need for referral of patients for arthroplasty. [14] It is hypothesised in this study that in haemophilia patients with

significant haemophilic arthropathy of the ankle, as defined by MRI scoring, two 2ml intra-articular injections 6 months apart will improve pain and functionality of the affected ankle joint. This pilot study will be used to inform a larger efficacy study.

This study is a pilot, single centre study that will address the question: does intra-articular Ostenil Plus improve pain and functionality in participants with haemophilic arthropathy of the ankle complex.

Ostenil Plus is an isotonic solution of highly purified sodium hyaluronate (hyaluronic acid) with added 0.5% mannitol. The hyaluronic acid is non-animal in origin and is derived from bacterial fermentation. The Ostenil Plus formulation offers the option to reduce the number of injections to only one injection per treatment cycle (6 months). It is administered as a prefilled syringe containing 2mls (40mg) of hyaluronic acid. In a multicentre, open, non-comparative study in 79 patients, Ostenil Plus treatment led to significant reductions in joint pain, stiffness and functional disability compared with baseline up to 6 months. In addition, rescue medication intake decreased from 58.2% at baseline to 2.5% on Day 90. [16] In addition to the known benefit to participants of taking part in a clinical study, there are several potential benefits from the intervention which include: reduction of pain and increase in function (i.e. improved range of movement, improved gait) in the affected joint. These improvements may influence quality of life measures for participants.

Intra-articular injection of hyaluronic acid is known to cause short-lived side effects in some patients. The side effects include: stiffness and pain. Participants with known allergy to the excipients of hyaluronic acid will not be included in this study. Participants with unknown allergy may potentially be entered and any allergic symptoms will be treated in the standard manner. The potential risks will be evaluated with the safety outcome data.

5. OBJECTIVES AND OUTCOME MEASURES

Objectives	**Outcome Measures**	**Timepoint(s) of evaluation of this outcome measure (if applicable)**
Primary Objective To determine whether Ostenil Plus improves pain in participants with haemophilic arthropathy of the ankle.	VAS (visual analogue score) for pain.	VAS will be assessed at all of the following timepoints: 3, 6, 9, 12 months.
Secondary Objectives To determine whether Ostenil Plus improves the functionality of the haemophilia ankle and to assess the safety of treatment in adult patients	Changes to ankle functionality as defined by changes to the ankle HJHS score; the foot and ankle mobility measure (FAAM)	These assessments will be completed at:

with haemophilia and arthropathy of the ankle	and the global HJHS score. Changes to annualised bleeding rate Changes to quality of life using the EQ-5D-5L and Haemophilia Activity List (HAL) Safety measures including increased pain and stiffness to the injected joint	3, 6, 9, 12 months.

6. TRIAL DESIGN

This is a single centre, open-label, pilot study.

The trial will enroll 20 participants and the recruitment phase will last 12 months.

Follow-up will be for 12 months from the date of enrolment of the last participant.

The number of visits for a participant is set out below, in the trial assessment schedule.

Trial Assessment Schedule:

Timepoint*	***Screening***	***Intervention and follow-up***				
	T_0	T_1	T_2	T_3	T_4	T_5
SCREENING						
Eligibility Screen	*X*					
Informed Consent	*X*					
MRI showing arthropathy, within 6 months of enrolment	*X*					
BASELINE VISIT						
Baseline characteristics		*X*				
Details of Haemophilia, including ABR, factor concentrate usage , previous joint injections, and a global HJHS within 6 months of enrolment		*X*				
Medications including anti-inflammatory drugs		*X*				
VAS score		*X*				
INTERVENTION		↔		↔		
Ankle HJHS score		*X*				

Factor concentrate replacement		*X*		*X*		
Ostenil Plus injection		*X*		*X*		
FOLLOW-UP ASSESSMENTS						
VAS score			*X*	*X*	*X*	*X*
Medications including anti-inflammatory drugs			*X*	*X*	*X*	*X*
Ankle HJHS						*X*
EQ-5D-5L		*X*	*X*	*X*	*X*	*X*
HAL score		*X*	*X*	*X*	*X*	*X*
FAAM score		*X*	*X*	*X*	*X*	*X*
Adverse events		*X*	*X*	*X*	*X*	*X*
End of study assessment – including ABR and factor concentrate usage						*X*
**Time points are:*	*T_o – Screening (within 1 month of intervention and may take place with T_1)* *T_1 – Baseline and Ostenil Plus injection* *T_2 – 3 months post intervention (± 14 days)* *T_3 – Ostenil Plus injection #2, 6 months review* *T_4 – 9 months post intervention (± 14 days)* *T_5 – 12 months post intervention (± 14 days)*					

Data will be collected onto a study specific electronic database.

7. PARTICIPANT IDENTIFICATION

7.1. Trial Participants

Adult (18 years or older) participants with haemophilia A or B of any severity and who have haemophilic arthropathy including synovitic and/or degenerative changes to one or both ankle joints, as determined by MRI.

Participants will be known to the haemophilia team at either Oxford or Basingstoke Comprehensive Care Centres and will be easily identifiable. Basingstoke will act as a PIC such that they will identify potential participants and will inform participants of the study, as well as offer interested patients a PIL. However, all study procedures will be performed at Oxford.

Patients will be assessed for eligibility to enter the trial according to the criteria set out below. If patients are eligible for entry into the study following initial screening, consent for entry into the study will be sought.

There will be no exceptions to eligibility requirements at the time of enrolment.

Participants will be considered eligible for enrolment in this trial if they fulfil all the inclusion criteria and none of the exclusion criteria detailed below.

7.2. Inclusion Criteria

Patients are eligible for this trial if:

1. Written informed consent is obtained before any study related activity
2. The participant is an adult (age 18 years or older) and has haemophilia A or haemophilia B of any severity, including those with inhibitors
3. There are MRI ankle changes consistent with haemophilic arthropathy – showing synovitic and/or degenerative changes to one or both ankle joints

7.3. Exclusion Criteria

A patient will not be eligible for this trial if he fulfils one or more of the following criteria:

1. The patient has evidence of infection, including those patients taking antibiotic therapy
2. The patient has known inflammatory joint disease, including crystal disease
3. The patient has received an intra-articular steroid injection within the preceding 6 months
4. The patient is known to be allergic to any of the excipients of Ostenil Plus

8. TRIAL PROCEDURES

8.1. Recruitment

Participants will be identified by the staff at the Oxford Haemophilia and Thrombosis Centre or Basingstoke Haemophilia Centre. Both haemophilia centres look after all adult patients with haemophilia in the Thames Valley region. Every adult patient is reviewed 6 – 12 monthly by the clinical staff and any patient who has clinical evidence of ankle arthropathy will be considered for the study. It is standard clinical practice to request an MRI for these individuals and if the MRI confirms haemophilic arthropathy, the research staff will approach the patient either in person or by telephone to offer participation in this

study. The patient will receive a patient information leaflet (PIL) which will be given to them, either in person in clinic by a member of the research team, or if the first discussion about the trial is by telephone the patient will receive the PIL in the post with an accompanying invitation letter. Basingstoke will act as a PIC such that they will identify potential participants and will inform participants of the study, as well as offer interested patients a PIL. However, all other study procedures will be performed at Oxford.

Oxford Haemophilia & Thrombosis Centre (OHTC) has 158 adult patients with severe and moderate haemophilia A and B (and 150 mild patients) which is a large cohort of patients, many of whom will be eligible for this study. Basingstoke has over 80 severe haemophilia patients. There is an excellent clinical infrastructure at OHTC and at Basingstoke, which includes dedicated haemostasis doctors, nurses, a physiotherapist and a rheumatologist once a month for clinic. The research infrastructure is equally strong and OHTC and Basingstoke Haemophilia Centre have run many observational and interventional haemophilia trials. These local resources and facilities will support recruitment, and there are adequate numbers of qualified staff to conduct the study properly and safely.

Adult haemophilia patients with ankle arthropathy will be identified as follows: (1) in clinic by the haemophilia doctors at OHTC or Basingstoke; (2) by the physiotherapist at OHTC or Basingstoke.

8.1. Screening and Eligibility Assessment

A screening log will be completed at OHTC whenever a potential patient is screened for this study, which will record all patients considered for eligibility to the trial. The log will include age, gender, inclusion/exclusion criteria and other reasons for non-enrolment. The screening log will include patients approached but in whom consent was not obtained for the trial (with reasons). The local principal investigator and research team will be responsible for completing the screening log after an eligible patient has been identified and considered for participation in the trial.

The following assessments will be performed at screening:

- Assessment of inclusion/exclusion criteria
- Confirmation that an MRI showing haemophilic arthropathy is available and has been conducted within 6 months of enrolment

Once final eligibility is confirmed the research team will obtain fully informed, written consent. At this point the participant will be enrolled into the study.

No longer than 12 weeks is permitted between screening and intervention.

8.2. Informed Consent

The participant must personally sign and date the latest approved version of the Informed Consent form before any trial specific procedures are performed.

Written and verbal versions of the Participant Information and Informed Consent will be presented to the participants detailing no less than: the exact nature of the trial; what it will involve for the participant; the implications and constraints of the protocol; the known side effects and any risks involved in taking part. It will be clearly stated that the participant is free to withdraw from the trial at

any time for any reason without prejudice to future care, without affecting their legal rights and with no obligation to give the reason for withdrawal.

The participant will be allowed as much time as wished to consider the information, and the opportunity to question the Investigator, their GP or other independent parties to decide whether they will participate in the trial. Written Informed Consent will then be obtained by means of participant dated signature and dated signature of the person who presented and obtained the Informed Consent. The person who obtained the consent must be suitably qualified and experienced, and have been authorised to do so by the Chief/Principal Investigator. At OHTC the clinicians and the research nurses will be able to take written, informed consent. A copy of the signed Informed Consent will be given to the participant. The original signed form will be retained at the trial site and a copy will be filed in the participants notes.

8.3. Baseline Assessments

At the baseline visit the following assessments will be completed prior to the intra-articular injection of Ostenil Plus.

Demographic data (patient characteristics) will be collected and will include:

- Severity of haemophilia
- Type of haemophilia (e.g. haemophilia A or B)
- Patient age, weight, height, presence of inhibitors (current or historical)
- Treatment regimen for haemophilia: e.g. prophylaxis or on-demand therapy
- If a participant uses prophylaxis, the following information will be recorded:
    - dose of factor given for prophylaxis
    - frequency of factor treatment
    - trough level
- Documentation of the severity of the haemophilic arthropathy will be made
- Documentation of previous joint injections

Clinical data will also be collected and will include:

- Annualised bleeding rate for the 12 months prior to the baseline assessment date. The ABR can be determined usi ng data from HaemTrack and the clinical notes.
- HJHS score (completed within 6 months of screening)
- VAS pain score for the affected ankle
- VAS stiffness score for the affected ankle
- Analgesia used including anti-inflammatories and opiate medication
- All concomitant medications
- QofL measurements will also be documented and will include the following QofL questionnaires: EQ-5D-5L and HAL
- The following functionality score will be documented: FAAM score
- Factor concentrate usage for the 6 months preceding study entry will be calculated using data from HaemTrack

These assessments will take approximately 30 minutes and will be performed in the clinic rooms at OHTC.

8.4. Treatment of participants

This is an open-label study and all participants will receive Ostenil Plus. The patient's eligibility criteria MUST be confirmed to ensure they are still eligible prior to administration of the trial device.

The device is Ostenil Plus (20 mg/mL) and will be supplied as vials of fully reconstituted 2mL (20mg/mL) per bottle by TRB Chemedica UK. One or two vials will be used for each ankle that is injected (one participant may have both ankles injected). One ankle complex may have both the tibio-talar and the subtalar joints affected and therefore a participant may have two injections of 2mL into the same ankle complex – with one injection into each part of the joint.

Otenil Plus will be stored according to manufacturer's instructions (OSTENIL PLUS® Instructions For use). All vials will be provided to OHTC for storage from TRB Chemedica UK.

The trial device will be administered to a participant in the joint haemophilia/rheumatology clinic at OHTC. It is likely that the participant will be scheduled for an additional clinic appointment for this procedure to be completed, over and above their standard 6 monthly clinic appointments if they are an Oxford patient, although occasionally these clinic appointments can coincide. For patients attending OHTC from Basingstoke, they will require three appointments at OHTC – at time 0, 6 and 12 months. The data collected for all patients at 3 and 9 months can be collected by post or electronically and via a telephone call.

Prior to injection of the Ostenil Plus, each patient will receive factor concentrate replacement, or other haemostatic therapy (such as DDAVP or bypassing agent therapy), according to clinical need to ensure safe haemostasis is achieved around the joint injection. The standard OHTC guidelines will be followed.

The IA preparation of Ostenil Plus will be administered as a single bolus into one of the ankle joint(s) – up to four injections if the participant has affected tibio-talar and subtalar joints in both ankles. It will be administered over 10-15 seconds. The participant will be asked to remain in the clinic for 30 minutes after the injection and will be reviewed by the clinical staff for signs of allergy immediately after injection and then at 15 and 30 minutes after the injection.

Ostenil Plus may be injected with lignocaine 1%.

8.5. Subsequent Visits

Four subsequent visits will be completed:

<u>Visit 1: 3 months ± 14 days</u>

The following study interventions will be conducted. These include questionnaires to complete and a telephone consultation with the participant to document adverse events.

The participant will have the following questionnaires sent via post or e-mail (according to participant preference) and they will be asked to complete the questionnaires within a 14 day period. The participant will be asked to return the questionnaires by post (return envelope provided) or e-mail to the research team.

The following questionnaires will be completed by the participant:

- HAL score
- EQ-5D-5L
- FAAM score

A member of the research team will contact the participant by telephone to complete the following three interventions:

- VAS score – the participant will be asked to score their pain on a 0 – 10 score
- The participant will be asked to list their current medications, including anti-inflammatory medications
- The participant will be asked if they have suffered any pain, stiffness or swelling to their affected ankle joint

Visit 2: 6 months ± 14 days

The following study interventions will be conducted.

These include questionnaires to complete and a second clinic appointment to receive a second injection to the affected joint(s).

Prior to injection of the Ostenil Plus, each patient will receive factor concentrate replacement, or other haemostatic therapy (such as DDAVP or bypassing agent therapy), according to clinical need to ensure safe haemostasis is achieved around the joint injection. The standard OHTC guidelines will be followed.

2mL Ostenil Plus (20mg/mL) will be injected into each of the affected joint(s) – up to four injections if the participant has affected tibio-talar and subtalar joints in both ankles. 1% lignocaine may be administered with the Ostenil Plus.

The participant will be asked to complete the following questionnaires when they attend clinic:

- HAL score
- EQ-5D-5L
- FAAM score

A member of the research team will collect the following data:

- VAS score – the participant will be asked to score their pain on a 0 – 10 score
- The participant will be asked to list their current medications, including anti-inflammatory medications
- The participant will be asked if they have suffered any pain, stiffness or swelling to their affected ankle joint

Visit 3: 9 months ± 14 days

The following study interventions will be conducted. These include questionnaires to complete and a telephone consultation with the participant to document adverse events.

The participant will have the following questionnaires sent via post or e-mail (according to participant preference) and they will be asked to complete the questionnaires within a 14 day period. The participant will be asked to return the questionnaires by post (return envelope provided) or e-mail to the research team.

The following questionnaires will be completed by the participant:

- HAL score
- EQ-5D-5L
- FAAM score

A member of the research team will contact the participant by telephone to complete the following three interventions:

- VAS score – the participant will be asked to score their pain on a 0 – 10 score
- The participant will be asked to list their current medications, including anti-inflammatory medications
- The participant will be asked if they have suffered any pain, stiffness or swelling to their affected ankle joint

Visit 4: 12 months ± 14 days

The following study interventions will be conducted. This will also include a clinical assessment.

The participant will be asked to attend the OHTC for visit 4.

The participant will complete the following questionnaires whilst at OHTC:

- HAL score
- EQ-5D-5L
- FAAM score

The following clinical assessments will be completed and will constitute the end of study assessment:

- VAS score – the participant will be asked to score their pain on a 0 – 10 score
- The participant will be asked to list their current medications, including anti-inflammatory medications
- The participant will be asked if they have suffered any pain, stiffness or swelling to their affected ankle joint
- The OHTC physiotherapist will assess the affected ankle and will calculate their ankle HJHS
- The participant's ABR will be calculated using the data from the 6 months since their Ostenil Plus injection and the result will be used to extrapolate to an annualised bleeding rate.

8.6. Procedures for Assessing Safety

Safety outcomes will be assessed for all participants until week 52, at all the time points set out above. The following outcomes will be assessed:

a) Pain in the affected joint (as measured by VAS scale)
b) Stiffness in the affected joint (as measured by VAS scale)

8.7. Discontinuation/Withdrawal of Participants from Trial Treatment

Each participant has the right to withdraw from the trial at any time. In addition, the Investigator may discontinue a participant from the trial at any time if the Investigator considers it necessary for any reason including:

- Ineligibility (either arising during the trial or retrospectively having been overlooked at screening)
- Significant protocol deviation
- Significant non-compliance with treatment regimen or trial requirements
- An adverse event which requires discontinuation of the trial device or results in inability to continue to comply with trial procedures
- Disease progression which requires discontinuation of the trial device or results in inability to continue to comply with trial procedures
- Withdrawal of Consent
- Loss to follow up

Safety data will be sought until the end of the 12 month period, even if a participant were to withdraw from the study. If an adverse event does occur after withdrawal, or at the time of withdrawal, the Investigator will arrange for follow-up visits or telephone calls until the adverse event has resolved or stabilised.

8.8. Definition of End of Study

The end of trial is the date of the last visit of the last participant.

9. INVESTIGATIONAL DEVICE

9.1. Device Description

Active treatment will be 2ml Ostenil Plus provided as a solution in a single syringe per affected joint in each participant. Ostenil Plus will be supplied as vials of 2ml (20mg/ml) per bottle by TRB Chemedica UK. All participants will receive active intervention. No placebo arm is included in this study. There are no dose adjustments for this study.

The device is ready made for intra-articular (IA) injection. The solution is pre-packaged in a 2ml sterilized syringe and will be administered as a single bolus into each of the affected ankle joint(s). It will be administered over 10-15 seconds. Dr Joel David, Consultant Rheumatologist will perform all joint injections. The participant will receive the injections at OHTC, in one of the scheduled haemophilia/rheumatology clinics.

9.2. Storage of Ostenil Plus

Ostenil Plus will be stored according to manufacturer's instructions. Ostenil Plus will be stored at OHTC. OHTC has a long track record of storing trial products in its centre. There are trial fridges with temperature control monitoring and storage capabilities. The temperature is monitored daily in the week by research staff and out of hours there is an alarm that triggers OHTC staff to attend the centre, where required.

9.3. Accountability of the Trial Treatment

Ostenil Plus will be administered by the research team in clinic. The Ostenil Plus administration will be recorded on EPR, as a source document for the study.

9.4. Concomitant Medication

There are no contra-indicated medications in this study. All concomitant medications will be recorded throughout the study.

9.5. Post-trial Treatment

There will not be provision of the device beyond the trial period.

10. SAFETY REPORTING

10.1. Definitions

Adverse Event (AE)	Any untoward medical occurrence, unintended disease or injury or any untoward clinical signs (including an abnormal laboratory findings) in participants, users or other persons whether or not related to the investigational medical device. This includes events related to the investigational device or comparator, events related to the procedures involved (any procedure in the protocol). For users or other persons this is restricted to events related to the investigational medical device.
Adverse Device effect (ADE)	An adverse event related to the use of an investigational medical device. This definition includes any events resulting from insufficient or inadequate instructions for use, deployment, implantation, installation, or operation, or any malfunction of the investigational device. This definition also includes any event resulting from user error or form intentional misuse of the investigational device.
Serious Adverse Event (SAE)	An adverse event that: • Led to death

	• Resulted in serious deterioration in the health of the subject that: o resulted in a life-threatening illness or injury o resulted in a permanent impairment of a body structure or a body function o required in-patient care or prolongation of hospitalisation o resulted in medical or surgical intervention to prevent life-threatening illness or injury or permanent impairment to a body structure or a body function. This includes device deficiencies that might have led to a serious adverse event if: a) suitable action had not been taken or b) intervention had not been made or c) circumstances had been less fortunate. These are handled under the SAE reporting system. Planned hospitalisation for a pre-existing condition, or a procedure required by the trial protocol, without serious deterioration in health, is not considered a serious adverse event.
Serious Adverse Device Effect (SADE)	Any untoward medical occurrence that can be attributed wholly or partly to the device, which resulted in any of the characteristics of a serious adverse event as described above. *Unanticipated Serious Adverse Device Effects (USADE)* Any serious adverse device effect which, by its nature, incidence, severity or outcome, has not been identified
Device deficiency	Inadequacy of a medical device with respect to its identity, quality, durability, reliability, safety or performance. Device deficiencies include malfunctions, use errors and inadequate labeling. Device deficiencies that did not lead to an adverse event, but could have led to a medical occurrence if suitable action had not been taken, or intervention had not been made or if circumstances had been less fortunate
User error	Act or omission of an act that results in a different medical device response than intended by the manufacturer or expected by the user. Use error includes slips, lapses and mistakes. An unexpected physiological response of the subject does not itself constitute a use error.

NB: to avoid confusion or misunderstanding of the difference between the terms “serious” and “severe”, the following note of clarification is provided: “Severe” is often used to describe intensity of a specific event, which may be of relatively minor medical significance. “Seriousness” is the regulatory definition supplied above.

Any pregnancy occurring during the clinical trial and the outcome of the pregnancy should be recorded and followed up for congenital abnormality or birth defect, at which point it would fall within the definition of “serious”.

10.2. Causality

The relationship of each adverse event to the trial device must be determined by a medically qualified individual according to the following definitions:

Related: The adverse event follows a reasonable temporal sequence from trial device administration. It cannot reasonably be attributed to any other cause.

Not Related: The adverse event is probably produced by the participant’s clinical state or by other modes of therapy administered to the participant.

10.3. Procedures for Recording Adverse Events

All AEs occurring during the trial and until the end of the 12 months follow-up period that are observed by the Investigator or reported by the participant and relate to the affected ankle will be recorded on the CRF.

Ostenil Plus has been used for many patients who have arthropathy due to conditions other than haemophilia, such as osteoarthritis and rheumatoid arthritis. Adverse events are not expected to occur outside local effects to the injected ankle and haemophilia is a condition that can cause symptoms in all large joints. We will not record symptoms of joint disease in other joints for this study, as these events would be expected in the normal course of a patient’s condition.

The following information will be recorded: description, date of onset and end date, severity, assessment of relatedness to device and action taken. Follow-up information should be provided as necessary.

The severity of events will be assessed on the following scale: 1 = mild, 2 = moderate, 3 = severe.

AEs/ADEs considered related to the device as judged by a medically qualified investigator or the Sponsor will be followed either until resolution, or the event is considered stable.

A participant may voluntarily withdraw from treatment due to what he or she perceives as an intolerable AE. If this occurs, the participant must undergo an end of trial assessment and be given appropriate care under medical supervision until symptoms cease, or the condition becomes stable.

10.4. Reporting Procedures for Serious Adverse Events

SAEs will be recorded from the time of taking informed consent until 6 months after the date of the second injection.

There are no SAEs expected in this study and therefore any SAEs must be reported within 24 hours of the study team becoming aware of the event.

All SAEs must be reported on the SAE reporting form to R&D within 24 hours of the Site Study Team becoming aware of the event. R&D will perform an initial check of the report, request any additional information, and ensure it is reviewed by the Medical Monitor on a weekly basis. It will also be reviewed at the next Trial Safety Group meeting. All SAE information must be recorded on an SAE form and emailed to R&D. Additional and further requested information (follow-up or corrections to the original case) will be detailed on a new SAE Report Form and emailed to R&D.

SAEs/SADEs that pose an immediate risk to patient health or safety, will be reported to the TSG immediately or no later than 24 hours after the Investigator is aware and to the device manufacturer, competent authority and the REC within 2 calendar days of the Chief Investigator becoming aware of the event.

All other reported SAEs/SADEs will be reported to the TSG and competent authority within 7 calendar days of notification, if appropriate. This will not include SAEs that may be expected as part of the risks of routine care. Adverse device events (SADEs, USADEs) and device deficiencies will also be reported to the device manufacturer. All SAEs will be followed up to resolution.

10.5. Expectedness

Expectedness will be determined according to the Manufacturer's Instructions.

10.6. Safety Monitoring Committee

The Oxford University Hospitals NHS Foundation Trust / University of Oxford Trials Safety Group (TSG) will conduct a review of all SAEs for the trial reported during the quarter and cumulatively. The aims of this committee include:

- To pick up any trends, such as increases in un/expected events, and take appropriate action
- To seek additional advice or information from investigators where required
- To evaluate the risk of the trial continuing and take appropriate action where necessary

11. STATISTICS

The analyses will be described in detail in a full Statistical Analysis Plan (SAP). This section summarises the main issues.

11.1. Description of Statistical Methods

Analysis of primary outcomes:

The results for the primary outcome of feasibility will be presented as the proportion of participants whose VAS pain score has decreased by at least 30% from baseline. Each time point (3 months, 6 months, 9 months and 12 months weeks) will be presented separately using basic summary statistics.

Analysis of secondary outcomes:

We will present information on the numbers of patients screened and the proportion of screened patients entered into the trial.

We will present basic summary statistics for VAS pain scores, Ankle HJHS, HAL and FAAM scores for the participant group at each time point. Changes to these scores from baseline and throughout the study will be explored using a repeated measures test.

Numbers of AEs and SAEs reported will be presented for patients.

Quality of life scores will be compared across the time points.

Annualised bleeding rates will be compared between the baseline measure and the measure at 12 months.

Analysis of safety outcomes:

The number of symptomatic events up to 12 months will be presented.

The total number of adverse and serious adverse events will also be presented.

There will not be an interim analysis due to the small size of the study.

11.2. The Number of Participants

This is a pilot feasibility study and therefore does not require a formal sample size calculation.

The primary endpoint explores whether two Ostenil Plus injections leads to a clinically meaningful reduction in pain score, as measured by the VAS scale. A clinically meaningful reduction in pain has been defined as a decrease in VAS by 30% from baseline score. For this pilot trial to be successful, we would expect that 80% of the patients will achieve at a least a 30% reduction in their VAS pain score. If the proportion of participants whose VAS scores decreases by 30% is 80%, a sample size of 20 will yield a 95% confidence interval for this estimate of between 62.5% and 97.5%.

11.3. The Level of Statistical Significance

A level of 0.05 will be deemed as significant.

11.4. Criteria for the Termination of the Trial

This is a pilot trial using a device that is used as a therapeutic treatment for patients with arthropathy due to different clinical conditions. It is not expected that this study will need to be terminated due to safety reasons, however, the trial team will be guided by the TSG and if a safety signal is evident, the trial will be terminated for safety reasons. The main potential reason for safety concern would be an increase in bleeds into the injected ankle.

11.5. Procedure for Accounting for Missing, Unused, and Spurious Data.

Sensitivity to missing data for the VAS pain scores at each time point will be assessed by re-calculating the proportion, treating cases with missing data as no improvement in pain score (worst-case scenario) and as improvement in pain score of 50% (best-case scenario).

Missing data for secondary or safety outcomes will be assumed to be missing-at-random.

11.6. Inclusion in Analysis

All analyses will be performed according to the intention-to-treat principle and will include all patients.

11.7. Procedures for Reporting any Deviation(s) from the Original Statistical Plan

Deviations from the statistical plan will be documented in the final publication, including reasons for the deviation.

12. DATA MANAGEMENT

12.1. Source Data

Source documents are where data are first recorded, and from which participants' CRF data are obtained. These include, but are not limited to, hospital records (from which medical history and previous and concurrent medication may be summarised into the CRF), clinical and office charts, laboratory and pharmacy records, diaries, microfiches, radiographs, and correspondence.

CRF entries will be considered source data if the CRF is the site of the original recording (e.g. there is no other written or electronic record of data). All documents will be stored safely in confidential conditions. On all trial-specific documents, other than the signed consent, the participant will be referred to by the trial participant number/code, not by name.

12.2. Access to Data

Direct access will be granted to authorised representatives from the Sponsor, host institution and the regulatory authorities to permit trial-related monitoring, audits and inspections.

12.3. Data Recording and Record Keeping

All trial data will be entered on to paper CRFs and/or an Excel trial specific spreadsheet.

The participants will be identified by a unique trial specific number and/or code in any database. The name and any other identifying detail will NOT be included in any trial data electronic file.

13. QUALITY ASSURANCE PROCEDURES

The trial will be conducted in accordance with the current approved protocol, GCP, relevant regulations and standard operating procedures.

The study may be monitored, or audited in accordance with the current approved protocol, GCP, relevant regulations and standard operating procedures.

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14. SERIOUS BREACHES

A serious breach is defined as "A breach of GCP or the trial protocol which is likely to affect to a significant degree –

(a) the safety or physical or mental integrity of the subjects of the trial; or

(b) the scientific value of the trial".

In the event that a serious breach is suspected the Sponsor must be contacted within 1 working day. In collaboration with the C.I., the serious breach will be reviewed by the Sponsor and, if appropriate, the Sponsor will report it to the REC committee, Regulatory authority and the NHS host organisation within seven calendar days.

15. ETHICAL AND REGULATORY CONSIDERATIONS

15.1. Declaration of Helsinki

The Investigator will ensure that this trial is conducted in accordance with the principles of the Declaration of Helsinki.

15.2. Guidelines for Good Clinical Practice

The Investigator will ensure that this trial is conducted in accordance with relevant regulations and with Good Clinical Practice.

15.3. Approvals

The protocol, informed consent form, participant information sheet and any proposed advertising material will be submitted to an appropriate Research Ethics Committee (REC), HRA (where required), regulatory authorities (MHRA in the UK), and host institution(s) for written approval.

The Investigator will submit and, where necessary, obtain approval from the above parties for all substantial amendments to the original approved documents.

15.4. Reporting

The CI shall submit once a year throughout the clinical trial, or on request, an Annual Progress Report to the REC, HRA (where required), host organisation and Sponsor. In addition, an End of Trial notification and final report will be submitted to the MHRA, the REC, host organisation and Sponsor.

15.5. Participant Confidentiality

The trial staff will ensure that the participants' anonymity is maintained. The participants will be identified only by a participant ID number on all trial documents and any electronic database, with the exception of the CRF, where participant initials may be added. All documents will be stored securely and only accessible by trial staff and authorised personnel. The trial will comply with the Data Protection Act, which requires data to be anonymised as soon as it is practical to do so.

15.6. Expenses and Benefits

Reasonable travel expenses for any visits for participants additional to normal care will be reimbursed on production of receipts, or a mileage allowance provided as appropriate.

16. FINANCE AND INSURANCE

16.1. Funding

The device is supplied by TRB Chemedica. No other funding is required for this study.

16.2. Insurance

NHS bodies are legally liable for the negligent acts and omissions of their employees. If you are harmed whilst taking part in a clinical trial as a result of negligence on the part of a member of the trial team this liability cover would apply.

Non-negligent harm is not covered by the NHS indemnity scheme. The Oxford University NHS Foundation Trust, therefore, cannot agree in advance to pay compensation in these circumstances.

In exceptional circumstances an ex-gratia payment may be offered.

17. PUBLICATION POLICY

The final study data set will be analysed and results published as soon as possible following completion of study follow up, final data checks and database lock. The research team will form the basis of the Writing Committee and will advise on the nature of publications

Authorship for any publications arising from this study will follow the rules set out by the International Committee of Medical Journal Editors definitions of Authorship and Contributorship, http://www.icmje.org/ethical_1author.html

Study results will be embargoed and not disseminated until authorised by the CI. Final manuscripts and presentations will be approved by the CI prior to publication.

For the main report of this study submitted for publication, together with associated methodology and posters/presentations, the International Committee of Medical Journal Editors definitions of Authorship and Contributorship will be used, http://www.icmje.org/ethical_1author.html. The Funder will be acknowledged in all publications/presentations.

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19. APPENDIX A: AMENDMENT HISTORY

Amendment No.	Protocol Version No.	Date issued	Author(s) of changes	Details of Changes made

Protocol amendments must be submitted to the Sponsor for approval prior to submission to the REC committee or MHRA.