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Can we use estrogen-containing therapy to improve pain in women after menopause with hand osteoarthritis? (HOPE-e study)

Submission date
15/01/2019

Recruitment status
No longer recruiting

Registration date
11/03/2019

Overall study status
Completed

Last Edited
08/11/2022

Condition category
Musculoskeletal Diseases

[X] Prospectively registered

[X] Protocol

[_] Statistical analysis plan

[X] Results

[_] Individual participant data

Plain English summary of protocol

Background and study aims
Hand osteoarthritis (OA) affects over 2 million people in the UK, causing pain and functional difficulties for many. Painful hand OA affects 8% of women and 3% of men over the age of 45 years. Currently there is no cure. There are few evidence-based interventions other than pain relief and exercise, which are often inadequate. Around 90% of those seeking specialist care for symptomatic hand OA are female. Hand OA is more common in women, especially around the time of menopause, when levels of the hormone estrogen fall. Estrogen-containing therapy appears to protect from progression of knee and hip OA. However, to date there have been no randomised trials testing estrogen-containing therapy in individuals with symptomatic hand OA. The study aims to find out whether it is acceptable to women with painful hand OA to take this type of treatment, and what is the best way of collecting some of the information in order to facilitate planning a full size trial. The long-term aim is to find out whether giving estrogen-containing therapy to women after the menopause improves hand OA symptoms.

Who can participate?
Women aged 40-65 with painful hand OA who are already menopausal but not taking HRT

What does the study involve?
Participants are randomly allocated to take either a hormone containing therapy (HRT) tablet daily for 6 months or a dummy tablet that looks similar to the HRT tablets but does not contain any hormones. Measurements of hand pain, function, quality of life and menopause symptoms are collected and the acceptability of taking the drug everyday is assessed. The study involves five study visits and one telephone call over a 7-month period. In addition, some participants are invited to an optional focus group.

What are the possible benefits and risks of participating?
Participants may not benefit directly from taking part in this study. 1 in 2 individuals will receive an inactive treatment. During the study participants will be monitored closely by a consultant who is an expert in osteoarthritis. Sometimes, conditions are detected that would otherwise have been undetected, for example, high blood pressure. In this situation, the study team will

give the participant advice on treatment. Joining the study can therefore have indirect health benefits. The study will give us useful information which may be of benefit to others in the future and help the development of new treatments for OA. Participants may experience side effects as a result from taking the study medication. Some participants may have minor bruising because of the needle puncture required for blood testing.

Where is the study run from?
1. Nuffield Orthopaedic Centre, Oxford (UK)
2. Charing Cross Hospital, London (UK)
3. White Horse Medical Practice, Faringdon (UK)

When is the study starting and how long is it expected to run for?
Recruitment phase: April 2019 – December 2020 (updated 28/04/2020, previously: April 2020) (updated 14/10/2019, previously: February 2020)
Follow-up phase: January 2021 - July 2021 (updated 28/04/2020, previously: March 2020 – September 2020)
Analysis phase: August 2021 - December 2021 (updated 28/04/2020, previously: September 2020 – April 2021)

Who is funding the study?
National Institute for Health Research (NIHR) (UK)

Who is the main contact?
Jennifer Williams
ouh-tr.hope-e@nhs.net

Contact information

Type(s)
Scientific

Contact name
Dr Jennifer Williams

Contact details
Trial Manager
Kennedy Institute of Rheumatology
NDORMS – University of Oxford
Roosevelt Drive
Oxford
United Kingdom
OX3 7FY
+44 (0)1865 612661
HOPE-e@kennedy.ox.ac.uk

Additional identifiers

Clinical Trials Information System (CTIS)
Nil known

Integrated Research Application System (IRAS)
236463

ClinicalTrials.gov (NCT)
NCT04036929

Protocol serial number
CPMS 39726, IRAS 236463

Study information

Scientific Title
Hand Osteoarthritis: investigating Pain Effects in a randomised placebo-controlled feasibility study of Estrogen-containing therapy (HOPE-e)

Acronym
HOPE-e

Study objectives
It is hypothesised that an estrogen-selective estrogen receptor modulator (SERM) combination 'Duavive' will improve average hand pain in post-menopausal symptomatic hand osteoarthritis (OA). Estrogens and SERMs are both likely to have beneficial effects on OA. In hand OA, which appears more closely related to estrogen deficiency, this effect may be greater and more discernible. The individual components, estrogen and bazedoxifene (SERM), cannot easily be tested in view of safety/tolerability considerations. The use of this estrogen-SERM combination may not only be more acceptable but also more effective than either treatment alone. The researchers need to test the hypothesis that a trial of this therapy in this population is feasible before proceeding to a full trial.

Ethics approval required
Old ethics approval format

Ethics approval(s)
Approved 08/10/2018 by North of Scotland Research Ethics Committee 2 – Chair Helen Galley, North of Scotland Research Ethics Service, NHS Grampian, Summerfield House, 2 Eday Road, Aberdeen, AB15 6RE, Tel: +44 (0)1224 558458 (Ethics Administrator) or 01224 558474 (REC Manager), Email: nosres@nhs.net, ref: 18/NS/0100

Study design
Randomised; Interventional; Design type: Treatment, Drug

Primary study design
Interventional

Study type(s)
Treatment

Health condition(s) or problem(s) studied
Osteoarthritis of the hand

Interventions

The primary research question is whether carrying out a full randomised controlled trial of estrogen-containing therapy in post-menopausal women with symptomatic hand OA is feasible. This is because this is the first time that a study of this nature has been carried out in symptomatic hand OA. Like most interventional trials, the study is proposed because we believe there may be benefit to patients, but we have no direct evidence to support the drug's routine use for OA in general, or hand OA in particular. There were a number of uncertainties identified at the time of designing the study around the feasibility of recruitment, retention and acceptability to participants, and need for refinement of outcome measures to be used which meant that a feasibility study design was recommended and selected (following Research and Design Service (RDS) RDAP review January–April 2016). The study has been designed to systematically address these feasibility questions.

The results of this study will also significantly build on existing knowledge, being the first time that estrogen-containing therapy has been given in a controlled trial setting to those with symptomatic hand OA. As such it will also provide important 'proof of concept' data, and estimates of the effect of the study medication (although the study is not designed to definitely detect the presence or absence of an effect).

Study population

We have closely mirrored the inclusion criteria of the previous clinical trials of the combination drug under test, with similar inclusion and exclusion criteria regarding age, time from menopause and other medical contraindications etc. This is to maximise safety in the study, based on previous experience. Several aspects have been discussed with the drug company who were involved in these trials. As the trial does not require the presence of menopausal symptoms, but does require the presence of hand pain secondary to OA, the use of this medication is outside of its existing European license for use. One option was to also require the presence of significant menopausal symptoms such as regular, debilitating flushing in addition (so that the drug would be being used within existing license). However, the study investigators felt that this would make the study unfeasible, as the restrictive criteria would make recruitment too challenging, and did not reflect the primary study question.

We do not have sensitive imaging tools for diagnosing hand OA. For this reason, we will include those who fulfil clinical diagnostic criteria without X-ray change. This is to include as many people with painful hand OA as possible. There is good evidence that the clinical diagnostic criteria alone are specific for hand OA, so we feel this is justified. We will still X-ray all those who have not had OA evident on an X-ray in the last 3 years, as many will have supporting X-ray change, which strengthens the diagnosis. This is standard practice in OA clinical trials. Some may also have existing ultrasound which documents the presence of osteophytes, which further supports diagnosis (there is some support for this approach, but no agreed ultrasound diagnostic criteria for OA, hence we will not require this).

Sample number

We will recruit up to 90 participants. This sample size allows us to fully test the rates of recruitment at study sites over a period of time. It has been calculated on feasibility grounds, not on statistical grounds. If numbers of minimum participants recruited which have been pre-specified are not reached as below, we would not pursue proceeding to a full study.

Minimum stop-go criteria for a full study:

1. Recruitment of ≥30 participants at 2 sites in the defined period
2. Drop-out rate of ≤30% of randomised individuals
3. Acceptability to the majority of participants including acceptable rates of adverse events

Our non-essential success criterion is an apparent difference in outcomes between the treatment and placebo.

Choice of study agent

We wish to test estrogen-containing therapy. Estrogens cannot be given without combination with other drugs, such as progestins or SERMs, in those with a womb, because of cancer risk. SERMs, as opposed to the usually used progestins, appear to potentially offer additional benefit in pre-clinical models of OA. In selecting an agent to test, we also considered availability and use within the UK, available safety data, acceptability to patients and feasibility of blinded delivery (tablets, versus gel or patch). Duavive was selected as the only available licensed estrogen-containing therapy combined with a SERM in the EU. The administration of a daily tablet to all participants was feasible and acceptable to the patient discussion group. The initial plan and hope was that Pfizer would support a drug only request (through their IIR funding scheme) in which we had advanced to a late stage. This would have provided study medication and identical matching placebo for use in the study. Unfortunately, Pfizer withdrew their support for this request on financial grounds, following the study being funded by NIHR. Therefore, no commercial bodies who could benefit are supporting this study in any way or contributing to the protocol, which avoids a potential conflict of interest.

Design of study

We will run a miniaturised version of a full randomised controlled trial with the same outcome measures so that we can fully test feasibility and acceptability, and refine how we would carry out a full trial. The data will also enable us to accurately calculate a sample size for a future study. This means including an active and a control arm, with the same anticipated ratio for randomisation (1:1) to assess the acceptability to participants of this approach. This approach was supported by our patient discussion group (April 2016).

Placebo control

There are two reasons why it is important that we include a placebo arm; 1) In any drug trial measuring pain, there is a placebo response – this is a well-recognised feature of being in a clinical trial and taking a tablet. Pain improves somewhat, even if that tablet is inactive. Without a placebo control arm in a full trial, we would over-estimate the effects of a drug, and we wish this feasibility study to mirror the design of a full study as closely as possible. 2) Because not everyone will receive active medication in this study, this can affect individual decisions to participate or not. Without the chance of placebo more people may choose to participate which could be misleading in regards to feasibility of recruitment.

Various strategies to produce an alternative source of matched placebo to the one which would have been provided by Pfizer were examined including over-encapsulation and re-blistering, or synthesis of a close-match placebo, with dispensing of tablets in identical opaque pots. However, because of issues with lack of stability of medication outside of the blister packaging and the costs of stability testing of over-encapsulated drug (which were prohibitive, >£150K), a practical decision was made to provide similar active and placebo medication in blisters. These are placed in identical over-packaging of study medication to maintain blinded participants and investigators. Study procedures will maintain the blind as far as possible. Participants will be asked at the end of the study whether they knew which arm of the study they were in. Given that this is a feasibility study, this approach has been supported as reasonable by our collaborating clinical trials unit (OCTRU) and our Trials Pharmacy. We have also involved Pfizer and the MHRA in discussions around IMP stability in coming to these decisions.

The study investigators in consultation with the RDAP review and patient discussion group initially proposed a further, third arm of traditional (estrogen +/- progesterone) HRT, with participants in this arm stratified to this on the presence of absence of a uterus. However, first round peer review by NIHR Research for Patient Benefit (which included multiple scientific and lay reviewers) found this design overly complex for the size and aims of the study, and simplification to a 2 arm approach was encouraged and subsequently supported in the second round application. The active arm (estrogen plus SERM, Duavive) was selected on the basis that it was most likely to give patient benefit, based on existing data. We believe that this simplified 2-arm study is more ethical as it is more achievable and an effect is more likely to be seen. This is balanced against less post-marketing surveillance for Duavive than other forms of HRT.
The finalised protocol has since been reviewed by members of the trial steering committee, and our participant information leaflet and consent form have also been reviewed by a lay co-applicant and a patient reviewer.

The outcome measures have been reviewed by the patient discussion group, who found them acceptable.

Recruitment and Randomisation
A number of standard routes to recruitment will be used such as secondary care clinics, and GP surgeries as PICs. In some cases, the treating physician may be a study investigator. In other cases, identifying physicians may refer individuals with their consent for consideration of the study. At this point, minimal contact details would be passed on. We will ensure that this process is free from undue influence or inducement and make no therapeutic promises (the reason for the study is that there is uncertainty about effect and this is made clear in the participant information leaflet).

A computerised randomised system will be used for allocation of participants, to ensure equipoise.

Eligibility Criteria
Rationale for both inclusion and exclusion criteria have been carefully considered by the investigator team and have scientific and/or medical justification in terms of a) those fulfilling adequate diagnostic criteria for hand OA, without other conditions/medications which would affect the outcome of the study; b) a population with sufficient hand pain to justify their inclusion in a study of this type; and c) a population who may safely be prescribed Duavive/HRT as per SmPC and international guidance. Key criteria have also been considered by a patient discussion group.

Inclusion criteria
The age and time from menopause, and history of lack of use of other hormonal therapy, are from the SmPC for Duavive and also after review by our gynaecologist co-applicant (little experience in those >65 years would lead to safety concerns). We will perform pregnancy tests in those at any risk of pregnancy at the discretion of the clinician investigator as many participants by definition, will not be at risk of this.

Previous:
The inclusion of hand OA in this study is restricted to interphalangeal disease (we have no evidence that base of thumb OA would respond in the same way to this therapy, and it has other treatments) and in those with regular pain, and of moderate severity (4/10). This mirrors eligibility criteria for similar previous CTIMPs in hand OA, to ensure that a pain response is detectable if present in a full study.

Updated 28/02/2020:
The inclusion of hand OA in this study is restricted to those with regular pain, and of moderate severity (4/10). This mirrors eligibility criteria for similar previous CTIMPs in hand OA, to ensure that a pain response is detectable if present in a full study.

Exclusion criteria reflect exclusions for HRT use in clinical practice, and for Duavive in particular, and have been informed by the SmPC for the study medication. This is to maximise safety of the study, and test in a similar population to those who would be prescribed Duavive in usual clinical care as far as possible.

Exclusions include alternative reasons for hand pain (as this would dilute the findings of the study) and those who would be using treatments which would interfere with the outcome in a full study.

It is important to stress that we are not excluding those without a womb, as would have been the case in the HRT trials. This is because we are not giving the SERM purely for womb protection (as it would be in standard HRT use) but because we want to test if the SERM may have some additional clinical benefit. This requires us to test the effect of the combination in all participants, irrespective of presence/absence of a womb.

Timetable for the study
The study lasts for 36 months. The first 6 months will be involved in study set up including HRA approval, manufacture and QP release of placebo, and set up of research sites.

The following 24 months will involve study activity, 18 months of active recruitment, and a following 6 months until the last participant's face-to-face visit.

The last 6 months will include focus groups, database clean and lock down, analysis and initial study reporting and publication. There will be no interim analyses. The trial steering committee will meet at planned times during the study to review progress and safety.

What is involved for the participant who takes part in the study:
There are 5 face-to-face study visits and one remote visit over a 7 month period.
The visits will take place in a research outpatient clinic setting in the two hospital sites, and in a clinic room in the primary care site.
Those participants that have not had an X-ray in the past 3 years will also be required to go for an X-ray which may be on a different day to the screening visit depending on which site they have been recruited to.

Visits will take no longer than 3 hours and often be shorter: Visit 1 - screening (-14 to -42 days before baseline) (3 h), Visit 2 – baseline (2.5 h), Visit 3 – week 4 (1 h), Visit 4 – week 12 (2 h), Visit 5 – week 24 (2 h) and follow-up telephone call - week 28 (30 min).

Face-to-face visits are necessary to assess for adverse events, provide new prescriptions and perform blood test monitoring. Self-complete questionnaires will be the main method of assessment. Participants can be seen outside of study visits if medically required. One of the questionnaires does look at the possibility of research bias, in terms of the possibility of inadvertent un-blinding in the study.

At Visit 5 - week 24, participants will be advised on how to wean off the study medication over a 4 week period from the day after Visit 5 to the Week 28 telephone call. During the first 2 weeks, the participant should take 1 tablet on alternate days and for the third and fourth weeks, the

participant should take 1 tablet on every third day or less before stopping. It is advisable to wean off the study medication gradually like this because it will decrease the chances of the participant experiencing spotting or vaginal bleeding during this time.

Some participants will also attend an optional focus group which will occur 1-3 months after the last participant has finished the study. The focus group will be led by an experienced facilitator who is trained on the protocol and who can be unblinded. Two focus groups will be organised, one at the Oxford site and one at the London site. Each focus group will not last longer than 2 h.

No participant samples will be kept or stored linked to this consent.

Data collection will be primarily via paper Case Report Forms (pCRFs): investigator and participant, for entry into a secure electronic database hosted on a secure University server.

For daily rating of average hand pain, 2 different methods of capturing this data remotely will be tested. These will compare the collection of data via either direct entry into the study database accessed via SMS (text) message link to a participant's phone, or the completion of a paper diary, with a telephone call reminder.

Travel expenses incurred for study visit attendance will be refunded.

Intervention Type
Other

Primary outcome(s)
Feasibility outcome measures:
1. Rates of eligible participant identification: frequency, and relationship to the study medication, recorded throughout the study
2. Rates of recruitment/randomisation from different sources, recorded throughout the study
3. Retention rates, recorded throughout the study
4. Tolerability/adverse events, recorded at weeks 4, 12, 24 and 28
5. Likelihood that participant or Investigator have become unblinded, measured using Bang's Blinding Index (likelihood of unblinding) self-complete questionnaire at week 24
6. Study medication compliance monitored via diaries at weeks 4, 12 and 24

Key secondary outcome(s))
Measured at baseline, week 4 (average hand pain and remote pain rating only), week 12 and week 24:
1. Pain and function:
1.1. Average hand pain over last 14 days, measured using NRS 0-to-10, where 0 is "no pain" and 10 is "pain as bad as you can imagine"
1.2. Remote pain-rating (recorded via LimeSurvey, or in paper diary) prior to a visit, NRS 0-to-10, where 0 is "no pain" and 10 is "pain as bad as you can imagine"
1.3. Prevalence of joint pain in other joints in last 4 weeks, measured using pain manikin
1.4. Hand OA-related functional impairment, measured using Functional Index for Hand OA (FIHOA). It includes 10 questions scored according to a 4-grade scale. The score ranges from 0 (no functional impairment) to 30 points (maximal impairment).
1.5. Quality of life measured using EQ-5D-5L. Validated measurement of quality of life across five dimensions and their associated levels of severity on a 1 (no problems) to 5 (extreme problems) scale.
2. Menopause symptoms, measured using:

2.1. The Menopause Specific Quality of Life Questionnaire (MENQOL). Validated measurement of menopausal symptoms and their associated degree of severity; 30 items in a Likert-scale format. Items are rated as present or not present and if present how bothersome, on a 0 (not bothersome) to 6 (extremely bothersome) scale. The interventional version is being used here, which includes an additional 3 questions relevant to HRT use which has been used in a trials setting.
2.2. Greene Climacteric scale. A 21-item validated questionnaire that measures a variety of menopausal symptoms on a 4-point Likert scale (0 = “not at all” to 3 = “extremely”), plus one sexual function probe.
3. Joint appearance, measured using:
3.1. Cosmesis score of Michigan Hand Questionnaire (4 questions, questions 28-31). Subdomain of hand-specific outcomes instrument that measures outcomes of patients with conditions of, or injury to, the hand or wrist
3.2. Investigator-recorded tender and swollen joint counts, binary recording (1 swollen, 0 not swollen)
3.3. Photographic recording of swollen hand joints; standardised digital photography of hands
4. Joint function: Jamar grip strength – average of three measurements. Handgrip strength will be measured in kilograms to the nearest hundred grams in both hands using a Jamar dynamometer. Both hands will be alternately assessed three times and the average score recorded.
5. Acceptability measured using End of Treatment study-specific questionnaire at week 24

Completion date
10/12/2021

Eligibility

Key inclusion criteria
Current inclusion criteria as of 28/02/2020:
1. Able to give informed written consent
2. Female, aged 40-65 years old
3.1. In those with an intact uterus: At least 12 months of spontaneous amenorrhea (without any menstrual bleeding in last 12 months) and last menstrual period not more than 10 years ago
3.2. In those who have undergone hysterectomy or are/were using an intrauterine contraceptive device with progesterone local therapy (such as Mirena): Follicle-stimulating hormone (FSH) ≥30 milli-International Units per millilitre (mIU/ml) on screening blood test AND a history of menopausal symptoms in the last 1 to 10 years, in keeping with appropriate timing of menopausal status
4. Hand pain, aching or stiffness on most days in the last 3 months
5. At least two painful hand joints of any type (interphalangeal joints (IPJ) or base of thumbs)
6. Fulfils ACR (American College of Rheumatology) clinical diagnostic criteria for hand OA (3 or more of following):
6.1 Hard tissue enlargement of 2 or more of the following joints: 2nd or 3rd distal interphalangeal joints (DIPJ), 2nd or 3rd proximal interphalangeal joints (PIPJ), first carpometacarpal joints (CMCJ)
6.2 Hard tissue enlargement of 2 or more of the DIPJs
6. 3 Less than 3 swollen metacarpophalangeal joints (MCPJ)
6.4 Deformity of at least one of the joints listed in first point
OR, for those with base of thumb osteoarthritis only not fulfilling these criteria, has clinical symptoms and examination findings consistent with base of thumb osteoarthritis
7. Hand pain has not responded adequately to NICE core guidance for management of OA,

including the use of paracetamol or non-steroidal anti-inflammatory drug (NSAID) gel, except where there is contraindication or intolerance
8. Average hand pain is reported as typically more than 4 out of 10 in severity, OR average hand pain in the last 7 days of 4/10 or more on a visual analogue scale
9. In the Investigator's opinion, is able and willing to comply with all trial requirements

Previous inclusion criteria:
1. Able to give informed written consent
2. Female, aged 40-65 years old
3.1. In those with an intact uterus: At least 12 months of spontaneous amenorrhea (without any menstrual bleeding in last 12 months) and last menstrual period not more than 10 years ago
3.2. In those who have undergone hysterectomy or are using an intrauterine contraceptive device with progesterone local therapy (such as Mirena): Follicle stimulating hormone (FSH) ≥30 milli-International Units per millilitre (mIU/ml) on screening blood test AND a history of menopausal symptoms in the last 1 to 10 years, in keeping with appropriate timing of menopausal status (added 11/10/2019)
4. Hand pain, aching or stiffness on most days in the last 3 months and fulfils ACR (American College of Rheumatology) clinical diagnostic criteria for hand OA (3 or more of following):
4.1. Hard tissue enlargement of 2 or more of the following joints: 2nd or 3rd distal interphalangeal joints (DIPJ), 2nd or 3rd proximal interphalangeal joints (PIPJ), first carpometacarpal joints (CMCJ)
4.2. Hard tissue enlargement of 2 or more of the DIPJs
4.3. Less than 3 swollen metacarpophalangeal joints (MCPJ)
4.4. Deformity of at least one of the joints listed above
5. Minimum of 2 affected, painful interphalangeal joints (IPJ)
6. Hand pain has not responded adequately to National Institute for Health and Care Excellence (NICE) core guidance for management of OA, including the use of paracetamol or non-steroidal anti-inflammatory drug (NSAID) gel, except where there is contraindication or intolerance
7. Average hand pain in the last 7 days of 4/10 or more on a visual analogue scale
8. In the Investigator's opinion, is able and willing to comply with all trial requirements

Participant type(s)
Patient

Healthy volunteers allowed
No

Age group
Adult

Sex
Female

Total final enrolment
28

Key exclusion criteria
1. Other cause of hand pain, including inflammatory arthritis, connective tissue disorder, chronic pain or alternative clinical diagnosis such as tenosynovitis or carpal tunnel syndrome
2. Pregnancy or breastfeeding, or risk of this during study
3. Use of one or more prohibited treatments within specified time frame, or not willing to avoid

treatment for the duration of the study:
3.1. Oral contraceptive pill, or systemic HRT within the last 6 months
3.2. Anti-estrogen medication within the last 6 months
3.3. Oral, intramuscular or intraarticular steroid within the last 3 months
3.4. Intraarticular hyaluronan to a hand joint within the last 6 months
3.5. Initiation of new oral analgesia within last 4 weeks
3.6. Initiation of glucosamine, chondroitin, hand exercises or other relevant non-pharmacological therapy within last 6 weeks
3.7. Hand surgery within the last 6 months, or planned within the next 6 months
3.8. Medications likely to increase hepatic metabolism of study medication, including:
3.8.1. St John's Wort
3.8.2. Anti-convulsants (phenobarbital, phenytoin, carbamazepine, lamotrigine)
3.8.3. Some anti-infectives (rifampicin, rifabutin, nevirapine, efavirenz, ritonavir and nelfinavir)
4. Presence of one or more medical contraindications to the use of systemic hormonal replacement therapy:
4.1. Any history of breast, endometrial, ovarian or skin cancer
4.2. Any other history of other cancer within 5 years (except treated Basal Cell Carcinoma)
4.3. Relevant breast issue on routine national breast screening in prior 3 years
4.4. Undiagnosed genital bleeding, or untreated endometrial hyperplasia, active uterine fibroids or endometriosis
4.5. Active or past history of venous thromboembolism (VTE) (including deep venous thrombosis, pulmonary embolism and retinal vein thrombosis), or at high risk of VTE (such as known thrombophilic disorders (such as Protein C, S or anti-thrombin deficiency) or presence of a strong family history of VTE¥)
4.6. Active or past history of arterial thrombo-embolic disease (such as myocardial infarction, angina or stroke) or strong family history of stroke¥)
4.7. Clinically significant immobility
4.8. Migraine or active epilepsy
4.9. Uncontrolled hypertension (or diastolic pressure greater than 90 mmHg or systolic pressure greater than 145 mmHg at screening visit)
4.10. Uncontrolled diabetes mellitus or uncontrolled hypertriglyceridaemia
4.11. Body Mass Index greater than 30
4.12. Active malabsorption syndrome or clinically significant small bowel disease
4.13. Acute liver disease, clinically significant abnormal liver function, active gallbladder disease or porphyria
4.14. Clinically significant renal impairment
4.15. Intolerance to lactose, fructose or glucose (including galactose intolerance, lactase deficiency, fructose intolerance, glucose-galactose malabsorption or sucrase-isomaltase insufficiency)
4.16.Known sensitivity to either conjugated equine estrogens, bazedoxifene or the combination
5. Any other significant or uncontrolled disease or disorder which, in the opinion of the Investigator, may either put the participants at risk because of participation in the trial, or may influence the result of the trial, or the participant's ability to participate in the trial.
6. Participants who have participated in another research trial involving an investigational product in the past 8 weeks.
Use of an intrauterine contraceptive device with progesterone local therapy (Mirena) or vaginal topical estrogen use (known low systemic absorption) are not exclusions to participation.
¥Women with a first degree relative with a history of VTE, or other strong family history of VTE at the investigators discretion

Date of first enrolment

01/04/2019

Date of final enrolment
31/12/2020

Locations

Countries of recruitment
United Kingdom

England

Study participating centre
Nuffield Orthopaedic Centre (lead site)
Oxford University Hospitals NHS Foundation Trust
Windmill Rd
Oxford
United Kingdom
OX3 7HE

Study participating centre
Charing Cross Hospital
Imperial College Healthcare NHS Trust
Fulham Palace Rd
Hammersmith
London
United Kingdom
W6 8RF

Study participating centre
White Horse Medical Practice
Faringdon Medical Centre
Volunteer Way
Faringdon
United Kingdom
SN7 7YU

Sponsor information

Organisation
University of Oxford

ROR
https://ror.org/052gg0110

Funder(s)

Funder type
Government

Funder Name
NIHR Central Commissioning Facility (CCF); Grant Codes: PB-PG-0416-20023

Results and Publications

Individual participant data (IPD) sharing plan

Current individual participant data (IPD) sharing statement as of 31/03/2022:
Access to the de-identified dataset for purposes of research other than this study, would be at the discretion of the Chief Investigator, Dr Fiona Watt and OCTRU. All participants have consented to the information collected about them from the study may be used in a de-identified form to support other research on hand osteoarthritis in the future and may in certain circumstances be passed on to other collaborators of the research team in organisations other than the University of Oxford, which may include those outside the EU and commercial organisations. Requests for the de-identified dataset generated during the current study should be made to the Chief Investigator, Dr Fiona Watt (fiona.watt@kennedy.ox.ac.uk) or OCTRU (octrutrialshub@ndorms.ox.ac.uk). Dr Fiona Watt and OCTRU will consider requests once the main results from the study have been published up until 10 Dec 2036. All requests must relate to bone fide research into hand osteoarthritis research.

Previous individual participant data (IPD) sharing statement:
The datasets generated during the current study and its analysis are not expected to be made publically available. This is because intellectual property and scientific know-how arising from this feasibility study will inform a future full study. (The study medication is to be used in the commercially available combination and dose, and is subject to composition of matter protection by Pfizer until March 2027. Any full study or subsequent commercialisation would likely be through them and would involve the extension of the label relating to this drug.)

IPD sharing plan summary

Available on request

Study outputs

Output type	Details	Date created	Date added	Peer reviewed?	Patient-facing?
Results article		21/09/2022	08/11/2022	Yes	No
Protocol article		24/06/2021	28/06/2021	Yes	No
HRA research summary			28/06/2023	No	No
Participant information sheet	Participant information sheet Study website	11/11/2025	11/11/2025	No	Yes

Study website	11/11/2025	11/11/2025	No	Yes