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An experimental medicine study to investigate the short-term effects of retinoic acid metabolism blockade by oral talarozole on molecular outcomes in the joint tissues of those with hand osteoarthritis (RAMBOH-1): protocol for a double- blind randomised placebo-controlled feasibility study

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Study protocol

Keywords: hand osteoarthritis, retinoic acid, clinical trial, inflammation, cartilage, RAMBA, disease-modifying, genetic, ALDH1A2, Experimental Medicine

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An experimental medicine study to investigate the short-term effects of retinoic acid metabolism blockade by oral talarozole on molecular outcomes in the joint tissues of those with hand osteoarthritis (RAMBOH-1): protocol for a double-blind randomised placebo-controlled feasibility study

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ABSTRACT

Background: Hand osteoarthritis (OA) is one of the most common musculoskeletal conditions. A genetic variant in an enzyme (ALDH1A2) lowers retinoic acid levels and is associated with hand osteoarthritis. A developmental drug class, including the agent talarozole, inhibits the degradation of retinoic acid and reduces inflammatory gene expression in preclinical studies, representing a potential therapeutic for hand osteoarthritis. This experimental medicine study will investigate the effect of talarozole on molecular readouts in the articular cartilage of individuals with hand osteoarthritis who are undergoing a surgical procedure as part of their planned clinical care.

Methods: A feasibility study of a double-blind placebo-controlled intervention with 1:1 randomisation to either oral talarozole 2 mg once daily or placebo. The target population is those with symptomatic radiographic thumb joint osteoarthritis undergoing trapeziectomy. The objective is to test whether systemic administration of talarozole decreases inflammatory gene expression in the trapezium articular cartilage compared to placebo. Participants will take the study medication for 10-21 days prior to their surgery. The primary outcome is the difference in mean cartilage expression of a panel of pre-defined inflammatory genes (including, but not limited to ADAMTS4, MMP13 and MMP1) when comparing the intervention and placebo arms. Secondary outcomes include measures of feasibility such as recruitment, safety, acceptability, retinoic acid dependent gene expression and clinical outcomes such as average hand pain.

Discussion: Identifying new treatments that improve symptoms and slow progression of hand osteoarthritis remains a top research priority. This study is not definitive but will provide data including mechanistic data on the molecular effects of pharmacological retinoic acid metabolism blockade in participants with hand osteoarthritis. The study will generate data to inform progression criteria to a fully powered randomised controlled efficacy trial. The findings will be published in a peer-reviewed journal and presented at relevant conferences.

Trial registration: ISRCTN, ISRCTN16717773. Registered 16 February 2022,

https://www.isrctn.com/ISRCTN16717773

Key words: hand osteoarthritis, retinoic acid, clinical trial, inflammation, cartilage, RAMBA, disease-modifying, genetic, ALDH1A2, Experimental Medicine

BACKGROUND

8.75 million people are affected by osteoarthritis (OA) in the UK alone and the joints in the hand are most commonly affected (1, 2). Hand OA represents a huge societal burden through pain and loss of hand function (3). Hand OA can affect the base of thumb (also referred to as OA of the first carpometacarpal (CMC) joint) and the interphalangeal joints (small joints of the fingers).

Unlike rheumatoid arthritis, there are no disease-modifying treatments available for OA. Current management approaches in hand OA include lifestyle advice, exercises, splinting, topical or oral non-steroidal anti-inflammatory drugs, intra-articular steroid injection, or surgical approaches (3-5). In the case of base of thumb OA, a well-recognised operative treatment is trapeziectomy, where the trapezium (the bone at the base of the thumb where it meets the wrist) is removed (6). This procedure is reserved for those with advanced painful disease and leads to improvement in function and symptoms (7). The RAMBOH-1 (Retinoic Acid Metabolism Blocking agents to treat Osteoarthritis of the Hand) study seeks to test for the mechanistic effects and feasibility of a drug by studying those with base of thumb OA undergoing trapeziectomy.

One of the earliest changes seen in the joint in OA is progressive damage to the articular cartilage. An important causative factor in OA is abnormal mechanical load or injury (3). Chondrocytes are the only cells in cartilage, responsible for its maintenance. Our work has demonstrated that sterile mechanical injury activates inflammatory signalling and increases inflammatory response gene expression in chondrocytes including proteases such as metalloproteinases (MMPs) that break down the matrix of articular cartilage (8-10) and that such inflammatory gene expression can change rapidly with intervention, as is seen with mechanical offloading (11). Despite evidence of inflammatory change in the joint, several recent randomised controlled trials (RCTs) of existing anti-rheumatic agents, targeting synovial inflammation in rheumatoid arthritis, have failed to show improvement in pain or function in patients with hand OA (12-14). This supports the search for druggable pathways driving the inflammatory response specifically in OA tissues.

Heritability of hand OA is high (at around 87%), so genetic studies provide important insights into disease mechanism (15). In 2014, an Icelandic genome-wide association study (GWAS) found that common polymorphic variants in aldehyde dehydrogenase 1 family member A2 gene (*ALDH1A2*), associated with its lower expression, were associated with severe hand OA (16). These variants were present in ~50% of the Icelandic population and conferred a 1.4-fold increased risk of disease at all hand joints including thumb CMC joint and interphalangeal joints. *ALDH1A2* encodes the key enzyme responsible for cellular synthesis of retinoic acid (17). This genetic finding suggested that lower levels of retinoic acid may confer susceptibility to hand OA development.

All trans Retinoic Acid (atRA) is described to have anti-inflammatory roles in human tissues (18). Levels of atRA can be enhanced indirectly using pharmacological agents that inhibit atRA-degrading enzymes belonging to the CYP26 family. These CYP26 inhibitors or so called "Retinoic Acid Metabolism Blocking Agents" (RAMBAs) were developed for several potential medical indications (19). Measuring atRA levels directly is challenging as it is unstable, so levels are often inferred by expression levels of atRA-dependent genes e.g. retinoic acid receptors (RARs), CYP19A, CYP26A, RARα, RARβ, and RARγ. Drugs of the tetracycline class such as doxycycline, and certain anti-fungal agents such as ketoconazole, are known to inhibit CYP26: this may account for their described anti-inflammatory effects (20). Newer drugs with more specific CYP26 inhibitory action include talarozole and liarozole (21).

We have previously shown that chondrocytes are highly sensitive to atRA, that atRA is strongly down-regulated by mechanical injury of cartilage, and that there is a strong inverse relationship between atRA-dependent and inflammatory genes upon cartilage injury that can be attenuated by talarozole (22). Furthermore, in human hand OA cartilage we have shown an inverse relationship between *ALDH1A2* gene expression and inflammatory response gene expression (22). The upregulated expression of several of these genes in human OA articular cartilage, such as ADAMTS4, MMP1 and MMP13 has been established previously by others (23, 24) and directly linked to OA pathogenesis (25-

29). Therefore, increasing levels of atRA, using talarozole might suppress tissue inflammation associated with cartilage damage in OA(22, 30).

The RAMBA talarozole (GlaxoSmithKline, GSK) has undergone phase I and phase II clinical trials for both oral and topical treatment of keratinisation disorders, such as psoriasis, ichthyosis and acne. No studies have been carried out in participants with OA. From its known mechanism of action and available trial data, it has a safety profile compatible with use in an OA population (31). Some adverse events (AEs) would be expected including on the mucocutaneous system (19).

We aim to determine whether the RAMBA agent talarozole will increase atRA associated gene expression and reduce inflammatory gene expression in the articular cartilage of trapezia of individuals with symptomatic thumb CMC joint OA compared to placebo. Given the lack of prior evidence for use of talarozole for this indication, the study has been designed to test for a signal of molecular change in tissue with talarozole, including other measures of feasibility, safety and acceptability. Evidence of feasibility, including of mechanistic effect, will be required for progression to a definitive randomised controlled efficacy trial of a RAMBA in a hand OA population.

METHODS/DESIGN

Study design

RAMBOH-1 is a stand-alone 2-arm parallel group, double-blind randomised placebo-controlled feasibility study testing a pharmacological intervention in those with symptomatic thumb CMC joint OA. The study examines changes in a molecular panel of predefined specific mRNAs in cartilage, serving as a laboratory primary outcome measure. There are four study visits (two in-person plus two telephone appointments) over a period of 3-16 weeks (Figure 1). Patient and public involvement actively informed the rationale, design and development of protocol and patient facing materials of this study. The study is managed by the Experimental Medicine and Rheumatology group within the Oxford Clinical Trials Research Unit (OCTRU).

Primary objective

To test whether systemic administration of talarozole can decrease inflammatory gene expression in the trapezium articular cartilage of individuals with symptomatic thumb CMC joint OA. Specifically, we will test the difference in mean cartilage expression of a panel of pre-defined inflammatory gene mRNA levels between the intervention and placebo arms (Table 1, Supplementary Table 1).

*Secondary objective*s

There are three secondary objectives, each comparing various measures before and after intervention, in the intervention and placebo arms. These are:

- To inform the feasibility of a definitive future trial.
- To test exploratory molecular outcomes by examining the difference in mean levels of other biological measures of inflammation or of the retinoic acid pathway activity.
- To collect clinical outcome data to inform the design of a definitive future efficacy trial.

All outcome measures to address these primary and secondary objectives are listed in Table 1.

179 **Table 1. Outcome measures**

Primary objective outcome measures	**Secondary objectives outcome measures**		
	Feasibility	**Exploratory molecular**	**Clinical**[¥]
The difference in mean cartilage expression of a panel of pre-defined inflammatory- genes mRNA levels[θ] when comparing the intervention and placebo arms.	a) Recruitment and randomisation rates b) Acceptability to patients (% dropouts) c) Acceptability of study medication assessed by End of Study questionnaire and adverse events	a) Cartilage expression of atRA associated genes (including, but not limited to CYP19A, CYP26A, RARα, RARβ, and RARγ) b) Cartilage expression of atRA associated or inflammatory response genes when considering ALDH1A2 genotype c) Synovial fluid and blood (plasma and cellular) molecular outcomes which may include inflammatory genes and response	a) Average daily hand pain on numerical rating scale, recorded by paper diary* b) Patient Evaluation Measure c) EQ-5D-5L, a measure of health-related quality of life

		proteins, retinoic acid and drug levels	

All outcome measures will be compared between intervention and placebo arms.

[θ]The pre-defined full list of 10 inflammatory gene mRNAs can be found in Supplementary Table 1.

*Average hand pain will be recorded daily for up to 2 weeks prior to the Baseline visit (before intervention) and up to 2 weeks prior to the Day of Surgery visit (on intervention).

[¥]The difference in change of each of the following measures will be compared between Screening/Baseline (before intervention) and Day of Surgery (on intervention) (see Figure 1 for collection Time Points). Note that these data will not test clinical efficacy, as the study is not designed for this purpose.

Abbreviations: ALDH1A2 - Aldehyde Dehydrogenase 1 Family Member A2; atRA - All-trans retinoic acid; CYP19A - Cytochrome P450 19A; CYP26 - Cytochrome P450 26; mRNA – messenger Ribonucleic Acid; RAR - Retinoic acid receptor.

The protocol follows the Standard Protocol Items: Recommendations for Interventional Trials (SPIRIT) guidelines. The SPIRIT checklist is provided as Supplementary Table 2 (Additional File 1) (32).

Study setting

The study will take place in two National Health Service (NHS) hospitals in the UK, which will perform all study activities from recruitment to provision of intervention and follow-up. The central laboratory activities will take place at the University of Oxford. A list of the study sites can be provided on request from the RAMBOH-1 study office.

Eligibility criteria

In order to be eligible for the study, participants must:

- Be able to understand English, and willing and able to give written informed consent for participation in the study including agreement to provide blood samples and donate tissue sample at surgery.
- Be male or female, aged 18 to 79 years.
- Have symptomatic and radiographic thumb CMC joint OA and be scheduled for trapeziectomy surgery as part of usual care.
- Additionally, female participants have to fulfil either of criteria (a) or (b):

a) Are of non-childbearing potential, defined as:

1. Aged 45 or over and definitely postmenopausal (defined as ≥2 years without any menses) prior to screening.

OR

2. Documented as surgically sterile.

b) Are of childbearing potential and fulfil **all** four of these criteria as well as the fifth, where relevant:

1. Are not pregnant and have a negative pregnancy test at screening, and
2. Agree not to try to become pregnant during the study and for 33 days after the final study medication administration, and
3. Agree not to breastfeed from screening until 33 days after the final study medication administration.
4. Agree not to donate ova from screening until 33 days after the final study medication administration.
5. If heterosexually active, agree to consistently use one form of highly effective birth control from screening until 33 days after the final study medication administration (see Supplementary Table 3 for definition and list of acceptable methods, Additional File 1).

- Additionally, male participants have to fulfil both criteria (a) and (b) below:

a) They and their female spouse/partner(s) who are of childbearing potential agree to use one form of highly effective birth control from screening until 93 days after the final study medication administration.

b) They agree not to donate sperm from screening until 93 days after the final study medication administration.

- Agrees not to consume grapefruit or grapefruit juice for the duration of the study.
- In the Investigator's opinion, is able and willing to comply with all study requirements.

Participants may not enter the study if any of the following apply (see Supplementary Table 4 for a full list of sub-criteria for some of these exclusions, Additional File 1):

- Other cause of hand pain including inflammatory arthritis (such as rheumatoid arthritis, psoriatic arthritis, gout).
- Use of one or more prohibited treatments within specified timeframe prior to screening, or not willing to avoid treatment for the duration of the study and for 75 hours after last dose.
- Presence of one or more medical contraindications to the use of talarozole or placebo.
- Presence of other exclusionary medical conditions or states
- Participation in another interventional study within the last 3 months, or treatment with an investigational drug within 1 month or 5 half-lives (whichever is longer) of Baseline.
- Any other significant or uncontrolled disease or disorder which, in the opinion of the Investigator, may either put the participant at risk because of participation in the study, or may influence the result of the study, or the participant's ability to participate in the study.

Pregnancy and contraception

Given its stage of development and mode of action, talarozole is contraindicated in women who are, or may become pregnant or men who are planning to father a pregnancy. Talarozole has the potential for foetal teratogenicity and could affect spermatogenesis. Those at risk of pregnancy may not enter the study unless willing to use highly effective contraception and have been on the medication for a sufficient time for it to be fully effective – see Supplementary Table 3 for further details, Additional File 1.

All participants who fulfil the criteria as a woman of child-bearing potential (WOCBP) will be tested to ensure they are not pregnant at screening and have not become pregnant during the study. A process is in place in the unlikely event that a participant or participant's partner becomes pregnant whilst on study medication.

Interventions

Talarozole is an unlicensed drug, owned by GSK and will be gifted by them. Following recrystallisation and testing, the drug will be manufactured for the study as 1 mg hard gelatin capsules, along with matching placebo, by Upperton Pharma Solutions (Nottingham, UK) with Qualified Person certification of manufacture to EU Good Manufacturing Practice standards.

Placebo excipients are gelatin, polyethylene glycol (PEG) 400, PEG 4000. Participating site pharmacies will be supplied with bottles of talarozole and placebo capsules and will be responsible for dispensing of the study medication as per the randomisation allocation. Talarozole and placebo capsules will be identical and supplied in identical packaging.

Two capsules (2 x 1mg capsules of talarozole/placebo) are to be taken orally, once a day in the morning for 10-14 days prior to surgery (with last dose taken on day of surgery). Participants will be provided with a 21-day supply of study medication to enable dosing to be extended in the event of short (<7 days) delays to surgery. In the case of longer delays, study medication will be stopped and restarted

14 days (or if less than 14 days of medication is left the appropriate number of days) prior to new surgery date with participant agreement.

At the discretion of the Investigator, participants reporting AEs will have the option to reduce the dose to 1 mg (1 capsule) once daily; this will be recorded. The duration of study treatment will remain the same: the selected treatment duration of 10-21 days considered available pharmacokinetic data, preclinical laboratory study data, as well as practical considerations regarding study conduct within the pre-operative setting.

Participant timeline

The timeline and visits for participants are illustrated in Figure 1 and Table 2.

[**TABLE 2 HERE**]

Recruitment

Potentially eligible participants that have been placed on the waiting list for trapeziectomy according to usual NHS care will be approached by members of their direct healthcare team (or in Patient Identification Centres identified via database searches of patients who are on waiting lists for this surgery). In either case, they will be given a Participant Information Leaflet (PIL) and can contact the site study team if interested.

Potential participants will be given the opportunity to discuss the study with their family and healthcare professionals before deciding to take part in the study. If a patient has read the PIL and continues to express interest in the study, a pre-screen will be carried out by telephone. If no reasons for ineligibility are identified, the patient will be invited to proceed to a screening visit with a study Investigator.

Consent

A medically qualified, Good Clinical Practice (GCP) trained study Investigator will receive written informed consent from the patient at the screening visit.

Screening assessment

Full eligibility will be confirmed by a medically qualified doctor prior to randomisation. Should an individual fail to meet certain eligibility criteria at screening assessment based on a reversible criterion (e.g., liver function test abnormality), re-screening may be carried out if the participant agrees.

Randomisation

Eligible participants will be randomised 1:1 to either the study medication or placebo at Visit 2 Baseline (Day 0) and will be prescribed study medication on that day. Randomisation to the interventions will be carried out via a secure online computer-based service, hosted by OCTRU. Randomisation will be performed using a minimisation algorithm including a random element to ensure balanced allocation of participants across the two treatment groups, stratified by study site and sex. Full details will be available at the end of the study and are stored in the confidential randomisation and blinding plan in the statistical section of the Trial Master File, available only to the statistician during the study.

Blinding and unblinding

Study participants, care providers, study team (except the site pharmacists, Trial Manager/delegate and the statistician) and outcome assessors will all be blinded to intervention.

24-hour unblinding (emergency and non-emergency) via the randomisation system will be available (participants will be given an emergency contact card). A letter will be sent by the site team to the participant's GP to notify them of their patient's participation. Site Principal Investigators (PIs), the trial manager/delegate, and site pharmacy have the ability to unblind individual patient allocations, during office hours, on a need-to-know basis. Non-emergency requests for unblinding will require prior approval by the CI or delegate. Out of hours emergency unblinding will be available via delegated team members.

Tissue collection and processing

The trapezium bone (including articular cartilage) will be obtained at the time of the participant's

standard care trapeziectomy surgery either under general or local anaesthetic (Day of Surgery visit) (Table 3) and transferred on ice to the laboratory. Tissue will be processed as soon as possible after surgery by removing cartilage from the articular surface. Both bone and articular cartilage will be snap frozen prior to storage at -70^{o}C before onwards processing including DNA and RNA extraction and storage respectively by the central laboratory (22).

Table 3. Biological samples and related measurements

	Visit 1 Screening (-70 to –1 days, target -14 days)	Visit 2 Baseline (Day 0)	Visit 3 Day of Surgery (Day 10-21, target 14 days)	Visit 4 Post-surgery follow up (Visit 3 + 7 -21 days)
Samples for eligibility and safety (tested at NHS site for study purposes)				
BLOOD	x		x	
Blood screening FBC, U&E, LFT, CRP, fasting glucose, HbA1c and fasting lipid profile.	x			
Safety tests FBC, U&E, LFTs, fasting lipid profile, CRP			x	
Hormone tests (for male participants only) Testosterone, FSH and LH	x		x	
URINE	x	x*^	x*	x*
Research samples (testing to be carried out at central laboratory)				
BLOOD Plasma Whole blood RNA	x		x	
TRAPEZIUM DNA genotyping (bone) RNA extraction (articular cartilage)			X	
SYNOVIAL FLUID (if available)			X	

*Women of childbearing potential (WOCBP) only. ^WOCBP will be required to complete a urine pregnancy test at home within 24 hours prior to starting the study medication

Abbreviations: CRP – C-reactive Protein; DNA - Deoxyribonucleic acid; FBC - Full blood count; FSH - Follicle Stimulating Hormone; HbA1c – Haemoglobin A1c; LFTs - Liver function tests; LH - Luteinising Hormone; RNA – Ribonucleic Acid; U & E - Urea & Electrolytes

Blood, urine and synovial fluid collection and processing

Fasting blood samples will be taken at screening as part of the eligibility process and at Day of Surgery for a variety of tests for monitoring of treatment safety (Table 3). Further safety bloods will be taken at visit 3 (Day of surgery).

Whole blood (in an EDTA tube and in a Tempus Blood RNA collection tube) will also be transferred at room temperature to the laboratory. Processed plasma and Tempus tubes will be stored at -70^{o}C. Whole blood RNA will be extracted at the end of the study for analysis.

A mid-stream urine sample will be tested by dipstick for blood, protein and glucose at screening. Urine samples will also be used to perform Beta Human Chorionic Gonadotropin (β-HCG) testing by test stick to exclude pregnancy in women of childbearing potential (WOCBP) at screening, within 24 hours prior to starting study medication and during the study.

In addition, up to 1 ml of synovial fluid may be collected at the time of the participant's trapeziectomy surgery using a needle and syringe, where this is available. Synovial fluid will be frozen at -70^{o}C within 4 hours of the time of collection.

Data collection methods

Study outcome data will be collected during two in-person study visits, two telephone appointments and a paper diary completed at home. Details of visit timings and outcomes are presented in Figure 1 and Table 2.

Post surgery in-person visits will be only necessary in the event of the need for assessment of any AEs, including to perform additional safety blood tests (Figure 1, Figure 2 and Table 3). (We will report AEs and any other relevant changes noted on safety bloods from screening to the end of treatment).

Outcome data will be mostly collected via electronic Case Report Forms (eCRFs) completed by the Investigator and participant directly on a study specific REDCap database, designed and managed by OCTRU. The database will have in-built validation such as range checks to improve data quality.

Participants will be asked to record their average daily hand pain (0-10 numerical rating scale (NRS), 0 = no pain, 10 = worst pain possible) on a paper study diary for up to 14 days prior to the Baseline visit and for up to 14 days prior to Day of Surgery. Participant questionnaires and/or diaries completed on paper will be entered onto the study database manually.

Data management

All electronic and paper study data will be kept securely for 5 years after the end of the study, including all pre-screening information. Biological samples will be stored for 12 months following the end of the study before being transferred to the Oxford Musculoskeletal Biobank with participant consent, otherwise samples will be destroyed. Consent forms will be retained for the life of the sample to meet Human Tissue Authority traceability requirements. A Data Management Plan which covers data management, monitoring activities and plans for sharing the data has been produced for the study.

Concomitant medications and allowed care

Participants will be allowed to continue with their usual concomitant medications. These will be recorded at each visit. Contraindicated medications which require the participant to be immediately discontinued from study medication when used between Baseline and the Day of surgery visit, and those which are discouraged during the study are listed in Supplementary Table 5 (Additional File 1).

Compliance with the study medication

Participants will be asked to record adherence with study medication by paper medication diary. Any reduction in dose and its timing will also be recorded. They will also be instructed to return any unused study medication to the site study team at the time of surgery for counting of returned capsules, prior to return to site pharmacy for destruction. Full compliance is defined as:

- A minimum of 10 days of study medication taken

AND

- Study medication is taken for all three final days of dosing which includes the two days prior to surgery, plus the day of surgery, as reported by the participant (at least one of verbally, via the study compliance diary or the corresponding amount of study medication returned).

All participants who have received at least one dose of study medication will be included in the study analysis (i.e. that tissue and data is collected) whether fully compliant or not. Participants who have not received at least one dose of study medication will be withdrawn from the study (their withdrawals recorded in a log) and tissue will not be collected.

Full accountability records will be completed to record receipt, dispensing, return and destruction of the study medication.

Laboratory analysis

All laboratory procedures are stated in a study laboratory manual, using established procedures in the central laboratory by experienced staff. Briefly, DNA extracted from the bone will be used for *ALDH1A2* variant genotyping (22). RNA extracted from the dissected cartilage will undergo quantification of mRNA by RNA sequencing and/or real time Polymerase Chain Reaction (RT-PCR), to measure the pre-specified molecular responses to drug treatment (compared to placebo) (22), Supplementary Table 1. RNA sequence data will be normalised using the DESeq2 (R Bioconductor package), which includes a predefined, standardised workflow. Where gene expression is measured by quantitative RT-PCR, normalisation will be by comparison with housekeeper gene expression as per standard laboratory protocol.

Plasma and whole blood RNA will be analysed for exploratory molecular outcomes (Table 3). All laboratory analysis and results will undergo quality control, documentation by standardised procedures and be analysed as part of the analysis of data.

Statistical methods

Standard descriptive statistics will be used to describe the demographics between the treatment groups, reporting means and standard deviations or medians and interquartile ranges as appropriate for continuous variables, and numbers and percentages for binary and categorical variables. We will also summarise in this way treatment duration, dosing and report participant adherence. All comparative outcomes will be presented as summary statistics and reported together with 95% confidence intervals (CIs).

Results will be reported as per Figure 2 and in accordance with the Consolidated Standards of Reporting Trials (CONSORT) guidelines, including the extension to randomised pilot and feasibility trials (33, 34).

Analysis populations: Primary analyses will use the fully compliant population. Compliance with trial treatment with all available data will be analysed as randomised.

Additional analyses will be undertaken in the intention-to-treat the population and potentially other subsets, unless surgery did not take place, the participant did not take any treatment or the participant withdrew before donating tissue. No interim analysis is planned and no stopping rules reliant on futility on primary outcome or lack of power will be employed. Missing data will be reported and summarised by treatment arm. All available data will be summarised and analysed and every effort will be undertaken to ensure as little missing data as possible. No imputation will be undertaken. Any protocol deviations will be reported and justified in the final report, overseen by the statistician.

The primary outcomes are the difference in mean cartilage mRNA expression of a panel of pre-defined 10 inflammatory genes in human articular cartilage from tissue taken at surgery after 10-21 days of treatment (Supplementary Table 1). The difference in means between the two treatment arms will be reported for each pre-defined inflammatory gene mRNA level, together with 95% CIs and will be tested using unadjusted t-tests for normally distributed variables with 5% (2-sided) significance. (No multiplicity adjustment will be made, given that these are exploratory endpoints, which have been defined *a priori)*. Supplementary analysis will be undertaken using multi-variable linear regression

methods adjusting for genotype, sex and other predefined important factors. Secondary outcome measures will utilise the same methods with multivariable logistic regression used for binary outcomes. For all secondary analyses, only 95% CIs will be reported (no p values provided), to note these are not powered definitive analyses. For example, the change in average hand pain score (calculated from a minimum of 3 ratings over a seven-day period - the seven days preceding Baseline compared to the seven days preceding Day of surgery) will be reported for placebo and talarozole arms together with 95% CIs. (The collection of clinical outcomes and their reporting are for feasibility purposes).

A trial statistician will oversee all the statistical aspects of the study. Key details of the planned statistical analysis are presented here but will be supplemented by an outline of the outcomes and tables for reporting. Stata (StataCorp LP, release 16, 2019) or other appropriate validated statistical software will be used for analysis.

Two progression criteria will be considered based on these analyses, to support a decision to progress to a full trial, relating to:

(i) confirmation of signal detection of a molecular change in OA tissue with talarozole (where a statistically significant difference in 3 out of 10 pre-defined mRNA levels when comparing the active arm with the placebo arm will be considered sufficient evidence);

AND

(ii) evidence of likely feasibility and acceptability based on proportions of participants randomised and retained, meeting both of:

- Proportion randomised of >0.5 (those randomised/those eligible after screening)
- Proportion withdrawing of <0.4 (those withdrawn after randomisation for any reason/those completing)

(Those completing here include those who are adherent to medication but have no tissue sample at surgery, as tissue sampling would not be sought in a future trial).

Both progression criteria must be met, one is not sufficient. The Trial Oversight Committee will advise on whether these progression criteria are met as part of their review and recommendations at the end of the study. Specifically, they will advise on (i) whether this current study design was feasible, and (ii) if a future trial is therefore likely feasible, considering all available data and any changes that could be made reasonably when scaling up and designing a full RCT.

Sample size justification

A number of different datasets were considered to identify the most robust inflammatory genes suppressed by atRA (22). Based on the variation in fold change (the change in expression level) of the mRNA of *ADAMTS4* in articular cartilage relative to the expression level of a house-keeping (control) gene, or genes, in human cartilage stratified by treatment group (talarozole vs placebo), it was judged from these and other biological data that a large standardised effect size of 1.0 could be tested for reasonably. Considering this effect size, 34 tissue samples were estimated to provide 80% power to detect a difference in the normalised ADAMTS4 mRNA level between the active and placebo group with 5% 2-sided significance (assuming that the effect of talarozole versus placebo is equivalent to the variability in the outcome measure) (35). To allow for potential 20% loss to follow-up (including withdrawal and non-compliance) and 20% insufficient tissue for analysis up to 56 participants will be recruited (28 per arm). Recruitment will cease after 34 participants have been recruited who remain fully compliant with protocol (see *Compliance with study medication*) and for whom a viable cartilage sample is obtained. The study is not powered to detect clinically important change in patient reported outcomes but differences in means will be reported, alongside 95% CIs. Collection of 34 or more evaluable participant samples will be sufficient to detect a large effect size for the primary laboratory outcome and address our progression criteria. The sample size is also sufficient to assess total proportion randomised, as a feasibility outcome. A sample size of 34 will enable estimation of a 95%

CI for an assumed 0.5 proportion randomised of those eligible, with a margin of error (half-width of the 95% CI) of approximately ± 0.18 (95% CI [0.32, 0.68]). This 2-sided 95% CI calculation uses the Clopper-Pearson formula. This sample size is adequate to maintain this level of precision or greater (95% CI width 0.4 or less), for a wide range of randomised proportions (0.2-0.7) that can be assumed for differing recruitment rates (36, 37).

Data monitoring

Regular monitoring will be performed to verify that the clinical study is conducted and data are generated, documented and reported in compliance with the protocol, GCP and the applicable regulatory requirements.

A Trial Oversight Committee (TOC) will oversee the overall conduct of the study and will meet and report during the study at least annually, and ad hoc as needed. The TOC will comprise of invited expert members, including at least one medically qualified person and a patient representative. A separate medically qualified Safety Oversight Clinician (SOC) (with appropriate clinical experience and independent to the study) will be appointed to safeguard the interests of the study participants. The SOC can advise the chair of the TOC at any time, if in their view, the study should be stopped due to concerns over participant safety.

Withdrawals

Participants asking to stop treatment or unable to tolerate the study medication or comply with study procedures will be withdrawn. The Investigator may discontinue a participant from the study medication at any time if they consider it necessary for any reason. These include and are not limited to pregnancy, ineligibility arising of a contraindicated medication post-screening, significant non-compliance, cancellation of surgery. Reasons for withdrawal will be documented and reported by treatment arm. Those withdrawn from treatment will continue to be followed up unless they withdraw consent from the study entirely.

Participants have the right to withdraw from the study at any time and without giving reason. If the participant has received any amount of study medication prior to withdrawing consent, they will be strongly encouraged to complete a safety follow up call/visit, including AE recording, safety blood testing and pregnancy follow up (where applicable).

Safety

From information available about these agents (and similar agents such as retinoids), talarozole is expected to be generally well-tolerated but may cause some side effects. These include dry lips or skin, or soreness around the corners of the mouth. Less commonly, dry eyes, skin itching, skin irritation or hair loss may occur. Occasionally there may be an increase in blood lipids. All AEs will be recorded. Given the stage of development and relatively low numbers of participants exposed to talarozole to date, additional precautionary safety screening and monitoring, including mental health and suicide ideation, effects on male gonadal function (assessed by blood testing) are necessary.

The safety reporting window will be from time of the participant starting the study medication, until the point that the participant completes the study, or where applicable the relevant pregnancy window (final dose of study medication + 33 days (female participants) or + 93 days (male participants). Investigator follow-up of Serious Adverse Events (SAEs) will be until resolution.

AEs occurring during the safety window that are observed by the Investigator or reported by the participant will be reported on the eCRF, whether or not attributed to study medication.

Their description, date of onset and end date, severity, assessment of relatedness to study medication, other suspect drug or device, and action taken will be recorded. The relationship of each AE to the study medication will be determined by a medically qualified individual. AEs considered related to the study medication will be followed up until event resolution or stabilisation.

SAEs will be reported within 24 hours following knowledge of the event being defined as serious to OCTRU. Reports of unblinded SAEs in participants exposed to talarozole (de-identified data only) will

be shared with GSK. SAEs will be reported to the Research Ethics Committee (REC) and Medicines and Healthcare Products Regulatory Agency (MHRA) (via the Yellow Card Scheme) if the Chief Investigator believes the event was 'related' and 'unexpected'. These data will be summarised and reviewed by the SOC and the TOC.

In the event of a Serious Adverse Reaction (SAR) or any suspicion of an SAR, the study medication will be stopped immediately. AEs of special interest for this study include mood change, dry lips, dry eyes, sore or gritty eyes, sore mouth/cheilitis and changes in male hormonal levels (testosterone, Follicle stimulating hormone, Luteinising hormone) from within normal range at screening to outside of normal range on day of surgery.

Some events have also been defined as exempt from AE reporting, relating to hospitalisation and expected symptoms or complications related to surgery and anaesthesia related to trapeziectomy as part of planned usual care and expected symptoms in the 48 hours following influenza or COVID-19 vaccination.

Auditing

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

Ancillary and post-trial care

There is no provision for continuation of this unlicensed medication beyond the end of the study. The final dose of study medication is taken on the Day of surgery.

Dissemination policy

Reporting of RAMBOH-1 will be in line with CONSORT guidelines, including the extension to randomised pilot and feasibility trials and the funder terms (33, 34). The results of the study will be published and disseminated via oral reports at international meetings and on University of Oxford

websites. Study results will be disseminated to study participants, via email or letter following end of study and analysis.

Protocol amendments

The original REC approved protocol was dated 16 August 2021. A history of the protocol amendments since is presented in Supplementary Table 6 (Additional File 1). Should any further protocol changes be required, approval from REC and/or Health Research Authority (HRA) will be obtained and relevant parties updated.

Confidentiality

The study staff will ensure that the participants' confidentiality is maintained. The study will comply with the UK General Data Protection Regulation (GDPR) and Data Protection Act 2018, which require data to be anonymised as soon as it is practical to do so. The processing of personal data of participants will be minimised by making use of a unique participant identification number on all study documents, samples, and study database. Personal data (name, contact information) will be held in REDCap, for the purpose of sending questionnaires and results of the study by email or post. In compliance with GDPR this will be deleted when no longer needed. All documents and data will be stored securely with inbuilt user permissions meaning personal and other data will only be accessible to authorised personnel.

Declaration of interests

This research study is supported by a grant from the Medical Research Council (MRC). GSK are providing talarozole compound for the study free of charge. The selection of study medication was on academic grounds. GSK had no part in the conception of this study.

DISCUSSION

Pharmacological therapies to improve pain or target underlying disease processes in OA, slowing its progression, remain elusive despite the pressing clinical need (38, 39). Experimental medicine studies, which offer efficient and cost-effective early readouts compared to full efficacy trials, could provide the necessary traction for developing OA therapeutics, enabling earlier stop-go decisions based on mechanistic readouts.

Here, we aim to augment joint tissue retinoic acid levels and reduce inflammatory signalling in a non-stratified group of patients with advanced hand OA. This drug targeting, based on our prior data, makes two key assumptions. That even those with no copies of the disease related *ALDH1A2* allele may still benefit from the mechanism of action of this agent; and that in individuals with a wildtype genotype, there will not be an increase to supra-physiological levels of retinoic acid (in tissues or systemically). The latter seems unlikely, given atRA's tight regulation in the body. Depending on secondary analysis of genotype effects on the molecular response, stratified or personalised medicine may be important for treating responsive subgroups. However, this is difficult to predict now, leading us to a more inclusive initial approach.

Choosing the right agent is crucial. Talarozole was selected for its target specificity, suitable safety profile, accessibility, and synthesis/manufacture cost. Patients with OA prefer oral agents (40), and an involvement panel in 2021 responded positively. We know of no other RAMBAs in active development. Depending on our findings, re-establishing pharmaceutical programs for more selective CYP26A inhibitors might be attractive.

Talarozole was previously developed for congenital ichthyosis and tested in clinical trials for keratinization disorders (19). It has never been tested in an OA population, making safety monitoring paramount in this small study. Not having mucocutaneous barrier issues, unlike populations previously tested, may help avoid some adverse reactions associated with retinoids.

A particular strength of this study is the direct translation of a human genetic finding into a targeted intervention, allowing mechanistic validation of a genetically proven pathway in human osteoarthritic tissue (16, 22). Other particular strengths include the randomised, double-blind, placebo-controlled design; the use of human osteoarthritic cartilage obtained during clinically indicated surgery; and the strong translational rationale linking genetic, mechanistic and pharmacological evidence. The study also benefits from assessment of cartilage as the target tissue for molecular outcomes, which is the tissue with a strong expression-genetic (expression quantitative trait locus) signal. Also, the use of this tissue closely aligns with our preclinical studies and the proposed mechanism of action of talarozole (22). The study also benefits from its parallel collection of feasibility, acceptability and safety data to inform progression decisions on a future full trial. We also build on our experience in other studies, which showed that collecting daily average hand pain is more acceptable and meaningful to patients and feasible to do (41). To our knowledge the study is unique in the field, aiming to harness tissue from consenting patients undergoing usual care operative procedures to interrogate the effects of a potential novel drug, enabling a human experimental medicine system for OA. (16, 22).

There are a number of recognised limitations of a study of this type. Firstly, given the short two-week dosing duration in patients needing imminent surgery, symptomatic benefit is not anticipated. The study is not powered (or intended) to determine clinical efficacy and this will not be tested (we are making assumptions from the known biology that a molecular change will reflect disease relevant processes that could eventually lead to a clinical benefit if taken over a longer time). We are also assuming that there will be a measurable molecular shift that will be detectable in the cartilage between treatment and placebo groups, irrespective of variations in an individual's biology. These are generic limitations of experimental medicine studies. Secondly, the nature of the study means that recruitment is limited to those with advanced thumb carpometacarpal osteoarthritis choosing to undergo surgical trapeziectomy allowing study of tissue changes after treatment at a single point in time. This does not allow us to test the drug in an earlier disease group who may be more responsive

to treatment, or to establish what the pre-treatment 'baseline' tissue molecular measures were (we rely on detecting differences between arms after treatment).

We also recognise that our treatment duration window is relatively short (10-21 days) and this may be an insufficient time to reverse established biology in the tissue. There is limited direct evidence defining the optimal duration of talarozole exposure required to reverse established molecular responses in human osteoarthritic cartilage *in vivo*. Having said this, the prediction from our preclinical studies is that drug effects are likely to be rapid (11, 22) and it is reassuring that the short half-life of talarozole means that steady state will have been reached after just a few days. Extending treatment duration was considered but would introduce additional logistical challenges, including increased participant burden and complexities associated with longer-term dosing in patients awaiting surgery.

Dose and delivery choice is critical. We lacked capacity for dose-ranging or further pharmacokinetic (PK) studies and needed to ensure sufficient concentration and tissue penetration while minimising toxicity. Based on available data including PK data from early phase studies, we opted for a middle range dose of 2 mg. This dose, while well-tolerated, is expected to achieve higher systemic concentration and joint tissue penetration than 0.5 and 1 mg doses, with flexibility to halve the dose if needed. Based on this and known safety data, good adherence is anticipated. The clinical manufacture aims to recapitulate as closely as possibly a gel capsule previously used in trials, aiming to maximise pharmacodynamics to enable once daily dosing, given short half-life.

We note that drug effects will also be affected by the absolute circulating concentrations of talarozole, which are likely to be variable across participants due to a variety of individual biological factors beyond adherence or dosing. If no molecular effect is observed or the result is inconclusive, it may be challenging to distinguish definitively between insufficient biological activity on the target and insufficient treatment exposure as the underlying reason. Drug levels will be measured from stored plasma samples to investigate this if the study results are null or inconclusive. Although measuring

these or retinoic acid may be challenging biochemically, this provides an opportunity for further exploration in this situation.

Finally, our study is unlikely to be able to add substantive data on safety and tolerability in this study population as drug exposure times are intentionally so short, though we intend to report carefully the data we acquire.

Experimental medicine studies are not designed to detect clinical benefit, sometimes making recruitment challenging, so this needs to be considered in the interpretation of feasibility testing. RAMBOH-1 aims to gather critical data to enable a decision on whether progression to a larger efficacy RCT for symptomatic hand OA of this novel agent or drug class is justified.

The study opened to recruitment in January 2024 and is anticipated to close to recruitment in 2026.

List of abbreviations

ADAMTS	A Disintegrin and Metalloproteinase with Thrombospondin Motif
AE	Adverse Event
ALDH1A2	Aldehyde Dehydrogenase 1 Family Member A2
ALT	Alanine aminotransferase
API	Active pharmaceutical ingredient
atRA	All-trans retinoic acid
β-HCG	Beta-Human Chorionic Gonadotropin
95% CI	95% Confidence Interval
CMC	Carpometacarpal
CONSORT	Consolidated Standards of Reporting Trials
CRP	C-reactive protein
C-SSRS	Columbia-Suicide Severity Rating Scale
CYP19A	Cytochrome P450 19A
CYP26	Cytochrome P450 26
DNA	Deoxyribonucleic acid
ECG	Electrocardiogram

eCRF	Case Report Form
EDTA	Ethylenediaminetetraacetic Acid
FBC	Full blood count
GCP	Good Clinical Practice
GDPR	General Data Protection Regulation
GP	General Practitioner
GWAS	Genome-wide association study
GSK	GlaxoSmithKline
HDL	High-density lipoprotein
HDPE	High-density polyethylene
HRA	Health Research Authority
HRT	Hormone Replacement Therapy
IRAS	Integrated Research Application System
ISRCTN	International Standard Randomised Controlled Trials Number
LFT	Liver function test
LH	Luteinising hormone
MHRA	Medicines and Healthcare products Regulatory Agency
MMP	Matrix metalloproteinase
MRC	Medical Research Council
mRNA	Messenger ribonucleic acid
NDORMS	Nuffield Department of Orthopaedics, Rheumatology, and Musculoskeletal Sciences
NHS	National Health Service
NIHR	National Institute for Health Research
NRS	Numerical Rating Scale
OA	Osteoarthritis
OCTRU	Oxford Clinical Trials Research Unit
PEG	Polyethylene glycol
PEM	Patient Evaluation Measure
PI	Principal Investigator
PIL	Participant/ Patient Information Leaflet
PK	Pharmacokinetic
RAMBA	Retinoic Acid Metabolism Blocking Agent
RAMBOH-1	Retinoic Acid Metabolism Blocking Agents to treat Osteoarthritis of the Hand
RAR	Retinoic acid receptor

RCT	Randomised Controlled Trial
REC	Research Ethics Committee
RNA	Ribonucleic acid
RT-PCR	Real-time Polymerase Chain Reaction
SAE	Serious Adverse Event
SAR	Serious Adverse Reaction
SMS	Short Message Service
SOC	Safety Oversight Clinician
SPIRIT	Standard Protocol Items: Recommendations for Interventional Trials
TOC	Trial Oversight Committee
U&E	Urea & Electrolytes
WOCBP	Women of childbearing potential

DECLARATIONS

Ethics approval and consent to participate

This is an experimental medicine randomised feasibility study of an unlicensed study medication. This study is not a Clinical Trial of an Investigational Medicinal Product as defined by the EU Directive 2001/20/EC, given that the outcomes are molecular rather than efficacy. At the time that the study was designed and seeking its approvals, the MHRA confirmed that as currently designed this study did not fall under their remit.

A favourable ethical opinion has been obtained from the East Midlands-Nottingham 2 REC (UK REC 21/EM/0220). HRA approval was obtained on 05/Oct/2021, (IRAS ID 291242). The study has already undergone full external peer review as part of the ethics approval process and funding process by the MRC. The study is registered on the ISRCTN registry, https://www.isrctn.com/ISRCTN16717773.

Written informed consent will be obtained from all participants prior to their participation in the study (Informed Consent Form, Supplementary material provided for review).

This manuscript reports version 9.0 dated 21/11/2025 of the approved current study protocol. A summary of amendments to protocol can be found in Supplementary Table 6 (Additional File 1).

Consent for publication

Sponsor and GSK agreed that a public summary of the protocol would be made available. Results of the study will be submitted to all investigators and to GSK for review and comment prior to submission for peer-reviewed publication. A summary of results summary will be posted within 12 months of the conclusion of the study in publicly accessible, worldwide registers.

Availability of data and materials

Following the end of study and primary publication of the study findings, a de-identified study dataset will be created and stored for as long as it is useful and may be shared with other researchers or collaborators (this may include commercial organisations) and/or uploaded into a research data repository. Access to this dataset will be made available to other bone fide researchers on reasonable request, by application to the chief investigator and OCTRU, contact octrutrialshub@ndorms.ox.ac.uk.

Competing interests

The authors declare that:

JAEW – none

AF – none

AL – none

LZ – none

MG -none

SL - none

VSB – none

JB – none

DR - none

DK – none

MDG – none

DF - none

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FEW - consulting fees in last 5 years from Pfizer, Novartis and GSK for unrelated agents/research.

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In addition, support in kind was received from GSK due to their gifting of the active pharmaceutical ingredient (API) for this research project, via an investigator-initiated collaboration. No other funding was received from GSK.

None of the funders had any explicit role in the study design and will not have any role in data collection, management, analysis, interpretation and report writing.

The University of Oxford is the Sponsor of the study and has ultimate authority over study activities. OCTRU act on behalf of the sponsor, contact RGEA.Sponsor@admin.ox.ac.uk.

FEW was supported by a UKRI Future Leaders Fellowship which directly supported her time on this research (MR/S016538/1, MR/S016538/2 and MR/Y003470/1). She is also a member of the Arthritis UK Centre for Sport, Exercise and Osteoarthritis, University of Oxford (Grant 21595).

Authors' contributions

All authors contributed to the drafting of the manuscript and have read and approved the final manuscript. TLV is the grant holder of the funding from MRC. FEW was the chief investigator at the time of design, funding and set up of the study and the primary protocol author. DF has been chief investigator since April 2023. DF and MDG are site PIs and grant co-applicants, in addition to SL. DK participated in the statistical design of the study. LZ inputted on the design of laboratory aspects of the study. MG, JAEW, AL and AF are Trial Management staff and assisted in writing the protocol, obtaining ethical permissions and managing the study. DR advised on various aspects including study medication and its manufacture. VSB and JB are senior trials unit staff and were involved in planning the design and governance of the study, its risk assessment and its data management.

Acknowledgements

This study will be conducted as part of the portfolio of trials in the UK Clinical Research Collaboration registered clinical trials unit – OCTRU at the University of Oxford. It will follow their Standard Operating

Procedures ensuring compliance with the principles of GCP and the Declaration of Helsinki and any applicable regulatory requirements.

Additional support will also be received from the NIHR local Clinical Research Networks at both Oxford University Hospitals NHS Foundation Trust and Frimley Health NHS Foundation Trust.

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856 **Table 2. Timing of visits and data collection (SPIRIT)**

Procedures	**Visit 1 Screening** **-70 to -1 day** **(Target -14 days)**	**Visit 2 Baseline** *(Telephone)* **Day 0**	**Visit 3** **Day of Surgery** **Day 10 -21** **(Target 14 days)**	**Visit 4** **Post-surgery follow-up** *(Telephone)* **Visit 3 + 7-21 days**
Informed consent	x			
Inclusion/exclusion	x	x	x	x
Demographics	x			
Medical history	x	x		
Concomitant medication	x	x	x	
Physical examination	x			
Measurement of height and weight	x			
Vital signs	x			
ECG	x			
Blood screening	x			
Hormone blood testing (males only)	x		x	
Research bloods	x		x	
Pregnancy testing (urine, if applicable)	x	x^	x	x^^
Hand pain symptoms & severity	x			
C-SSRS*	x		x	x
Eligibility assessment	x			
Key pinch	x			
Grip strength test	x			
Training in remote pain rating	x			
Randomisation		x		

Instructions for taking study medication		x		
Prescription/dispense study medication		x		
Remote medication compliance diary		x	x	
Remote daily hand pain rating (0-10 NRS)		x	x	
Questionnaires (PEM, EQ-5D-5L)		x	x	
Joint tissue sample			x	
Synovial fluid sample			x	
Urine sample (dipstick)	x			
End of Study questionnaire				x
Study medication compliance			x	
Adverse event assessments		AE reporting window**		
Safety blood monitoring			x	
Investigator Blinding Index			x	

*C-SSRS Screen Lifetime/Recent version to be used at Visit 1 (Screening visit). C-SSRS Screen Recent version to be used at Visit 3 (Day of Surgery) and Visit 4 (Post-surgery Follow-up). This is Investigator administered.

**AE reporting window is from time the participant starts study medication until the participant completes the study (or where applicable, the relevant pregnancy window)

^ Urine pregnancy test to be completed by WOCBP at home within 24 hours prior to starting study medication

^^ Urine pregnancy test to be completed by WOCBP at home, ideally on the same day as the post-surgery follow-up visit and, if not, at least within the visit 4 window (i.e. visit 3 Day of Surgery +7-21 days) and inform the study team of the result.

AE – Adverse Event; C-SSRS - Columbia-Suicide Severity Rating Scale; ECG – Electrocardiogram; NRS - Numerical Rating Scale; PEM - Patient Evaluation Measure; WOCBP – Woman of Child-Bearing Potential

Supplementary Files

This is a list of supplementary files associated with this preprint. Click to download.

- RAMBOH1ProtocolPaperSuppTablesV2.0R21August2026Clean.docx