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Metformin treatment for patients with hand osteoarthritis: protocol for the multicentre, randomised, placebo-controlled METRO trial

Kasper Staberg Madsen ,[1] Marius Henriksen,[1] Anna Døssing,[1] Asbjørn S Poulsen,[1] Rasmus Oscar,[2] Tue Kragstrup,[2,3] Karen Ellegaard,[1] Filip K Knop ,[4,5,6] Mikael Boesen,[6,7] David J Hunter ,[8,9] Robin Christensen,[1,10] Henning Bliddal[1,6]

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For numbered affiliations see end of article.

Correspondence to
Mr Kasper Staberg Madsen; kasper.staberg.madsen@regionh.dk

ABSTRACT

Introduction Hand osteoarthritis (OA) is a prevalent joint disorder with limited treatment options. Accumulating evidence suggests that the antidiabetic drug metformin has beneficial effects on knee OA and may likewise be beneficial for hand OA. The objective of this randomised, double-blinded, placebo-controlled trial is to investigate the effect of metformin 1000 mg two times a day, or maximum tolerated dose, compared with placebo on reducing finger joint pain after 16 weeks of treatment.

Methods and analysis The participants will be enrolled from the OA clinic at the Parker Institute at Copenhagen University Hospital - Bispebjerg and Frederiksberg, Copenhagen, Denmark and from the Department of Rheumatology, Hospitalsenhed Midt, Silkeborg, Denmark. 150 participants with painful hand OA according to the American College of Rheumatology criteria will be randomly allocated in a 1:1 ratio to receive either metformin or a matching placebo for 16 weeks. The initial dose of 500 mg of metformin or placebo once daily is increased by 500 mg every week until the target dose of 1000 mg two times a day, or the maximum tolerated dose, is reached. The participants will have clinical visits every 4 weeks, except the week 12 visit, which is by telephone. The primary endpoint is the between-group difference in least squares means for the change in the Visual Analogue Scale (VAS) finger joint pain scores between the metformin and placebo groups at 16 weeks. The main analysis will be conducted on the intention-to-treat population, comprising all participants assessed and randomly assigned at baseline. Least squares means and the differences between them, along with their respective 95% CIs, will be derived from a mixed-effects model for repeated measurements (outcomes collected at baseline and at weeks 4, 8, 12 and 16). Adverse events will be registered systematically.

Ethics and dissemination Approval has been obtained from the European Medicines Agency (EudraCT: 2023-509181-38-00), which also includes approval from the local health research ethics committee. Written informed consent will be obtained from all participants. Study findings will be published in international peer-reviewed journals and will be presented in relevant media and at international scientific conferences.

Trial registration number EudraCT, 2023-509181-38-00; ClinicalTrials.gov, NCT06367283.

STRENGTHS AND LIMITATIONS OF THIS STUDY

⇒ This is a multicentre, randomised, double-blinded, placebo-controlled trial.
⇒ This study is adequately powered to address whether metformin can reduce pain over 16 weeks in people with painful hand osteoarthritis.
⇒ Due to the exclusion criteria, the generalisability of the study results will be limited to people without, for example, diabetes, renal failure or psoriasis.

INTRODUCTION

The prevalence of hand osteoarthritis (OA) has been estimated to be 26% among women and 13% among men above 70 years.[1] People with hand OA experience pain, stiffness and decreased grip strength that results in difficulties in undertaking everyday activities and poor self-reported general health.[2–4] The aetiology of hand OA remains to be fully elucidated. Inflammation may play a role in the pathogenesis, supported by recent studies showing that treatment with oral prednisolone or methotrexate was efficacious for the treatment of painful hand OA.[5 6] Although colchicine is known to have anti-inflammatory properties, it did not effectively relieve pain.[7] Previous studies have shown conflicting results on the associations between body mass index (BMI) and symptomatic hand OA or hand pain; however, in people with hand OA, higher BMI is associated with greater pain severity in the hands, which could be explained by systemic low-grade inflammation.[8 9] The treatment of hand OA includes

non-pharmacological (eg, exercise and splints) and pharmacological treatments (eg, topical or oral non-steroidal anti-inflammatory drugs (NSAIDs)).[10] With regards to oral NSAIDs, precautions should be taken in elderly people due to their gastrointestinal (GI), cardiovascular and renal side effects.[11 12] Furthermore, oral glucocorticoids cannot be recommended for prolonged periods of time.[11]

Metformin is best known as a recommended first-line therapy in the treatment of type 2 diabetes; however, metformin seems to have beneficial effects beyond its effect on glucose control.[13] Within OA, cohort studies have shown a decrease in knee cartilage loss, a reduction in the development of OA and a decrease in total knee arthroplasty frequency among people taking metformin compared with matched control groups.[14–17] Furthermore, three small randomised controlled trials with participants having knee OA showed an improvement in symptoms in people randomised to treatment with metformin.[18–20] Recently, a systematic review found consistent evidence across preclinical (cell studies and animal models) and human studies to support a favourable effect of metformin on chondroprotection, immunomodulation and pain reduction in knee OA.[21] Metformin is considered a safe and tolerable drug. The most frequent adverse event is GI symptoms, which typically occur in the beginning of treatment.[22] Long-term treatment is associated with a small risk of vitamin B_{12} deficiency.[23]

In relation to OA, preclinical studies suggest that the beneficial effects of metformin are mainly mediated via the activation of the adenosine monophosphate-activated protein kinase (AMPK) enzyme.[21 24] Additionally, the mammalian/mechanistic target of rapamycin complex 1 and sirtuin 3 have been suggested as potential pathways in metformin's mechanisms of action.[25 26] The purpose of the present study protocol is to evaluate the effect of metformin in people with painful hand OA after 16 weeks of treatment. As metformin has shown body weight loss in some trials, studying the effect in people with hand OA may allow for evaluation aside from the potential benefit of reduced mechanical stress by weight loss. The primary efficacy objective is to compare the effect of metformin 1000 mg two times a day, relative to placebo, on changes in finger joint pain from baseline to week 16 in patients with hand OA.

METHODS AND ANALYSIS

Study design and hypothesis

The METRO (Metformin treatment for patients with hand osteoarthritis: protocol for the multicentre, randomised, placebo-controlled trial) trial is a multicentre, randomised, double-blinded, placebo-controlled, superiority trial in people with painful hand OA to investigate the effect of metformin 1000 mg two times a day, or maximum tolerated dose, compared with placebo on reducing finger joint pain after 16 weeks of treatment. We hypothesise that metformin is superior to placebo in reducing pain in patients with hand OA. The trial is registered at ClinicalTrials.gov on date 16 April 2024, with trial ID NCT06367283. The reporting of the trial will follow the Consolidated Standards of Reporting Trials Statement.[27]

Study setting and participants

The participants will be enrolled from the OA clinic at the Parker Institute at Copenhagen University Hospital - Bispebjerg and Frederiksberg, Copenhagen, Denmark and from the Department of Rheumatology, Hospitalsenhed Midt, Silkeborg, Denmark. Participants with painful hand OA will be recruited via the OA outpatient clinic and via an advertisement in the local media. Overarching inclusion criteria are as follows: metformin-naive men and women above 18 years of age, diagnosed with hand OA according to the American College of Rheumatology criteria[28] and with average finger (2–5) joint pain≥4 on a 0–10 numeric rating scale (where 10 is the worst pain) over the past 7 days.

Criteria that would exclude the possibility of enrolment are as follows: history of, or current signs of medical disease that may affect joints, for example, rheumatoid arthritis, gout, psoriatic arthritis; psoriasis; known malignancy (except successfully treated squamous or basal cell skin carcinoma); drug or alcohol abuse in the last year; existing nerve entrapment syndromes (eg, carpal tunnel syndrome); known diabetes; generalised pain syndromes such as fibromyalgia; known peripheral neuropathies; known allergies towards the interventions; gastric bypass or other malabsorption syndrome; in case of pharmacological weight loss medication (eg, glucagon-like peptide 1 (GLP-1) analogues) or pharmacological osteoporosis medication, dosage must have been stable for 3 months without any plan of up-titration during the study period; history of hand surgery in the target hand within 12 months prior to enrolment; history of arthroplasty, arthrodesis or surgical treatment of thumb base OA in the target hand; use of systemic corticosteroids equivalent of≥7.5 mg prednisolone daily within 3 months; treatment with denosumab (Prolia/Xgeva); participation in experimental device or experimental drug study 3 months prior to enrolment; intra-articular treatments of any kind of any joint of the target hand 3 months before inclusion; current use of synthetic or non-synthetic opioids; planning to start other treatment for hand OA in the study participation period; planned CT scan with iodine contrast; scheduled surgery on upper extremity of the target hand during study participation; scheduled surgery requiring pause of metformin, for example, surgery in general anaesthesia, during study participation; pregnancy or planned pregnancy within the study period, 3 months after end of study treatment for female fertile participants and 6 months after end of study treatment for male participants; insufficient anticonception and breast-feeding; positive anticyclic citrullinated peptide (anti-CCP); estimated glomerular filtration rate<60 mL/min/1.73 m^2; vitamin B_{12} deficiency (< 125 pmol/L); haemoglobin A1c (Hba1c) ≥ 48 mmol/

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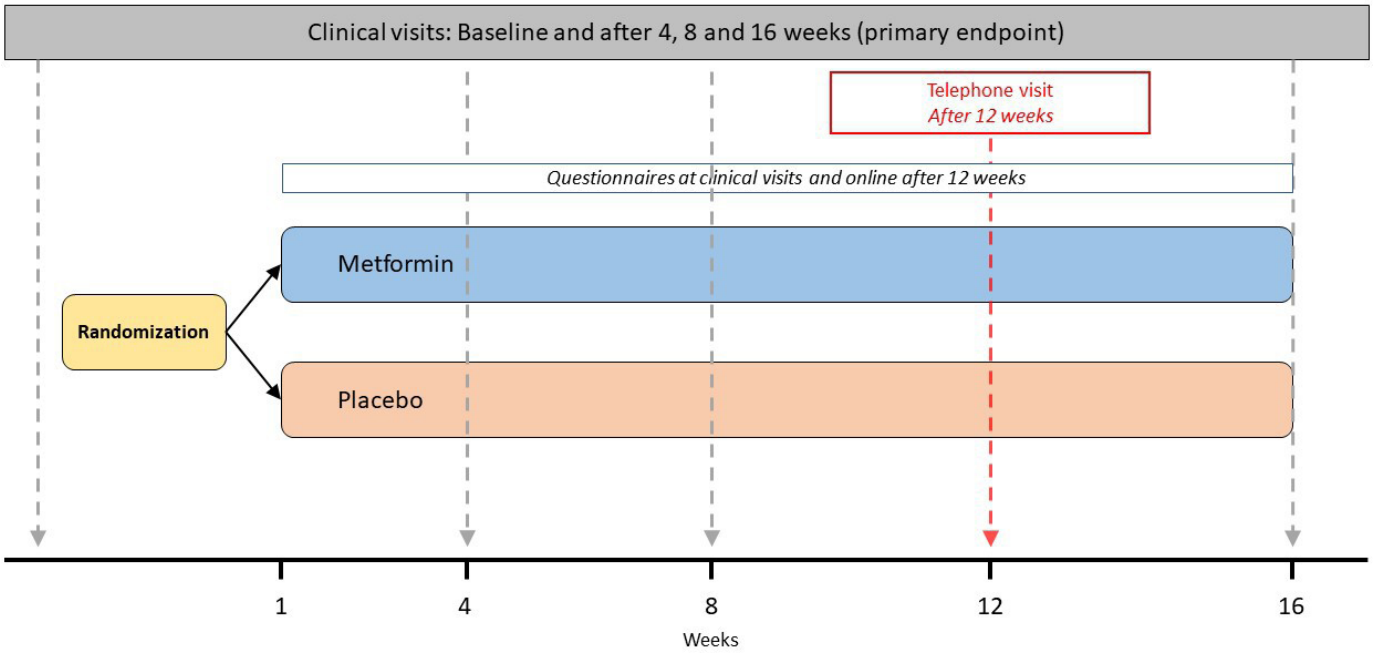

Figure 1 Trial design. Clinical assessment at baseline (before randomisation), after 4, 8 and 16 weeks (primary endpoint). Questionnaires at clinical visits (weeks 0, 4, 8 and 16) and online (via REDCap) in week 12. A telephone consultation is performed after 12 weeks.

mol or any other condition or impairment that, in the opinion of the investigator, makes a potential participant unsuitable for participation or obstructs participation, for example, psychiatric disorders.

For an overview of the trial, please see figure 1.

Study Timeline

The trial had the first patient first visit on 3 June 2024. The estimated last patient last visit is in December 2025. Figure 2 shows the flowchart of trial participation.

Randomisation, allocation concealment and blinding

A computer-generated randomisation sequence will be produced before patients are enrolled, allocating participants to treatment with metformin or placebo (1:1). Randomisation will be in permuted blocks in varying sizes of 2–4; block sizes will be unknown to the investigator and his/her delegate. The randomisation is stratified on sex (male/female) and carpometacarpal 1 (CMC-1) pain (yes/no). The randomisation sequence is generated by the central pharmacy of the capital region. Participants in the intervention group will receive tablets containing 500 mg metformin 'Orifarm', which is a round, vaulted and white tablet. Participants in the placebo group will receive an identical placebo tablet produced by the Central Pharmacy of the capital region (Marielundvej 25, DK-2730 Herlev). The metformin and placebo tablets will be packed in identical containers (high-density polyethylene (HDPE)). By providing a placebo identical to the intervention, we aim to achieve blinding of participants, care providers and outcome assessors. Data analysts will be blinded throughout the analysis. The data manager will provide a blinded data output for analyses. At the final follow-up visit, participants will be asked as to which group they think they were allocated.

Intervention and dosing

Metformin/placebo will be initiated at 500 mg once daily, preferably with breakfast. The dose will be increased by 500 mg every week until 2 g/day is reached, distributed as 1000 mg every morning and evening, together with a meal. If the subject cannot tolerate the maximum dose (2 g/day), the maximal tolerated dose will be given. The placebo group will receive a tablet identical to the metformin tablet and the same dosing regimen. The treatment period, including titration, is 16 weeks.

Safety and adherence

Any adverse or serious adverse events will be registered using the Common Terminology Criteria for Adverse Events V.5 developed by the National Cancer Institute at the National Institute of Health, every fourth week at the visits. The Copenhagen Unit of Good Clinical Practice will monitor the study. Unblinding can occur immediately and without restrictions, if necessary, by contacting an investigator. Study medications were handed out at baseline and at the week 8 visit. Adherence will be assessed at 16 weeks of treatment (primary endpoint) by pill count. Monthly clinical visits (except week 12, which is by telephone) will be conducted to address any concerns that might help to maintain adherence.

Concomitant medication

Non-pharmacological and pharmacological interventions for managing hand OA are allowed if use was stable for the 3 months before enrolment and will remain stable

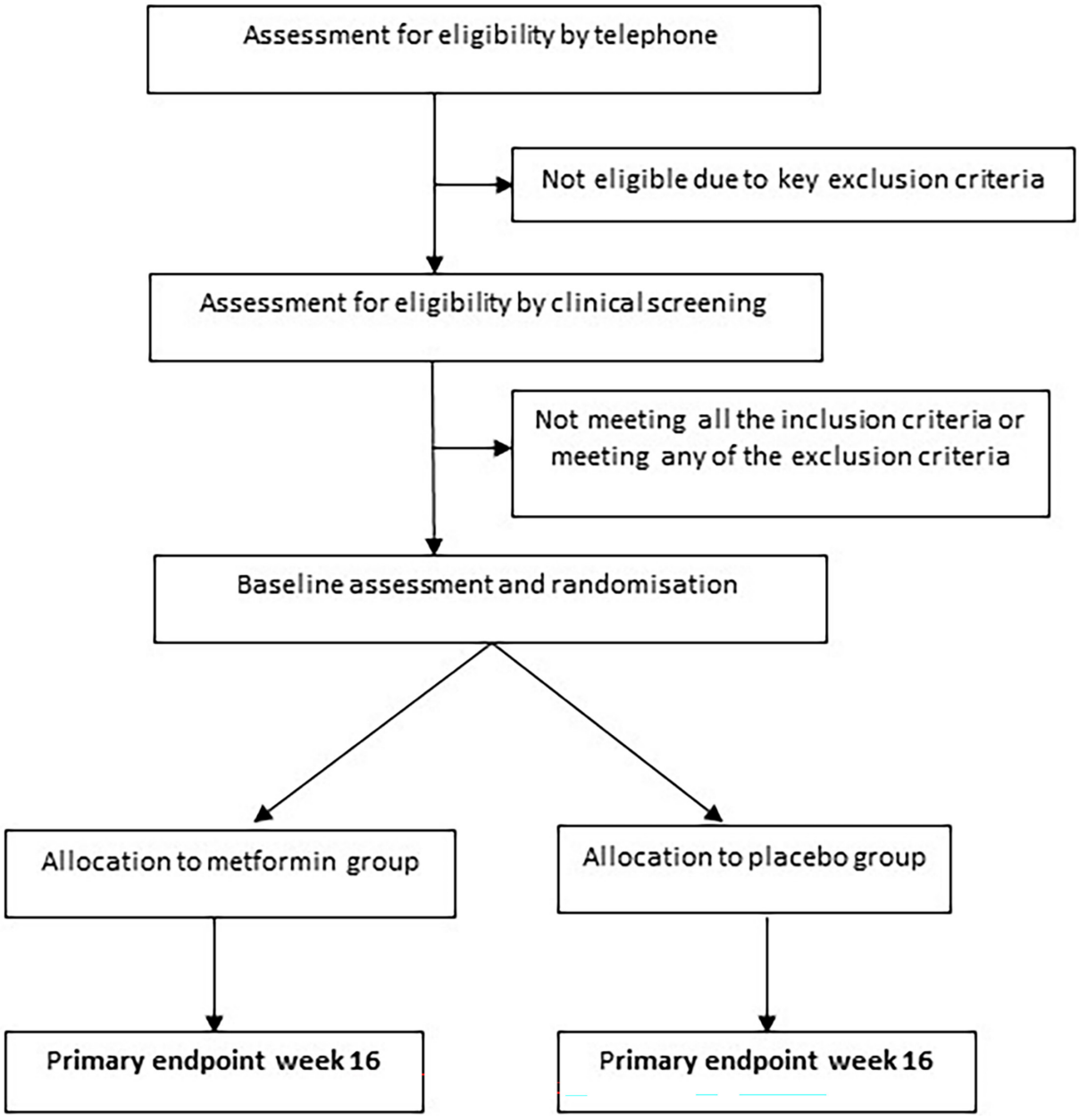

Figure 2 Trial participation flowchart.

throughout trial participation. Oral paracetamol and NSAIDs are allowed as rescue medication for the treatment of hand pain or any other pain (eg, headache) during study participation, excluding 24 hours prior to clinical study visits. A medical diary of paracetamol and NSAIDs is handed out to the participants.

Study procedures

Participants will be prescreened via the outpatient OA clinic at Bispebjerg Frederiksberg Hospital or via telephone by a questionnaire before attending a clinical screening visit. At screening, participants will have a physical examination and blood samples (renal and liver function, vitamin B_{12}, anti-CCP and HbA1c). A target hand will be selected for all outcome assessments. Selection of the target hand will adhere to the following, with advancement to the next step if unable to choose the target hand based on the given criteria:

1. The hand with the most overall finger pain (fingers 2–5).
2. The hand with the most swollen finger (2–5) joints, assessed by physician joint count.
3. The hand with the most tender finger (2–5) joints, assessed by physician joint count.
4. If unable to select a target hand based on the above criteria, a target hand will be randomly assigned.

At baseline, participants will have radiographs of both hands. At baseline and week 16 (primary endpoint), participants will have fasting blood samples drawn for later measurements of inflammation, metabolism and cartilage degradation, as well as questionnaires, physical

examination, grip strength and ultrasound of the target hand. At weeks 4, 8 and 12, participants will have questionnaires and safety recordings. Urine pregnancy screening will be conducted at all clinical visits for female fertile participants.

Outcomes and endpoints

We refer to outcome assessments as the actual measurement or evaluation performed to assess the outcome variable, while the primary endpoint represents the estimand being the specific outcome measurement at a specific timepoint designated as the primary focus of the study's analysis and interpretation. The outcomes follow the core domain set for clinical trials of symptom modification developed by the Outcome Measures in Rheumatology (OMERACT) hand OA working group.[29] Accordingly, the core outcome domains to be collected in the METRO trial will include pain, physical function, patient global assessment, hand stiffness and quality of life. Due to the trial's short-term design, structural damage will not be among our key secondary outcomes.

The primary outcome is the average Visual Analogue Scale (VAS) finger joint pain of the target hand in the past 7 days. The VAS scale is a 100 mm scale, where 0 mm equals no pain and 100 mm equals the worst imaginable pain. The primary endpoint is the between-group difference in least squares means for the change in VAS finger joint pain scores between the metformin and placebo groups at 16 weeks.

Secondary outcomes and endpoints

The secondary outcomes and endpoints include the following: the Australian/Canadian Hand Osteoarthritis Index (AUSCAN) subscales for (1) function and (2) pain[30]; (3) VAS thumb base pain of the target hand (ranging from 0 to 100 mm)[31]; (4) physician tender joint counts (ranging from 0 to 30)[32]; (5) VAS patient global assessment, referring to how much the OA of the target hand affects the participant in general (ranging from 0 to 100 mm)[31]; (6) quality of life assessed by the European Quality of Life – 5 Dimensions (ranging from −0.624 to 1.000[33]; (7) hand strength of the target hand assessed by a hand-held dynamometer (ranging from 0 to 80 kg)[34]; and finally, (8) responder indices defined according to the OMERACT/Osteoarthritis Research Society International responder criteria.[35] Outcome numbers 1, 2, 3, 5 and 6 will be collected at baseline and at 4, 8, 12 and 16 weeks of treatment, whereas outcome numbers 4, 7 and 8 will be collected at baseline and after 16 weeks of treatment.

Other outcome measures eligible for secondary publications

Other measures are change from baseline after 16 weeks of treatment in stiffness measured on AUSCAN; a combined composite measure of AUSCAN subscales (pain, function and stiffness); physical function of both hands assessed by the Health Assessment Questionnaire Disability Index; VAS physician global assessment of disease activity of hand OA in the target hand; physician swollen joint count of the target hand; VAS fatigue; sleep quality assessed by Pittsburgh Sleep Quality Index; inflammation of the target hand measured on ultrasound; use of analgesics measured as the use of paracetamol and NSAIDs and change in inflammatory and metabolic biomarkers, for example, high-sensitivity C-reactive protein, HbA1c, lipids, vitamin K, dephospho-uncarboxylated matrix Gla-protein and mass-spectrometry-based proteomics.

Sample size and power considerations

In OA research, interpreting clinical findings based on Cohen's d effect size helps standardise the assessment of treatment effects, informs clinical and research decisions, and highlights the magnitude of intervention impacts. However, it should be used in conjunction with other statistical measures and clinical judgement to fully understand the implications of the findings.[36] During the design phase of the trial protocol, it was determined that a distribution-based moderate effect size in the primary outcome (VAS finger joint pain) would be the minimum clinically relevant effect for this patient group.[37 38]

Based on a previous study at our institution, we assume that the pooled SD in our population is 20 mm VAS pain and, therefore, we would need 128 patients in total (ie, approximately 64 in each group) to achieve sufficient statistical power (at least 80%) to detect a group difference of 10 mm VAS pain, corresponding to a moderate effect size of 0.5[7]. To take a potential loss-to-follow-up into account, it was decided by the METRO trial steering committee to enrol a total sample size of 150 participants in the intention-to-treat (ITT) population (ie, approximately 75 participants in each group), corresponding to a statistical power of 86% to detect a target difference of 10 mm VAS.[36] As a consequence of potentially not being able to reject the null hypothesis (for the primary endpoint), the steering committee decided that a CI excluding differences greater than 5 units between groups would be interpreted as indicating the absence of a clinically meaningful difference.[39]

Statistical analyses

The main analysis will be based on the ITT population.[40] The ITT principle evaluates the effect of a treatment policy (ie, the planned treatment regimen) rather than the actual treatment administered, making it independent of treatment adherence. Accordingly, participants allocated to a treatment group (metformin or placebo) will be followed up, assessed and analysed as members of that group, regardless of missing data and adherence to the planned course of treatment (including withdrawals and cross-over occurrences). In the METRO trial, the outcome that establishes the effect of metformin (compared with placebo) and will be the basis for concluding that the study meets its primary objective is designated the primary endpoint family. In the METRO trial, there is a single prespecified primary endpoint (difference in VAS finger joint pain scores between the

metformin and placebo groups at the 16-week time point) and there are no multiple-endpoint-related multiplicity issues in the determination that the study achieves its objective.[41] All 95% CIs and p values will be two-sided. We will not apply explicit adjustments for multiplicity. Instead, we will analyse the key secondary outcomes in a prioritised order.[41 42] The analysis of the key secondary outcomes will be interpreted sequentially until one analysis fails to show a statistically significant difference or until all analyses have been completed at a significance level of 0.05 ($p<0.05$).

For continuous outcome measures, our main analysis will estimate between-group differences in the continuous outcomes after 16 weeks for both primary and key secondary outcomes. Repeated measurements at baseline (t=0), 4, 8, 12 and 16 weeks will be used in a linear mixed-effects model, with randomised treatment, stratification groups and baseline value as covariates. Of particular interest is the treatment group, time point and their interaction (group×time) which will be included as fixed-effect factors, and participant identification as a random-effect parameter. All between-group differences based on the least square means with 95% CIs will be adjusted for baseline levels to reduce random variation. Missing data will be handled indirectly and statistically handled using the repeated-measures linear mixed models, that is, analysing repeated measurements using mixed models is valid under the assumption that data are missing at random.[43] Categorical endpoints assessed at week 16, such as the number of treatment responders, will be analysed using logistic regression with randomised treatment and stratification groups as factors. The OR with 95% CI will be derived from the logistic regression coefficients, representing the effect of metformin relative to placebo, adjusted for the covariates included in the model. For categorical efficacy endpoints, missing data will be handled conservatively using non-responder imputation. The statistician will remain blinded to group allocation (metformin vs placebo) throughout the analysis phases. Analyses will be done using SAS (V.4) and R (V.3.3.3, lme4 and mitml package; R Project for Statistical Computing).

Prespecified subgroup analyses (search for important contextual factors)

We have identified a range of baseline (pre-exposure) variables to be explored as potential effect modifiers and used them to create subgroups[44]: first, we will use the factors used for the stratified randomisation, sex (male vs female) and CMC-1 pain (yes vs no), and second, we will use erosive hand OA (yes vs no; estimated from baseline X-ray), metabolic syndrome (yes vs no), obesity (BMI≥30 kg/m^2: yes vs no) and old age (≥65 years of age; yes vs no).

The analyses will focus on the primary endpoint assessed at week 16 only. The ITT population, consisting of all randomised participants, will be used for the analyses. Missing data at week 16 will be conservatively replaced with the baseline observation (ie, non-responder imputation). The statistical approach for this evaluation of potential effect modifiers is a test for statistical interaction to evaluate whether the treatment effect varies across levels of the effect modifier (say X)[44]: Y=Group + X + Group×X, where the difference between two (net benefit) estimates can be derived from least squares means and SEs.[45] For presenting the results of subgroup analyses graphically, forest plots are useful. These plots will include a bold vertical line at the overall treatment effect rather than at the null (ie, 'no effect') to guide correct interpretation regarding heterogeneity of treatment effects across subgroups.[44]

Data integrity and management

Data management will adhere to the standard requirements for Good Clinical Practice (GCP)-compliant data management in clinical trials. The sponsor will organise GCP monitoring together with the GCP unit in Copenhagen. The frequency of the audits will depend on the pace of recruitment of trial participants. The study will use electronic case report forms (eCRF) using MS SQL database technology. The eCRF (database) will be stored physically on a server hosted by the Capital Region of Denmark.

The eCRF is linked to an in-house custom-built electronic data capture system used for questionnaire answers via touch screens in the OA outpatient clinic where the clinical visits will be performed. The eCRF is also linked to the online web-based research data capture application (REDCap) that is stored physically on a dedicated server hosted by the Capital Region of Denmark. REDCap will be used for the online questionnaires at the 12-week time point.

Patient and public involvement

Two patient research partners (PRPs) with hand OA were involved in the designing process of this study, which follows the European Alliance of Associations for Rheumatology recommendations.[46] The PRPs' work is voluntary. They were identified at the Parker Institute outpatient clinic and invited to participate. The PRPs' will prospectively be invited to discuss the results and contribute to the core publication.

ETHICS AND DISSEMINATION

Approval has been obtained from the European Medicines Agency (EMA), study ID EudraCT: 2023-509181-38-00, which includes approval from the local health research ethics committee, including for the full protocol, the informed consent form, written patient information, any anticipated advertising materials and relevant supporting information. Written informed consent for participation in the trial is obtained from all participants and is given based on the written and oral information (the consent form, in Danish, is provided in the online supplemental material).

Irrespective of the trial's outcome, within 1 year from the trial's end, the sponsor will submit a summary of the results to EMA, including a summary that is understandable to laypersons. The project's findings will furthermore be published in international peer-reviewed journals and presented in relevant media and at international scientific conferences.

DISCUSSION

Despite the high prevalence, hand OA has gained surprisingly little attention in clinical research agendas globally, and there is an unmet need for effective and tolerable pharmacological therapies for this patient group. Due to the well-known and mild safety profile, metformin could be an important therapeutic approach to manage the symptoms of patients with hand OA. The aim of this randomised controlled trial is to investigate if metformin 2000 mg/day over 16 weeks of treatment will reduce hand pain in participants with painful hand OA.

Little is known about the aetiology of OA, reflecting the relatively few effective pharmacological therapies. At least in knee OA, consistent evidence from preclinical and clinical studies suggests that metformin could be used in both the protection and treatment of the disease.[21] As knee and hand OA share a lot of similarities, such as risk factors, symptoms and radiographic features, metformin could likewise be beneficial in people with hand OA. Studying the effect in people with hand OA may allow for evaluation aside from the potential benefit of reduced mechanical stress by weight loss.

Although metformin has been used for the treatment of type 2 diabetes for more than 60 years, its mechanism of action remains to be completely elucidated. Research over the past years has suggested a switch from the liver to the gut as the primary site of glucoregulatory action mediated via AMPK-dependent and independent pathways.[47]

Within OA, weight management is one of the key recommendations. Metformin is known to cause a modest weight loss, which recently has been suggested to be mediated via an increase in the appetite-suppressing metabolite *N*-lactoyl phenylalanine (Lac-Phe).[48 49] Whether Lac-Phe mediates the potential beneficial effects of metformin in OA is still unknown.

Both ageing and OA are associated with a decreased activity of the AMPK enzyme.[50] Several preclinical studies suggest that metformin exerts its beneficial effects in OA via activation of the AMPK enzyme.[21] Also, other pharmacological drugs activate the AMPK enzyme, including salicylate, quercetin (a plant flavanol), canagliflozin (a sodium–glucose co-transporter 2 inhibitor), GLP-1 receptor agonism and methotrexate.[51] Of importance, all these drugs have shown possible beneficial effects in the prevention and/or treatment of OA in either preclinical or clinical studies, thus suggesting the AMPK enzyme as an important target in the prevention and/or management of OA.[6 52–55]

The main strength of this study is its design as a multicentre, randomised double-blind, placebo-controlled clinical trial that is adequately powered. A key limitation is the impact on generalisability of the rigorous exclusion criteria.

In summary, hand OA is a disease mainly affecting elderly women and with limited treatment options due to side effects. Increasing evidence suggests that metformin may have beneficial effects in the prevention and/or treatment of knee OA acting via the AMPK pathway. As knee and hand OA share a lot of similarities, the potential of metformin for treating hand OA needs to be clarified. This study will provide high-quality evidence for the possible effect of metformin in painful hand OA, which will benefit both the patients and society.

Author affiliations
[1]The Parker Institute, Bispebjerg and Frederiksberg Hospital, University of Copenhagen, Frederiksberg, Copenhagen, Denmark
[2]Medical Diagnostic Center, Regional Hospital Silkeborg, Silkeborg, Denmark
[3]Department of Biomedicine, Aarhus University, Aarhus, Denmark
[4]Center for Clinical Metabolic Research, Gentofte Hospital, University of Copenhagen, Hellerup, Denmark
[5]Novo Nordisk A/S, Søborg, Denmark
[6]Department of Clinical Medicine, Faculty of Health and Medical Sciences, University of Copenhagen, Copenhagen, Denmark
[7]Department of Radiology, Copenhagen University Hospital, Bispebjerg and Frederiksberg, Bispebjerg, Copenhagen, Denmark
[8]Rheumatology Department, Royal North Shore Hospital, St Leonards, Sydney, New South Wales, Australia
[9]Sydney Musculoskeletal Health, Kolling Institute of Medical Research, The University of Sydney, Sydney, New South Wales, Australia
[10]Research Unit of Rheumatology, Department of Clinical Research, University of Southern Denmark, Odense University Hospital, Odense, Denmark

X Kasper Staberg Madsen @KasperStaberg, Filip K Knop @Filip_Knop and David J Hunter @ProfDavidHunter

Contributors Conception and design: KSM, MH, AD, KE, FKK, MB, DJH, RC, HB. Study execution and data acquisition: KSM, MH, ASP, KE, MB, RO, TK, HB. Drafting of the manuscript: KSM, MH, RC, HB. Critical revision of the manuscript for important and intellectual content and approval of the final manuscript: KSM, MH, AD, ASP, KE, FKK, MB, RO, TK, DJH, RC, HB. Obtaining of funding: KSM, MH, HB. Guarantor: HB.

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Patient and public involvement Patients and/or the public were involved in the design, conduct, reporting or dissemination plans of this research. Refer to the Methods section for further details.

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Provenance and peer review Not commissioned; externally peer reviewed.

ORCID iDs
Kasper Staberg Madsen http://orcid.org/0009-0009-8311-0101
Filip K Knop http://orcid.org/0000-0002-2495-5034
David J Hunter http://orcid.org/0000-0003-3197-752X

REFERENCES

1 Zhang Y, Niu J, Kelly-Hayes M, *et al*. Prevalence of symptomatic hand osteoarthritis and its impact on functional status among the elderly: The Framingham Study. *Am J Epidemiol* 2002;156:1021–7.
2 Bukhave EB, Huniche L. Activity problems in everyday life--patients' perspectives of hand osteoarthritis: "try imagining what it would be like having no hands". *Disabil Rehabil* 2014;36:1636–43.
3 Bromann Bukhave E, la Cour K, Huniche L. The meaning of activity and participation in everyday life when living with hand osteoarthritis. *Scand J Occup Ther* 2014;21:24–30.
4 van Schoor NM, Zambon S, Castell MV, *et al*. Impact of clinical osteoarthritis of the hip, knee and hand on self-rated health in six European countries: the European Project on OSteoArthritis. *Qual Life Res* 2016;25:1423–32.
5 Kroon FPB, Kortekaas MC, Boonen A, *et al*. Results of a 6-week treatment with 10 mg prednisolone in patients with hand osteoarthritis (HOPE): a double-blind, randomised, placebo-controlled trial. *Lancet* 2019;394::1993–2001:.
6 Wang Y, Jones G, Keen HI, *et al*. Methotrexate to treat hand osteoarthritis with synovitis (METHODS): an Australian, multisite, parallel-group, double-blind, randomised, placebo-controlled trial. *Lancet* 2023;402:1764–72.
7 Døssing A, Henriksen M, Ellegaard K, *et al*. Colchicine twice a day for hand osteoarthritis (COLOR): a double-blind, randomised, placebo-controlled trial. 2023;5::e254–62:.
8 De Roover A, Escribano-Núñez A, Monteagudo S, *et al*. Fundamentals of osteoarthritis: Inflammatory mediators in osteoarthritis. *Osteoarthr Cartil* 2023;31:1303–11.
9 Gløersen M, Steen Pettersen P, Neogi T, *et al*. Associations of Body Mass Index With Pain and the Mediating Role of Inflammatory Biomarkers in People With Hand Osteoarthritis. *Arthritis Rheumatol* 2022;74:810–7.
10 Marshall M, Watt FE, Vincent TL, *et al*. Hand osteoarthritis: clinical phenotypes, molecular mechanisms and disease management. *Nat Rev Rheumatol* 2018;14:641–56.
11 Kloppenburg M, Kroon FP, Blanco FJ, *et al*. 2018 update of the EULAR recommendations for the management of hand osteoarthritis. *Ann Rheum Dis* 2019;78:16–24.
12 Harirforoosh S, Asghar W, Jamali F. Adverse effects of nonsteroidal antiinflammatory drugs: an update of gastrointestinal, cardiovascular and renal complications. *J Pharm Pharm Sci* 2013;16:821–47.
13 ElSayed NA, Aleppo G, Aroda VR, *et al*. 9. Pharmacologic Approaches to Glycemic Treatment: Standards of Care in Diabetes-2023. *Diabetes Care* 2023;46:S140–57.
14 Lai FTT, Yip BHK, Hunter DJ, *et al*. Metformin use and the risk of total knee replacement among diabetic patients: a propensity-score-matched retrospective cohort study. *Sci Rep* 2022;12:11571.
15 Lu C-H, Chung C-H, Lee C-H, *et al*. Combination COX-2 inhibitor and metformin attenuate rate of joint replacement in osteoarthritis with diabetes: A nationwide, retrospective, matched-cohort study in Taiwan. *PLoS ONE* 2018;13:e0191242.
16 Wang Y, Hussain SM, Wluka AE, *et al*. Association between metformin use and disease progression in obese people with knee osteoarthritis: data from the Osteoarthritis Initiative-a prospective cohort study. *Arthritis Res Ther* 2019;21:127.
17 Baker MC, Sheth K, Liu Y, *et al*. Development of Osteoarthritis in Adults With Type 2 Diabetes Treated With Metformin vs a Sulfonylurea. *JAMA Netw Open* 2023;6:e233646.
18 M. Mohammed M, J. Al-Shamma K, A. Jassim N. Evaluation of the Clinical use of Metformin or Pioglitazone in Combination with Meloxicam in Patients with Knee Osteoarthritis; using Knee Injury and Osteoarthritis outcome Score. *IJPS* 2014;23:13–23.
19 Alimoradi N, Tahami M, Firouzabadi N, *et al*. Metformin attenuates symptoms of osteoarthritis: role of genetic diversity of Bcl2 and CXCL16 in OA. *Arthritis Res Ther* 2023;25:35.
20 Aiad AAE, El-Haggar SM, El-Barbary AM, *et al*. Metformin as adjuvant therapy in obese knee osteoarthritis patients. *Inflammopharmacology* 2024;32:2349–59.
21 Lim YZ, Wang Y, Estee M, *et al*. Metformin as a potential disease-modifying drug in osteoarthritis: a systematic review of pre-clinical and human studies. *Osteoarthr Cartil* 2022;30:1434–42.
22 Bonnet F, Scheen A. Understanding and overcoming metformin gastrointestinal intolerance. *Diabetes Obes Metab* 2017;19:473–81.
23 de Jager J, Kooy A, Lehert P, *et al*. Long term treatment with metformin in patients with type 2 diabetes and risk of vitamin B-12 deficiency: randomised placebo controlled trial. *BMJ* 2010;340:c2181.
24 Li J, Zhang B, Liu W-X, *et al*. Metformin limits osteoarthritis development and progression through activation of AMPK signalling. *Ann Rheum Dis* 2020;79:635–45.
25 Feng X, Pan J, Li J, *et al*. Metformin attenuates cartilage degeneration in an experimental osteoarthritis model by regulating AMPK/mTOR. *Aging (Milano)* 2020;12:1087–103.
26 Wang C, Yang Y, Zhang Y, *et al*. Protective effects of metformin against osteoarthritis through upregulation of SIRT3-mediated PINK1/Parkin-dependent mitophagy in primary chondrocytes. *Biosci Trends* 2019;12:605–12.
27 Moher D, Hopewell S, Schulz KF, *et al*. CONSORT 2010 explanation and elaboration: updated guidelines for reporting parallel group randomised trials. *BMJ* 2010;340:c869.
28 Altman R, Alarcón G, Appelrouth D, *et al*. The American College of Rheumatology criteria for the classification and reporting of osteoarthritis of the hand. *Arthritis Rheum* 1990;33:1601–10.
29 Kloppenburg M, Bøyesen P, Visser AW, *et al*. Report from the OMERACT Hand Osteoarthritis Working Group: Set of Core Domains and Preliminary Set of Instruments for Use in Clinical Trials and Observational Studies. *J Rheumatol* 2015;42:2190–7.
30 Bellamy N, Campbell J, Haraoui B, *et al*. Clinimetric properties of the AUSCAN Osteoarthritis Hand Index: an evaluation of reliability, validity and responsiveness. *Osteoarthr Cartil* 2002;10:863–9.
31 Revill SI, Robinson JO, Rosen M, *et al*. The reliability of a linear analogue for evaluating pain. *Anaesthesia* 1976;31:1191–8.
32 Van Riel P, *et al*. *EULAR handbook of clinical assessments in rheumatoid arthritis: on behalf of the EULAR standing committee for international clinical studies including therapeutic trials-ESCISIT*. Chairman, Piet LCM Van Riel Van Zuiden, 2000.
33 Wittrup-jensen K, Lauridsen JT, Gudex C, *et al*. Estimating danish eq-5d tariffs using the time-trade-off (tto) and visual analogue scale (vas) methods. 2002.
34 Rijk JM, Roos PR, Deckx L, *et al*. Prognostic value of handgrip strength in people aged 60 years and older: A systematic review and meta-analysis. *Geriatr Gerontol Int* 2016;16:5–20.
35 Pham T, van der Heijde D, Altman RD, *et al*. OMERACT-OARSI Initiative: Osteoarthritis Research Society International set of responder criteria for osteoarthritis clinical trials revisited. *Osteoarthr Cartil* 2004;12:389–99.
36 Cook JA, Julious SA, Sones W, *et al*. DELTA^2 guidance on choosing the target difference and undertaking and reporting the sample size calculation for a randomised controlled trial. *BMJ* 2018;363:k3750.
37 Bliddal H, Christensen R. The treatment and prevention of knee osteoarthritis: a tool for clinical decision-making. *Expert Opin Pharmacother* 2009;10:1793–804.
38 Devji T, Carrasco-Labra A, Qasim A, *et al*. Evaluating the credibility of anchor based estimates of minimal important differences for patient reported outcomes: instrument development and reliability study. *BMJ* 2020;369:m1714.

39 Christensen R, Ranstam J, Overgaard S, *et al*. Guidelines for a structured manuscript: Statistical methods and reporting in biomedical research journals. *Acta Orthop* 2023;94:243–9.
40 Detry MA, Lewis RJ. The intention-to-treat principle: how to assess the true effect of choosing a medical treatment. *JAMA* 2014;312:85–6.
41 Cao J, Zhang S. Multiple comparison procedures. *JAMA* 2014;312:543–4.
42 Yadav K, Lewis RJ. Gatekeeping Strategies for Avoiding False-Positive Results in Clinical Trials With Many Comparisons. *JAMA* 2017;318:1385–6.
43 Detry MA, Ma Y. Analyzing Repeated Measurements Using Mixed Models. *JAMA* 2016;315:407–8.
44 Christensen R, Bours MJL, Nielsen SM. Effect Modifiers and Statistical Tests for Interaction in Randomized Trials. *J Clin Epidemiol* 2021;134::174–7:.
45 Altman DG, Bland JM. Interaction revisited: the difference between two estimates. *BMJ* 2003;326:219.
46 de Wit MPT, Berlo SE, Aanerud GJ, *et al*. European League Against Rheumatism recommendations for the inclusion of patient representatives in scientific projects. *Ann Rheum Dis* 2011;70:722–6.
47 Foretz M, Guigas B, Viollet B. Metformin: update on mechanisms of action and repurposing potential. *Nat Rev Endocrinol* 2023;19:460–76.
48 Xiao S, Li VL, Lyu X, *et al*. Lac-Phe mediates the effects of metformin on food intake and body weight. *Nat Metab* 2024;6:659–69.
49 Scott B, Day EA, O'Brien KL, *et al*. Metformin and feeding increase levels of the appetite-suppressing metabolite Lac-Phe in humans. *Nat Metab* 2024;6:651–8.
50 Loeser RF, Collins JA, Diekman BO. Ageing and the pathogenesis of osteoarthritis. *Nat Rev Rheumatol* 2016;12:412–20.
51 Steinberg GR, Carling D. AMP-activated protein kinase: the current landscape for drug development. *Nat Rev Drug Discov* 2019;18:527–51.
52 Døssing A, Nielsen SM, Kroon FP, *et al*. Comparative effectiveness of pharmacological interventions for hand osteoarthritis: a systematic review and network meta-analysis of randomised trials. *RMD Open* 2023;9:e003030.
53 S. Reza Jafarzadeh KM, Peloquin CE, Felson D. SGLT2 inhibitors vs. In: *GLP1 AGONISTS AS TREATMENTS FOR OSTEOARTHRITIS*. OARSI World Congress on Osteoarthritis Vienna, 2024.
54 Yamaura K, Nelson AL, Nishimura H, *et al*. Therapeutic potential of senolytic agent quercetin in osteoarthritis: A systematic review and meta-analysis of preclinical studies. *Ageing Res Rev* 2023;90:101989.
55 Bliddal H, Bays H, Czernichow S, *et al*. Semaglutide 2.4 mg efficacy and safety in people with obesity and knee osteoarthritis: Results: from the STEP 9 randomised clinical trial. *Osteoarthr Cartil* 2024;32:745–6.