





# BMJ Open Protocol for the RETHINK study: a randomised, double-blind, parallel-group, non-inferiority clinical trial comparing acetaminophen and NSAIDs for treatment of chronic pain in elderly patients with osteoarthritis of the hip and knee

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## ABSTRACT

**Introduction** In patients with chronic pain, oral analgesics are essential treatment options to manage pain appropriately, improve activities of daily living abilities and achieve a higher quality of life (QOL). It is desirable to select analgesics for elderly patients based on comparative data on analgesic effect and risk of adverse events; however, there are few comparative studies so far. The purpose of this study is to determine whether the efficacy and safety of acetaminophen are non-inferior to non-steroidal anti-inflammatory drugs (NSAIDs) in the treatment of chronic pain associated with osteoarthritis of the hip and knee in elderly patients.

**Methods and analysis** This study is a multicentre, randomised controlled, double-blind, parallel-group study to compare the analgesic effect and adverse events between acetaminophen or NSAIDs (loxoprofen or celecoxib). A total of 400 elderly patients with osteoarthritis of the hip and knee will be recruited from five institutions in Japan. Patients of 65 years or older with osteoarthritis-related pain will be registered and randomly assigned to acetaminophen, loxoprofen or celecoxib with 2:1:1 allocation. The primary endpoint is change in the Brief Pain Inventory (BPI) item 3 (worst pain) score from baseline to week 8. The secondary endpoints are BPI item 3 score change from baseline to week 4, health-related QOL measured by Short Form-8 Health Survey, and occurrence of adverse events including gastrointestinal disorders and abnormal liver function. Data will be analysed in accordance with a predefined statistical analysis plan.

**Ethics and dissemination** This study protocol was approved by the Kyushu University Hospital Certified Institutional Review Board for Clinical Trials on 28 January 2021 (KD2020004) and the chief executive of each participating hospital. The results of the study will be

## STRENGTHS AND LIMITATIONS OF THIS STUDY

- ⇒ This study will prospectively investigate the efficacy and safety of analgesics for treatment of chronic pain in elderly patients with osteoarthritis of the hip and knee.
- ⇒ The study medications (acetaminophen, loxoprofen and celecoxib) are double-blinded and randomly assigned.
- ⇒ Data on pain intensity, gastrointestinal disorders and quality of life are collected by participants on an electronic device using electronic patient-reported outcomes.
- ⇒ Gastrointestinal disorders are assessed with the Gastrointestinal Symptom Rating Scale; endoscopy is not mandatory to confirm the diagnosis of gastrointestinal disorder.
- ⇒ Patients with severe pain who cannot accept a 3-day wash-out period for any analgesics before starting the study medication will not be eligible for this study.

submitted to international peer-reviewed journals, and the main findings will be presented at international scientific conferences.

**Trial registration number** jRCTs071200112.

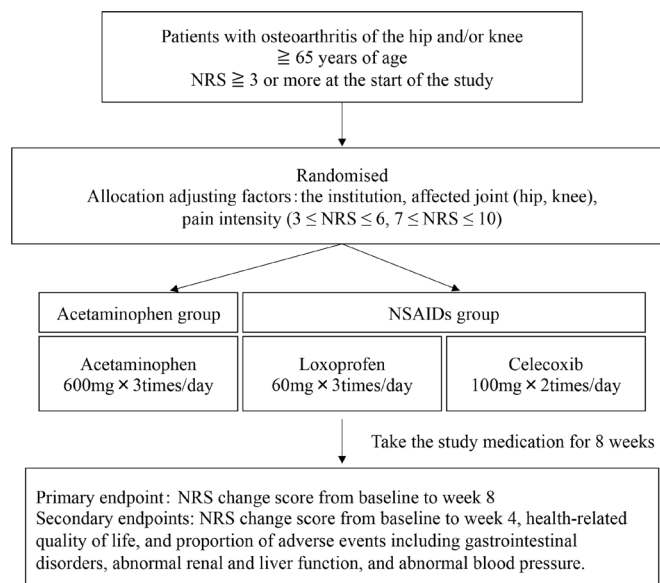
## INTRODUCTION

Pain is defined as ‘an unpleasant sensory and emotional experience associated with, or resembling that associated with, actual or potential tissue damage,’ and prolonged pain causes immobilisation of joints and atrophy

of muscles, resulting in decreased activities of daily living (ADL) and quality of life (QOL);<sup>1</sup> therefore, appropriate medical intervention to treat and manage pain is necessary. The therapeutic goal in patients with chronic pain is to manage their pain appropriately and to improve their ADL abilities and QOL, and oral analgesics are one of the essential treatment options. Frequently used oral non-opioid analgesics are acetaminophen; non-selective non-steroidal anti-inflammatory drugs (NSAIDs), such as loxoprofen, ibuprofen and diclofenac; and selective cyclooxygenase-2 (COX-2) inhibitors, such as celecoxib.<sup>2</sup> Several clinical trials have been conducted to compare these drugs; however, there are differences in dosage of the drug and eligibility criteria in each trial, and which drug is most preferable remains controversial. Gastrointestinal complications and cardiovascular disorders are known to be major adverse events of these analgesics, and the risk of gastrointestinal complications is reported to be higher for NSAIDs, especially in elderly patients. The share of oral analgesics varies from country to country because there are no clear international standards for selecting the appropriate drug. For example, acetaminophen is prescribed less frequently than NSAIDs such as loxoprofen and celecoxib in Japan,<sup>2</sup> while acetaminophen is frequently prescribed, particularly to elderly patients in Europe.<sup>3</sup> One possible reason for this discrepancy is that the regular daily dosage of acetaminophen varies from country to country. A survey of prescriptions has revealed that the daily dosage of acetaminophen in Japan is lower than that in Europe and the USA.<sup>2,4</sup> Until 2011 in Japan, the daily dosage upper limit had been set at a low dose of 1500 mg. The upper limit has now been raised to 4000 mg; however, the daily dosage in clinical settings has not increased sufficiently.<sup>2</sup> Acetaminophen is routinely used at low dosage, and its efficacy is not properly evaluated in clinical practice in Japan. As a result, NSAIDs are used more frequently in Japan than acetaminophen when compared with Western countries.

Osteoarthritis is a major cause of chronic musculoskeletal pain and is a leading cause of physical disability in the elderly. The hip and knee joints are the most common sites of osteoarthritis, and its prevalence increases with age, reaching about 17% at age 65.<sup>5</sup> The main treatment methods include medications such as analgesics, exercise therapy, orthotic therapy and surgery.<sup>6</sup> Oral analgesics is one of the essential treatment options for osteoarthritis; however, in elderly patients, adverse events are more likely to be a problem due to age-related pharmacokinetic changes and polypharmacy. From this viewpoint, it is desirable to select analgesics for elderly patients with osteoarthritis based on prospective comparative data that assesses efficacy and safety. However, few such high-quality comparative studies have been conducted.

Given this gap in the literature, we planned a multicentre, randomised, double-blind, parallel-group study to compare acetaminophen with NSAIDs. The purpose of this study is to determine whether the efficacy and safety of acetaminophen is non-inferior to NSAIDs in the



**Figure 1** The flow chart of the RETHINK study. NRS, Numerical Rating Scale; NSAID, non-steroidal anti-inflammatory drug.

treatment for chronic pain associated with osteoarthritis of the hip and knee in elderly patients.

## METHODS AND ANALYSIS

### Trial design

The study is a multicentre, randomised, double-blind, parallel-group study to examine the efficacy and safety of acetaminophen and NSAIDs, which are standard oral analgesics for osteoarthritis-related pain in elderly patients, and to verify the non-inferiority of acetaminophen to NSAIDs (loxoprofen, celecoxib) in analgesic effect (figure 1). Also, this study will examine the toxicity of acetaminophen and NSAIDs by comparing the incidence rates of gastrointestinal disorders, abnormal renal and liver function, and abnormal blood pressure.

### Study setting

This study will be conducted across five institutions in Japan, which are Kyushu University Hospital, Fukuoka Orthopaedic Hospital, Aso Iizuka Hospital, Hamanomachi Hospital and Kyushu Rosai Hospital. In all of these institutions, patients with osteoarthritis of the hip and knee are being treated as part of the daily practice. The attending orthopaedic surgeons recruit participants by offering the potentially eligible patients to participate in the study. The study protocol was approved by the Kyushu University Hospital Certified Institutional Review Board for Clinical Trials (CRB: Certification No. CRB718005) prior to patient enrolment.

### Inclusion criteria

The inclusion criteria for this study are (1): age 65 years or older at the time of providing consent; (2) diagnosis of osteoarthritis of the hip and/or knee joint; (3) osteoarthritis-related pain intensity score  $\geq 3$  on the

Numerical Rating Scale (NRS); (4) aspartate aminotransferase (AST) level  $\leq 60$  U/L, alanine transaminase (ALT) level  $\leq 84$  U/L in men and 46 U/L in women, gamma-glutamyl transpeptidase ( $\gamma$ -GTP) level  $\leq 128$  U/L in men and 64 U/L in women, total bilirubin (T-Bil)  $\leq 3.0$  mg/dL and estimated glomerular filtration rate (eGFR)  $\leq 30$  mL/min/1.73 m<sup>2</sup>; (5) ability to visit hospital for at least two or more months continuously; (6) ability to take the study medication for 8 weeks; (7) 3-day wash-out period for concomitant drugs that may affect pain assessment before starting the study medication and (8) voluntary written consent to participate in the study.

### Exclusion criteria

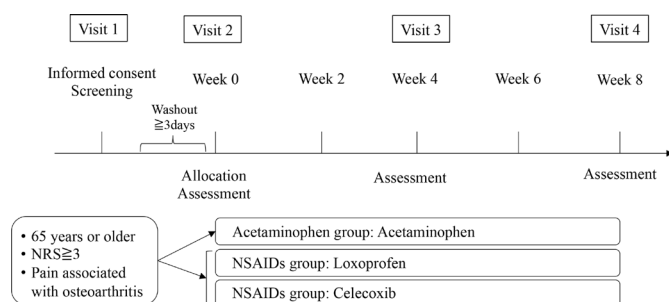
The exclusion criteria for this study are: (1) scheduled to undergo surgery during study period; (2) contraindication or hypersensitivity to the study medications; (3) coexisting pain requiring medication caused by a condition other than osteoarthritis; (4) inflammatory bowel disease such as ulcerative colitis; (5) acute or chronic kidney disease; (6) serious coagulopathy; (7) diagnosis within 3 months of or undergoing treatment for ulcer(s) of the upper gastrointestinal tract or reflux esophagitis; (8) poorly controlled hypertension; (9) heavy use of alcohol; (10) clinically problematic mental illness or dementia and (11) deemed ineligible at the discretion of the investigator(s).

### Interventions

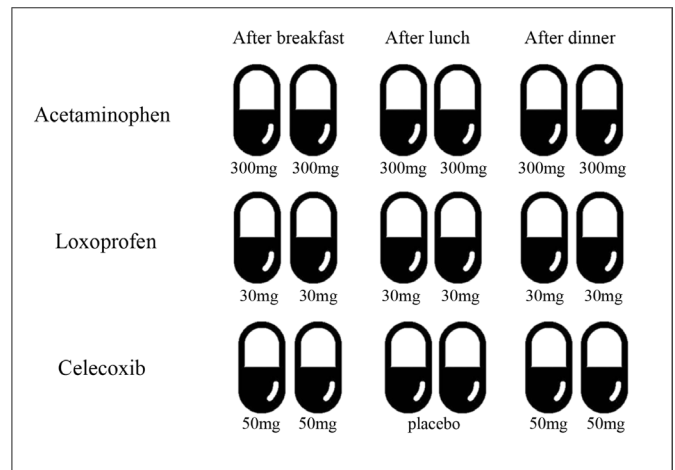
Patients will undergo at least 3-day drug wash-out period if necessary and will take the assigned study medication (acetaminophen: 600 mg $\times$ 3 times/day or loxoprofen: 60 mg $\times$ 3 times/day or celecoxib: 100 mg $\times$ 2 times/day and placebo: 1 time/day) for 8 weeks (figure 2). All the study medications will have the same appearance, and the study will be conducted under double blinded conditions such that neither the physician nor the patient will know which study medication is assigned. The study medication will be terminated after 8 weeks, and patients will return to their routine treatments under supervision of the physician.

### Study medication blinding

The study medications were prepared by filling each drug (300 mg of acetaminophen, 30 mg of loxoprofen, 50 mg of celecoxib) into empty capsules, which were made to



**Figure 2** The study treatment schedule of the RETHINK study. NRS, Numerical Rating Scale; NSAID, non-steroidal anti-inflammatory drug.



**Figure 3** The study treatment used in the RETHINK study.

be indistinguishable from each other by colour and size (figure 3). As only celecoxib is taken twice daily, a placebo capsule filled with 300 mg of lactose was prepared for patients assigned to the celecoxib group to take after lunch. The study medications were provided by Ayumi Pharmaceuticaln.


### Prohibited concomitant medications/treatments

The following drugs/therapies are prohibited from the start of drug wash-out to the termination of the study medication: (1) additional acetaminophen and/or NSAIDs to the study medication, including the intravenous administration; (2) analgesic adjuvants such as pregabalin, mirogabalin, duloxetine and neurotrophin; (3) opioids including tramadol and buprenorphine; (4) steroid (topical use is allowed); (5) over-the-counter combination cold remedy (only the day before and on the day of answering the questionnaire); (6) surgical treatment; (7) intra-articular and local administration of hyaluronic acid, steroids, local anaesthetics; (8) acupuncture, moxibustion, chiropractic treatment; (9) any other drugs and therapies prohibited for concomitant use and (10) prophylactic use of proton-pump inhibitors (PPIs), H<sub>2</sub> receptor antagonists and gastric mucosal protective agents (the therapeutic use is allowed after the start of study treatment).

### Participant timeline

Candidates who consent to participate will be checked for eligibility based on the inclusion/exclusion criteria, and enrolment will be completed after verification of participant eligibility (Visit 1) (table 1). Participants will begin the study within 30 days from the consent, undergo the 3-day drug wash-out prior to beginning the study treatment if necessary, and take the study medication for 8 weeks starting from week 0 (visit 2). Participants will visit the clinic at weeks 0, 4 (0, 4 (visit 3) and 8 (visit 4) for a medical interview and blood and urine examinations. Furthermore, they will use the electronic device to answer a questionnaire on Brief Pain Inventory (BPI),<sup>7</sup> Gastrointestinal Symptom Rating Scale (GSRs)<sup>8</sup>

**Table 1** The assessment schedule

	Visit 1 Screening	Visit 2 Week 0	Week 2	Visit 3 Week 4	Visit 4 Week 8
Informed consent	X				
Inclusion/exclusion criteria	X				
Wash-out instructions	X				
Demographics	X				
Randomisation		X			
Study interventions (acetaminophen/loxoprofen/cerecoxib)					
Study medication history				X	X
Concomitant medication	X	X		X	X
Physical examination	X	X		X	X
Medical interview	X	X		X	X
Vital signs	X	X		X	X
Blood/urine examination	X	X		X	X
PRO(BPI)	X	X		X	X
PRO(GSRS)		X	X	X	X
PRO(SF-8)		X		X	X
Adverse events				X	X

BPI, Brief Pain Inventory; GSRS, Gastrointestinal Symptom Rating Scale; SF-8, Short Form-8.

and SF-8 scores<sup>9</sup> on their own at the time of each visit. An assistant, who is blind to the assigned medication, will help with input procedure if needed. The scores and the data collection date will be recorded on the electronic device. As gastrointestinal haemorrhages can be caused by the study medication within a short period of time, GSRS data will be collected at week two in addition to weeks 4 and 8.

The investigator will discontinue the study treatment if any of the following events occur:

(1) an adverse event that makes it impossible to continue the study; (2) use of prohibited concomitant medications/treatments; (3) inability to perform necessary examinations and observations identified after participation in the study; (4) deterioration of NRS value by four or more from baseline during study treatment; (5) opening of the blinding process and (6) refusal to continue the study by the study participant for any reason.

### Primary endpoint

The primary endpoint is BPI item 3 (worst pain) score change from baseline to week 8. BPI-Short Form will be used to assess the pain intensity by the 11-point NRS from 0 (no pain) to 10 (worst possible pain) with a recall period of past 24 hours. It has been widely used, self-administered questionnaire, and validated in chronic pain condition of osteoarthritis and also linguistically validated in Japanese language.<sup>10 11</sup> The score change is calculated based on electronic patient-reported outcomes (ePROs) recorded by participants using an electronic device.

### Secondary endpoints

The secondary endpoints include (1) BPI item 3 score change from baseline to week 4; (2) the incidence of gastrointestinal disorders evaluated by the changes in the mean GSRS score from baseline to weeks 2, 4 and 8; (3) the proportion of patients with elevated laboratory values in AST, ALT,  $\gamma$ -GTP, ALP and T-Bil; (4) the changes in estimated eGFR from baseline to weeks 4 and 8; (5) the changes in Short Form-8 scores and (6) the changes in blood pressure.

Data of the primary endpoint and secondary endpoints (1), (2) and (5) will be recorded by participants using ePROs on an electronic device.

### Sample size calculation

The primary endpoint of this study is change in BPI item three score from baseline to week 8. Previous studies on pain intensity changes evaluated through a Visual Analogue Scale (VAS) reported the following mean VAS scores: NSAIDs (ibuprofen), -27.6 (SD, 19.6) and acetaminophen, -21.2 (SD, 17.2)<sup>12</sup> and NSAIDs (celecoxib), -16.7 (SD, 24.9) and acetaminophen, -11.5 (SD, 24.1).<sup>13</sup> The margin was set to 8 to 10 in the previous non-inferiority studies.<sup>14-19</sup> As these VAS scores correlate with BPI item three scores, the values were converted to BPI item three scores by dividing them by 10.<sup>20</sup> With an BPI item three score change of -2 during the study period and minimal clinically important difference of -1 based on previous studies,<sup>21 22</sup> we considered that a non-inferiority margin of 0.6 was acceptable.

Based on the above, the change in pain intensity in both groups was set to  $-2$ , the SD to  $2$ , and non-inferiority margin to  $-0.6$ , and with a one-sided significance level of  $2.5\%$  and statistical power of  $80\%$ , the calculated sample size was  $176$  patients per group. Taking into consideration a drop-out rate of approximately  $10\%$  in the previous trials,<sup>12 13</sup> we set the target number of cases to  $200$  patients per group resulting in a total of  $400$  patients for this study.

### Allocation

After verifying participant eligibility, they will be randomised through the Electronic Data Capture (EDC) system, Datatrak Enterprise Cloud (Datatrak International, Ohio, USA). Allocation to acetaminophen, loxoprofen or celecoxib will be performed by the minimisation method with a ratio of  $2:1:1$ . The detailed minimisation procedure will not be disclosed to the researchers at the participating institutions. The institution, site (hip joint, knee joint) and pain intensity ( $3 \leq \text{BPI item 3 score} \leq 6$ ,  $7 \leq \text{BPI item 3 score} \leq 10$ ) will serve as allocation adjusting factors. The allocation will be performed in a double-blind manner. After randomisation, the participants, the investigators and all other involved individuals will not know the results of allocation until the data are fixed.

### Masking

After confirming participant eligibility through the EDC system, participants will be randomly allocated to receive a study medication under blinded conditions. Unblinding will be performed after database fixing, following the study's end. Only in certain emergency situations requiring appropriate medical intervention for a serious adverse event or to ensure participant safety, individual participants may be unblinded using the blind code at the discretion of the principal investigator.

### Data collection methods

The individual records, including a copy of informed consent, patient registration forms, medical records and laboratory data, for each patient will be maintained as source materials at each site. Data entry to the electronic case report form is performed by investigators using EDC at each site. PRO data are collected electronically from patients through an electronic tablet device, expect GSRS assessment at week 2 will be conducted using a paper questionnaire. The adverse events will be closely monitored by site investigators. The severe adverse events will be reported by site investigators to the institutional administrator and the principal investigator, and then to the Kyushu University Hospital CRB and the sponsor as appropriate. Personal information, such as names, addresses and medical IDs, will not be collected.

### Data management, monitoring and auditing

The data centre is located at the Fukuoka Data Centre of Clinical Trial. Enrolment, randomisation, clinical data entry, PRO assessment data management and central monitoring will be performed using the EDC and ePRO system, Datatrak Enterprise Cloud (Datatrak

International). The data manager will prepare the central data monitoring report annually after the start of the study, which will be submitted to the principal investigator who will confirm the accuracy of this report and analyse and evaluate the appropriateness and problems associated with the study. An audit will be performed at the study's end. The collected raw data and fixed dataset for statistical analysis will be archived by the principal investigator for up to 10 years from the study's end.

### Statistical methods of analysis

Full analysis set (FAS) is defined as all patients included in this study, excluding the following: (1) patients of non-eligibility; (2) patients who were allocated but did not receive the study medication and (3) patients without any baseline or assessment data. Per-protocol set (PPS) is defined as all patients excluding those with serious breaches of the study protocol and those with a medication compliance rate of less than  $75\%$ . Safety analysis set (SAS) is defined as all patients who have received at least one dose of the study medication. Efficacy analyses are performed based on the FAS, unless otherwise specified. For the primary endpoint, PPS analyses will also be performed.

A BPI item 3 score change from baseline to week 8 will be calculated in the main analysis. Non-inferiority testing will be conducted through a mixed-effect model with repeated measures (MMRM) using the baseline value, treatment group (acetaminophen group vs NSAIDs group), evaluation time point, interaction between treatment group and evaluation time point, and allocation adjusting factors as covariates. The non-inferiority test will be performed with a non-inferiority margin of  $0.6$  and one-sided significance level of  $0.025$ . In case of missing data, these data will be implicitly complemented by the MMRM model, assuming that the data are missing due to a random missing data mechanism. In subjects who received drugs or therapies prohibited for concomitant use, data collection will be discontinued from the moment they receive such drugs or therapies. Data of subjects who stopped the study medication but did not receive any drugs or therapies prohibited for concomitant use even after discontinuing the study medication may be included in the analysis. No interim analyses are planned.

### Patient and public involvement

The patients and the public were not involved in this research.

### ETHICS AND DISSEMINATION

All patients receive verbal and written information and provide their written informed consent before enrolment. This study is conducted in accordance with the ethical principles stipulated in the 'Declaration of Helsinki' (revised October 2013) and 'Clinical Trials Act' (announced 14 April 2017, enacted 1 April 2018)



established by Japan's Ministry of Health, Labour and Welfare. This study was approved by the Kyushu University Hospital CRB on 28 January 2021 (KD2020004).

The results of the study will be submitted to international peer-reviewed journals, and the main findings will be presented at international scientific conferences. The authors are attributed according to the guidance of the International Committee of Medical Journal Editors.

Any amendments to the protocol will undergo a review by the Kyushu University Hospital CRB. This study protocol was corrected in September 2021 (V.1.3) due to the amendment of investigators.

## DISCUSSION

This study will compare the efficacy and safety of acetaminophen with those of NSAIDs for the treatment of osteoarthritis-related pain in elderly patients in whom chronic pain is highly prevalent and drug safety is of importance because this population is more likely to use several drugs concomitantly. The study medications (acetaminophen, loxoprofen and celecoxib) are double-blinded and randomly assigned in order to avoid bias in subject selection and allocation and to eliminate the influence of the placebo effect in this trial. There are no prospective randomised trials on the use of different analgesics for chronic pain derived from osteoarthritis restricted to the elderly, and it is expected that valuable data will be obtained. Data on pain intensity, gastrointestinal disorders and QOL will be collected by participants using ePROs recorded on an electronic device. We have built an ePRO system specifically for this trial, and it is hoped that the ePRO system will be useful for gathering more accurate and complete data. Gastrointestinal complications are the most worrisome complication of acetaminophen and NSAIDs administration. In this study, prophylactic use of PPIs, H<sub>2</sub> receptor antagonists, and gastric mucosal protective agents is not allowed because prophylactic use is not officially approved in Japan. However, therapeutic administration of these agents is not prohibited. If they were administered therapeutically, they are supposed to be recorded as gastrointestinal complications.

There are several limitations in this study. In order to accurately assess the analgesic effect of the study medication, a 3-day wash-out period for concomitant drugs that may affect pain assessment is required before starting the study medication. Patients with very severe pain who cannot meet this requirement will not be eligible for this study. Patients with coexisting pain requiring medication caused by a condition other than osteoarthritis of the hip and knee are excluded to accurately evaluate the analgesic effect on arthralgia caused by osteoarthritis. Patients with coexisting pain in other parts of the body, such as low back pain, will not be enrolled in this study. In order to ensure the safety of the study, we have established criteria for eligibility in terms of liver function, kidney function and other internal organ functions. Patients who do not meet these criteria will not be allowed to enter the study,

which means that patients enrolled in this trial have a slightly different profile from those in the real world. We would think that these are unavoidable issues in conducting a clinical trial and does not necessarily reduce the value of this trial.

In summary, the study medication will be taken under double-blinded conditions, which would eliminate the effects of any preconception related to the drug. Pain intensity will be evaluated by the patients through ePROs, implying that the researchers would not know the assessment results and would be unlikely to influence them, thereby avoiding bias. There are many open-label studies on existing therapeutic agents, and these biases are likely to occur; therefore, this study may contribute higher quality research data to the clinical field.

## Trial status

The study is ongoing, and patients are currently being enrolled. Having started enrolment in May 2021, 169 patients have been enrolled as of the end of January 2022. We plan to complete recruitment by June 2023.

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**Contributors** ME, SZ, TMI, MS and YN were involved in conception of trial. ME, SK, TS, MT, TH, TMa, TK, SZ, TMI, MS, SS, TT, MM, HA and YN were involved in trial design. ME, SZ, TMI, SS, MS and YN wrote the first draft of this manuscript. ME, SK, TS, MT, TH, TMa, TK, SZ, TMI, MS, SS, TT, MM, HA and YN contributed to revisions of this manuscript and approved the final manuscript.

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**Competing interests** ME receives honoraria from Daiichi Sankyo. SZ receives consulting fees from Maruho and honoraria from Merck Biopharma, Bristol Myers Squibb Company, and Ono Pharmaceutical. TMI receives consulting fees from AYUMI Pharmaceutical Corporation. TT, MM, and HA are employees of AYUMI Pharmaceutical Corporation. YN receives honoraria from Daiichi Sankyo and Pfizer.

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**Patient consent for publication** Not applicable.

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