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Complete List of Authors:	Zhuang, Qiangyu; Peking Union Medical College Hospital, Orthopedics Bian, Yanyan; Peking Union Medical College Hospital, Orthopedics Department Wang, Wei; Peking Union Medical College Hospital, Orthopaedics Department Jiang, Jingmei; Chinese Academy of Medical Sciences Feng, Bin; Peking Union Medical College Hospital, Orthopedics Department Sun, Tiezheng; Peking University People\'s Hospital, Department of Orthopaedics Lin, Jianhao; Peking University People\'s Hospital Zhang, Miaofeng; The Second Affiliated Hospital of Zhejiang University, Department of Orthopaedics Yan, Shigui; The Second Affiliated Hospital of Zhejiang University, Department of Orthopaedics Shen, Bin; West China Hospital, Sichuan University, Department of Orthopaedics Pei, Fuxing; West China Hospital, Sichuan University, Department of Orthopaedics Weng, Xisheng; Peking Union Medical College Hospital, Orthopedics Department;
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Efficacy and Safety of Postoperative Intravenous Parecoxib Sodium Followed by Oral Celecoxib Post Total Knee Arthroplasty in Osteoarthritis Patients (PIPFORCE): Study Protocol for a Multicenter, Double Blind, Parallel-group Trial

Qianyu Zhuang[1], Yanyan Bian[1], Wei Wang[1], Jingmei jiang[2], Bin Feng[1], Tiezheng Sun[3], Jianhao Lin[3], Miaofeng Zhang[4], Shigui Yan[4], Bin Shen[5], Fuxing Pei[5], Xisheng Weng[1#]

Affiliations:

1. Department of Orthopaedics, Peking Union Medical College Hospital, No.1 Shuaifuyuan, Wangfujing, Beijing 100730, China
2. Department of Epidemiology and Biostatistics, Institute of Basic Medical Sciences Chinese Academy of Medical Sciences/School of Basic Medicine, Peking Union Medical College, Beijing, China .
3. Department of Orthopaedics, Peking University People's Hospital, No. 11 Xizhimen South Street, Xicheng District, Beijing 100044, P. R. China
4. Department of Orthopaedics, The Second Affiliated Hospital of Zhejiang University, Qingchun street No. 79, Hangzhou, Zhejiang Province, 310003, China
5. Department of Orthopaedics, West China Hospital, Sichuan University, No. 37, Guoxue Street, Wuhou district, Chengdu, Sichuan 610041, China

[#] Corresponding Authors:

Xisheng Weng, MD & Professor
Peking Union Medical College Hospital
1 Shuai Fu Yuan Beijing 100730 P. R. China
Telephone Number: 86-13366200018
Fax Number: 86-10-69152810
Email: wengxishengpumch@126.com

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Abstract:

Introduction: Total knee arthroplasty (TKA) has been regarded as a most painful orthopedic surgery. Although many surgeons sequentially use parecoxib and celecoxib as a routine strategy for controlling pain post TKA, high quality evidence is still lacking to prove the effect of this sequential regimen, especially at the medium or long-term follow-up. The purpose of this study, therefore, is to evaluate efficacy and safety of postoperative intravenous parecoxib sodium followed by oral celecoxib in OA patients undergoing TKA. The hypothesis is that compared to placebo with opioids as rescue treatment, sequentially use of parecoxib and celecoxib can achieve not only less morphine consumption over postoperatively 2 weeks, but also better pain control, quicker functional recovery over postoperatively 6 weeks, and less opioid related adverse events over 12-week recovery phase.

Methods and Analysis: This study is designed as multicenter, randomized, double blind, parallel-group, placebo control. Target sample size is 246. All subjects who meet the study inclusion and exclusion criteria will be randomly assigned in a 1:1 ratio to either parecoxib/celecoxib group or placebo group. The allocation or randomization will be study site based. All subjects will be recruited from 4 study centers in China. The study will consist of 3 phases: an initial screening phase; a 6-week double blind treatment phase; and a 6 week follow up phase. The primary outcome is cumulative opioid consumption till 2 weeks post operation. Secondary outcomes consist of postoperative VAS score, knee joint function, quality of life, local skin temperature, ESR and CRP, Cytokines, and blood coagulation parameters.

Ethics and dissemination: Ethics approval for this study has been obtained from the Ethics Committee, Peking Union Medical College Hospital, China. (Protocol number: S-572) Study results will be made available in the form of manuscripts for publication and presentations at national and international meetings.

Strengths and limitations of this study

- This is the first study to target the efficacy and safety of the clinical use of the sequential analgesia regimen of intravenous parecoxib followed by oral celecoxib after TKA surgery.
- Explore the benefits of prolonged sequential treatment of parecoxib and celecoxib in this population on the medium or long-term function recovery.
- The results will assist in the process of optimizing the NSAIDs drug use that can be incorporated into the standard multimodal analgesic regimen for managing postoperative pain.
- Potential limitations relate to the need for validation studies in data sets from other institutions outside of China.

1. Introduction

Osteoarthritis (OA) is a chronic degenerative joint disorder which is frequently occurred in the elderly.[1, 2] In mainland China, knee OA is the leading cause of disability in elderly patients. Total knee arthroplasty (TKA) is now generally regarded as an effective treatment for end-stage knee OA in pain alleviation, joint deformity correction and life quality improvement.[3, 4]

However, TKA has been regarded as a most painful orthopedic surgery due to the weight bearing characteristics of knee joint and the high demand of functional exercise within the 6-8 weeks post operation.[5, 6] Firstly, TKA induces massive tissue damage and severe perioperative pain which jointly hampers the early postoperative rehabilitation and exerts negative effects on surgical outcome and patient satisfaction.[7] Secondly, postoperative pain, as the most suffering experience for TKA patients, may prolong postoperative bedbound duration and increase the risks for pulmonary infection, deep venous thrombosis (DVT), pulmonary embolism (PE) etc. [8] Thirdly, previous findings suggested that local inflammation trigged by tissue damage not only increases the central and peripheral pain sensitivity, but also leads to acute hemorrhage and swelling, which poses greater challenges to the postoperative rehabilitation. [9, 10]

The targeted treatment with selective cyclooxygenase (COX-2) inhibitor, such as parecoxib or celecoxib, can significantly reduce the inflammatory reaction level within two days post operation. [11-14] In addition, perioperative administration of celecoxib can relieve postoperative pain and improve articular function, thereby improving life quality of the patients. Recently, sequential therapy of intravenous-to-oral COX-2 inhibitor

administration has been demonstrated as effective in many post-operative pain control models. [15-19] Significant morphine sparing effect and reduction of opioid related complications were also observed. [15-19] In China, it's becoming a routine at many institutions that 40mg parecoxib be administered intravenously twice daily for the first 3 days after surgery, followed by 200mg celecoxib administered orally bid for 2 weeks or longer. Although satisfactory results of the sequential therapy on short-term pain alleviation and functional recovery have been preliminarily observed in clinical practice, high quality evidence is still lacking, especially at the medium/ long-term follow-up.

PIPFORCE study (Trial registration number: ClinicalTrails.gov identifier: NCT02198924) aims to investigate the sequential analgesia regimen with intravenous parecoxib followed by oral celecoxib for post-surgical analgesic treatment in osteoarthritis patients undergoing TKA surgery. Subjects will receive double-blinded study medication consisting of parecoxib injection in analgesic doses or matching placebo followed by oral Celecoxib in acute pain doses or matching placebo. The hypothesis is that subjects treated with parecoxib/celecoxib will consume less morphine over postoperative 2 weeks, achieve better pain control, quicker functional recovery over postoperative 6 weeks, and has less opioid adverse events than those treated with opioids alone over 12-week recovery phase.

2. Aim and objectives

2.1. Primary objectives

The primary objective of this study is to evaluate the morphine-sparing effects of the sequential treatment with parecoxib and celecoxib versus placebo in subjects undergoing TKA.

2.2. Secondary objectives

The secondary objective for the study is to compare the effects of the sequential treatment versus placebo on pain relief, inflammation control and functional rehabilitation after TKA.

3. Design and methods

3.1. Study Design

This study is an investigator initiated post marketing study which is designed as multicenter, randomized, double blind, parallel-group, and placebo-controlled.

3.2. Study Setting

This study is being conducted at Peking Union Medical College Hospital (PUMCH), China as the coordinating center, and 3 participating centers including 1)West China Hospital of Sichuan University, Sichuan Province, China, 2) People's Hospital of Peking University, Beijing, China, and 3)Second Affiliated Hospital of Zhejiang University College of Medicine, Zhejiang Province, China.

3.3. Study participants

3.3.1. Inclusion Criteria

Subject eligibility should be reviewed and documented by an appropriately qualified member of the investigator's study team before subjects are included in the study.

Subjects must meet all of the following inclusion criteria to be eligible for enrollment into the study:

1) The subject is scheduled to undergo elective unilateral total knee arthroplasty because of OA, performed under a standardized regimen of spinal anesthesia, as specified in this protocol.
2) Evidence of a personally signed and dated informed consent document indicating that the subject (or a legal representative) has been informed of all pertinent aspects of the study.
3) The subject is a male or female over 18 years of age.
4) Male and female subjects of childbearing potential must agree to use an effective method of contraception throughout the study and for 42 days after the last dose of assigned treatment. A subject is of childbearing potential if, in the opinion of the investigator, he/she is biologically capable of having children and is sexually active.
5) Total duration of the surgical procedure is four hours or less.
6) ASA grade 1-3 subjects.
7) Subjects who are willing and able to comply with scheduled visits, treatment plan, laboratory tests, standardized rehabilitation scheme, and other study procedures.
8) The subject is in satisfactory health as determined by the investigator on the basis of medical history and physical exam.
9) The subject must demonstrate sufficient psychomotor dexterity and cognitive capacity to use intravenous (IV) PCA.
10) The subject who live near to the hospital may be considered prior for the concern of convenient and sufficient follow-up.

3.3.2 Exclusion Criteria

The subjects will be excluded with any condition listed below:

1) The subject requires a revision to previous knee arthroplasty and/or is having a bilateral knee arthroplasties.
2) The subject requires an emergency knee arthroplasty.
3) Addiction to using any non-steroidal anti-inflammatory drugs (NSAIDs) and opioids
4) Subject has a known hypersensitivity to COX-2 specific inhibitors, sulfonamides, lactose, NSAIDs, opioids or acetaminophen/paracetamol. Subjects who have experienced asthma, urticaria or allergic type reactions after taking aspirin or other NSAIDs.
5) The subject has a history of any of the following arthritis: (i.e. rheumatoid arthritis, ankylosing spondylitis, psoriatic arthritis), chronic pain (e.g. fibromyalgia), metastasis, and Paget's disease.
6) The subject received any investigational medication within 30 days prior to the first dose of study medication or is scheduled to receive any investigational drug other than those described in the protocol during the study.
7) The subject has any known laboratory abnormality, which in the opinion of the investigator, would contraindicate study participation including ALT (SGPT), AST (SGOT), blood urea nitrogen or Creatinine ≧1.5 times the upper limit of the normal reference range.
8) The subject has an active malignancy of any type, or history of a malignancy (Subjects who have a history of basal cell carcinoma that has been successfully treated can be entered into the study. Subjects with a history of other malignancies that have been surgically removed and who have no evidence of recurrence for at least five years before study enrollment can also be entered into the study).
9) Subject had inflammatory bowel disease (e.g. Crohn's disease or ulcerative colitis), a chronic or acute renal or hepatic disorder, a significant coagulation defect, or any condition, which could preclude use of NSAIDs or COX-2 specific inhibitors.
10) The subject has active or suspected esophageal, gastric, pyloric channel, or duodenal ulceration history.
11) The subject has received warfarin or other anticoagulants during the 30 days preceding the first dose of study medication (Cardioprotective aspirin, ≦or 325 mg/day is permitted, when the dose has been stable for at least the month prior to entering the study). Anticoagulation is permitted when related to the surgery, with such medicines as low molecular weight heparin including Lovenox and Fragmin.
12) Subject is anticipated to require or requires treatment with lithium.
13) Subject is ASA grade 4-5.

14) The subject has a history of a psychiatric disorder requiring new or changing treatment (A subject with a psychiatric disorder who has been stable on therapy may enter the study if they have not required any changes in their therapy for the 4 weeks prior to study entry and it is anticipated they will not need any changes for the 2-week duration of this study).
15) The subject has a history of uncontrolled chronic disease or a concurrent clinically significant illness, medical condition, which in the investigators' opinion, would contraindicate study participation or confound interpretation of the result. Including, but not exclusive to the following: uncontrolled hypertension, uncontrolled ischemic heart disease, uncontrolled cardiac insufficiency, history of coronary artery bypass graft (CABG) surgery, history of heart valve surgery or coronary stent implantation, history of peripheral vascular disease or cerebrovascular disease, moderate or severe hepatic impairment, fluid retention, heart failure, abdominal pain of unknown etiology (or where study medication could mask symptoms) or any other condition which in the opinion of the Investigator, would contraindicate study participation or confound interpretation of the results.
16) The subject has any cognitive impairment or other characteristics that would in the investigator's opinion preclude study participation or compliance with protocol mandated procedures.
17) Subject has a history of asthma or bronchospasm, which requires treatment with glucocorticoids.
18) Subject had a history of alcohol, analgesic or narcotic abuse.
19) Subject has been previously randomized into the study
20) Subjects who are investigational site staff members or relatives of those site staff
21) Participation in other studies within 3 months before the current study begins and/or during study participation
22) Other severe acute or chronic medical or psychiatric condition or laboratory abnormality that may increase the risk associated with study participation or investigational product administration or may interfere with the interpretation of study results and, in the judgment of the investigator, would make the subject inappropriate for entry into this study.
23) Pregnant females, breastfeeding females, or males and females of childbearing potential not using effective contraception or not agreeing to continue effective contraception from screening through 42 days after last dose of investigational product will not enter into this study.

3.3.3. Withdrawal criteria

At any stage of the study, subjects are free to consent withdraw from the study with their medication and or treatment to the disease and their well beings be taken care of by the investigator/hospital without any negative impact.

The investigator may decide that a subject needs to be withdrawn from the study based on evaluations of individual conditions and balancing of the potential benefit/risk caused by the study treatment to the subject.

3.4 Intervention measures

3.4.1. Allocation to Treatment

All subjects who meet the study inclusion and exclusion criteria will be randomly assigned in a 1:1 ratio to either parecoxib/celecoxib group or placebo group. The allocation or randomization will be study site based.

The Electronic Data Capture (EDC) system will automatically generate subject identification numbers in sequence at baseline, which is subsequently linked to the treatment assignments at randomization. A copy of the randomization code will be maintained by the investigator designated a person(s) who is independent of the trial conduct. It is the responsibility of the Principal Investigator (PI) to ensure that the subject is eligible for participation in the study before requesting randomization.

The study will consist of 3 phases: an initial screening phase which must be completed within 30 days prior to randomization; a 6-week double-blind treatment phase; and a 6-week follow-up phase. (**Figure 1**)

Firstly, the investigator will initiate the required screening procedures after obtaining written informed consent. All qualified patients after selection by inclusive/exclusive criteria will be assigned in the order in which they are enrolled into the study, to receive their allocated treatment sequence according to a computer-generated randomization schedule prepared prior to the start of the study.

Secondly, after completion of screening, subjects that remain eligible will enter a 6 week double-blind randomized treatment period. Patients in the study group are supplied sequential treatment with parecoxib 40 mg intravenously (IV) twice daily (Q12h) for the first 3 days post-surgery followed by celecoxib 200mg orally twice daily (Q12h) for up to 6 weeks post-surgery; whereas control patients are supplied with the corresponding placebo with the same instructions. Patient-controlled intravenous analgesia (PCIA) with morphine is administrated to all the subjects starting immediately post-anesthesia and ending at 24h after operation. As long as oral intake is feasible, both the two groups may

receive centrally-acting analgesic tramadol hydrochloride in oral form as rescue analgesia if VAS score≧3. With the support of sufficient pain management, patients will be educated to perform functional exercise according to the standardized post-TKA exercise plan. The investigator will use patient diary at every visit to track the patient exercise, pain score, the study medication, and the rescue therapy.

Lastly, a telephone safety follow up visit at 12-week post-surgery will be taken to reveal any adverse events that may happen during the follow-up phase. All participants and all assessment operators were blinded to the identity of the treatments until all study data had been collated in a database.

3.4.2. Drug preparation and administration

3.4.2.1. Drug Supplies

Due to the non-competing design of subject recruitment, the study drug will be shipped to the study sites prior to study start once for all. Drug labeling and packaging will be performed by medicine supplier's facility, and shipped to Principal Investigator in 4 batches; one batch for one site. On the drug labeling, there will be a unique drug ID that is generated by an un-blind study statistician.

3.4.2.2 **Formulation and Packaging**

Parecoxib lyophilized presentation will be supplied in 40 mg per vial for intravenous administration; liquid presentation of placebo will be 0.9% saline in 2 ml per vial provided on site for intravenous administration. 2ml of 0.9% saline is used for reconstitution of parecoxib before administration.

Celebrex/Placebo 200 mg capsule presentation will be supplied in bottles for oral administration, and the number of capsule in each bottle are 12 for the first week post-surgery, 22 for the second week, 44 for the following two weeks scheduled respectively.

The label of "Clinical Trial Only" should be added on the parecoxib vials and boxes.

Labeling of celebrex bottle and box are being conducted by the medicine provider.

3.4.2.3. **Preparation and Dispensing**

Only qualified personnel who are familiar with procedures that minimize undue exposure to them and to the environment should undertake the preparation, handling, and safe disposal of chemotherapeutic agents. This includes the pharmacist for the trial and the nurse who helps in preparation for administration of trial medication.

The study is designed as randomized and double blind, preparation of the study medication will be performed by medicine supplier in its GMP facility, according to the random list a unique random code will be labeled to each vial/bottle of the

medicine/placebo allowing no recognition of the real ingredients by trial operating nurse and or subjects.

Reconstitution of parecoxib will be performed by nurse who does not have access of direct contact with administration field and or subjects.

2 ml 0.9% saline is used for reconstitution with the steps clearly defined in the package insert, as well as the procedure of administration of liquid placebo, another 2 ml of saline.

Dispensing of the trial medication/placebo will be based on random code kept by the nurse for reconstitution of parecoxib or the label of the bottle for celecoxib by strictly following the sequence of the medicine identification number on the labels.

3.4.2.4. Administration

Parecoxib/placebo will be administered via intravenous route, after reconstitution, the medication or placebo will be transferred to the field nurse for administration, and the infusion will be twice daily in twelve hours interval, the medication should not be given simultaneously with any other medication, and bolus injection is recommended after using 1 - 2ml of saline washing of infusion route in advance. .

Administration of parecoxib/placebo will be witnessed by the field nurse with checking and recoding of subject ID, case number, medicine identification number, starting time/date, finishing time/date, and signed/dated by the operator and witness.

During the in-ward phase of subject, celebrex/placebo will be administered orally, twice daily in twelve hours interval, such as at 8:00 and 20:00 respectively, with a cup of water, and witnessed by the field nurse with checking and recoding of subject ID, code for the medication, administration time/date, and signed/dated by the operator and witness. While discharged from hospital, the subjects are required to record the oral intake of celebrex/placebo by themselves on the diary card proved at each visit keeping the time points of administration as same as in ward.

3.4.2.5. Drug Storage and Drug Accountability

Parecoxib and placebo will be shipped and stored at a temperature below 25°C, and celebrex and placebo will be shipped and stored at 10 - 25 °C.

The Investigator or an approved representative (e.g., pharmacist) will ensure that all investigational products are stored in a strictly controlled, secure area, at appropriate temperatures and in accordance with applicable regulatory requirements.

The Investigator or designated personnel must maintain adequate records documenting the receipt, use, loss, or other disposition of the investigational products. In either case, the forms must identify the investigational product, including batch or code numbers,

and account for its disposition on a subject by subject basis, including specific dates and quantities. The forms must be signed by the individual who dispensed the drug.

At the end of the trial, all bottles distributed to the subjects must be returned to the investigator site by the subjects. The Investigator must ensure that the materials are destroyed in compliance with applicable environmental regulations and institutional policy. Destruction must be adequately documented.

Investigators and site staff are reminded to check temperatures daily and ensure that thermometers are working correctly as required for proper storage of investigational products. These include thermometers for both the room storage and refrigerator storage. Any temperature excursions should be reported immediately.

Both vials for parecoxib and bottles for celcoxib will not be returned to sponsor, nor the medicine supplier from the study sites, the vials and bottles will be checked by CRA after each visit, while subjects are asked to bring the bottle for Celecoxib together with unused capsules to the investigator at each time of visits 7, 8 and 9. The investigator will check the number of capsules inside the bottle against the record on the diary, and have this fully recorded, followed by issuing the subject with a bottle of medicine for the next visit.

3.4.2.6. Concomitant Medication(s)

The use of permitted concomitant therapy must be explained in detail, including prescription and nonprescription drugs, non-drug therapy, and dietary supplements and herbal preparations, as appropriate. Clearly state the types of medications that will and will not be permitted before, during, and after the study, as appropriate.

The name, dose, date, and exact time of administration must be recorded in the CRF and appropriate medical records as source data for each medication administered to thepatient.

Prohibited medications

The following medications are prohibited for the duration of the study:

- NSAIDs and other analgesics (including steroid), by any route (i.e. oral, inhaled, topical, injected, rectal) within 5 days prior to TKA until the end of the study.
- Fluconazole, and/or lithium
- Hypnotics, anxiolytics, sedatives, tranquilizers, SSRIs, tricyclic anti-depressants, or benzodiazepines unless the subject's prescribed daily dose has remained unchanged throughout the previous 4 weeks and will remain unchanged throughout the study period.
- Herbal and alternative medicines such as: garlic, ginko biloba, ginseng.

- Local infiltration of the surgical site with anesthetic is prohibited.

Permitted medications

- Pre-medication, if required, will be a short-acting benzodiazepine (e.g. temazepam)
- Anesthesia will be a standardized spinal regimen using a unique dose of 10-20 mg bupivacaine. Levobupivacaine (chirocaine) may also be used.
- If intra-operative sedatives are necessary, midazolam (0.5 to 1 mg dose) or propofol (less than 6 mg/kg/hour) is allowed. Administration of the intra-operative sedative has to be stopped approximately 30 minutes prior to the end of the operation. Midazolam or propofol can be titrated to provide adequate sedation but the titration will be done such that the subject is able to participate in adequately assessing their post-surgical pain shortly after the procedure.
- Anti-coagulants: Low molecular weight heparin is permitted for post-surgical anticoagulant treatment, 2 -4 hours after spinal anesthesia.
- Aspirin＜325 mg/day is permitted for cardiovascular prophylaxis, if used at a stable dose for the 30 days prior to randomization.
- Anti-emetic drugs may be given, if needed. The dose and total number of doses of the anti-emetic treatment should be documented on the CRF.

3.4.3. Rescue Therapy

Intravenous rescue medication- PCA: After surgery, all subjects will be connected to patient-controlled analgesia (PCA) within 150 minutes of time 0, defined as wound closure at application of last stitch and may start administration of morphine after 30 minutes of time 0. The PCA pump will contain morphine (1 mg/ml), set to a lockout time of 6 minutes and will administer 1.0 ml per dose. The Investigator may limit the administration of Morphine by PCA to a maximum dose/4 hours; this limit should not be lower than 30 mg/4 hours. A 2 mg bolus of morphine may be given at any time after the end of surgery to control breakthrough pain. The safe administration of Morphine is the responsibility of the Investigator.

All doses of morphine (PCA and bolus) must be recorded precisely with the date and time of administration and the amount of morphine given. If a subject is unable to use the PCA pump he/she must be withdrawn from the study and provided with appropriate analgesia.

Oral rescue medication: After PCA is discontinued, all subjects with a VAS more than 3 may take open-label oral rescue medication, tramadol 100mg each time as needed, not to exceed 400mg per day.

Consumption of both morphine and tramadol will be calculated together and converted to morphine equivalent dosage, the converting of tramadol to morphine equivalents is estimated as 200mg tramadol equals to 40mg of morphine.

3.4.4. Life Style Guidelines

Subjects should maintain their normal daily routine, including stable doses of permitted medications and exercise program. Subjects may continue with stable non-pharmacologic activities (e.g., physiotherapy massage, psychological therapy) during the trial but those activities must be collected and recorded in the trial predefined Case Report Form (CRF). Subjects should be cautioned against initiating or altering strenuous exercise regimens during the study as this may influence efficacy and laboratory results.

All male and female subjects who, in the opinion of the investigator, are biologically capable of having children and are sexually active, must agree to use a highly effective method of contraception consistently and correctly for the duration of the active treatment period and for 42 days after the last dose of investigational product. The investigator, in consultation with the subject, will select the most appropriate method of contraception for the individual subject from the permitted list of contraception methods, and instruct the subject in its consistent and correct use. The investigator, at each study visit, will confirm and document consistent and correct use. In addition, the investigator will instruct the subject to call immediately if the selected birth control method is discontinued or if pregnancy is known or suspected.

In the event of indeterminate or anomalous results on pregnancy testing or issues surrounding contraceptive requirements, study management should be contacted and will make the final decision as to the adequacy/need for contraception.

3.5. Outcome measures

3.5.1. Primary endpoint

Cumulative opioid consumption till 2 weeks post operation. It can be calculated as the sum of the cumulative Morphine consumption over the first 24 hours postsurgical period and the narcotic drug consumption till 2w post operation. The converting of Tramadol to morphine equivalents is estimated as 200mg Tramadol equals to 40mg of morphine

3.5.2. Secondary endpoints

3.5.2.1. Key secondary endpoints

Knee Society Score (KSS) at 6w post operation.

3.5.2.2. Other secondary endpoints

- Western Ontario and McMaster Universities Osteoarthritis Index (WOMAC) index prior to operation and at 2w,4w and 6w post operation
- Knee Society Score (KSS) prior to operation and at 2w and 4w post operation
- Total morphine use: The cumulative morphine consumption over the first 24 hours postsurgical period.
- Total narcotic use till 72h, 4w, 6w post operation. For example, total narcotic use till 72h post operation will be calculated as the sum of the cumulative morphine consumption over the first 24 hours postsurgical period and the narcotic drug consumption (converted to morphine equivalents) till 72h post operation.
- VAS (0-10) prior to operation and at 24h, 48h, 72h, 2w, 4w and 6w post operation, with 0 representing no pain and 100 mm representing the worst imaginable pain.
- EQ-5D and patient satisfaction prior to operation and 72h, 2w, 4w and 6w post operation. EQ-5D is a standard instrument for use as a measure of health outcome. It is cognitively simple, taking only a few minutes to complete.

3.5.3. Exploratory endpoints

- Knee circumference (measured 1cm proximal to the base of the patella) prior to operation and at 72h, 2w, 4w and 6w post operation. The measurements were performed in a quiet room, with a recording clerk and a physician present who measured and recorded dimensions of the knee circumference of both legs. Circumferential measurements were recorded to the nearest 0.1 cm with an ordinary tape measure.
- Knee skin temperature prior to operation and at 72h, 2w, 4w and 6w post operation.
- ESR and CRP at preoperative and at 72h, 2w, 4w and 6w post operation.
- Synovial fluid cytokine (including IL-6, IL-8, IL-10 and PGE2) concentration at 0h, 24h and 48h post operation.
- Peripheral blood cytokine (including IL-6, IL-8, IL-10 and PGE2) concentration prior to operation and at 72h, 2w, 4w and 6w post operation.
- Blood coagulation Tests prior to operation and at 72h, 2w, 4w and 6w post operation.

3.6. Adverse event reporting

3.6.1. Adverse Event Definition

An adverse event (AE) is any untoward medical occurrence in a clinical investigation subject administered a product or medical device; the event need not necessarily have a causal relationship with the treatment or usage. Examples of AEs include but are not

limited to: abnormal test findings, clinically significant symptoms and signs, changes in physical examination findings, hypersensitivity, progression/worsening of underlying disease, drug abuse, drug dependency, etc.

3.6.2. Serious Adverse Events (SAE)

An SAE is any untoward medical occurrence at any dose that:

- Results in death;
- Is life-threatening (immediate risk of death);
- Requires inpatient hospitalization or prolongation of existing hospitalization;
- Results in persistent or significant disability/incapacity (substantial disruption of the ability to conduct normal life functions);
- Results in congenital anomaly/birth defect.
- Lack of efficacy should be reported as an AE when it is associated with an SAE.

Medical and scientific judgment is exercised in determining whether an event is an important medical event. An important medical event may not be immediately life-threatening and/or result in death or hospitalization. However, if it is determined that the event may jeopardize the subject or may require intervention to prevent one of the other AE outcomes, the important medical event should be reported seriously.

3.6.3. Severity Assessment

If required on the AE case report forms (CRFs), the investigator will use the adjectives MILD, MODERATE, or SEVERE to describe the maximum intensity of the AE. For purposes of consistency, these intensity grades are defined as follows: 1) MILD: Does not interfere with subject's usual function. 2) MODERATE: Interferes to some extent with subject's usual function.3) SEVERE: Interferes significantly with subject's usual function.

3.6.4. Causality Assessment

The investigator's assessment of causality must be provided for all AEs (serious and non-serious); the investigator must record the causal relationship in the CRF, as appropriate, and report such an assessment in accordance with the serious adverse reporting requirements if applicable. An investigator's causality assessment is the determination of whether there exists a reasonable possibility that the investigational product caused or contributed to an AE; generally the facts (evidence) or arguments to suggest a causal relationship should be provided. If the investigator does not know whether or not the investigational product caused the event, then the event will be handled as "related to investigational product" for reporting purposes, as defined by the investigator. If the investigator's causality assessment is "unknown but not related to investigational product", this should be clearly documented on study records. In addition, if the

investigator determines an SAE is associated with study procedures, the investigator must record this causal relationship in the source documents and CRF, as appropriate, and report such an assessment in accordance with the SAE reporting requirements, if applicable.

3.6.5. Withdrawal Due to Adverse Events

Withdrawal due to AE should be distinguished from withdrawal due to insufficient response according to the definition of AE noted earlier, and recorded on the appropriate AE CRF page.

When a subject withdraws due to an SAE, the SAE must be reported in accordance with the reporting requirements defined below.

3.7. Study procedures

There will be altogether 10 visits in the study for a certain subject. (**Table 1**) Screening will be performed at visit 1, and the day for TKA operation will be considered as Day 0. There is a visit on one day before operation, the visit 2, when the qualification of subject to the study will be evaluated again before operation, and the visit right after operation is visit 3. Those on day 1, 2 and 3 post-surgery will be regarded as visits 4, 5 and 6 respectively, then there will be visits 7, 8 and 9 at 2 weeks, 4 weeks and 6 weeks post-surgery, and the last visit will be at 12 weeks post-surgery, the visit 10.

3.7.1. Screening and wash-out

Screening will be performed between visits 1 and 2, where the potential subjects will be evaluated by inclusion/exclusion criteria, demography and medical history recording, evaluation of the background diseases as well as OA for the knee to be operated on, physical examination and laboratory examinations including routine tests of blood and urine, biochemical, X-ray (chest, two lower limbs, and the knee joint), 12-lead ECG, echocardiogram, pulmonary function, ultrasound for lower extremities venous and arteria, blood transfusion test (8 items), blood type and pregnancy test for female subjects, ESR and CRP, peripheral blood cytokine concentration (IL6, IL8, IL10 and PEG2) and blood coagulation, WOMAC index and KSS, VAS and EQ-5D, knee circumference and skin temperature at baseline.

Before any trial required assessments been conducted, a written Informed Consent must be signed by the subject, witness to the signing is needed when the subject is unable to read or write.

There is a two-week wash-out period after the screening at visit 1 and before visit 2, in which subjects who have been receiving any NSAIDs will be stopped for using of these medicines for two weeks and asked to replace their NSAIDs with Tramadol when needed. All required data must be recorded on CRF for verification and archiving. In this study, e-CRF will be applied allowing online source data verification.

Qualification of subject to the study will be evaluated again at visit 2 which is the day before operation, and randomization of the subject to receive either parecoxib or placebo in the first three days post-surgery, and either clebrex or placebo in the following 6 weeks will also be determined on the same visit.

3.7.2. Study Period

At visits 3 which is right after operation, physical examination will be performed, infusion of parecoxib or placebo 40mg Q12h in the first three days and recording of morphine consumption for 24 hours starts, and synovial fluid cytokine concentration will be tested. Safety evaluations are also conducted for the subjects.

At visits 4 and 5 the recording of accumulative morphine consumption stops, while that for tramadol starts at visit 4, physical examination and safety evaluations are also conducted for the subjects. Synovial fluid cytokine concentration is tested at 24 h and 48h post operation.

At visit 6 which is 72 hours after operation, infusion of parecoxib 40mg Q12 or placebo stops, and oral administration of celebrex 200mg Q12h /placebo starts on Day 4, while recording the cumulative tramadol consumption continues. Evaluations of VAS and EQ-5D will be performed, while testing of ESR, CRP, peripheral blood cytokine concentration and blood coagulation will also be performed. Safety evaluations are also conducted for the subjects.

3.7.3. Follow-up Visits

This period covers visits 7 through 9, where recording the cumulative Tramadol consumption at 2w, 4w and 6w after operation, WOMAC index and KSS at 2w, 4w and 6w post operation, evaluations of VAS and EQ-5D at 2w, 4w and 6w post operation, knee circumference and skin temperature at 2w, 4w and 6w post operation, ESR and CRP at 2w, 4w and 6w post operation, peripheral blood cytokine concentration at 2w, 4w and 6w post operation, and tests of blood coagulation at 2w, 4w and 6w post operation. Safety evaluations are also conducted for the subjects at each visit.

3.7.4. Post-Study Subject Telephone Interview

At 12 weeks post-surgery, only safety evaluations will be conducted for the subjects by a telephone follow-up.

All data required by above visits must be recorded on CRF for verification and archiving.

3.8. Breaking the Blind

This is a double-blind study. The subjects, investigators, study coordinators, clinical site staff, Clinical Research Associate (CRA), and staff directly involved with the study and its designees will be blinded to subject treatment assignment.

At the initiation of the study, the study site will be instructed on the method of breaking the blind. Blinding should only be broken in emergency situations for reason of subject safety. Whenever possible, the investigator or sub-investigator consults with a member of the study team prior to breaking the blind. When the blind is broken, the reason must be fully documented and entered on the CRF.

3.9. Stop Criteria

The subjects involved in this study have the right to quit at any time. In addition, subjects will be discontinued from the study if they meet any of the following criteria:

1) Clinical interventions (e.g. systemic or topical application of glucocorticoids, other NSAIDs used within six weeks after TKA) which may affect the study results within the observation period;
2) Occurrence of serious adverse event (SAE, e.g. malignant tumors, serious perioperative complications) which, in the opinion of the investigator, may complicate assessment of the effects of study drugs.

3.10. Ethical review and informed consent

Ethics approval for this study has been obtained from the Ethics Committee, Peking Union Medical College Hospital, China. The benefits and risks of participation in the trial will be explained to each patient, legal deputy, or witness by the investigators or their designee, and written informed consent will be obtained before the trial. The informed consent with the signature of the patient, legal deputy, and person who explained the benefits or risks will be preserved by the researchers. The trial will be conducted in accordance with the Declaration of Helsinki.

3.11. Sample Size Determination

Total 86 subjects per group would have 90% power in detecting 100 mg or more in mean difference of morphine use on Day 14 between the two groups, assuming a common

standard deviation of 200, and a two-sided alpha level of 0.05. This would result in a total 172 subjects. In consideration of 30% drop outs, 246 subjects would be adequate for the study.

Due to lacking prospective studies for this type of endpoint, and in review of a retrospective evaluation of inpatient Celecoxib use after total hip and knee arthroplasty [15], our assumptions in the sample size estimation are conservatively stipulated.

3.12. Data collection, management, and statistical analysis

Data will be collected through EDC (Electronic Data Capture) system under intent-to-treat principals, i.e., all the data of the subjects who signed inform consent form will be included in the study database.

Data Quality Assurance will be achieved through

- Online Edit Checks at the time of data entry
- Database Edit Checks performed by Data Management (DM)
- Online query issuance/resolution among/between PI, CRA and DM
- Medical review of data listing by the project team

For this study, the following definitions of analysis population will be followed:

ITT (Intent-to-treat)

All the randomized subjects who signed ICF, and satisfied all inclusion/exclusion criteria at visit 2 will be included in ITT analysis set.

Analyses on demographics and baseline characters will be based on ITT analysis set, and the listings of subjects' information will also be based on ITT.

EAP (Effective Analysis Population)

All the subjects in ITT who have complete demographics data and evaluable baseline morphine use, and at least 1 post-baseline cumulative use of Tramadol.

All the analyses on efficacy will be based on EAP.

PP (Per-protocol Population)

All the subjects in EAP who don't have any major protocol deviation, no forbidden concomitant use, have the data of cumulative use of Tramadol in the first 2 weeks after operation, and the compliance in treatment use in the first 2 weeks after operation is in 80%~120%.

PP will be only used in primary efficacy analysis.

SS (Safety Set)

All the randomized subjects who had received at least one dose will be included in safety set. Analysis on adverse events, laboratory, ECG, and vital sign will be based on safety set.

All data collected at follow-up visits for patients in the study and control groups are compared by an independent statistician using SAS 9.3 statistical analysis software. Continuous variables will be summarized by treatment groups using descriptive statistics including number of subjects, mean, standard deviation, median, Q1, Q3, minimum and maximum. The statistics of t test, Welch-Satterthwaite t test or Mann-Whitney U test will be used in comparison between 2 groups based on the results of normality test and homogeneity of variance test. Paired t test will be used in comparison within each group if the variable normally distributed; otherwise signed rank test will be used. The statistical significance level of normality test and homogeneity of variance test is 0.05. Nominal categorical variables will be presented as “frequency (percentage)”. The statistics of Pearson Chi-Squared test, continuity adjusted Chi-Squared test or Fisher's exact test will be used in comparison between 2 groups based on the distribution of the variable considered. Ordinal categorical variables will be presented as “frequency (percentage)”. Mann-Whitney U test will be used in comparison between 2 groups. Two-sided p value will be used in the statistical tests, and the difference between groups will be considered statistically significant if $p < 0.05$.

For primary endpoint analysis, statistical methods for continuous variable analysis will be used in the superiority test of study group over control group on reducing morphine use. Additionally, ANCOVA will be used in primary endpoint analysis as supplemental analysis, the covariates include the subjects’ dosed days, gender, age, and weight.

In additional to general statistical methods, mixed model for repeated measures (MMRM) will also be used in secondary endpoints analysis.

For safety analysis, the adverse events, abnormal findings in laboratory tests will be listed with the relationship to the study treatments. Fisher’s exact test will be used to compare the rates of subjects who have at least one adverse event between study and control groups.

3.13. Quality control and quality assurance

During study conduct, investigator or its contracted agent will conduct periodic monitoring visits to ensure that the protocol and Good Clinical Practices (GCPs) are being followed. The monitors may review source documents to confirm that the data

recorded on CRFs is accurate. The investigator and institution will allow monitors directly accessed to source documents to perform this verification.

Each step will be strictly performed according to the trial protocol. Each step of quality control of measured outcomes will be performed according to the standard operating and quality control procedure.

4. Discussion

Total knee arthroplasty is associated with significant postoperative pain, which adversely affects patients' ability and desire to effectively rehabilitate their knee. [5, 6] Inadequate pain control has been correlated with prolonged postoperative bed time, increased incidence of pulmonary infection, deep venous thrombosis (DVT), pulmonary embolism (PE) and poor functional recovery in some patients after TKA.[8]

The current standard care for postoperative pain management consists of opioids alone or with adjunctive use of nonsteroidal anti-inflammatory drugs (NSAIDs) (multimodal analgesia) [1]. Although both opioids and NSAIDs are effective analgesics, neither is without safety and tolerability concerns. Opioids are associated with nausea, vomiting, constipation, paralytic ileus, and respiratory depression, all of which can potentially cause or exacerbate postsurgical complications. [20] In addition, nonselective NSAIDs may cause gastrointestinal (GI) and hematologic adverse events, compromise platelet function [21], and are associated with increased postoperative bleeding and increased blood transfusion requirements after joint arthroplasty surgery[22].

Selective cyclo-oxygenase-2 (COX-2) inhibitors display similar anti-inflammatory properties with traditional NSAIDs, but lack many of the side effects associated with NSAIDs because they spare the COX-1 enzyme and have no clinically significant effect on platelet or gastrointestinal function. [21, 23, 24] parecoxib sodium (parecoxib), is the injectable prodrug of valdecoxib and is the only parenteral formulation of a selective COX-2 inhibitor NSAID.[25] It has been demonstrated as effective in several models of postoperative pain[26] with no effect on platelet function or gastric mucosa at doses up to 40 mg twice daily.[27] Celecoxib, another oral specific COX-2 inhibitor, was shown as not only have short-term pain reduction and morphine sparing effect in patients undergoing total knee arthroplasty[13], but also improve functionality recovery if prolonged use up to 6 weeks postoperatively[11].

Treatment of postoperative pain with intravenous with or without subsequent oral COX-2 specific inhibitor has been demonstrated as effective in many post-operative pain

models.[15-19] Significant morphine sparing effect and reduction of opioid distressed symptoms were also observed. Combination of intravenous parecoxib and oral valdecoxib was used for less than 2 weeks in most of previous studies. In these studies [15-19], short-term postoperative pain control and morphine sparing effect were evaluated. However, to the best of our knowledge, no study has investigated the effect of prolonged (6 weeks) sequential treatment of intravenous parecoxib and oral celecoxib on the medium or long-term functionality recovery.

PIPFORCE study is being conducted to investigate the sequential analgesia regimen with intravenous parecoxib followed by oral celecoxib for post-surgical analgesic treatment in osteoarthritis patients undergoing TKA. Subjects will receive study medication consisting of parecoxib injection in analgesic doses or matching placebo followed by oral celecoxib in acute pain doses or matching placebo in a double-blind fashion. The hypothesis is that subjects treated with parecoxib/celecoxib will consume less morphine over 2 weeks postoperative period, achieve improved pain control over study period, quicker return to functionality, and has less opioid adverse events than those treated with opioids alone over the 12-week recovery phase. Both treatment groups will be able to use open-label rescue medication with opioids.

The contribution from PIPFORCE study is expected to be a comprehensive understanding of how the sequential regimen with intravenous parecoxib followed by oral celecoxib affects postoperative pain relief, inflammation control and functional rehabilitation in osteoarthritis patients undergoing TKA. The completion of this study will provide solid evidence for the efficacy and safety of the clinical use of the sequential regimen of COX-2 specific inhibitors after TKA surgery. The results will assist in optimizing the NSAIDs use as a part of standard multimodal analgesic regimen for managing postoperative pain. Furthermore, this project will provide insight into the benefits of prolonged sequential treatment of parecoxib and celecoxib in this population on the medium or long-term functionality recovery.

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Contributors

WXS contribute as the senior author and the principle investigator (PI) of this study. ZQY, as the sub PI, wrote the first draft of the manuscript and contributed to the design of the study. BYY, WW, FB, STZ, ZMF advised on the study design. LJH, YSG, SB, PFX refined the protocol. JJM, as the medical statistician for the study, contributed to the statistical design, acquisition and analysis of data for the work. All authors revised the protocol critically for important intellectual content and approved the final manuscript.

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Competing interests

None declared.

Ethics approval

Ethics Committee, Peking Union Medical College Hospital, China. (Protocol number: S-572).

Trial status

The trial is currently in the data collection phase. Recruitment to the study started in December, 2013. It is anticipated that full post and follow-up data will be finalized in September, 2016.

REFERENCES

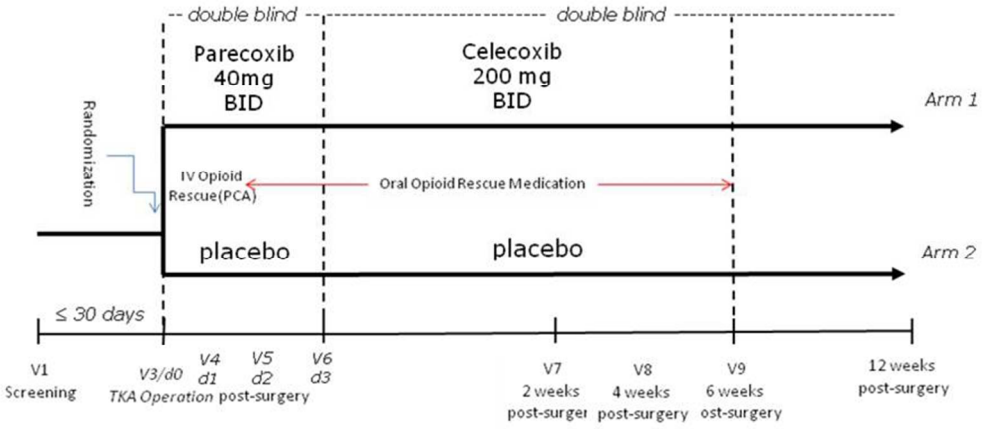
1. Bennell KL, Hunter DJ, Hinman RS. Management of osteoarthritis of the knee. *Bmj*. 2012;345:e4934
2. Bijlsma JW, Berenbaum F, Lafeber FP. Osteoarthritis: An update with relevance for clinical practice. *Lancet*. 2011;377:2115-2126
3. Carr AJ, Robertsson O, Graves S, Price AJ, Arden NK, Judge A, et al. Knee replacement. *Lancet*. 2012;379:1331-1340
4. Skou ST, Roos EM, Laursen MB, Rathleff MS, Arendt-Nielsen L, Simonsen O, et al. A randomized, controlled trial of total knee replacement. *The New England journal of medicine*. 2015;373:1597-1606
5. Lavand'homme P, Thienpont E. Pain after total knee arthroplasty: A narrative review focusing on the stratification of patients at risk for persistent pain. *The bone & joint journal*. 2015;97-B:45-48
6. Thomazeau J, Rouquette A, Martinez V, Rabuel C, Prince N, Laplanche JL, et al. Acute pain factors predictive of post-operative pain and opioid requirement in multimodal analgesia following knee replacement. *European journal of pain*. 2015
7. Elmallah RK, Cherian JJ, Pierce TP, Jauregui JJ, Harwin SF, Mont MA. New and common perioperative pain management techniques in total knee arthroplasty. *The journal of knee surgery*. 2015
8. Capdevila X, Barthelet Y, Biboulet P, Ryckwaert Y, Rubenovitch J, d'Athis F. Effects of perioperative analgesic technique on the surgical outcome and duration of rehabilitation after major knee surgery. *Anesthesiology*. 1999;91:8-15
9. Holm B, Kristensen MT, Bencke J, Husted H, Kehlet H, Bandholm T. Loss of knee-extension strength is related to knee swelling after total knee arthroplasty. *Archives of physical medicine and rehabilitation*. 2010;91:1770-1776
10. Honsawek S, Deepaisarnsakul B, Tanavalee A, Sakdinakiattikoon M, Ngarmukos S, Preativatanyou K, et al. Relationship of serum il-6, c-reactive protein, erythrocyte sedimentation rate, and knee skin temperature after total knee arthroplasty: A prospective study. *International orthopaedics*. 2011;35:31-35
11. Schroer WC, Diesfeld PJ, LeMarr AR, Reedy ME. Benefits of prolonged postoperative cyclooxygenase-2 inhibitor administration on total knee arthroplasty recovery: A double-blind, placebo-controlled study. *The Journal of arthroplasty*. 2011;26:2-7
12. Hubbard RC, Naumann TM, Traylor L, Dhadda S. Parecoxib sodium has opioid-sparing effects in patients undergoing total knee arthroplasty under spinal anaesthesia. *British journal of anaesthesia*. 2003;90:166-172
13. Huang YM, Wang CM, Wang CT, Lin WP, Horng LC, Jiang CC. Perioperative celecoxib administration for pain management after total knee arthroplasty - a randomized, controlled study. *BMC musculoskeletal disorders*. 2008;9:77
14. Rasmussen GL, Steckner K, Hogue C, Torri S, Hubbard RC. Intravenous parecoxib sodium foracute pain after orthopedic knee surgery. *American journal of orthopedics*. 2002;31:336-343
15. Nussmeier NA, Whelton AA, Brown MT, Joshi GP, Langford RM, Singla NK, et al. Safety and efficacy of the cyclooxygenase-2 inhibitors parecoxib and valdecoxib after noncardiac surgery. *Anesthesiology*. 2006;104:518-526

16. Joshi GP, Viscusi ER, Gan TJ, Minkowitz H, Cippolle M, Schuller R, et al. Effective treatment of laparoscopic cholecystectomy pain with intravenous followed by oral cox-2 specific inhibitor. *Anesthesia and analgesia*. 2004;98:336-342, table of contents
17. Gan TJ, Joshi GP, Viscusi E, Cheung RY, Dodge W, Fort JG, et al. Preoperative parenteral parecoxib and follow-up oral valdecoxib reduce length of stay and improve quality of patient recovery after laparoscopic cholecystectomy surgery. *Anesthesia and analgesia*. 2004;98:1665-1673, table of contents
18. Gan TJ, Joshi GP, Zhao SZ, Hanna DB, Cheung RY, Chen C. Presurgical intravenous parecoxib sodium and follow-up oral valdecoxib for pain management after laparoscopic cholecystectomy surgery reduces opioid requirements and opioid-related adverse effects. *Acta anaesthesiologica Scandinavica*. 2004;48:1194-1207
19. Langford RM, Joshi GP, Gan TJ, Mattera MS, Chen WH, Revicki DA, et al. Reduction in opioid-related adverse events and improvement in function with parecoxib followed by valdecoxib treatment after non-cardiac surgery: A randomized, double-blind, placebo-controlled, parallel-group trial. *Clinical drug investigation*. 2009;29:577-590
20. Bovill JG, Sebel PS, Stanley TH. Opioid analgesics in anesthesia: With special reference to their use in cardiovascular anesthesia. *Anesthesiology*. 1984;61:731-755
21. Leese PT, Hubbard RC, Karim A, Isakson PC, Yu SS, Geis GS. Effects of celecoxib, a novel cyclooxygenase-2 inhibitor, on platelet function in healthy adults: A randomized, controlled trial. *Journal of clinical pharmacology*. 2000;40:124-132
22. Robinson CM, Christie J, Malcolm-Smith N. Nonsteroidal antiinflammatory drugs, perioperative blood loss, and transfusion requirements in elective hip arthroplasty. *The Journal of arthroplasty*. 1993;8:607-610
23. Deeks JJ, Smith LA, Bradley MD. Efficacy, tolerability, and upper gastrointestinal safety of celecoxib for treatment of osteoarthritis and rheumatoid arthritis: Systematic review of randomised controlled trials. *Bmj*. 2002;325:619
24. Silverstein FE, Faich G, Goldstein JL, Simon LS, Pincus T, Whelton A, et al. Gastrointestinal toxicity with celecoxib vs nonsteroidal anti-inflammatory drugs for osteoarthritis and rheumatoid arthritis: The class study: A randomized controlled trial. Celecoxib long-term arthritis safety study. *Jama*. 2000;284:1247-1255
25. Cheer SM, Goa KL. Parecoxib (parecoxib sodium). *Drugs*. 2001;61:1133-1141; discussion 1142-1133
26. Barton SF, Langeland FF, Snabes MC, LeComte D, Kuss ME, Dhadda SS, et al. Efficacy and safety of intravenous parecoxib sodium in relieving acute postoperative pain following gynecologic laparotomy surgery. *Anesthesiology*. 2002;97:306-314
27. Graff J, Arabmotlagh M, Cheung R, Geisslinger G, Harder S. Effects of parecoxib and dipyrone on platelet aggregation in patients undergoing meniscectomy: A double-blind, randomized, parallel-group study. *Clinical therapeutics*. 2007;29:438-447

Table 1. Schedule of activities

The Schedule of Activities table provides an overview of the protocol visits and procedures. Refer to Study Procedures (Section 6) and Assessments (Section 7) for detailed information on each procedure and assessment required for compliance with the protocol.											
Protocol Activity	**Screen**	**Baseline Randomization Day-1**	**Surgery Day 0**	**Day 1**	**Day 2**	**Day 3**	**Day 4**	**Week 2**	**Week 4**	**Week 6**	**Week 12**
Visit	**1**	**2**	**3**	**4**	**5**	**6**		**7**	**8**	**9**	**10**
Informed Consent	X										
Demography	X										
Medical and Surgical History	X										
Physical Examination	X		X	X	X	X					
Vital signs	X	X	X	X	X	X	X	X	X	X	
Hematology	X			X				X			
Blood Chemistry	X			X				X			
Urinalysis	X			X				X			
Pregnancy test [a]	X									X	
ECG	X			X				X			
ESR and CRP	X					X		X	X	X	
Blood coagulation	X					X		X	X	X	
Peripheral blood cytokine concentration	X			X	X	X		X	X	X	
VAS	X			X	X	X		X	X	X	
EQ-5D	X					X		X	X	X	
Knee circumference and skin temperature	X			X	X	X		X	X	X	
X-ray	X										
Echocardiogram	X										
Pulmonary Function	X										
Ultrasound tests	X										
Blood transfusion tests	X										
WOMAC & KSS	X					X		X	X	X	
Inclusion/exclusion criteria	X	X									
Registration/Randomization		X	X								
Hospital Admission	X										
Surgery – Total Knee Arthroplasty			X								
Synovial fluid cytokine concentration			X	X	X						
Infusion of Parecoxib or placebo 40mg BID				X	X	X					
Record Morphine consumption				X							

The Schedule of Activities table provides an overview of the protocol visits and procedures. Refer to Study Procedures (Section 6) and Assessments (Section 7) for detailed information on each procedure and assessment required for compliance with the protocol.											
Protocol Activity	**Screen**	**Baseline Randomization Day-1**	**Surgery Day 0**	**Day 1**	**Day 2**	**Day 3**	**Day 4**	**Week 2**	**Week 4**	**Week 6**	**Week 12**
Celebrex/placebo 200mg BID							X----------X				
Recording the cumulative tramadol consumption					X	X	X	X	X	X	
Adverse Event		X	X	X	X	X	X	X	X	X	X[b]



Flowchart of the "PIPFORCE" trial design.
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Table 1. **SPIRIT 2013 Checklist: Recommended Items to Address in a Clinical Trial Protocol and Related Documents***

Section/Item	Item Number	Description	
Administrative information			
Title	1	Descriptive title identifying the study design, population, interventions, and, if applicable, trial acronym	Yes, please see the "Title " part.
Trial registration	2a	Trial identifier and registry name. If not yet registered, name of intended registry	Yes, please see the "Abstract" Part
	2b	All items from the World Health Organization Trial Registration Data Set (**Appendix Table**, available at www.annals.org)	
Protocol version	3	Date and version identifier	Yes, please see the "Abstract" Part
Funding	4	Sources and types of financial, material, and other support	Yes, please see the "Funding" part
Roles and responsibilities	5a	Names, affiliations, and roles of protocol contributors	Yes, please see the "Contributors" part
	5b	Name and contact information for the trial sponsor	Yes, please see the "Funding" part
	5c	Role of study sponsor and funders, if any, in study design; collection, management, analysis, and interpretation of data; writing of the report; and the decision to submit the report for publication, including whether they will have ultimate authority over any of these activities	Yes, please see the "Funding" part
	5d	Composition, roles, and responsibilities of the coordinating center, steering committee, end point adjudication committee, data management team, and other individuals or groups overseeing the trial, if applicable (see item 21a for DMC)	Yes, please see the "Contributors" part
Introduction			
Background and rationale	6a	Description of research question and justification for undertaking the trial, including summary of relevant studies (published and unpublished) examining benefits and harms for each intervention	Yes, , Please see the "Introduction" Part
	6b	Explanation for choice of comparators	Yes, , Please see the "Introduction" Part
Objectives	7	Specific objectives or hypotheses	
Trial design	8	Description of trial design, including type of trial (e.g., parallel group, crossover, factorial, single group), allocation ratio, and framework (e.g., superiority, equivalence, noninferiority, exploratory)	Yes, , Please see the "Introduction" Part Yes, , Please see the "Introduction" Part
Methods			
Participants, interventions, and outcomes			
Study setting	9	Description of study settings (e.g., community clinic, academic hospital) and list of countries where data will be collected. Reference to where list of study sites can be obtained	Yes, please see the "3.2 Study setting"
Eligibility criteria	10	Inclusion and exclusion criteria for participants. If applicable, eligibility criteria for study centers and individuals who will perform the interventions (e.g., surgeons, psychotherapists)	Yes, please see the "3.3 Study Participants"
Interventions	11a	Interventions for each group with sufficient detail to allow replication, including how and when they will be administered	Yes, please see the "3.4 Intervention measures"
	11b	Criteria for discontinuing or modifying allocated interventions for a given trial participant (e.g., drug dose change in response to harms, participant request, or improving/worsening disease)	Yes, please see the "3.3.3 withdrawal criteria"
	11c	Strategies to improve adherence to intervention protocols, and any procedures for monitoring adherence (e.g., drug tablet return, laboratory tests)	Yes, please see the "3.4 Intervention measures"
	11d	Relevant concomitant care and interventions that are permitted or prohibited during the trial	Yes, please see the "3.4 Intervention measures"
Outcomes	12	Primary, secondary, and other outcomes, including the specific measurement variable (e.g., systolic blood pressure), analysis metric (e.g., change from baseline, final value, time to event), method of aggregation (e.g., median, proportion), and time point for each outcome. Explanation of the clinical relevance of chosen efficacy and harm outcomes is strongly recommended	Yes, please see the "3.5 Outcome measures"
Participant timeline	13	Time schedule of enrollment, interventions (including any run-ins and washouts), assessments, and visits for participants. A schematic diagram is highly recommended (**Figure**).	Yes, please see the "3.6 Study procedures" and Figure 1(Flowchart of the trial design)
Sample size	14	Estimated number of participants needed to achieve study objectives and how it was determined, including clinical and statistical assumptions supporting any sample size calculations	Yes, please see the "3.10 Sample size"
Recruitment	15	Strategies for achieving adequate participant enrollment to reach target sample size	Yes, please see the "3. Design and Methods"
Assignment of interventions (for controlled trials)			
Allocation			
Sequence generation	16a	Method of generating the allocation sequence (e.g., computer-generated random numbers), and list of any factors for stratification. To reduce predictability of a random sequence, details of any planned restriction (e.g., blocking) should be provided in a separate document that is unavailable to those who enroll participants or assign interventions	Yes, please see the "3.4.1 Allocation to treatment"
Allocation concealment mechanism	16b	Mechanism of implementing the allocation sequence (e.g., central telephone; sequentially numbered, opaque, sealed envelopes), describing any steps to conceal the sequence until interventions are assigned	Yes, please see the "3.4.1 Allocation to treatment"
Implementation	16c	Who will generate the allocation sequence, who will enroll participants, and who will assign participants to interventions	Yes, please see the "3.4.1 Allocation to treatment"
Blinding (masking)	17a	Who will be blinded after assignment to interventions (e.g., trial participants, care providers, outcome assessors, data analysts), and how	Yes, please see the "3.4.1 Allocation to treatment"
	17b	If blinded, circumstances under which unblinding is permissible, and procedure for revealing a participant's allocated intervention during the trial	Yes, please see the "3.4.1 Allocation to treatment"

Continued on following page

Table 1—**Continued**

Section/Item	Item Number	Description	
Data collection, management, and analysis			
Data collection methods	18a	Plans for assessment and collection of outcome, baseline, and other trial data, including any related processes to promote data quality (e.g., duplicate measurements, training of assessors) and a description of study instruments (e.g., questionnaires, laboratory tests) along with their reliability and validity, if known. Reference to where data collection forms can be found, if not in the protocol.	Yes, please see the "3.11. Data collection, management, and statistical analysis"
	18b	Plans to promote participant retention and complete follow-up, including list of any outcome data to be collected for participants who discontinue or deviate from intervention protocols	Yes, please see the "3.11. Data collection, management, and statistical analysis"
Data management	19	Plans for data entry, coding, security, and storage, including any related processes to promote data quality (e.g., double data entry; range checks for data values). Reference to where details of data management procedures can be found, if not in the protocol.	Yes, please see the "3.11. Data collection, management, and statistical analysis"
Statistical methods	20a	Statistical methods for analyzing primary and secondary outcomes. Reference to where other details of the statistical analysis plan can be found, if not in the protocol.	Yes, please see the "3.11. Data collection, management, and statistical analysis"
	20b	Methods for any additional analyses (e.g., subgroup and adjusted analyses)	Yes, please see the "3.11. Data collection, management, and statistical analysis"
	20c	Definition of analysis population relating to protocol nonadherence (e.g., as-randomized analysis), and any statistical methods to handle missing data (e.g., multiple imputation)	Yes, please see the "3.11. Data collection, management, and statistical analysis"
Monitoring			
Data monitoring	21a	Composition of DMC; summary of its role and reporting structure; statement of whether it is independent from the sponsor and competing interests; and reference to where further details about its charter can be found, if not in the protocol. Alternatively, an explanation of why a DMC is not needed.	Yes, please see the "3.11. Data collection, management, and statistical analysis"
	21b	Description of any interim analyses and stopping guidelines, including who will have access to these interim results and make the final decision to terminate the trial	Yes, please see the "3.11. Data collection, management, and statistical analysis"
Harms	22	Plans for collecting, assessing, reporting, and managing solicited and spontaneously reported adverse events and other unintended effects of trial interventions or trial conduct	Yes, please see the "3.5 Adverse Events Reporting"
Auditing	23	Frequency and procedures for auditing trial conduct, if any, and whether the process will be independent from investigators and the sponsor	Yes, please see the "3.12 Quality control and quality assurance"
Ethics and dissemination			
Research ethics approval	24	Plans for seeking REC/IRB approval	Yes, please see the supplemental ethics approval certificate
Protocol amendments	25	Plans for communicating important protocol modifications (e.g., changes to eligibility criteria, outcomes, analyses) to relevant parties (e.g., investigators, REC/IRBs, trial participants, trial registries, journals, regulators)	Yes, please see the "Ethics and dissemination"
Consent or assent	26a	Who will obtain informed consent or assent from potential trial participants or authorized surrogates, and how (see item 32)	Yes, please see the supplemental consent inform
	26b	Additional consent provisions for collection and use of participant data and biological specimens in ancillary studies, if applicable	Yes, please see the supplemental consent inform
Confidentiality	27	How personal information about potential and enrolled participants will be collected, shared, and maintained in order to protect confidentiality before, during, and after the trial	Yes, please see the supplemental consent inform
Declaration of interests	28	Financial and other competing interests for principal investigators for the overall trial and each study site	Yes, please see the "Competing interests"
Access to data	29	Statement of who will have access to the final trial data set, and disclosure of contractual agreements that limit such access for investigators	Yes, please see the "3.11. Data collection, management, and statistical analysis"
Ancillary and post-trial care	30	Provisions, if any, for ancillary and post-trial care, and for compensation to those who suffer harm from trial participation	Yes, please see the supplemental consent inform
Dissemination policy	31a	Plans for investigators and sponsor to communicate trial results to participants, health care professionals, the public, and other relevant groups (e.g., via publication, reporting in results databases, or other data-sharing arrangements), including any publication restrictions	Yes, please see the "Ethics and dissemination"
	31b	Authorship eligibility guidelines and any intended use of professional writers	Yes, please see the "Ethics and dissemination"
	31c	Plans, if any, for granting public access to the full protocol, participant-level data set, and statistical code	Yes, please see the "Ethics and dissemination"
Appendices			
Informed consent materials	32	Model consent form and other related documentation given to participants and authorized surrogates	Yes, please see the supplemental consent inform
Biological specimens	33	Plans for collection, laboratory evaluation, and storage of biological specimens for genetic or molecular analysis in the current trial and for future use in ancillary studies, if applicable	Yes, please see the supplemental consent inform

DMC = data monitoring committee; IRB = institutional review board; REC = research ethics committee; SPIRIT = Standard Protocol Items: Recommendations for Interventional Trials.
* It is strongly recommended that this checklist be read in conjunction with the SPIRIT 2013 Explanation and Elaboration (31) for important clarification on the items. Amendments to the protocol should be tracked and dated. The SPIRIT checklist is copyrighted by the SPIRIT Group and is reproduced with permission.

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Efficacy and Safety of Postoperative Intravenous Parecoxib Sodium Followed by Oral Celecoxib Post Total Knee Arthroplasty in Osteoarthritis Patients (PIPFORCE): Study Protocol for a Multicenter, Double Blind, Parallel-group Trial

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Complete List of Authors:	Zhuang, Qiangyu; Peking Union Medical College Hospital, Orthopedics Bian, Yanyan; Peking Union Medical College Hospital, Orthopedics Department Wang, Wei; Peking Union Medical College Hospital, Orthopaedics Department Jiang, Jingmei; Chinese Academy of Medical Sciences Feng, Bin; Peking Union Medical College Hospital, Orthopedics Department Sun, Tiezheng; Peking University People\'s Hospital, Department of Orthopaedics Lin, Jianhao; Peking University People\'s Hospital Zhang, Miaofeng; The Second Affiliated Hospital of Zhejiang University, Department of Orthopaedics Yan, Shigui; The Second Affiliated Hospital of Zhejiang University, Department of Orthopaedics Shen, Bin; West China Hospital, Sichuan University, Department of Orthopaedics Pei, Fuxing; West China Hospital, Sichuan University, Department of Orthopaedics Weng, Xisheng; Peking Union Medical College Hospital, Orthopedics Department;
Primary Subject Heading:	Surgery
Secondary Subject Heading:	Surgery
Keywords:	parecoxib, celecoxib, total knee arthroplasty, postoperative pain, cumulative opioid consumption, opioid sparing

Efficacy and Safety of Postoperative Intravenous Parecoxib Sodium Followed by Oral Celecoxib Post Total Knee Arthroplasty in Osteoarthritis Patients (PIPFORCE): Study Protocol for a Multicenter, Double Blind, Parallel-group Trial

Qianyu Zhuang[1], Yanyan Bian[1], Wei Wang[1], Jingmei jiang[2], Bin Feng[1], Tiezheng Sun[3], Jianhao Lin[3], Miaofeng Zhang[4], Shigui Yan[4], Bin Shen[5], Fuxing Pei[5], Xisheng Weng[1#]

Affiliations:

1. Department of Orthopaedics, Peking Union Medical College Hospital, No.1 Shuaifuyuan, Wangfujing, Beijing 100730, China
2. Department of Epidemiology and Biostatistics, Institute of Basic Medical Sciences Chinese Academy of Medical Sciences/School of Basic Medicine, Peking Union Medical College, Beijing, China .
3. Department of Orthopaedics, Peking University People's Hospital, No. 11 Xizhimen South Street, Xicheng District, Beijing 100044, P. R. China
4. Department of Orthopaedics, The Second Affiliated Hospital of Zhejiang University, Qingchun street No. 79, Hangzhou, Zhejiang Province, 310003, China
5. Department of Orthopaedics, West China Hospital, Sichuan University, No. 37, Guoxue Street, Wuhou district, Chengdu, Sichuan 610041, China

[#] Corresponding Authors:

Xisheng Weng, MD & Professor
Peking Union Medical College Hospital
1 Shuai Fu Yuan Beijing 100730 P. R. China
Telephone Number: 86-13366200018
Fax Number: 86-10-69152810
Email: wengxishengpumch@126.com

Key Words: parecoxib; celecoxib; total knee arthroplasty; postoperative pain; cumulative opioid consumption

Word Count: 7614

Abstract:

Introduction: Total knee arthroplasty (TKA) has been regarded as a most painful orthopedic surgery. Although many surgeons sequentially use parecoxib and celecoxib as a routine strategy for controlling pain post TKA, high quality evidence is still lacking to prove the effect of this sequential regimen, especially at the medium-term follow-up. The purpose of this study, therefore, is to evaluate efficacy and safety of postoperative intravenous parecoxib sodium followed by oral celecoxib in OA patients undergoing TKA. The hypothesis is that compared to placebo with opioids as rescue treatment, sequentially use of parecoxib and celecoxib can achieve not only less morphine consumption over postoperatively 2 weeks, but also better pain control, quicker functional recovery over postoperatively 6 weeks, and less opioid related adverse events over 12-week recovery phase.

Methods and Analysis: This study is designed as multicenter, randomized, double blind, parallel-group, placebo control. Target sample size is 246. All subjects who meet the study inclusion and exclusion criteria will be randomly assigned in a 1:1 ratio to either parecoxib/celecoxib group or placebo group. The allocation or randomization will be study site based. The study will consist of 3 phases: an initial screening phase; a 6-week double blind treatment phase; and a 6 week follow up phase. The primary endpoint is cumulative opioid consumption till 2 weeks post operation. Secondary endpoints consist of postoperative VAS score, knee joint function, quality of life, local skin temperature, ESR and CRP, Cytokines, and blood coagulation parameters. Safety endpoints will be monitored, too.

Ethics and dissemination: Ethics approval for this study has been obtained from the Ethics Committee, Peking Union Medical College Hospital, China. (Protocol number: S-572) Study results will be made available in the form of manuscripts for publication and presentations at national and international meetings.

Trial registration number: ClinicalTrails.gov identifier: NCT02198924

Strengths and limitations of this study

- This is the first study to target the efficacy and safety of the clinical use of the sequential analgesia regimen of intravenous parecoxib followed by oral celecoxib after TKA surgery.
- Explore the benefits of prolonged sequential treatment of parecoxib and celecoxib in this population on the medium-term function recovery.
- The results will assist in the process of optimizing the NSAIDs drug use that can be incorporated into the standard multimodal analgesic regimen for managing postoperative pain.
- Potential limitations include the need for further validation studies from other institutions outside of China, lack of investigation of the long-term (e.g. >3 months) effects of the sequential treatment, lack of evaluation of the anxiety levels as endpoints, and compromise of the test accuracy of cytokines of synovial fluid.

1. Introduction

Osteoarthritis (OA) is a chronic degenerative joint disorder which is frequently occurred in the elderly.[1, 2] In mainland China, knee OA is the leading cause of disability in elderly patients. Total knee arthroplasty (TKA) is now generally regarded as an effective treatment for end-stage knee OA in pain alleviation, joint deformity correction and life quality improvement.[3, 4]

However, TKA has been regarded as a most painful orthopedic surgery due to the weight bearing characteristics of knee joint and the high demand of functional exercise within the 6-8 weeks post operation.[5, 6] Firstly, TKA induces massive tissue damage and severe perioperative pain which jointly hampers the early postoperative rehabilitation and exerts negative effects on surgical outcome and patient satisfaction.[7] Secondly, postoperative pain, as the most suffering experience for TKA patients, may prolong postoperative bedbound duration and increase the risks for pulmonary infection, deep venous thrombosis (DVT), pulmonary embolism (PE) etc. [8] Thirdly, previous findings suggested that local inflammation trigged by tissue damage not only increases the central and peripheral pain sensitivity, but also leads to acute hemorrhage and swelling, which poses greater challenges to the postoperative rehabilitation. [9, 10]

The targeted treatment with selective cyclooxygenase (COX-2) inhibitor, such as parecoxib or celecoxib, can significantly reduce the inflammatory reaction level within two days post operation. [11-14] In addition, perioperative administration of celecoxib can

relieve postoperative pain and improve articular function, thereby improving life quality of the patients. Recently, sequential therapy of intravenous-to-oral COX-2 inhibitor administration has been demonstrated as effective in many post-operative pain control models. [15-19] Significant morphine sparing effect and reduction of opioid related complications were also observed. [15-19] In China, it's becoming a routine at many institutions that 40mg parecoxib be administered intravenously twice daily for the first 3 days after surgery, followed by 200mg celecoxib administered orally bid for 2 weeks or longer. Although satisfactory results of the sequential therapy on short-term pain alleviation and functional recovery have been preliminarily observed in clinical practice, high quality evidence is still lacking, especially at the medium/ long-term follow-up.

PIPFORCE study (Trial registration number: ClinicalTrails.gov identifier: NCT02198924) aims to investigate the sequential analgesia regimen with intravenous parecoxib followed by oral celecoxib for post-surgical analgesic treatment in osteoarthritis patients undergoing TKA surgery. Subjects will receive double-blinded study medication consisting of parecoxib injection in analgesic doses or matching placebo followed by oral Celecoxib in acute pain doses or matching placebo. The hypothesis is that subjects treated with parecoxib/celecoxib will consume less morphine over postoperative 2 weeks, achieve better pain control, quicker functional recovery over postoperative 6 weeks, and has less opioid adverse events than those treated with opioids alone over 12-week recovery phase.

2. Aim and objectives

2.1. Primary objectives

The primary objective of this study is to evaluate the morphine-sparing effects of the sequential treatment with parecoxib and celecoxib versus placebo in subjects undergoing TKA.

2.2. Secondary objectives

- To compare the effects of the sequential treatment versus placebo on pain relief, inflammation control and functional rehabilitation after TKA.
- To investigate the safety of the sequential treatment with parecoxib and celecoxib versus placebo post TKA.

3. Design and methods

3.1. Study Design

This study is an investigator initiated post marketing study which is designed as multicenter, randomized, double blind, parallel-group, and placebo-controlled.

3.2. Study Setting

This study is being conducted at Peking Union Medical College Hospital (PUMCH), China as the coordinating center, and 3 participating centers including 1)West China Hospital of Sichuan University, Sichuan Province, China, 2) People's Hospital of Peking University, Beijing, China, and 3)Second Affiliated Hospital of Zhejiang University College of Medicine, Zhejiang Province, China.

3.3. Study participants

3.3.1. Inclusion Criteria

Subject eligibility should be reviewed and documented by an appropriately qualified member of the investigator's study team before subjects are included in the study.

Subjects must meet all of the following inclusion criteria to be eligible for enrollment into the study:

1) The subject is scheduled to undergo elective unilateral total knee arthroplasty because of OA, performed under a standardized regimen of general anesthesia, as specified in this protocol.
2) Evidence of a personally signed and dated informed consent document indicating that the subject (or a legal representative) has been informed of all pertinent aspects of the study.
3) The subject is a male or female over 18 years of age.
4) Male and female subjects of childbearing potential must agree to use an effective method of contraception throughout the study and for 42 days after the last dose of assigned treatment. A subject is of childbearing potential if, in the opinion of the investigator, he/she is biologically capable of having children and is sexually active.
5) Total duration of the surgical procedure is four hours or less.
6) ASA grade 1-3 subjects.
7) Subjects who are willing and able to comply with scheduled visits, treatment plan, laboratory tests, standardized rehabilitation scheme, and other study procedures.
8) The subject is in satisfactory health as determined by the investigator on the basis of medical history and physical exam.
9) The subject must demonstrate sufficient psychomotor dexterity and cognitive capacity to use intravenous (IV) PCA.

10) The subject who live near to the hospital may be considered prior for the concern of convenient and sufficient follow-up.

3.3.2 Exclusion Criteria

The subjects will be excluded with any condition listed below:

1) The subject requires a revision to previous knee arthroplasty and/or is having a bilateral knee arthroplasties.
2) The subject requires an emergency knee arthroplasty.
3) Addiction to using any non-steroidal anti-inflammatory drugs (NSAIDs) and opioids
4) Subject has a known hypersensitivity to COX-2 specific inhibitors, sulfonamides, lactose, NSAIDs, opioids or acetaminophen/paracetamol. Subjects who have experienced asthma, urticaria or allergic type reactions after taking aspirin or other NSAIDs.
5) The subject has a history of any of the following arthritis: (i.e. rheumatoid arthritis, ankylosing spondylitis, psoriatic arthritis), chronic pain (e.g. fibromyalgia), metastasis, and Paget's disease.
6) The subject received any investigational medication within 30 days prior to the first dose of study medication or is scheduled to receive any investigational drug other than those described in the protocol during the study.
7) The subject has any known laboratory abnormality, which in the opinion of the investigator, would contraindicate study participation including ALT (SGPT), AST (SGOT), blood urea nitrogen or Creatinine ≧1.5 times the upper limit of the normal reference range.
8) The subject has an active malignancy of any type, or history of a malignancy (Subjects who have a history of basal cell carcinoma that has been successfully treated can be entered into the study. Subjects with a history of other malignancies that have been surgically removed and who have no evidence of recurrence for at least five years before study enrollment can also be entered into the study).
9) Subject had inflammatory bowel disease (e.g. Crohn's disease or ulcerative colitis), a chronic or acute renal or hepatic disorder, a significant coagulation defect, or any condition, which could preclude use of NSAIDs or COX-2 specific inhibitors.
10) The subject has active or suspected esophageal, gastric, pyloric channel, or duodenal ulceration history.
11) The subject has received warfarin or other anticoagulants during the 30 days preceding the first dose of study medication (Cardioprotective aspirin, ≦or 325 mg/day is permitted, when the dose has been stable for at least the month prior to

entering the study). Anticoagulation is permitted when related to the surgery, with such medicines as low molecular weight heparin including Lovenox and Fragmin.

12) Subject is anticipated to require or requires treatment with lithium.
13) Subject is ASA grade 4-5.
14) The subject has a history of a psychiatric disorder requiring new or changing treatment (A subject with a psychiatric disorder who has been stable on therapy may enter the study if they have not required any changes in their therapy for the 4 weeks prior to study entry and it is anticipated they will not need any changes for the 2-week duration of this study).
15) The subject has a history of uncontrolled chronic disease or a concurrent clinically significant illness, medical condition, which in the investigators' opinion, would contraindicate study participation or confound interpretation of the result. Including, but not exclusive to the following: uncontrolled hypertension, uncontrolled ischemic heart disease, uncontrolled cardiac insufficiency, history of coronary artery bypass graft (CABG) surgery, history of heart valve surgery or coronary stent implantation, history of peripheral vascular disease or cerebrovascular disease, moderate or severe hepatic impairment, fluid retention, heart failure, abdominal pain of unknown etiology (or where study medication could mask symptoms) or any other condition which in the opinion of the Investigator, would contraindicate study participation or confound interpretation of the results.
16) The subject has any cognitive impairment or other characteristics that would in the investigator's opinion preclude study participation or compliance with protocol mandated procedures.
17) Subject has a history of asthma or bronchospasm, which requires treatment with glucocorticoids.
18) Subject had a history of alcohol, analgesic or narcotic abuse.
19) Subject has been previously randomized into the study
20) Subjects who are investigational site staff members or relatives of those site staff
21) Participation in other studies within 3 months before the current study begins and/or during study participation
22) Other severe acute or chronic medical or psychiatric condition or laboratory abnormality that may increase the risk associated with study participation or investigational product administration or may interfere with the interpretation of study results and, in the judgment of the investigator, would make the subject inappropriate for entry into this study.

23) Pregnant females, breastfeeding females, or males and females of childbearing potential not using effective contraception or not agreeing to continue effective contraception from screening through 42 days after last dose of investigational product will not enter into this study.

3.3.3. Withdrawal criteria

At any stage of the study, subjects are free to consent withdraw from the study with their medication and or treatment to the disease and their well beings be taken care of by the investigator/hospital without any negative impact.

The investigator may decide that a subject needs to be withdrawn from the study based on evaluations of individual conditions and balancing of the potential benefit/risk caused by the study treatment to the subject. For example, in case that even max dose of oral tramadol could not give good rescue-pain control, we may withdraw the patient from the study to guarantee the pain control quality and clinical safety.

3.4 Intervention measures

3.4.1. Allocation to Treatment

All subjects who meet the study inclusion and exclusion criteria will be randomly assigned in a 1:1 ratio to either parecoxib/celecoxib group or placebo group. The allocation or randomization will be study site based.

The Electronic Data Capture (EDC) system will automatically generate subject identification numbers in sequence at baseline, which is subsequently linked to the treatment assignments at randomization. A copy of the randomization code will be maintained by the investigator designated a person(s) who is independent of the trial conduct. It is the responsibility of the Principal Investigator (PI) to ensure that the subject is eligible for participation in the study before requesting randomization.

The study will consist of **3 phases**: an initial screening phase which must be completed within 30 days prior to randomization; a 6-week double-blind treatment phase; and a 6-week follow-up phase. (**Figure 1**)

In the 1st phase, the investigator will initiate the required screening procedures after obtaining written informed consent. All qualified patients after selection by inclusive/exclusive criteria will be assigned in the order in which they are enrolled into the study, to receive their allocated treatment sequence according to a computer-generated randomization schedule prepared prior to the start of the study.

In the 2nd phase, after completion of screening, subjects that remain eligible will enter a 6 week double-blind randomized treatment period. All the participants will undergo

standard TKA on unilateral side under general anesthesia. Patients in the study group are supplied sequential treatment with parecoxib 40 mg intravenously (IV) twice daily (Q12h) for the first 3 days post-surgery followed by celecoxib 200mg orally twice daily (Q12h) for up to 6 weeks post-surgery; whereas control patients are supplied with the corresponding placebo with the same instructions. Patient-controlled intravenous analgesia (PCIA) with morphine is administrated to all the subjects starting immediately post-anesthesia and ending at 24h after operation. As long as oral intake is feasible, both the two groups may receive centrally-acting analgesic tramadol hydrochloride in oral form as rescue analgesia if VAS score ≧ 3. With the support of sufficient pain management, patients will be educated to perform functional exercise according to the standardized post-TKA exercise plan. The investigator will use patient diary at every visit to track the patient exercise, pain score, the study medication, and the rescue therapy.

- Surgical techniques: A standard medial parapatellar approach was used through a midline skin incision, and a tourniquet was used which was inflated (280mmHg) following limb exsanguination immediately before skin preparation. Bone cuts and soft tissue balancing were done in the same sequence. The joint capsule and wound layers were closed in layers. A wool and crepe dressing was applied to the wound from mid-calf to mid-thigh at which point the tourniquet was then released.
- Anesthesia regimen: All 4 centers in this study will adopt the same anesthesia protocol (as presented above) and same anesthesia drugs to minimize difference among centers and ensure the comparability between the two study groups. The general anesthesia protocol is as follows: Patients will be operated under general anesthesia (GA) with tracheal intubation. GA induction will be conducted with intravenous administration of 1-2 ug/kg sufentanil, 0.6-0.8mg/kg rocuronium, 0.02mg/kg midazolam, 4mg ondansetron and target-controlled infusion (TCI) of propofol at 4.0- 6.0μg/ml. GA will be maintained with propofol TCI at 3-5ug/ml and continuous infusion of sufentanil at 0.1-0.2ug/kg. Rocuronium and 1ug/kg of sufentanil will be given when necessitated. Parecoxib or placebo drug will be dripped at suture, and neostigmine plus atropine will be given as muscle relaxant reversal before extubation. Total amount of intraoperative sufentanil consumption will be documented at GA conclusion.

In the 3rd phase, a telephone safety follow up visit at 12-week post-surgery will be taken to reveal any adverse events that may happen during the follow-up phase. All participants and all assessment operators were blinded to the identity of the treatments until all study data had been collated in a database.

3.4.2. Drug preparation and administration

3.4.2.1. Drug Formulation and Packaging

Parecoxib lyophilized presentation will be supplied in 40 mg per vial for intravenous administration; liquid presentation of placebo will be 0.9% saline in 2 ml per vial provided on site for intravenous administration. 2ml of 0.9% saline is used for reconstitution of parecoxib before administration.

Celebrex/Placebo 200 mg capsule presentation will be supplied in bottles for oral administration, and the number of capsule in each bottle are 12 for the first week post-surgery, 22 for the second week, 44 for the following two weeks scheduled respectively.

3.4.2.2. Preparation and Dispensing

Preparation of the study medication will be performed by medicine supplier in its GMP facility. According to the random list, a unique random code will be labeled to each vial/bottle of the medicine/placebo allowing no recognition of the real ingredients by trial operating nurse and or subjects.

Dispensing of the trial medication/placebo will be based on random code kept by the nurse for reconstitution of parecoxib or the label of the bottle for celecoxib by strictly following the sequence of the medicine identification number on the labels.

3.4.2.3. Administration

Parecoxib/placebo will be administered via intravenous route twice daily in twelve hours interval, the medication should not be given simultaneously with any other medication, and bolus injection is recommended after using 1 - 2ml of saline washing of infusion route in advance. The first iv administration of Parecoxib 40mg or placebo will be performed at the beginning of wound suture during the TKA surgery, followed by Parecoxib 40mg or placebo every 12 hours for 3 consecutive days.

Thereafter, celebrex/placebo will be administered orally, twice daily in twelve hours interval, such as at 8:00 and 20:00 respectively, with a cup of water. While discharged from hospital, the subjects are required to record the oral intake of celebrex/placebo by themselves on the diary card proved at each visit keeping the time points of administration as same as in ward.

3.4.2.5. Drug Storage

Parecoxib and placebo will be shipped and stored at a temperature below 25°C, and celebrex and placebo will be shipped and stored at 10 - 25 °C. Investigators and site staff are reminded to check temperatures daily and ensure that thermometers are working correctly as required for proper storage of investigational products.

3.4.2.6. Concomitant Medication(s)

The use of permitted concomitant therapy must be explained in detail, including prescription and nonprescription drugs, non-drug therapy, and dietary supplements and herbal preparations, as appropriate. The name, dose, date, and exact time of administration must be recorded in the CRF and appropriate medical records as source data for each medication administered to thepatient.

Prohibited medications

The following medications are prohibited for the duration of the study:

- NSAIDs and other analgesics (including steroid), by any route (i.e. oral, inhaled, topical, injected, rectal) within 5 days prior to TKA until the end of the study.
- Fluconazole, and/or lithium
- Hypnotics, anxiolytics, sedatives, tranquilizers, SSRIs, tricyclic anti-depressants, or benzodiazepines unless the subject's prescribed daily dose has remained unchanged throughout the previous 4 weeks and will remain unchanged throughout the study period.
- Herbal and alternative medicines such as: garlic, ginko biloba, ginseng.
- Local infiltration of the surgical site with anesthetic is prohibited.

Permitted medications

- Pre-medication, if required, will be a short-acting benzodiazepine (e.g. temazepam)
- Anesthesia will be a standardized general anesthesia regimen as described above.
- Midazolam and propofol are given only intraoperatively with no administration after the surgery, thus avoiding the potential opioid sparing effect for the postoperative hours.
- Anti-coagulants: Low molecular weight heparin is permitted for post-surgical anticoagulant treatment.
- Aspirin＜325 mg/day is permitted for cardiovascular prophylaxis, if used at a stable dose for the 30 days prior to randomization.
- Anti-emetic drugs may be given, if needed. The dose and total number of doses of the anti-emetic treatment should be documented on the CRF.

3.4.3. Rescue Therapy

Intravenous rescue medication- PCA: After surgery, all subjects will be connected to patient-controlled analgesia (PCA) at the last stich of wound closure. The PCA pump setting protocol is as follows: Sixty milligrams morphine in 240ml normal saline (NS) (morphine 1mg/4ml) will be prescribed for postoperative patient control analgesia (PCA). The background infusion rate of PCA is set at 4ml/hr (morphine 1mg/hr), and 4ml

bolus infusion (morphine 1mg/bolus) is available with 15min lockout interval. A dosage limit of 60ml within 4hr is applied for preventing the potential adverse events.

All doses of morphine (PCA and bolus) must be recorded precisely with the date and time of administration and the amount of morphine given. If a subject is unable to use the PCA pump he/she must be withdrawn from the study and provided with appropriate analgesia.

Oral rescue medication: After PCA is discontinued, all subjects with a VAS more than 3 may take open-label oral rescue medication, tramadol 100mg each time as needed, not to exceed 400mg per day.

Only tramadol will be used as rescue medication post discharge from the hospital. Doctor and research nurse will give the participants very thorough and clear education on how to take tramadol as rescue medication (all subjects with a VAS equal to or more than 3 may take tramadol 100mg each time as needed, not to exceed 400mg per day), how to record on the patient diary, and how to return the left tramadol at each visit. They will also assess the use and consumption of the participants at each follow-up visit. No other analgesics will be allowed to taken by the participants post hospital discharge.

Consumption of both morphine and tramadol will be calculated together and converted to morphine equivalent dosage, the converting of tramadol to morphine equivalents is estimated as 300mg oral administered tramadol equals to 20mg of intravenous morphine.[20-23]

3.5. Outcome measures

3.5.1. Primary endpoint

Cumulative opioid consumption till 2 weeks post operation. It can be calculated as the sum of the cumulative Morphine consumption over the first 24 hours postsurgical period and the opioid drug consumption till 2w post operation. The converting of Tramadol to morphine equivalents is estimated as 300mg Tramadol equals to 20mg of morphine

3.5.2. Secondary endpoints

3.5.2.1. Key secondary endpoints

Knee Society Score (KSS) at 6w post operation.

3.5.2.2. Other secondary endpoints

- Western Ontario and McMaster Universities Osteoarthritis Index (WOMAC) index[24] prior to operation and at 2w,4w and 6w post operation
- Knee Society Score (KSS)[25] prior to operation and at 2w, 4w and 6w post operation

- Total morphine use: The cumulative morphine consumption over the first 24 hours postsurgical period.
- Cumulative opioid consumption till 24h, 72h, 2w, 4w, 6w post operation. For example, total narcotic use till 72h post operation will be calculated as the sum of the cumulative morphine consumption over the first 24 hours postsurgical period and the opioid drug consumption (converted to morphine equivalents) till 72h post operation.
- VAS (0-10)[26] prior to operation and at 24h, 48h, 72h, 2w, 4w and 6w post operation, with 0 representing no pain and 100 mm representing the worst imaginable pain.
- EQ-5D[27] and patient satisfaction prior to operation and 72h, 2w, 4w and 6w post operation. EQ-5D is a standard instrument for use as a measure of health outcome. It is cognitively simple, taking only a few minutes to complete.

3.5.3. Exploratory endpoints

- Knee circumference (measured 1cm proximal to the base of the patella) prior to operation and at 24h, 48h, 72h, 2w, 4w, 6w post operation. The measurements were performed in a quiet room, with a recording clerk and a physician present who measured and recorded dimensions of the knee circumference of both legs. Circumferential measurements were recorded to the nearest 0.1 cm with an ordinary tape measure.
- Knee skin temperature prior to operation and at 24h, 48h, 72h, 2w, 4w, 6w post operation.
- ESR and CRP at preoperative and at 72h, 2w, 4w and 6w post operation.
- Synovial fluid cytokine (including IL-6, IL-8, IL-10 and PGE2) concentration at 0h, 24h and 48h post operation.
- Peripheral blood cytokine (including IL-6, IL-8, IL-10 and PGE2) concentration prior to operation and at 24h, 48h, 72h, 2w, 4w, 6w post operation.
- Blood coagulation tests prior to operation and at 72h, 2w, 4w and 6w post operation.

3.5.3 Safety endpoints

The nature, incidence, duration, and severity of adverse events; discontinuation due to adverse events; adverse events occurring during and after trial medication discontinuation; body weight, clinical safety laboratory, 12-lead ECGs, physical exams, and vital signs will be monitored in this study.

3.6. Adverse event reporting

3.6.1. Adverse Event Definition

An adverse event (AE) is any untoward medical occurrence in a clinical investigation subject administered a product or medical device; the event need not necessarily have a causal relationship with the treatment or usage. Examples of AEs include but are not limited to: abnormal test findings, clinically significant symptoms and signs, changes in physical examination findings, hypersensitivity, progression/worsening of underlying disease, drug abuse, drug dependency, etc.

3.6.2. Serious Adverse Events (SAE)

An SAE is any untoward medical occurrence at any dose that:

- Results in death;
- Is life-threatening (immediate risk of death);
- Requires inpatient hospitalization or prolongation of existing hospitalization;
- Results in persistent or significant disability/incapacity (substantial disruption of the ability to conduct normal life functions);
- Results in congenital anomaly/birth defect.
- Lack of efficacy should be reported as an AE when it is associated with an SAE.

Medical and scientific judgment is exercised in determining whether an event is an important medical event. An important medical event may not be immediately life-threatening and/or result in death or hospitalization. However, if it is determined that the event may jeopardize the subject or may require intervention to prevent one of the other AE outcomes, the important medical event should be reported seriously.

3.6.3. Severity Assessment

If required on the AE case report forms (CRFs), the investigator will use the adjectives MILD, MODERATE, or SEVERE to describe the maximum intensity of the AE. For purposes of consistency, these intensity grades are defined as follows: 1) MILD: Does not interfere with subject's usual function. 2) MODERATE: Interferes to some extent with subject's usual function.3) SEVERE: Interferes significantly with subject's usual function.

3.6.4. Causality Assessment

The investigator's assessment of causality must be provided for all AEs (serious and non-serious); the investigator must record the causal relationship in the CRF, as appropriate, and report such an assessment in accordance with the serious adverse reporting requirements if applicable. If the investigator determines an SAE is associated with study procedures, the investigator must record this causal relationship in the source

documents and CRF, as appropriate, and report such an assessment in accordance with the SAE reporting requirements, if applicable.

3.6.5. Withdrawal Due to Adverse Events

Withdrawal due to AE should be distinguished from withdrawal due to insufficient response according to the definition of AE noted earlier, and recorded on the appropriate AE CRF page.

When a subject withdraws due to an SAE, the SAE must be reported in accordance with the reporting requirements defined below.

3.7. Study procedures

There will be altogether 10 visits in the study for a certain subject. (**Table 1**) Screening will be performed at visit 1, and the day for TKA operation will be considered as Day 0. There is a visit on one day before operation, the visit 2, when the qualification of subject to the study will be evaluated again before operation, and the visit right after operation is visit 3. Those on day 1, 2 and 3 post-surgery will be regarded as visits 4, 5 and 6 respectively, then there will be visits 7, 8 and 9 at 2 weeks, 4 weeks and 6 weeks post-surgery, and the last visit will be at 12 weeks post-surgery, the visit 10.

3.7.1. Screening and wash-out

Screening will be performed between visits 1 and 2, where the potential subjects will be evaluated by inclusion/exclusion criteria, demography and medical history recording, evaluation of the background diseases as well as OA for the knee to be operated on, physical examination and laboratory examinations including routine tests of blood and urine, biochemical, X-ray (chest, two lower limbs, and the knee joint), 12-lead ECG, echocardiogram, pulmonary function, ultrasound for lower extremities venous and arteria, blood transfusion test (8 items), blood type and pregnancy test for female subjects, ESR and CRP, peripheral blood cytokine concentration (IL6, IL8, IL10 and PEG2) and blood coagulation, WOMAC index and KSS, VAS and EQ-5D, knee circumference and skin temperature at baseline.

Before any trial required assessments been conducted, a written Informed Consent must be signed by the subject, witness to the signing is needed when the subject is unable to read or write.

There is a two-week wash-out period after the screening at visit 1 and before visit 2, in which subjects who have been receiving any NSAIDs will be stopped for using of these medicines for two weeks and asked to replace their NSAIDs with Tramadol when needed.

All required data must be recorded on CRF for verification and archiving. In this study, e-CRF will be applied allowing online source data verification.

Qualification of subject to the study will be evaluated again at visit 2 which is the day before operation, and randomization of the subject to receive either parecoxib or placebo in the first three days post-surgery, and either clebrex or placebo in the following 6 weeks will also be determined on the same visit.

3.7.2. Study Period

At visits 3 which is right after operation, physical examination will be performed, infusion of parecoxib or placebo 40mg Q12h in the first three days and recording of morphine consumption for 24 hours starts, and synovial fluid cytokine concentration will be tested. Safety evaluations are also conducted for the subjects.

At visits 4 and 5 the recording of accumulative morphine consumption stops, while that for tramadol starts at visit 4, physical examination and safety evaluations are also conducted for the subjects. Synovial fluid cytokine concentration is tested at 24 h and 48h post operation.

At visit 6 which is 72 hours after operation, infusion of parecoxib 40mg Q12 or placebo stops, and oral administration of celebrex 200mg Q12h /placebo starts on Day 4, while recording the cumulative tramadol consumption continues. Evaluations of VAS and EQ-5D will be performed, while testing of ESR, CRP, peripheral blood cytokine concentration and blood coagulation will also be performed. Safety evaluations are also conducted for the subjects.

3.7.3. Follow-up Visits

This period covers visits 7 through 9, where recording the cumulative Tramadol consumption at 2w, 4w and 6w after operation, WOMAC index and KSS at 2w, 4w and 6w post operation, evaluations of VAS and EQ-5D at 2w, 4w and 6w post operation, knee circumference and skin temperature at 2w, 4w and 6w post operation, ESR and CRP at 2w, 4w and 6w post operation, peripheral blood cytokine concentration at 2w, 4w and 6w post operation, and tests of blood coagulation at 2w, 4w and 6w post operation. Safety evaluations are also conducted for the subjects at each visit.

3.7.4. Post-Study Subject Telephone Interview

At 12 weeks post-surgery, only safety evaluations will be conducted for the subjects by a telephone follow-up.

All data required by above visits must be recorded on CRF for verification and archiving.

3.8. Breaking the Blind

This is a double-blind study. The subjects, investigators, study coordinators, clinical site staff, Clinical Research Associate (CRA), and staff directly involved with the study and its designees will be blinded to subject treatment assignment.

At the initiation of the study, the study site will be instructed on the method of breaking the blind. Blinding should only be broken in emergency situations for reason of subject safety. Whenever possible, the investigator or sub-investigator consults with a member of the study team prior to breaking the blind. When the blind is broken, the reason must be fully documented and entered on the CRF.

3.9. Stop Criteria

The subjects involved in this study have the right to quit at any time. In addition, subjects will be discontinued from the study if they meet any of the following criteria:

1) Clinical interventions (e.g. systemic or topical application of glucocorticoids, other NSAIDs used within six weeks after TKA) which may affect the study results within the observation period;
2) Occurrence of serious adverse event (SAE, e.g. malignant tumors, serious perioperative complications) which, in the opinion of the investigator, may complicate assessment of the effects of study drugs.

3.10. Ethical review and informed consent

Ethics approval for this study has been obtained from the Ethics Committee, Peking Union Medical College Hospital, China. The benefits and risks of participation in the trial will be explained to each patient, legal deputy, or witness by the investigators or their designee, and written informed consent will be obtained before the trial. The informed consent with the signature of the patient, legal deputy, and person who explained the benefits or risks will be preserved by the researchers. The trial will be conducted in accordance with the Declaration of Helsinki.

3.11. Sample Size Determination

Total 86 subjects per group would have 90% power in detecting 100 mg or more in mean difference of cumulative opioid consumption on Day 14 between the two groups, assuming a common standard deviation of 200, and a two-sided alpha level of 0.05. This would result in a total 172 subjects. In consideration of 30% drop outs, 246 subjects would be adequate for the study.

Due to lacking prospective studies for this type of endpoint, and in review of a retrospective evaluation of inpatient Celecoxib use after total hip and knee arthroplasty [15], our assumptions in the sample size estimation are conservatively stipulated.

3.12. Data collection, management, and statistical analysis

Data will be collected through EDC (Electronic Data Capture) system under intent-to-treat principals, i.e., all the data of the subjects who signed inform consent form will be included in the study database.

Data Quality Assurance will be achieved through

- Online Edit Checks at the time of data entry
- Database Edit Checks performed by Data Management (DM)
- Online query issuance/resolution among/between PI, CRA and DM
- Medical review of data listing by the project team

For this study, the following definitions of analysis population will be followed:

ITT (Intent-to-treat)

All the randomized subjects who signed ICF, and satisfied all inclusion/exclusion criteria at visit 2 will be included in ITT analysis set.

Analyses on demographics and baseline characters will be based on ITT analysis set, and the listings of subjects' information will also be based on ITT.

EAP (Effective Analysis Population)

All the subjects in ITT who have complete demographics data and evaluable baseline morphine use, and at least 1 post-baseline cumulative use of Tramadol.

All the analyses on efficacy will be based on EAP.

PP (Per-protocol Population)

All the subjects in EAP who don't have any major protocol deviation, no forbidden concomitant use, have the data of cumulative use of Tramadol in the first 2 weeks after operation, and the compliance in treatment use in the first 2 weeks after operation is in 80%~120%.

PP will be only used in primary efficacy analysis.

SS (Safety Set)

All the randomized subjects who had received at least one dose will be included in safety set. Analysis on adverse events, laboratory, ECG, and vital sign will be based on safety set.

All data collected at follow-up visits for patients in the study and control groups are compared by an independent statistician using SAS 9.3 statistical analysis software. Continuous variables will be summarized by treatment groups using descriptive statistics including number of subjects, mean, standard deviation, median, Q1, Q3, minimum and maximum. The statistics of t test, Welch-Satterthwaite t test or Mann-Whitney U test will be used in comparison between 2 groups based on the results of normality test and homogeneity of variance test. Paired t test will be used in comparison within each group if the variable normally distributed; otherwise signed rank test will be used. The statistical significance level of normality test and homogeneity of variance test is 0.05. Nominal categorical variables will be presented as “frequency (percentage)”. The statistics of Pearson Chi-Squared test, continuity adjusted Chi-Squared test or Fisher's exact test will be used in comparison between 2 groups based on the distribution of the variable considered. Ordinal categorical variables will be presented as “frequency (percentage)”. Mann-Whitney U test will be used in comparison between 2 groups. Two-sided p value will be used in the statistical tests, and the difference between groups will be considered statistically significant if $p < 0.05$.

For primary endpoint analysis, statistical methods for continuous variable analysis will be used in the superiority test of study group over control group on reducing morphine use. Additionally, ANCOVA will be used in primary endpoint analysis as supplemental analysis, the covariates include the subjects’ dosed days, gender, age, and weight.

In additional to general statistical methods, mixed model for repeated measures (MMRM) will also be used in secondary endpoints analysis.

For safety analysis, the adverse events, abnormal findings in laboratory tests will be listed with the relationship to the study treatments. Fisher’s exact test will be used to compare the rates of subjects who have at least one adverse event between study and control groups.

3.13. Quality control and quality assurance

During study conduct, investigator or its contracted agent will conduct periodic monitoring visits to ensure that the protocol and Good Clinical Practices (GCPs) are being followed. The monitors may review source documents to confirm that the data recorded on CRFs is accurate. The investigator and institution will allow monitors directly accessed to source documents to perform this verification.

Each step will be strictly performed according to the trial protocol. Each step of quality control of measured outcomes will be performed according to the standard operating

and quality control procedure.

4. Discussion

Total knee arthroplasty is associated with significant postoperative pain, which adversely affects patients' ability and desire to effectively rehabilitate their knee. [5, 6] Inadequate pain control has been correlated with prolonged postoperative bed time, increased incidence of pulmonary infection, deep venous thrombosis (DVT), pulmonary embolism (PE) and poor functional recovery in some patients after TKA.[8]

Multimodal analgesia is currently recommended for postoperative pain control after TKA.[7, 28-30] It basically refers to the administration, via the same route or by different routes, of multiple analgesics to provide superior analgesia and limit side effects and adverse events. Multimodal analgesia is achieved by combining different analgesics that act by different mechanisms (e.g., NSAIDs, opioids, and local anesthetics), resulting in additive or synergistic analgesia, lower total doses of analgesics, and fewer side effects.[28, 29] Among Multimodal analgesia modalities, NSAIDs, especially Selective cyclo-oxygenase-2 (COX-2) inhibitors play an important part in the postoperative pain control after TKA. [30]

Nonselective NSAIDs may cause gastrointestinal (GI) and hematologic adverse events, compromise platelet function [31], and are associated with increased postoperative bleeding and increased blood transfusion requirements after joint arthroplasty surgery[32]. Selective cyclo-oxygenase-2 (COX-2) inhibitors display similar anti-inflammatory properties with traditional NSAIDs, but lack many of the side effects associated with NSAIDs because they spare the COX-1 enzyme and have no clinically significant effect on platelet or gastrointestinal function. [31, 33, 34]

Parecoxib sodium (parecoxib) is the injectable prodrug of valdecoxib and is the only parenteral formulation of a selective COX-2 inhibitor NSAID.[35] It can be rapidly hydrolyzed *in vivo* to its active form, valdecoxib, which is approximately 28,000-fold more potent against COX-2 than COX-1.[36] Following IV injection, parecoxib is rapidly converted to valdecoxib, the pharmacologically active substance, by enzymatic hydrolysis in the liver. AUC and Cmax following twice daily administration is linear up to 50 mg IV and 20 mg IM. Following single IV and IM doses of parecoxib sodium 20 mg, Cmax of valdecoxib is achieved in approximately 30 minutes and approximately 1 hour,

respectively. After IV or IM dosing of parecoxib sodium, the elimination half-life (t1/2) of valdecoxib is about 8 hours. [37]

Parecoxib has been demonstrated as effective in several models of postoperative pain[38] with no effect on platelet function or gastric mucosa at doses up to 40 mg twice daily.[39] Celecoxib, another oral specific COX-2 inhibitor, was shown as not only have short-term pain reduction and morphine sparing effect in patients undergoing total knee arthroplasty[13], but also improve functionality recovery if prolonged use up to 6 weeks postoperatively[11].

Treatment of postoperative pain with intravenous with or without subsequent oral COX-2 specific inhibitor has been demonstrated as effective in many post-operative pain models.[15-19] Significant morphine sparing effect and reduction of opioid distressed symptoms were also observed. Combination of intravenous parecoxib and oral valdecoxib was used for less than 2 weeks in most of previous studies. In these studies [15-19], short-term postoperative pain control and morphine sparing effect were evaluated. However, to the best of our knowledge, no study has investigated the effect of prolonged (6 weeks) sequential treatment of intravenous parecoxib and oral celecoxib on the medium-term functionality recovery.

We present here the protocol of PIPFORCE study, which aims to investigate the sequential analgesia regimen with intravenous parecoxib followed by oral celecoxib for post-surgical analgesic treatment in osteoarthritis patients undergoing TKA. Subjects will receive study medication consisting of parecoxib injection in analgesic doses or matching placebo followed by oral celecoxib in acute pain doses or matching placebo in a double-blind fashion. The hypothesis is that subjects treated with parecoxib/celecoxib will consume less morphine over 2 weeks postoperative period, achieve improved pain control over study period, quicker return to functionality, and has less opioid adverse events than those treated with opioids alone over the 12-week recovery phase. Both treatment groups will be able to use open- label rescue medication with opioids.

The possible limitations of the PIPFORCE study are listed as follows: Firstly, Since the 4 study centers of this multicenter RCT study are all from mainland China, the future results of PIPFORCE study should be explained with this concern and require further validation studies in data sets from other institutions outside of China. Secondly, PIPFORCE study does not investigate the long-term (e.g. >3 months) effects of the sequential treatment on inflammation control and functional rehabilitation after TKA. Thirdly, several recent literatures[40, 41] reported parecoxib may exert positive influence on pain and anxiety levels in patients undergoing TKA. However, our

study design does not evaluate the anxiety levels as endpoints, which required further studies in the future to clarify. Lastly, cytokines of synovial fluid, as one of the exploratory endpoints, will be tested in this study aiming to observe the trend of change of local inflammation. However, the synovial fluid tested after surgery is actually obtained from the wound drainage and inevitably contains blood, which will compromise the test accuracy. We'll ensure that same technique is used to obtain the synovial fluid sample in both groups to guarantee the comparability. In addition, we will also observe peripheral blood cytokines as reference.

In spite of these possible limitations, the contribution from PIPFORCE study is expected to be a comprehensive understanding of how the sequential regimen with intravenous parecoxib followed by oral celecoxib affects postoperative pain relief, inflammation control and functional rehabilitation in osteoarthritis patients undergoing TKA. The completion of this study will provide solid evidence for the efficacy and safety of the clinical use of the sequential regimen of COX-2 specific inhibitors after TKA surgery. The results will assist in optimizing the NSAIDs use as a part of standard multimodal analgesic regimen for managing postoperative pain. Furthermore, this project will provide insight into the benefits of prolonged sequential treatment of parecoxib and celecoxib in this population on the medium-term functionality recovery.

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Contributors

WXS contribute as the senior author and the principle investigator (PI) of this study. ZQY, as the sub PI, wrote the first draft of the manuscript and contributed to the design of the study. BYY, WW, FB, STZ, ZMF advised on the study design. LJH, YSG, SB, PFX refined the protocol. JJM, as the medical statistician for the study, contributed to the statistical design, acquisition and analysis of data for the work. All authors revised the protocol critically for important intellectual content and approved the final manuscript.

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Competing interests

None declared.

Ethics approval

Ethics Committee, Peking Union Medical College Hospital, China. (Protocol number: S-572).

Trial status

The trial is currently in the data collection phase. Recruitment to the study started in December, 2013. It is anticipated that full post and follow-up data will be finalized in September, 2016.

REFERENCES

1. Bennell KL, Hunter DJ, Hinman RS. Management of osteoarthritis of the knee. *Bmj*. 2012;345:e4934
2. Bijlsma JW, Berenbaum F, Lafeber FP. Osteoarthritis: An update with relevance for clinical practice. *Lancet*. 2011;377:2115-2126
3. Carr AJ, Robertsson O, Graves S, Price AJ, Arden NK, Judge A, et al. Knee replacement. *Lancet*. 2012;379:1331-1340
4. Skou ST, Roos EM, Laursen MB, Rathleff MS, Arendt-Nielsen L, Simonsen O, et al. A randomized, controlled trial of total knee replacement. *The New England journal of medicine*. 2015;373:1597-1606
5. Lavand'homme P, Thienpont E. Pain after total knee arthroplasty: A narrative review focusing on the stratification of patients at risk for persistent pain. *The bone & joint journal*. 2015;97-B:45-48
6. Thomazeau J, Rouquette A, Martinez V, Rabuel C, Prince N, Laplanche JL, et al. Acute pain factors predictive of post-operative pain and opioid requirement in multimodal analgesia following knee replacement. *European journal of pain*. 2016;20:822-832
7. Elmallah RK, Cherian JJ, Pierce TP, Jauregui JJ, Harwin SF, Mont MA. New and common perioperative pain management techniques in total knee arthroplasty. *The journal of knee surgery*. 2016;29:169-178

8. Capdevila X, Barthelet Y, Biboulet P, Ryckwaert Y, Rubenovitch J, d'Athis F. Effects of perioperative analgesic technique on the surgical outcome and duration of rehabilitation after major knee surgery. *Anesthesiology*. 1999;91:8-15
9. Holm B, Kristensen MT, Bencke J, Husted H, Kehlet H, Bandholm T. Loss of knee-extension strength is related to knee swelling after total knee arthroplasty. *Archives of physical medicine and rehabilitation*. 2010;91:1770-1776
10. Honsawek S, Deepaisarnsakul B, Tanavalee A, Sakdinakiattikoon M, Ngarmukos S, Preativatanyou K, et al. Relationship of serum il-6, c-reactive protein, erythrocyte sedimentation rate, and knee skin temperature after total knee arthroplasty: A prospective study. *International orthopaedics*. 2011;35:31-35
11. Schroer WC, Diesfeld PJ, LeMarr AR, Reedy ME. Benefits of prolonged postoperative cyclooxygenase-2 inhibitor administration on total knee arthroplasty recovery: A double-blind, placebo-controlled study. *The Journal of arthroplasty*. 2011;26:2-7
12. Hubbard RC, Naumann TM, Traylor L, Dhadda S. Parecoxib sodium has opioid-sparing effects in patients undergoing total knee arthroplasty under spinal anaesthesia. *British journal of anaesthesia*. 2003;90:166-172
13. Huang YM, Wang CM, Wang CT, Lin WP, Horng LC, Jiang CC. Perioperative celecoxib administration for pain management after total knee arthroplasty - a randomized, controlled study. *BMC musculoskeletal disorders*. 2008;9:77
14. Rasmussen GL, Steckner K, Hogue C, Torri S, Hubbard RC. Intravenous parecoxib sodium foracute pain after orthopedic knee surgery. *American journal of orthopedics*. 2002;31:336-343
15. Nussmeier NA, Whelton AA, Brown MT, Joshi GP, Langford RM, Singla NK, et al. Safety and efficacy of the cyclooxygenase-2 inhibitors parecoxib and valdecoxib after noncardiac surgery. *Anesthesiology*. 2006;104:518-526
16. Joshi GP, Viscusi ER, Gan TJ, Minkowitz H, Cippolle M, Schuller R, et al. Effective treatment of laparoscopic cholecystectomy pain with intravenous followed by oral cox-2 specific inhibitor. *Anesthesia and analgesia*. 2004;98:336-342, table of contents
17. Gan TJ, Joshi GP, Viscusi E, Cheung RY, Dodge W, Fort JG, et al. Preoperative parenteral parecoxib and follow-up oral valdecoxib reduce length of stay and improve quality of patient recovery after laparoscopic cholecystectomy surgery. *Anesthesia and analgesia*. 2004;98:1665-1673, table of contents
18. Gan TJ, Joshi GP, Zhao SZ, Hanna DB, Cheung RY, Chen C. Presurgical intravenous parecoxib sodium and follow-up oral valdecoxib for pain management after laparoscopic cholecystectomy surgery reduces opioid requirements and opioid-related adverse effects. *Acta anaesthesiologica Scandinavica*. 2004;48:1194-1207
19. Langford RM, Joshi GP, Gan TJ, Mattera MS, Chen WH, Revicki DA, et al. Reduction in opioid-related adverse events and improvement in function with parecoxib followed by valdecoxib treatment after non-cardiac surgery: A randomized, double-blind, placebo-controlled, parallel-group trial. *Clinical drug investigation*. 2009;29:577-590
20. Lee CR, McTavish D, Sorkin EM. Tramadol. A preliminary review of its pharmacodynamic and pharmacokinetic properties, and therapeutic potential in acute and chronic pain states. *Drugs*. 1993;46:313-340

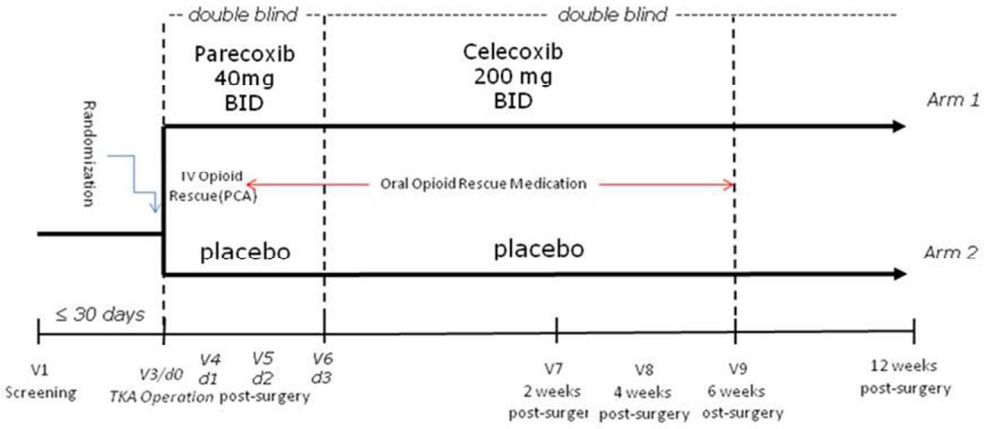
21. Silvasti M, Svartling N, Pitkanen M, Rosenberg PH. Comparison of intravenous patient-controlled analgesia with tramadol versus morphine after microvascular breast reconstruction. *European journal of anaesthesiology*. 2000;17:448-455
22. Hadi MA, Kamaruljan HS, Saedah A, Abdullah NM. A comparative study of intravenous patient-controlled analgesia morphine and tramadol in patients undergoing major operation. *The Medical journal of Malaysia*. 2006;61:570-576
23. Huang YG, Luo AL. Pain management drugs. ISBN-978-7-5062-8919-1. 2008.4
24. Symonds T, Hughes B, Liao S, Ang Q, Bellamy N. Validation of the chinese western ontario and mcmaster universities osteoarthritis index in patients from mainland china with osteoarthritis of the knee. *Arthritis care & research*. 2015;67:1553-1560
25. Liu D, He X, Zheng W, Zhang Y, Li D, Wang W, et al. Translation and validation of the simplified chinese new knee society scoring system. *BMC musculoskeletal disorders*. 2015;16:391
26. Brokelman RB, Haverkamp D, van Loon C, Hol A, van Kampen A, Veth R. The validation of the visual analogue scale for patient satisfaction after total hip arthroplasty. *European orthopaedics and traumatology*. 2012;3:101-105
27. Wang HM, Patrick DL, Edwards TC, Skalicky AM, Zeng HY, Gu WW. Validation of the eq-5d in a general population sample in urban china. *Quality of life research : an international journal of quality of life aspects of treatment, care and rehabilitation*. 2012;21:155-160
28. Baratta JL, Gandhi K, Viscusi ER. Perioperative pain management for total knee arthroplasty. *Journal of surgical orthopaedic advances*. 2014;23:22-36
29. Webb CA, Mariano ER. Best multimodal analgesic protocol for total knee arthroplasty. *Pain management*. 2015;5:185-196
30. Barrington JW, Halaszynski TM, Sinatra RS, Expert Working Group On A, Orthopaedics Critical Issues In H, Knee Replacement Arthroplasty FT. Perioperative pain management in hip and knee replacement surgery. *American journal of orthopedics*. 2014;43:S1-S16
31. Leese PT, Hubbard RC, Karim A, Isakson PC, Yu SS, Geis GS. Effects of celecoxib, a novel cyclooxygenase-2 inhibitor, on platelet function in healthy adults: A randomized, controlled trial. *Journal of clinical pharmacology*. 2000;40:124-132
32. Robinson CM, Christie J, Malcolm-Smith N. Nonsteroidal antiinflammatory drugs, perioperative blood loss, and transfusion requirements in elective hip arthroplasty. *The Journal of arthroplasty*. 1993;8:607-610
33. Deeks JJ, Smith LA, Bradley MD. Efficacy, tolerability, and upper gastrointestinal safety of celecoxib for treatment of osteoarthritis and rheumatoid arthritis: Systematic review of randomised controlled trials. *Bmj*. 2002;325:619
34. Silverstein FE, Faich G, Goldstein JL, Simon LS, Pincus T, Whelton A, et al. Gastrointestinal toxicity with celecoxib vs nonsteroidal anti-inflammatory drugs for osteoarthritis and rheumatoid arthritis: The class study: A randomized controlled trial. Celecoxib long-term arthritis safety study. *Jama*. 2000;284:1247-1255
35. Cheer SM, Goa KL. Parecoxib (parecoxib sodium). *Drugs*. 2001;61:1133-1141; discussion 1142-1133

36. Talley JJ, Brown DL, Carter JS, Graneto MJ, Koboldt CM, Masferrer JL, et al. 4-[5-methyl-3-phenylisoxazol-4-yl]- benzenesulfonamide, valdecoxib: A potent and selective inhibitor of cox-2. *Journal of medicinal chemistry*. 2000;43:775-777
37. Parecoxib sodium for injection package insert. Approval date: May 23, 2008. Revision date Sep25, 2012.
38. Barton SF, Langeland FF, Snabes MC, LeComte D, Kuss ME, Dhadda SS, et al. Efficacy and safety of intravenous parecoxib sodium in relieving acute postoperative pain following gynecologic laparotomy surgery. *Anesthesiology*. 2002;97:306-314
39. Graff J, Arabmotlagh M, Cheung R, Geisslinger G, Harder S. Effects of parecoxib and dipyrone on platelet aggregation in patients undergoing meniscectomy: A double-blind, randomized, parallel-group study. *Clinical therapeutics*. 2007;29:438-447
40. Sarridou DG, Chalmouki G, Braoudaki M, Siafaka I, Asmatzi C, Vadalouka A. Parecoxib possesses anxiolytic properties in patients undergoing total knee arthroplasty: A prospective, randomized, double-blind, placebo-controlled, clinical study. *Pain and therapy*. 2016
41. Vadalouca A, Moka E, Chatzidimitriou A, Siafaka I, Sikioti P, Argyra E. A randomized, double-blind, placebo-controlled study of preemptively administered intravenous parecoxib: Effect on anxiety levels and procedural pain during epidural catheter placement for surgical operations or for chronic pain therapy. *Pain practice : the official journal of World Institute of Pain*. 2009;9:181-194

Table 1. Schedule of activities

The Schedule of Activities table provides an overview of the protocol visits and procedures. Refer to Study Procedures (Section 6) and Assessments (Section 7) for detailed information on each procedure and assessment required for compliance with the protocol.											
Protocol Activity	**Screen**	**Baseline Randomization Day-1**	**Surgery Day 0**	**Day 1**	**Day 2**	**Day 3**	**Day 4**	**Week 2**	**Week 4**	**Week 6**	**Week 12**
Visit	**1**	**2**	**3**	**4**	**5**	**6**		**7**	**8**	**9**	**10**
Informed Consent	X										
Demography	X										
Medical and Surgical History	X										
Physical Examination	X		X	X	X	X					
Vital signs	X	X	X	X	X	X	X	X	X	X	
Hematology	X			X				X			
Blood Chemistry	X			X				X			
Urinalysis	X			X				X			
Pregnancy test [a]	X									X	
ECG	X			X				X			
ESR and CRP	X					X		X	X	X	
Blood coagulation	X					X		X	X	X	
Peripheral blood cytokine concentration	X			X	X	X		X	X	X	
VAS	X			X	X	X		X	X	X	
EQ-5D	X					X		X	X	X	
Knee circumference and skin temperature	X			X	X	X		X	X	X	
X-ray	X										
Echocardiogram	X										
Pulmonary Function	X										
Ultrasound tests	X										
Blood transfusion tests	X										
WOMAC & KSS	X					X		X	X	X	
Inclusion/exclusion criteria	X	X									
Registration/Randomization		X	X								
Hospital Admission	X										
Surgery – Total Knee Arthroplasty			X								
Synovial fluid cytokine concentration			X	X	X						
Infusion of Parecoxib or placebo 40mg BID				X	X	X					
Record Morphine consumption				X							

The Schedule of Activities table provides an overview of the protocol visits and procedures. Refer to Study Procedures (Section 6) and Assessments (Section 7) for detailed information on each procedure and assessment required for compliance with the protocol.											
Protocol Activity	**Screen**	**Baseline Randomization Day-1**	**Surgery Day 0**	**Day 1**	**Day 2**	**Day 3**	**Day 4**	**Week 2**	**Week 4**	**Week 6**	**Week 12**
Celebrex/placebo 200mg BID							X----------X				
Recording the cumulative tramadol consumption					X	X	X	X	X	X	
Adverse Event		X	X	X	X	X	X	X	X	X	X[b]



90x39mm (300 x 300 DPI)

SPIRIT 2013 Checklist: Recommended Items to Address in a Clinical Trial Protocol and Related Documents*

Section/Item	Item Number	Description	
Administrative information			
Title	1	Descriptive title identifying the study design, population, interventions, and, if applicable, trial acronym	**Yes, please see the "Title " part**
Trial registration	2a	Trial identifier and registry name. If not yet registered, name of intended registry.	**Yes, please see the "Abstract" Part**
	2b	All items from the World Health Organization Trial Registration Data Set (Appendix Table, available at www.annals.org)	
Protocol version	3	Date and version identifier	**Yes, please see the "Abstract" Part**
Funding	4	Sources and types of financial, material, and other support	**Yes, please see the "Funding" part**
Roles and responsibilities	5a	Names, affiliations, and roles of protocol contributors	**Yes, please see the "Contributors" part**
	5b	Name and contact information for the trial sponsor	**Yes, please see the "Funding" part**
	5c	Role of study sponsor and funders, if any, in study design; collection, management, analysis, and interpretation of data; writing of the report; and the decision to submit the report for publication, including whether they will have ultimate authority over any of these activities	**Yes, please see the "Funding" part**
	5d	Composition, roles, and responsibilities of the coordinating center, steering committee, end point adjudication committee, data management team, and other individuals or groups overseeing the trial, if applicable (see item 21a for DMC)	**Yes, please see the "Contributors" part**
Introduction			
Background and rationale	6a	Description of research question and justification for undertaking the trial, including summary of relevant studies (published and unpublished) examining benefits and harms for each intervention	**Yes, Please see the "Introduction" Part**

	6b	Explanation for choice of comparators	**Yes, Please see the "Introduction" Part**
Objectives	7	Specific objectives or hypotheses	**Yes, Please see the "Introduction" Part**
Trial design	8	Description of trial design, including type of trial (e.g., parallel group, crossover, factorial, single group), allocation ratio, and framework (e.g., superiority, equivalence, noninferiority exploratory)	**Yes, Please see the "Introduction" Part**
Methods			
Participants, interventions, and outcomes			
Study setting	9	Description of study settings (e.g., community clinic, academic hospital) and list of countries where data will be collected. Reference to where list of study sites can be obtained	**Yes, please see the "3.2 Study setting"**
Eligibility criteria	10	Inclusion and exclusion criteria for participants. If applicable, eligibility criteria for study centers and individuals who will perform the interventions (e.g., surgeons, psychotherapists)	**Yes, please see the "3.3 Study Participants"**
Interventions	11a	Interventions for each group with sufficient detail to allow replication, including how and when they will be administered	**Yes, please see the "3.4 Intervention measures**
	11b	Criteria for discontinuing or modifying allocated interventions for a given trial participant (e.g., drug dose change in response to harms, participant request, or improving/worsening disease)	**Yes, please see the "3.3.3 withdrawal criteria**
	11c	Strategies to improve adherence to intervention protocols, and any procedures for monitoring adherence (e.g., drug tablet return, laboratory tests)	**Yes, please see the "3.4 Intervention measures**
	11d	Relevant concomitant care and interventions that are permitted or prohibited during the trial	**Yes, please see the "3.4 Intervention measures**
Outcomes	12	Primary, secondary, and other outcomes, including the specific measurement variable (e.g., systolic blood pressure), analysis metric (e.g., change from baseline, final value, time to	**Yes, please see the "3.5 Outcome measures"**

		event), method of aggregation (e.g., median, proportion), and time point for each outcome. Explanation of the clinical relevance of chosen efficacy and harm outcomes is strongly recommended	
Participant timeline	13	Time schedule of enrollment, interventions (including any run-ins and washouts), assessments, and visits for participants. A schematic diagram is highly recommended (Figure).	**Yes, please see the "3.7 Study procedures" and Figure 1(Flowchart of the trial design)**
Sample size	14	Estimated number of participants needed to achieve study objectives and how it was determined, including clinical and statistical assumptions supporting any sample size calculations	**Yes, please see the "3.11 Sample Size Determination"**
Recruitment	15	Strategies for achieving adequate participant enrollment to reach target sample size	**Yes, please see the "3. Design and Methods"**
Assignment of interventions (for controlled trials)			
Allocation			
Sequence generation	16a	Method of generating the allocation sequence (e.g., computer-generated random numbers), and list of any factors for stratification. To reduce predictability of a random sequence, details of any planned restriction (e.g., blocking) should be provided in a separate document that is unavailable to those who enroll participants or assign interventions	**Yes, please see the "3.4.1 Allocation to treatment"**
Allocation concealment mechanism	16b	Mechanism of implementing the allocation sequence (e.g., central telephone; sequentially numbered, opaque, sealed envelopes), describing any steps to conceal the sequence until interventions are assigned	**Yes, please see the "3.4.1 Allocation to treatment"**
Implementation	16c	Who will generate the allocation sequence, who will enroll participants, and who will assign participants to interventions	**Yes, please see the "3.4.1 Allocation to treatment"**
Blinding (masking)	17a	Who will be blinded after assignment to interventions (e.g., trial participants, care providers, outcome assessors, data analysts), and how	**Yes, please see the "3.4.1 Allocation to treatment"**
	17b	If blinded, circumstances under which unblinding is permissible, and procedure for revealing a participant's allocated intervention during the trial	**Yes, please see the "3.4.1 Allocation to treatment"**

Data collection management, and analysis			
Data collection methods	18a	Plans for assessment and collection of outcome, baseline, and other trial data, including any related processes to promote data quality (e.g., duplicate measurements, training of assessors) and a description of study instruments (e.g., questionnaires, laboratory tests) along with their reliability and validity, if known. Reference to where data collection forms can be found, if not in the protocol.	**Yes, please see the "3.12. Data collection, management, and statistical analysis"**
	18b	Plans to promote participant retention and complete follow-up, including list of any outcome data to be collected for participants who discontinue or deviate from intervention protocols	**Yes, please see the "3.12. Data collection, management, and statistical analysis"**
Data management	19	Plans for data entry, coding, security, and storage, including any related processes to promote data quality (e.g., double data entry; range checks for data values). Reference to where details of data management procedures can be found, if not in the protocol	**Yes, please see the "3.12. Data collection, management, and statistical analysis"**
Statistical methods	20a	Statistical methods for analyzing primary and secondary outcomes. Reference to where other details of the statistical analysis plan can be found, if not in the protocol	**Yes, please see the "3.12. Data collection, management, and statistical analysis"**
	20b	Methods for any additional analyses (e.g., subgroup and adjusted analyses)	**Yes, please see the "3.12. Data collection, management, and statistical analysis"**
	20c	Definition of analysis population relating to protocol nonadherence (e.g., as-randomized analysis), and any statistical methods to handle missing data (e.g., multiple imputation)	**Yes, please see the "3.12. Data collection, management, and statistical analysis"**
Monitoring			
Data monitoring	21a	Composition of DMC; summary of its role and reporting structure; statement of whether it is independent from the sponsor and competing interests; and reference to where further details about its charter can be found, if not in the protocol. Alternatively, an explanation of why a DMC is not needed	**Yes, please see the "3.12. Data collection, management, and statistical analysis"**
	21b	Description of any interim analyses and stopping guidelines, including who will have access to these interim results and make the final decision to terminate the trial	**Yes, please see the "3.12. Data collection, management, and statistical analysis"**

Harms	22	Plans for collecting, assessing, reporting, and managing solicited and spontaneously reported adverse events and other unintended effects of trial interventions or trial conduct	**Yes, please see the "3.6 Adverse Events Reporting**
Auditing	23	Frequency and procedures for auditing trial conduct, if any, and whether the process will be independent from investigators and the sponsor	**Yes, please see the "3.13 Quality control and quality assurance**
Ethics and dissemination			
Research ethics approval	24	Plans for seeking REC/IRB approval	**Yes, please see the supplemental ethics approval certificate**
Protocol amendments	25	Plans for communicating important protocol modifications (e.g., changes to eligibility criteria, outcomes, analyses) to relevant parties (e.g., investigators, RECs/IRBs, trial participants, trial registries, journals, regulators)	**Yes, please see the "Ethics and dissemination"**
Consent or assent	26a	Who will obtain informed consent or assent from potential trial participants or authorized surrogates, and how (see item 32)	**Yes, please see the supplemental consent inform**
	26b	Additional consent provisions for collection and use of participant data and biological specimens in ancillary studies, if applicable	**Yes, please see the supplemental consent inform**
Confidentiality	27	How personal information about potential and enrolled participants will be collected, shared, and maintained in order to protect confidentiality before, during, and after the trial	**Yes, please see the supplemental consent inform**
Declaration of interests	28	Financial and other competing interests for principal investigators for the overall trial and each study site	**Yes, please see the "Competing interests"**
Access to data	29	Statement of who will have access to the final trial data set, and disclosure of contractual agreements that limit such access for investigators	**Yes, please see the "3.12. Data collection, management, and statistical analysis"**
Ancillary and post-trial care	30	Provisions, if any, for ancillary and post-trial care, and for compensation to those who suffer harm from trial participation	**Yes, please see the supplemental consent inform**
Dissemination policy	31a	Plans for investigators and sponsor to communicate trial results to participants, health care professionals, the public, and other relevant groups (e.g., via publication, reporting in results databases, or other data-sharing arrangements), including any publication	**Yes, please see the "Ethics and dissemination"**

		restrictions	
	31b	Authorship eligibility guidelines and any intended use of professional writers	**Yes, please see the "Ethics and dissemination"**
	31c	Plans, if any, for granting public access to the full protocol, participant-level data set, and statistical code	**Yes, please see the "Ethics and dissemination"**
Appendices			
Informed consent materials	32	Model consent form and other related documentation given to participants and authorized surrogates	**Yes, please see the supplemental consent inform**
Biological specimens	33	Plans for collection, laboratory evaluation, and storage of biological specimens for genetic or molecular analysis in the current trial and for future use in ancillary studies, if applicable	**Yes, please see the supplemental consent inform**

DMC = data monitoring committee; IRB = institutional review board; REC = research ethics committee; SPIRIT = Standard Protocol Items: Recommendations for Interventional Trials * It is strongly recommended that this checklist be read in conjunction with the SPIRIT 2013 Explanation and Elaboration (31) for important clarification on the items. Amendments to the protocol should be tracked and dated. The SPIRIT checklist is copyrighted by the SPIRIT Group and is reproduced with permission.

BMJ Open

Efficacy and Safety of Postoperative Intravenous Parecoxib Sodium Followed by Oral Celecoxib Post Total Knee Arthroplasty in Osteoarthritis Patients (PIPFORCE): Study Protocol for a Multicenter, Double Blind, Parallel-group Trial

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Complete List of Authors:	Zhuang, Qiangyu; Peking Union Medical College Hospital, Orthopedics Bian, Yanyan; Peking Union Medical College Hospital, Orthopedics Department Wang, Wei; Peking Union Medical College Hospital, Orthopaedics Department Jiang, Jingmei; Chinese Academy of Medical Sciences Feng, Bin; Peking Union Medical College Hospital, Orthopedics Department Sun, Tiezheng; Peking University People\'s Hospital, Department of Orthopaedics Lin, Jianhao; Peking University People\'s Hospital Zhang, Miaofeng; The Second Affiliated Hospital of Zhejiang University, Department of Orthopaedics Yan, Shigui; The Second Affiliated Hospital of Zhejiang University, Department of Orthopaedics Shen, Bin; West China Hospital, Sichuan University, Department of Orthopaedics Pei, Fuxing; West China Hospital, Sichuan University, Department of Orthopaedics Weng, Xisheng; Peking Union Medical College Hospital, Orthopedics Department;
Primary Subject Heading:	Surgery
Secondary Subject Heading:	Surgery
Keywords:	parecoxib, celecoxib, total knee arthroplasty, postoperative pain, cumulative opioid consumption, opioid sparing

Efficacy and Safety of Postoperative Intravenous Parecoxib Sodium Followed by Oral Celecoxib Post Total Knee Arthroplasty in Osteoarthritis Patients (PIPFORCE): Study Protocol for a Multicenter, Double Blind, Parallel-group Trial

Qianyu Zhuang[1], Yanyan Bian[1], Wei Wang[1], Jingmei jiang[2], Bin Feng[1], Tiezheng Sun[3], Jianhao Lin[3], Miaofeng Zhang[4], Shigui Yan[4], Bin Shen[5], Fuxing Pei[5], Xisheng Weng[1#]

Affiliations:

1. Department of Orthopaedics, Peking Union Medical College Hospital, No.1 Shuaifuyuan, Wangfujing, Beijing 100730, China
2. Department of Epidemiology and Biostatistics, Institute of Basic Medical Sciences Chinese Academy of Medical Sciences/School of Basic Medicine, Peking Union Medical College, Beijing, China .
3. Department of Orthopaedics, Peking University People's Hospital, No. 11 Xizhimen South Street, Xicheng District, Beijing 100044, P. R. China
4. Department of Orthopaedics, The Second Affiliated Hospital of Zhejiang University, Qingchun street No. 79, Hangzhou, Zhejiang Province, 310003, China
5. Department of Orthopaedics, West China Hospital, Sichuan University, No. 37, Guoxue Street, Wuhou district, Chengdu, Sichuan 610041, China

[#] Corresponding Authors:

Xisheng Weng, MD & Professor
Peking Union Medical College Hospital
1 Shuai Fu Yuan Beijing 100730 P. R. China
Telephone Number: 86-13366200018
Fax Number: 86-10-69152810
Email: wengxishengpumch@126.com

Key Words: parecoxib; celecoxib; total knee arthroplasty; postoperative pain; cumulative opioid consumption

Word Count: 7686

Abstract:

Introduction: Total knee arthroplasty (TKA) has been regarded as a most painful orthopedic surgery. Although many surgeons sequentially use parecoxib and celecoxib as a routine strategy for postoperative pain cotrol after TKA, high quality evidence is still lacking to prove the effect of this sequential regimen, especially at the medium-term follow-up. The purpose of this study, therefore, is to evaluate efficacy and safety of postoperative intravenous parecoxib sodium followed by oral celecoxib in osteoarthritis (OA) patients undergoing TKA. The hypothesis is that compared to placebo with opioids as rescue treatment, sequential use of parecoxib and celecoxib can achieve not only less morphine consumption over postoperative 2 weeks, but also better pain control, quicker functional recovery in postoperative 6 weeks, and less opioid related adverse events during 12-week recovery phase.

Methods and Analysis: This study is designed as a multicenter, randomized, double blind, parallel-group and placebo controlled trial. Target sample size is 246. All subjects who meet the study inclusion and exclusion criteria will be randomly assigned in a 1:1 ratio to either parecoxib/celecoxib group or placebo group. The randomization and allocation will be study site based. The study will consist of 3 phases: an initial screening phase; a 6-week double blind treatment phase; and a 6 week follow up phase. The primary endpoint is cumulative opioid consumption during 2 weeks post operation. Secondary endpoints consist of postoperative VAS score, knee joint function, quality of life, local skin temperature, ESR, CRP, cytokines, and blood coagulation parameters. Safety endpoints will be monitored, too.

Ethics and dissemination: Ethics approval for this study has been obtained from the Ethics Committee, Peking Union Medical College Hospital, China. (Protocol number: S-572) Study results will be available as published manuscripts and presentations at national and international meetings.

Trial registration number: ClinicalTrails.gov identifier: NCT02198924

Strengths and limitations of this study

- This is the first study to investigate the efficacy and safety of the sequential analgesia regimen of intravenous parecoxib followed by oral celecoxib after TKA surgery.
- Explore the benefits of prolonged sequential treatment of parecoxib and celecoxib in medium-term function recovery.
- The results will promote the NSAIDs drug incorporation into the standard multimodal analgesic regimen for postoperative pain control.
- Potential limitations include the need for further validation studies from other institutions outside China, lack of investigation of the long-term (e.g. >3 months) effects of the sequential treatment, and compromise of the test accuracy of synovial fluid cytokines.

1. Introduction

Osteoarthritis (OA) is a chronic degenerative joint disorder which frequently occurs in the elderly.[1, 2] In mainland China, knee OA is the leading cause of disability in elderly patients. Total knee arthroplasty (TKA) is now generally regarded as an effective treatment for end-stage knee OA in pain alleviation, joint deformity correction and life quality improvement.[3, 4]

However, TKA has been regarded as a most painful orthopedic surgery due to the weight bearing characteristics of knee joint and the high demand of functional exercise within the 6-8 weeks post operation.[5, 6] Firstly, TKA induces massive tissue damage and severe perioperative pain which jointly hamper the early postoperative rehabilitation and exerts negative effects on surgical outcome and patient satisfaction.[7] Secondly, postoperative pain, as the most suffering experience for TKA patients, may prolong postoperative bedbound duration and increase the risks for pulmonary infection, deep venous thrombosis (DVT), pulmonary embolism (PE) etc. [8] Thirdly, previous findings suggested that local inflammation triggerd by tissue damage not only increases the central and peripheral pain sensitivity, but also leads to acute hemorrhage and swelling, which poses greater challenges to the postoperative rehabilitation. [9, 10]

The targeted treatment with selective cyclooxygenase (COX-2) inhibitor, such as parecoxib or celecoxib, can significantly reduce the inflammatory reaction level within two days post operation. [11-14] In addition, perioperative administration of celecoxib can relieve postoperative pain and improve articular function, thereby improving life quality of the patients. Recently, sequential therapy of intravenous-to-oral COX-2 inhibitor

administration has been demonstrated as effective in many post-operative pain control models. [15-19] Significant morphine sparing effect and reduction of opioid related complications were also observed. [15-19] In China, it's becoming a routine at many institutions that 40mg parecoxib be administered intravenously twice daily for the first 3 days after surgery, followed by 200mg celecoxib administered orally twice daily for 2 weeks or longer. Although satisfactory results of the sequential therapy on short-term pain alleviation and functional recovery have been preliminarily observed in clinical practice, high quality evidence is still lacking, especially at the medium/ long-term follow-up.

PIPFORCE study (Trial registration number: ClinicalTrails.gov identifier: NCT02198924) aims to investigate the sequential analgesia regimen with intravenous parecoxib followed by oral celecoxib for post-surgical analgesic treatment in OA patients undergoing TKA surgery. Subjects will receive double-blinded study medication consisting of parecoxib injection in analgesic doses or matching placebo followed by oral Celecoxib in acute pain doses or matching placebo. The hypothesis is that subjects treated with parecoxib/celecoxib will consume less morphine during postoperative 2 weeks, achieve better pain control, quicker functional recovery during postoperative 6 weeks, and has less opioid adverse events than those treated with opioids alone during 12-week recovery phase.

2. Aim and objectives

2.1. Primary objectives

The primary objective of this study is to evaluate the morphine-sparing effects of the sequential treatment with parecoxib and celecoxib versus placebo in subjects undergoing TKA.

2.2. Secondary objectives

- To compare the effects of the sequential treatment versus placebo on pain relief, inflammation control and functional rehabilitation after TKA.
- To compare the safety of the sequential treatment versus placebo post TKA.

3. Design and methods

3.1. Study Design

This study is an investigator initiated post marketing study which is designed as multicenter, randomized, double blind, parallel-group, and placebo-controlled.

3.2. Study Setting

This study is being conducted by Peking Union Medical College Hospital (PUMCH), China as the coordinating center, and 3 other participating centers including 1)West China Hospital of Sichuan University, Sichuan Province, China, 2) People's Hospital of Peking University, Beijing, China, and 3)Second Affiliated Hospital of Zhejiang University College of Medicine, Zhejiang Province, China.

3.3. Study participants

3.3.1. Inclusion Criteria

Subject eligibility should be reviewed and documented by an appropriately qualified member of the investigator's study team before subjects are included in the study.

Subjects must meet all of the following inclusion criteria to be eligible for enrollment into the study:

1) The subject is scheduled to undergo elective unilateral total knee arthroplasty because of OA, performed under a standardized regimen of general anesthesia, as specified in this protocol.
2) Evidence of a personally signed and dated informed consent document indicating that the subject (or a legal representative) has been informed of all pertinent aspects of the study.
3) The subject is a male or female over 18 years of age.
4) Male and female subjects of childbearing potential must agree to use an effective method of contraception throughout the study and for 42 days after the last dose of assigned treatment. A subject is of childbearing potential if, in the opinion of the investigator, he/she is biologically capable of having children and is sexually active.
5) Total duration of the surgical procedure is four hours or less.
6) ASA grade 1-3 subjects.
7) Subjects who are willing and able to comply with scheduled visits, treatment plan, laboratory tests, standardized rehabilitation scheme, and other study procedures.
8) The subject is in satisfactory health as determined by the investigator on the basis of medical history and physical exam.
9) The subject must demonstrate sufficient psychomotor dexterity and cognitive capacity to use intravenous (IV) PCA.
10) Subjects who live near to the hospital may be considered prior for the concern of convenient and sufficient follow-up.

3.3.2 Exclusion Criteria

The subjects will be excluded with any condition listed below:

1) The subject requires a revision to previous knee arthroplasty and/or is having a bilateral knee arthroplasties.
2) The subject requires an emergency knee arthroplasty.
3) Addiction to using any non-steroidal anti-inflammatory drugs (NSAIDs) and opioids
4) Subject has a known hypersensitivity to COX-2 specific inhibitors, sulfonamides, lactose, NSAIDs, opioids or acetaminophen/paracetamol. Subjects who have experienced asthma, urticaria or allergic type reactions after taking aspirin or other NSAIDs.
5) The subject has a history of any of the following arthritis: (i.e. rheumatoid arthritis, ankylosing spondylitis, psoriatic arthritis), chronic pain (e.g. fibromyalgia), metastasis, and Paget's disease.
6) The subject received any investigational medication within 30 days prior to the first dose of study medication or is scheduled to receive any investigational drug other than those described in the protocol during the study.
7) The subject has any known laboratory abnormality, which in the opinion of the investigator, would contraindicate study participation including ALT (SGPT), AST (SGOT), blood urea nitrogen or creatinine ≧1.5 times the upper limit of the normal reference range.
8) The subject has an active malignancy of any type, or history of a malignancy (Subjects who have a history of basal cell carcinoma that has been successfully treated can be entered into the study. Subjects with a history of other malignancies that have been surgically removed and who have no evidence of recurrence for at least five years before study enrollment can also be entered into the study).
9) Subject had inflammatory bowel disease (e.g. Crohn's disease or ulcerative colitis), a chronic or acute renal or hepatic disorder, a significant coagulation defect, or any condition, which could preclude use of NSAIDs or COX-2 specific inhibitors.
10) The subject has active or suspected esophageal, gastric, pyloric channel, or duodenal ulceration history.
11) The subject has received warfarin or other anticoagulants during the 30 days preceding the first dose of study medication (Cardioprotective aspirin, ≦or 325 mg/day is permitted, when the dose has been stable for at least the month prior to entering the study). Anticoagulation is permitted when related to the surgery, with such medicines as low molecular weight heparin including Lovenox and Fragmin.

12) Subject is anticipated to require or requires treatment with lithium.
13) Subject is ASA grade 4-5.
14) The subject has a history of a psychiatric disorder requiring new or changing treatment (A subject with a psychiatric disorder who has been stable on therapy may enter the study if they have not required any changes in their therapy for the 4 weeks prior to study entry and it is anticipated they will not need any changes for the 2-week duration of this study).
15) The subject has a history of uncontrolled chronic disease or a concurrent clinically significant illness, medical condition, which in the investigators' opinion, would contraindicate study participation or confound interpretation of the result. Including, but not exclusive to: uncontrolled hypertension, uncontrolled ischemic heart disease, uncontrolled cardiac insufficiency, history of coronary artery bypass graft (CABG) surgery, history of heart valve surgery or coronary stent implantation, history of peripheral vascular disease or cerebrovascular disease, moderate or severe hepatic impairment, fluid retention, heart failure, abdominal pain of unknown etiology (or where study medication could mask symptoms) or any other condition which in the opinion of the Investigator, would contraindicate study participation or confound interpretation of the results.
16) The subject has any cognitive impairment or other characteristics that would in the investigator's opinion preclude study participation or compliance with protocol mandated procedures.
17) Subject has a history of asthma or bronchospasm, which requires treatment with glucocorticoids.
18) Subject had a history of alcohol, analgesic or narcotic abuse.
19) Subject has been previously randomized into the study
20) Subjects who are investigational site staff members or relatives of those site staff
21) Participation in other studies within 3 months before the current study begins and/or during study participation
22) Other severe acute or chronic medical or psychiatric condition or laboratory abnormality that may increase the risk associated with study participation or investigational product administration or may interfere with the interpretation of study results and, in the judgment of the investigator, would make the subject inappropriate for entry into this study.
23) Pregnant females, breastfeeding females, or males and females of childbearing potential not using effective contraception or not agreeing to continue effective

contraception from screening through 42 days after last dose of investigational product will not enter this study.

3.3.3. Withdrawal criteria

At any stage of the study, subjects are free to consent withdraw from the study with their medication and or treatment to the disease and their well beings be taken care of by the investigator/hospital without any negative impact.

The investigator may decide that a subject needs to be withdrawn from the study based on evaluations of individual conditions and balancing of the potential benefit/risk caused by the study treatment to the subject. For example, in case that even maximal dose of oral tramadol could not provide satisfying rescue-pain control, we may withdraw the patient from the study to guarantee the pain control quality and clinical safety. These patients will be shifted to NSAIDs or acetaminophen for pain treatment, and the details of altered treatments will be documented in the study.

3.4 Intervention measures

3.4.1. Allocation to Treatment

All subjects who meet the study inclusion and exclusion criteria will be randomly assigned in a 1:1 ratio to either parecoxib/celecoxib group or placebo group. The allocation or randomization will be study site based.

The Electronic Data Capture (EDC) system will automatically generate subject identification numbers in sequence at baseline, which is subsequently linked to the treatment assignments at randomization. A copy of the randomization code will be maintained by the investigator designated a person(s) who is independent of the trial conduct. It is the responsibility of the Principal Investigator (PI) to ensure that the subject is eligible for participation in the study before requesting randomization.

The study will consist of **3 phases**: an initial screening phase which must be completed within 30 days prior to randomization; a 6-week double-blind treatment phase; and a 6-week follow-up phase. (**Figure 1**)

In the 1st phase, the investigator will initiate the required screening procedures after obtaining written informed consent. All qualified patients after selection by inclusive/exclusive criteria will be assigned in the order in which they are enrolled into the study, to receive their allocated treatment sequence according to a computer-generated randomization schedule prepared prior to the start of the study.

In the 2nd phase, after completion of screening, subjects that remain eligible will enter a 6 week double-blind randomized treatment period. All the participants will undergo

standard TKA on unilateral side under general anesthesia. Patients in the study group are supplied sequential treatment with parecoxib 40 mg intravenously (IV) twice daily (Q12h) for the first 3 days post-surgery followed by celecoxib 200mg orally twice daily (Q12h) for up to 6 weeks post-surgery; whereas control patients are supplied with the corresponding placebo with the same instructions. Patient-controlled intravenous analgesia (PCIA) with morphine is administrated to all the subjects starting immediately post-anesthesia and ending at 24h after operation. As long as oral intake is feasible, both the two groups may receive centrally-acting analgesic tramadol hydrochloride in oral form as rescue analgesia if VAS score ≧ 3. With the support of sufficient pain management, patients will be educated to perform functional exercise according to the standardized post-TKA exercise plan. The investigator will use patient diary at every visit to track the patient exercise, pain score, the study medication, and the rescue therapy.

- Surgical techniques: A standard medial parapatellar approach was used through a midline skin incision, and a tourniquet was used which was inflated (280mmHg) following limb exsanguination immediately before skin preparation. Bone cuts and soft tissue balancing were done in the same sequence. The joint capsule and wound layers were closed in layers. A wool and crepe dressing was applied to the wound from mid-calf to mid-thigh at which point the tourniquet was then released.
- Anesthesia regimen: All 4 centers in this study will adopt the same anesthesia protocol (as presented above) and same anesthesia drugs to minimize difference among centers and ensure the comparability between the two study groups. The general anesthesia protocol is as follows: patients will be operated under general anesthesia (GA) with tracheal intubation. GA induction will be conducted with intravenous administration of 1-2 ug/kg sufentanil, 0.6-0.8mg/kg rocuronium, 0.02mg/kg midazolam, 4mg ondansetron and target-controlled infusion (TCI) of propofol at 4.0- 6.0μg/ml. GA will be maintained with propofol TCI at 3-5ug/ml and continuous infusion of sufentanil at 0.1-0.2ug/kg. Rocuronium and 1ug/kg of sufentanil will be given when necessitated. Parecoxib or placebo drug will be dripped at suture, and neostigmine plus atropine will be given as muscle relaxant reversal before extubation. Total amount of intraoperative sufentanil consumption will be documented at GA conclusion.

In the 3rd phase, a telephone safety follow up visit at 12-week post-surgery will be taken to reveal any adverse events that may happen during the follow-up phase. All participants and all assessment operators are blinded to the identity of the treatments until all study data have been collated in a database.

3.4.2. Drug preparation and administration

3.4.2.1. Drug Formulation and Packaging

Parecoxib lyophilized presentation will be supplied in 40 mg per vial for intravenous administration; liquid presentation of placebo will be 0.9% saline in 2 ml per vial provided on site for intravenous administration. 2ml of 0.9% saline is used for reconstitution of parecoxib before administration.

Celebrex/Placebo 200 mg capsule presentation will be supplied in bottles for oral administration, and the number of capsule in each bottle are 12 for the first week post-surgery, 22 for the second week, 44 for the following two weeks scheduled respectively.

3.4.2.2. Preparation and Dispensing

Preparation of the study medication will be performed by medicine supplier in its GMP facility. According to the random list, a unique random code will be labeled to each vial/bottle of the medicine/placebo allowing no recognition of the real ingredients by trial operating nurse and or subjects.

Dispensing of the trial medication/placebo will be based on random code kept by the nurse for reconstitution of parecoxib or the label of the bottle for celecoxib by strictly following the sequence of the medicine identification number on the labels.

3.4.2.3. Administration

Parecoxib/placebo will be administered via intravenous route twice daily at twelve hours interval, the medication should not be given simultaneously with any other medication, and bolus injection is recommended after using 1 - 2ml of saline washing of infusion route in advance. The first iv administration of Parecoxib 40mg or placebo will be performed at the beginning of wound suture during the TKA surgery, followed by Parecoxib 40mg or placebo every 12 hours for 3 consecutive days.

Thereafter, celebrex/placebo will be administered orally, twice daily in twelve hours interval, such as at 8:00 and 20:00 respectively, with a cup of water. While discharged from hospital, the subjects are required to record the oral intake of celebrex/placebo by themselves on the diary card proved at each visit keeping the time points of administration as same as in ward.

3.4.2.5. Drug Storage

Parecoxib and placebo will be shipped and stored at a temperature below 25°C, and celebrex and placebo will be shipped and stored at 10 - 25 °C. Investigators and site staff are reminded to check temperatures daily and ensure that thermometers are working correctly as required for proper storage of investigational products.

3.4.2.6. Concomitant Medication(s)

The use of permitted concomitant therapy must be explained in detail, including prescription and nonprescription drugs, non-drug therapy, and dietary supplements and herbal preparations, as appropriate. The name, dose, date, and exact time of administration must be recorded in the CRF and appropriate medical records as source data for each medication administered to thepatient.

Prohibited medications

The following medications are prohibited for the duration of the study:

- NSAIDs and other analgesics (including steroid), by any route (i.e. oral, inhaled, topical, injected, rectal) within 5 days prior to TKA until the end of the study.
- Fluconazole, and/or lithium
- Hypnotics, anxiolytics, sedatives, tranquilizers, SSRIs, tricyclic anti-depressants, or benzodiazepines unless the subject's prescribed daily dose has remained unchanged throughout the previous 4 weeks and will remain unchanged throughout the study period.
- Herbal and alternative medicines such as: garlic, ginko biloba, ginseng.
- Local infiltration of the surgical site with anesthetic is prohibited.

Permitted medications

- Pre-medication, if required, will be a short-acting benzodiazepine (e.g. temazepam)
- Anesthesia will be a standardized general anesthesia regimen as described above.
- Midazolam and propofol are given only intraoperatively with no administration after the surgery, thereby avoiding the potential opioid sparing effect for the postoperative hours.
- Anti-coagulants: Low molecular weight heparin is permitted for post-surgical anticoagulant treatment.
- Aspirin＜325 mg/day is permitted for cardiovascular prophylaxis, if used at a stable dose for the 30 days prior to randomization.
- Anti-emetic drugs may be given, if needed. The dose and total number of doses of the anti-emetic treatment should be documented on the CRF.

3.4.3. Rescue Therapy

Intravenous rescue medication- PCA: After surgery, all subjects will be connected to patient-controlled analgesia (PCA) at the last stich of wound closure. The PCA pump setting protocol is as follows: Sixty milligrams morphine in 240ml normal saline (NS) (morphine 1mg/4ml) will be prescribed for postoperative patient control analgesia (PCA). The background infusion rate of PCA is set at 4ml/hr (morphine 1mg/hr), and 4ml

bolus infusion (morphine 1mg/bolus) is available with 15min lockout interval. A dosage limit of 60ml within 4hr is applied for preventing the potential adverse events.

All doses of morphine (PCA and bolus) must be recorded precisely with the date and time of administration and the amount of morphine given. If a subject is unable to use the PCA pump he/she must be withdrawn from the study and provided with appropriate analgesia.

Oral rescue medication: After PCA is discontinued, all subjects with a VAS more than 3 may take open-label oral rescue medication, tramadol 100mg each time as needed, not to exceed 400mg per day.

Commercial product RYZOLT™ is used in this study which is tramadol hydrochloride extended-release tablets, a centrally acting analgesic composed of a dual-matrix delivery system with both immediate-release and extended-release characteristics. The median time to peak plasma concentrations of tramadol and O-demethylated metabolite (M1) after multiple-dose administration of RYZOLT™ 200 mg tablets to healthy subjects are attained at about 4 h and 5 h, respectively.

Only tramadol will be used as rescue medication post discharge from the hospital. Doctor and research nurse will give the participants very thorough and clear education on how to take tramadol as rescue medication (all subjects with a VAS equal to or more than 3 may take tramadol 100mg each time as needed, not to exceed 400mg per day), how to record on the patient diary, and how to return the left tramadol at each visit. They will also assess the use and consumption of the participants at each follow-up visit. No other analgesics will be allowed to taken by the participants post hospital discharge. Acetaminophen is not included in the rescue analgesia since it can inhibit cyclooxygenase-2 and thus influence the evaluation of inflammation-related endpoints.

Consumption of both morphine and tramadol will be calculated together and converted to morphine equivalent dosage, the converting of tramadol to morphine equivalents is estimated as 300mg oral administered tramadol equals to 20mg of intravenous morphine.[20-23]

3.5. Outcome measures

3.5.1. Primary endpoint

Cumulative opioid consumption till 2 weeks post operation. It can be calculated as the sum of the cumulative morphine consumption over the first 24 hours postsurgical period and the opioid drug consumption till 2w post operation. The converting of Tramadol to morphine equivalents is estimated as 300mg Tramadol equals to 20mg of morphine

3.5.2. Secondary endpoints

3.5.2.1. Key secondary endpoints

Knee Society Score (KSS) at 6w post operation.

3.5.2.2. Other secondary endpoints

- Western Ontario and McMaster Universities Osteoarthritis Index (WOMAC) index[24] prior to operation and at 2w,4w and 6w post operation
- Knee Society Score (KSS)[25] prior to operation and at 2w, 4w and 6w post operation
- Total morphine use: The cumulative morphine consumption over the first 24 hours postsurgical period.
- Cumulative opioid consumption till 24h, 72h, 2w, 4w, 6w post operation. For example, total narcotic use till 72h post operation will be calculated as the sum of the cumulative morphine consumption over the first 24 hours postsurgical period and the opioid drug consumption (converted to morphine equivalents) till 72h post operation.
- VAS (0-10)[26] prior to operation and at 24h, 48h, 72h, 2w, 4w and 6w post operation, with 0 point representing no pain and 10 points representing the worst imaginable pain.
- EQ-5D[27] and patient satisfaction prior to operation and 72h, 2w, 4w and 6w post operation. EQ-5D is a standard instrument for use as a measure of health outcome. It is cognitively simple, taking only a few minutes to complete.

3.5.3. Exploratory endpoints

- Knee circumference (measured 1cm proximal to the base of the patella) prior to operation and at 24h, 48h, 72h, 2w, 4w, 6w post operation. The measurements were performed in a quiet room, with a recording clerk and a physician present who measured and recorded dimensions of the knee circumference of both legs. Circumferential measurements were recorded to the nearest 0.1 cm with an ordinary tape measure.
- Knee skin temperature prior to operation and at 24h, 48h, 72h, 2w, 4w, 6w post operation.
- Erythrocyte sedation rate (ESR) and C-reaction protein (CRP) at preoperative and at 72h, 2w, 4w and 6w post operation.
- Synovial fluid cytokine (including IL-6, IL-8, IL-10 and PGE2) concentration at 0h, 24h and 48h post operation.
- Peripheral blood cytokine (including IL-6, IL-8, IL-10 and PGE2) concentration prior to operation and at 24h, 48h, 72h, 2w, 4w, 6w post operation.

- Blood coagulation tests prior to operation and at 72h, 2w, 4w and 6w post operation.

3.5.3 Safety endpoints

The nature, incidence, duration, and severity of adverse events; discontinuation due to adverse events; adverse events occurring during and after trial medication discontinuation; body weight, clinical safety laboratory, 12-lead ECGs, physical exams, and vital signs will be monitored in this study.

3.6. Adverse event reporting

3.6.1. Adverse Event Definition

An adverse event (AE) is any untoward medical occurrence in a clinical investigation where subjects are administered a product or medical device; the event need not necessarily have a causal relationship with the treatment or usage. Examples of AEs include but are not limited to: abnormal test findings, clinically significant symptoms and signs, changes in physical examination findings, hypersensitivity, progression/worsening of underlying disease, drug abuse, drug dependency, etc.

3.6.2. Serious Adverse Events (SAE)

An SAE is any untoward medical occurrence at any dose that:

- Results in death;
- Is life-threatening (immediate risk of death);
- Requires inpatient hospitalization or prolongation of existing hospitalization;
- Results in persistent or significant disability/incapacity (substantial disruption of the ability to conduct normal life functions);
- Results in congenital anomaly/birth defect.
- Lack of efficacy should be reported as an AE when it is associated with an SAE.

Medical and scientific judgment is exercised in determining whether an event is an important medical event. An important medical event may not be immediately life-threatening and/or result in death or hospitalization. However, if it is determined that the event may jeopardize the subject or may require intervention to prevent one of the other AE outcomes, the important medical event should be reported seriously.

3.6.3. Severity Assessment

If required on the AE case report forms (CRFs), the investigator will use the adjectives MILD, MODERATE, or SEVERE to describe the maximum intensity of the AE. For purposes of consistency, these intensity grades are defined as follows: 1) MILD: Does not

interfere with subject's usual function. 2) MODERATE: Interferes to some extent with subject's usual function.3) SEVERE: Interferes significantly with subject's usual function.

3.6.4. Causality Assessment

The investigator's assessment of causality must be provided for all AEs (serious and non-serious); the investigator must record the causal relationship in the CRF, as appropriate, and report such an assessment in accordance with the serious adverse reporting requirements if applicable. If the investigator determines an SAE is associated with study procedures, the investigator must record this causal relationship in the source documents and CRF, as appropriate, and report such an assessment in accordance with the SAE reporting requirements, if applicable.

3.6.5. Withdrawal Due to Adverse Events

Withdrawal due to AE should be distinguished from withdrawal due to insufficient response according to the definition of AE noted earlier, and recorded on the appropriate AE CRF page.

When a subject withdraws due to an SAE, the SAE must be reported in accordance with the reporting requirements defined below.

3.7. Study procedures

There will be altogether 10 visits in the study for a certain subject. (**Table 1**) Screening will be performed at visit 1, and the day for TKA operation will be considered as Day 0. There is a visit on one day before operation, the visit 2, when the qualification of subject to the study will be evaluated again before operation, and the visit right after operation is visit 3. Those on day 1, 2 and 3 post-surgery will be regarded as visits 4, 5 and 6 respectively, then there will be visits 7, 8 and 9 at 2 weeks, 4 weeks and 6 weeks post-surgery, and the last visit will be at 12 weeks post-surgery, the visit 10.

3.7.1. Screening and wash-out

Screening will be performed between visits 1 and 2, where the potential subjects will be evaluated by inclusion/exclusion criteria, demography and medical history recording, evaluation of the background diseases as well as OA for the knee to be operated on, physical examination and laboratory examinations including routine tests of blood and urine, biochemical, X-ray (chest, two lower limbs, and the knee joint), 12-lead ECG, echocardiogram, pulmonary function, ultrasound for lower extremities venous and arteria, blood transfusion test (8 items), blood type and pregnancy test for female subjects, ESR and CRP, peripheral blood cytokine concentration (IL-6, IL-8, IL-10 and

PEG2) and blood coagulation, WOMAC index and KSS, VAS and EQ-5D, knee circumference and skin temperature at baseline.

Before any trial required assessments are conducted, a written Informed Consent must be signed by the subject, witness to the signing is needed when the subject is unable to read or write.

There is a two-week wash-out period after the screening at visit 1 and before visit 2, in which subjects who have been receiving any NSAIDs will be stopped for using of these medicines for two weeks and asked to replace their NSAIDs with Tramadol when needed. All required data must be recorded on CRF for verification and archiving. In this study, e-CRF will be applied allowing online source data verification.

Qualification of subject to the study will be evaluated again at visit 2 which is the day before operation, and randomization of the subject to receive either parecoxib or placebo in the first three days post-surgery, and either clebrex or placebo in the following 6 weeks will also be determined on the same visit.

3.7.2. Study Period

At visit 3 which is right after operation, physical examination will be performed, infusion of parecoxib or placebo 40mg Q12h in the first three days and recording of morphine consumption for 24 hours starts, and synovial fluid cytokine concentration will be tested. Safety evaluations are also conducted for the subjects.

At visits 4 and 5 the recording of accumulative morphine consumption stops, while that for tramadol starts at visit 4, physical examination and safety evaluations are also conducted for the subjects. Synovial fluid cytokine concentration is tested at 24 h and 48h post operation.

At visit 6 which is 72 hours after operation, infusion of parecoxib 40mg Q12 or placebo stops, and oral administration of celebrex 200mg Q12h /placebo starts on Day 4, while recording the cumulative tramadol consumption continues. Evaluations of VAS and EQ-5D will be performed, while testing of ESR, CRP, peripheral blood cytokine concentration and blood coagulation will also be performed. Safety evaluations are also conducted for the subjects.

3.7.3. Follow-up Visits

This period covers visits 7 through 9, where recording the cumulative Tramadol consumption at 2w, 4w and 6w after operation, WOMAC index and KSS at 2w, 4w and 6w post operation, evaluations of VAS and EQ-5D at 2w, 4w and 6w post operation, knee circumference and skin temperature at 2w, 4w and 6w post operation, ESR and CRP at 2w, 4w and 6w post operation, peripheral blood cytokine concentration at 2w, 4w and

6w post operation, and tests of blood coagulation at 2w, 4w and 6w post operation. Safety evaluations are also conducted for the subjects at each visit.

3.7.4. Post-Study Subject Telephone Interview

At 12 weeks post-surgery, only safety evaluations will be conducted for the subjects by a telephone follow-up.

All data required by above visits must be recorded on CRF for verification and archiving.

3.8. Breaking the Blind

This is a double-blind study. The subjects, investigators, study coordinators, clinical site staff, Clinical Research Associate (CRA), and staff directly involved in the study and its designees will be blinded to subject treatment assignment.

At the initiation of the study, the study site will be instructed on the method of breaking the blind. Blinding should only be broken in emergency situations for reason of subject safety. Whenever possible, the investigator or sub-investigator consults with a member of the study team prior to breaking the blind. When the blind is broken, the reason must be fully documented and entered on the CRF.

3.9. Stop Criteria

The subjects involved in this study have the right to quit at any time. In addition, subjects will be discontinued from the study if they meet any of the following criteria:

1) Clinical interventions (e.g. systemic or topical application of glucocorticoids, other NSAIDs used within six weeks after TKA) which may affect the study results within the observation period;
2) Occurrence of serious adverse event (SAE, e.g. malignant tumors, serious perioperative complications) which, in the opinion of the investigator, may complicate assessment of the effects of study drugs.

3.10. Ethical review and informed consent

Ethics approval for this study has been obtained from the Ethics Committee, Peking Union Medical College Hospital, China. The benefits and risks of participation in the trial will be explained to each patient, legal deputy, or witness by the investigators or their designee, and written informed consent will be obtained before the trial. The informed consent with the signature of the patient, legal deputy, and person who explained the benefits or risks will be preserved by the researchers. The trial will be conducted in

accordance with the Declaration of Helsinki.

3.11. Sample Size Determination

Total 86 subjects per group would have 90% power in detecting 100 mg or more in mean difference of cumulative opioid consumption on Day 14 between the two groups, assuming a common standard deviation of 200, and a two-sided alpha level of 0.05. This would result in a total 172 subjects. In consideration of 30% drop outs, 246 subjects would be adequate for the study.

Due to lacking prospective studies for this type of endpoint, and in review of a retrospective evaluation of inpatient Celecoxib use after total hip and knee arthroplasty [15], our assumptions in the sample size estimation are conservatively stipulated.

3.12. Data collection, management, and statistical analysis

Data will be collected through EDC (Electronic Data Capture) system under intent-to-treat principals, i.e., all the data of the subjects who signed inform consent form will be included in the study database.

Data Quality Assurance will be achieved through

- Online Edit Checks at the time of data entry
- Database Edit Checks performed by Data Management (DM)
- Online query issuance/resolution among/between PI, CRA and DM
- Medical review of data listing by the project team

For this study, the following definitions of analysis population will be followed:

ITT (Intent-to-treat)

All the randomized subjects who signed ICF, and satisfied all inclusion/exclusion criteria at visit 2 will be included in ITT analysis set.

Analyses on demographics and baseline characters will be based on ITT analysis set, and the listings of subjects' information will also be based on ITT.

EAP (Effective Analysis Population)

All the subjects in ITT who have completed demographic data and evaluable baseline morphine use, and at least 1 post-baseline cumulative use of Tramadol.

All the analyses on efficacy will be based on EAP.

PP (Per-protocol Population)

All the subjects in EAP who have no any major protocol deviation, no forbidden concomitant use, have the data of cumulative use of Tramadol in the first 2 weeks after

operation, and the compliance in treatment use in the first 2 weeks after operation are in 80%~120%.

PP will be only used in primary efficacy analysis.

SS (Safety Set)

All the randomized subjects who have received at least one dose will be included in safety set. Analysis on adverse events, laboratory, ECG, and vital sign will be based on safety set.

All data collected at follow-up visits for patients in the study and control groups are compared by an independent statistician using SAS 9.3 statistical analysis software. Continuous variables will be summarized by treatment groups using descriptive statistics including number of subjects, mean, standard deviation, median, Q1, Q3, minimum and maximum. The statistics of t test, Welch-Satterthwaite t test or Mann-Whitney U test will be used in comparison between 2 groups based on the results of normality test and homogeneity of variance test. Paired t test will be used in comparison within each group if the variable normally distributed; otherwise signed rank test will be used. The statistical significance level of normality test and homogeneity of variance test is 0.05. Nominal categorical variables will be presented as “frequency (percentage)”. The statistics of Pearson Chi-Squared test, continuity adjusted Chi-Squared test or Fisher's exact test will be used in comparison between 2 groups based on the distribution of the variable considered. Ordinal categorical variables will be presented as “frequency (percentage)”. Mann-Whitney U test will be used in comparison between 2 groups. Two-sided p value will be used in the statistical tests, and the difference between groups will be considered statistically significant if $p < 0.05$.

For primary endpoint analysis, statistical methods for continuous variable analysis will be used in the superiority test of study group over control group on reducing morphine use. Additionally, ANCOVA will be used in primary endpoint analysis as supplemental analysis, the covariates include the subjects’ dosed days, gender, age, and weight.

In additional to general statistical methods, mixed model for repeated measures (MMRM) will also be used in secondary endpoints analysis.

For safety analysis, the adverse events, abnormal findings in laboratory tests will be listed with the relationship to the study treatments. Fisher’s exact test will be used to compare the rates of subjects who have at least one adverse event between study and control groups.

3.13. Quality control and quality assurance

During study conduct, investigator or its contracted agent will conduct periodic monitoring visits to ensure that the protocol and Good Clinical Practices (GCPs) are being followed. The monitors may review source documents to confirm that the data recorded on CRFs is accurate. The investigator and institution will allow monitors directly accessed to source documents for verification.

Each step will be strictly performed according to the trial protocol. Each step of quality control of measured outcomes will be performed according to the standard operating and quality control procedure.

4. Discussion

Total knee arthroplasty is associated with significant postoperative pain, which adversely affects patients' ability and desire to effectively rehabilitate their knee. [5, 6] Inadequate pain control has been correlated with prolonged postoperative bed time, increased incidence of pulmonary infection, deep venous thrombosis (DVT), pulmonary embolism (PE) and poor functional recovery in some patients after TKA.[8]

Multimodal analgesia is currently recommended for postoperative pain control after TKA.[7, 28-30] It basically refers to the administration, via the same route or by different routes, of multiple analgesics to provide superior analgesia and limit side effects and adverse events. Multimodal analgesia is achieved by combining different analgesics that act by different mechanisms (e.g., NSAIDs, opioids, and local anesthetics), resulting in additive or synergistic analgesia, lower total doses of analgesics, and fewer side effects.[28, 29] Among multimodal analgesia modalities, NSAIDs, especially selective cyclo-oxygenase-2 (COX-2) inhibitors play an important part in the postoperative pain control after TKA. [30]

Nonselective NSAIDs may cause gastrointestinal (GI) and hematologic adverse events, compromise platelet function [31], and are associated with increased postoperative bleeding and increased blood transfusion requirements after joint arthroplasty surgery[32]. Selective cyclo-oxygenase-2 (COX-2) inhibitors display similar anti-inflammatory properties with traditional NSAIDs, but lack many of the side effects associated with NSAIDs because they spare the COX-1 enzyme and have no clinically significant effect on platelet or gastrointestinal function. [31, 33, 34]

Parecoxib sodium (parecoxib) is the injectable prodrug of valdecoxib and is the only parenteral formulation of a selective COX-2 inhibitor NSAID.[35] It can be rapidly

hydrolyzed *in vivo* to its active form, valdecoxib, which is approximately 28,000-fold more potent against COX-2 than COX-1.[36] Following IV injection, parecoxib is rapidly converted to valdecoxib, the pharmacologically active substance, by enzymatic hydrolysis in the liver. AUC and Cmax following twice daily administration is linear up to 50 mg IV and 20 mg IM. Following single IV and IM doses of parecoxib sodium 20 mg, Cmax of valdecoxib is achieved in approximately 30 minutes and approximately 1 hour, respectively. After IV or IM dosing of parecoxib sodium, the elimination half-life (t1/2) of valdecoxib is about 8 hours. [37]

Parecoxib has been demonstrated as effective in several models of postoperative pain[38] with no effect on platelet function or gastric mucosa at doses up to 40 mg twice daily.[39] Some recent literature[40, 41] also revealed that 40 mg of intravenous administered parecoxib can alleviate the anxiety during perioperative period of TKA, which consequently led to better satisfaction scores and overall experiences for the patients. Celecoxib, another oral specific COX-2 inhibitor, was shown as not only have short-term pain reduction and morphine sparing effect in patients undergoing total knee arthroplasty[13], but also improve functionality recovery if prolonged use up to 6 weeks postoperatively[11].

Treatment of postoperative pain with intravenous with or without subsequent oral COX-2 specific inhibitor has been demonstrated as effective in many post-operative pain models.[15-19] Significant morphine sparing effect and reduction of opioid distressed symptoms were also observed. Combination of intravenous parecoxib and oral valdecoxib was used for less than 2 weeks in most of previous studies. In these studies [15-19], short-term postoperative pain control and morphine sparing effect were evaluated. However, to the best of our knowledge, no study has investigated the effect of prolonged (6 weeks) sequential treatment of intravenous parecoxib and oral celecoxib on the medium-term functionality recovery.

We present here the protocol of PIPFORCE study, which aims to investigate the sequential analgesia regimen with intravenous parecoxib followed by oral celecoxib for post-surgical analgesic treatment in osteoarthritis patients undergoing TKA. Subjects will receive study medication consisting of parecoxib injection in analgesic doses or matching placebo followed by oral celecoxib in acute pain doses or matching placebo in a double-blind fashion. The hypothesis is that subjects treated with parecoxib/celecoxib will consume less morphine over 2 weeks postoperative period, achieve improved pain control over study period, quicker return to functionality, and has less opioid adverse

events than those treated with opioids alone over the 12-week recovery phase. Both treatment groups will be able to use open- label rescue medication with opioids.

The possible limitations of the PIPFORCE study are listed as follows: Firstly, Since the 4 study centers of this multicenter RCT study are all from mainland China, the future results of PIPFORCE study should be explained with this concern and require further validation studies in data sets from other institutions outside China. Secondly, PIPFORCE study does not investigate the long-term (e.g. >3 months) effects of the sequential treatment on inflammation control and functional rehabilitation after TKA. Lastly, cytokines of synovial fluid, as one of the exploratory endpoints, will be tested in this study aiming to observe the trend of change of local inflammation. However, the synovial fluid tested after surgery is actually obtained from the wound drainage and inevitably contains blood, which will compromise the test accuracy. We'll ensure that same technique is used to obtain the synovial fluid sample in both groups to guarantee the comparability. In addition, we will also observe peripheral blood cytokines as reference.

In spite of these possible limitations, the contribution of PIPFORCE study is expected to provide a comprehensive understanding of how the sequential regimen with intravenous parecoxib followed by oral celecoxib affects postoperative pain relief, inflammation control and functional rehabilitation in OA patients undergoing TKA. The completion of this study will provide solid evidence for the efficacy and safety of the clinical use of the sequential regimen of COX-2 specific inhibitors after TKA surgery. The results will assist in optimizing the NSAIDs use as a part of standard multimodal analgesic regimen for managing postoperative pain. Furthermore, this project will provide insight into the benefits of prolonged sequential treatment of parecoxib and celecoxib in this population on the medium-term functionality recovery.

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Contributors

WXS contribute as the senior author and the principle investigator (PI) of this study. ZQY, as the sub PI, wrote the first draft of the manuscript and contributed to the design of the study. BYY, WW, FB, STZ, ZMF advised on the study design. LJH, YSG, SB, PFX refined the

protocol. JJM, as the medical statistician for the study, contributed to the statistical design, acquisition and analysis of data for the work. All authors revised the protocol critically for important intellectual content and approved the final manuscript.

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Competing interests

None declared.

Ethics approval

Ethics Committee, Peking Union Medical College Hospital, China. (Protocol number: S-572).

Trial status

The trial is currently in the data collection phase. Recruitment to the study started in December, 2013. It is anticipated that full post and follow-up data will be finalized in September, 2016.

REFERENCES

1. Bennell KL, Hunter DJ, Hinman RS. Management of osteoarthritis of the knee. *Bmj*. 2012;345:e4934
2. Bijlsma JW, Berenbaum F, Lafeber FP. Osteoarthritis: An update with relevance for clinical practice. *Lancet*. 2011;377:2115-2126
3. Carr AJ, Robertsson O, Graves S, Price AJ, Arden NK, Judge A, et al. Knee replacement. *Lancet*. 2012;379:1331-1340
4. Skou ST, Roos EM, Laursen MB, Rathleff MS, Arendt-Nielsen L, Simonsen O, et al. A randomized, controlled trial of total knee replacement. *The New England journal of medicine*. 2015;373:1597-1606
5. Lavand'homme P, Thienpont E. Pain after total knee arthroplasty: A narrative review focusing on the stratification of patients at risk for persistent pain. *The bone & joint journal*. 2015;97-B:45-48

6. Thomazeau J, Rouquette A, Martinez V, Rabuel C, Prince N, Laplanche JL, et al. Acute pain factors predictive of post-operative pain and opioid requirement in multimodal analgesia following knee replacement. *European journal of pain*. 2016;20:822-832
7. Elmallah RK, Cherian JJ, Pierce TP, Jauregui JJ, Harwin SF, Mont MA. New and common perioperative pain management techniques in total knee arthroplasty. *The journal of knee surgery*. 2016;29:169-178
8. Capdevila X, Barthelet Y, Biboulet P, Ryckwaert Y, Rubenovitch J, d'Athis F. Effects of perioperative analgesic technique on the surgical outcome and duration of rehabilitation after major knee surgery. *Anesthesiology*. 1999;91:8-15
9. Holm B, Kristensen MT, Bencke J, Husted H, Kehlet H, Bandholm T. Loss of knee-extension strength is related to knee swelling after total knee arthroplasty. *Archives of physical medicine and rehabilitation*. 2010;91:1770-1776
10. Honsawek S, Deepaisarnsakul B, Tanavalee A, Sakdinakiattikoon M, Ngarmukos S, Preativatanyou K, et al. Relationship of serum il-6, c-reactive protein, erythrocyte sedimentation rate, and knee skin temperature after total knee arthroplasty: A prospective study. *International orthopaedics*. 2011;35:31-35
11. Schroer WC, Diesfeld PJ, LeMarr AR, Reedy ME. Benefits of prolonged postoperative cyclooxygenase-2 inhibitor administration on total knee arthroplasty recovery: A double-blind, placebo-controlled study. *The Journal of arthroplasty*. 2011;26:2-7
12. Hubbard RC, Naumann TM, Traylor L, Dhadda S. Parecoxib sodium has opioid-sparing effects in patients undergoing total knee arthroplasty under spinal anaesthesia. *British journal of anaesthesia*. 2003;90:166-172
13. Huang YM, Wang CM, Wang CT, Lin WP, Horng LC, Jiang CC. Perioperative celecoxib administration for pain management after total knee arthroplasty - a randomized, controlled study. *BMC musculoskeletal disorders*. 2008;9:77
14. Rasmussen GL, Steckner K, Hogue C, Torri S, Hubbard RC. Intravenous parecoxib sodium foracute pain after orthopedic knee surgery. *American journal of orthopedics*. 2002;31:336-343
15. Nussmeier NA, Whelton AA, Brown MT, Joshi GP, Langford RM, Singla NK, et al. Safety and efficacy of the cyclooxygenase-2 inhibitors parecoxib and valdecoxib after noncardiac surgery. *Anesthesiology*. 2006;104:518-526
16. Joshi GP, Viscusi ER, Gan TJ, Minkowitz H, Cippolle M, Schuller R, et al. Effective treatment of laparoscopic cholecystectomy pain with intravenous followed by oral cox-2 specific inhibitor. *Anesthesia and analgesia*. 2004;98:336-342, table of contents
17. Gan TJ, Joshi GP, Viscusi E, Cheung RY, Dodge W, Fort JG, et al. Preoperative parenteral parecoxib and follow-up oral valdecoxib reduce length of stay and improve quality of patient recovery after laparoscopic cholecystectomy surgery. *Anesthesia and analgesia*. 2004;98:1665-1673, table of contents
18. Gan TJ, Joshi GP, Zhao SZ, Hanna DB, Cheung RY, Chen C. Presurgical intravenous parecoxib sodium and follow-up oral valdecoxib for pain management after laparoscopic cholecystectomy surgery reduces opioid requirements and opioid-related adverse effects. *Acta anaesthesiologica Scandinavica*. 2004;48:1194-1207

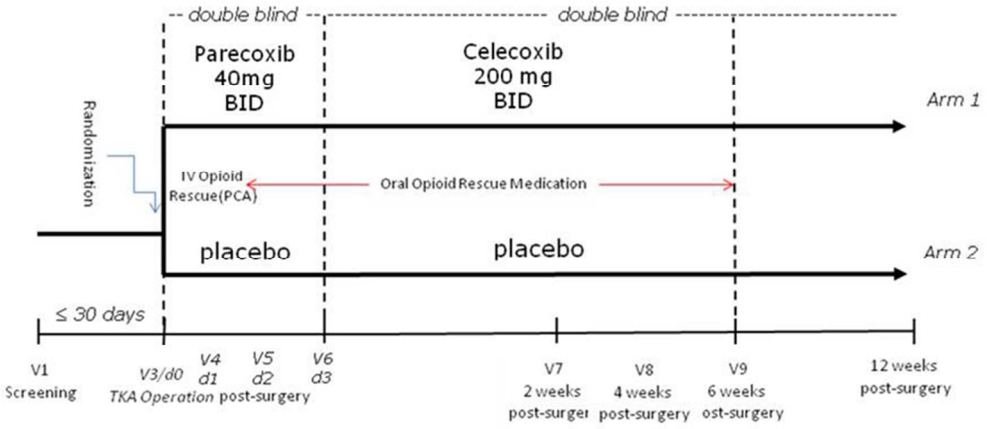
19. Langford RM, Joshi GP, Gan TJ, Mattera MS, Chen WH, Revicki DA, et al. Reduction in opioid-related adverse events and improvement in function with parecoxib followed by valdecoxib treatment after non-cardiac surgery: A randomized, double-blind, placebo-controlled, parallel-group trial. *Clinical drug investigation*. 2009;29:577-590
20. Lee CR, McTavish D, Sorkin EM. Tramadol. A preliminary review of its pharmacodynamic and pharmacokinetic properties, and therapeutic potential in acute and chronic pain states. *Drugs*. 1993;46:313-340
21. Silvasti M, Svartling N, Pitkanen M, Rosenberg PH. Comparison of intravenous patient-controlled analgesia with tramadol versus morphine after microvascular breast reconstruction. *European journal of anaesthesiology*. 2000;17:448-455
22. Hadi MA, Kamaruljan HS, Saedah A, Abdullah NM. A comparative study of intravenous patient-controlled analgesia morphine and tramadol in patients undergoing major operation. *The Medical journal of Malaysia*. 2006;61:570-576
23. Huang YG, Luo AL. Pain management drugs. ISBN-978-7-5062-8919-1. 2008.4
24. Symonds T, Hughes B, Liao S, Ang Q, Bellamy N. Validation of the chinese western ontario and mcmaster universities osteoarthritis index in patients from mainland china with osteoarthritis of the knee. *Arthritis care & research*. 2015;67:1553-1560
25. Liu D, He X, Zheng W, Zhang Y, Li D, Wang W, et al. Translation and validation of the simplified chinese new knee society scoring system. *BMC musculoskeletal disorders*. 2015;16:391
26. Brokelman RB, Haverkamp D, van Loon C, Hol A, van Kampen A, Veth R. The validation of the visual analogue scale for patient satisfaction after total hip arthroplasty. *European orthopaedics and traumatology*. 2012;3:101-105
27. Wang HM, Patrick DL, Edwards TC, Skalicky AM, Zeng HY, Gu WW. Validation of the eq-5d in a general population sample in urban china. *Quality of life research : an international journal of quality of life aspects of treatment, care and rehabilitation*. 2012;21:155-160
28. Baratta JL, Gandhi K, Viscusi ER. Perioperative pain management for total knee arthroplasty. *Journal of surgical orthopaedic advances*. 2014;23:22-36
29. Webb CA, Mariano ER. Best multimodal analgesic protocol for total knee arthroplasty. *Pain management*. 2015;5:185-196
30. Barrington JW, Halaszynski TM, Sinatra RS, Expert Working Group On A, Orthopaedics Critical Issues In H, Knee Replacement Arthroplasty FT. Perioperative pain management in hip and knee replacement surgery. *American journal of orthopedics*. 2014;43:S1-S16
31. Leese PT, Hubbard RC, Karim A, Isakson PC, Yu SS, Geis GS. Effects of celecoxib, a novel cyclooxygenase-2 inhibitor, on platelet function in healthy adults: A randomized, controlled trial. *Journal of clinical pharmacology*. 2000;40:124-132
32. Robinson CM, Christie J, Malcolm-Smith N. Nonsteroidal antiinflammatory drugs, perioperative blood loss, and transfusion requirements in elective hip arthroplasty. *The Journal of arthroplasty*. 1993;8:607-610
33. Deeks JJ, Smith LA, Bradley MD. Efficacy, tolerability, and upper gastrointestinal safety of celecoxib for treatment of osteoarthritis and rheumatoid arthritis: Systematic review of randomised controlled trials. *Bmj*. 2002;325:619

34. Silverstein FE, Faich G, Goldstein JL, Simon LS, Pincus T, Whelton A, et al. Gastrointestinal toxicity with celecoxib vs nonsteroidal anti-inflammatory drugs for osteoarthritis and rheumatoid arthritis: The class study: A randomized controlled trial. Celecoxib long-term arthritis safety study. *Jama*. 2000;284:1247-1255
35. Cheer SM, Goa KL. Parecoxib (parecoxib sodium). *Drugs*. 2001;61:1133-1141; discussion 1142-1133
36. Talley JJ, Brown DL, Carter JS, Graneto MJ, Koboldt CM, Masferrer JL, et al. 4-[5-methyl-3-phenylisoxazol-4-yl]- benzenesulfonamide, valdecoxib: A potent and selective inhibitor of cox-2. *Journal of medicinal chemistry*. 2000;43:775-777
37. Parecoxib sodium for injection package insert. Approval date: May 23, 2008. Revision date Sep25, 2012.
38. Barton SF, Langeland FF, Snabes MC, LeComte D, Kuss ME, Dhadda SS, et al. Efficacy and safety of intravenous parecoxib sodium in relieving acute postoperative pain following gynecologic laparotomy surgery. *Anesthesiology*. 2002;97:306-314
39. Graff J, Arabmotlagh M, Cheung R, Geisslinger G, Harder S. Effects of parecoxib and dipyrone on platelet aggregation in patients undergoing meniscectomy: A double-blind, randomized, parallel-group study. *Clinical therapeutics*. 2007;29:438-447
40. Sarridou DG, Chalmouki G, Braoudaki M, Siafaka I, Asmatzi C, Vadalouka A. Parecoxib possesses anxiolytic properties in patients undergoing total knee arthroplasty: A prospective, randomized, double-blind, placebo-controlled, clinical study. *Pain and therapy*. 2016
41. Vadalouca A, Moka E, Chatzidimitriou A, Siafaka I, Sikioti P, Argyra E. A randomized, double-blind, placebo-controlled study of preemptively administered intravenous parecoxib: Effect on anxiety levels and procedural pain during epidural catheter placement for surgical operations or for chronic pain therapy. *Pain practice : the official journal of World Institute of Pain*. 2009;9:181-194

Table 1. Schedule of activities

The Schedule of Activities table provides an overview of the protocol visits and procedures. Refer to Study Procedures (Section 6) and Assessments (Section 7) for detailed information on each procedure and assessment required for compliance with the protocol.											
Protocol Activity	**Screen**	**Baseline Randomization Day-1**	**Surgery Day 0**	**Day 1**	**Day 2**	**Day 3**	**Day 4**	**Week 2**	**Week 4**	**Week 6**	**Week 12**
Visit	**1**	**2**	**3**	**4**	**5**	**6**		**7**	**8**	**9**	**10**
Informed Consent	X										
Demography	X										
Medical and Surgical History	X										
Physical Examination	X		X	X	X	X					
Vital signs	X	X	X	X	X	X	X	X	X	X	
Hematology	X			X				X			
Blood Chemistry	X			X				X			
Urinalysis	X			X				X			
Pregnancy test [a]	X									X	
ECG	X			X				X			
ESR and CRP	X					X		X	X	X	
Blood coagulation	X					X		X	X	X	
Peripheral blood cytokine concentration	X			X	X	X		X	X	X	
VAS	X			X	X	X		X	X	X	
EQ-5D	X					X		X	X	X	
Knee circumference and skin temperature	X			X	X	X		X	X	X	
X-ray	X										
Echocardiogram	X										
Pulmonary Function	X										
Ultrasound tests	X										
Blood transfusion tests	X										
WOMAC & KSS	X					X		X	X	X	
Inclusion/exclusion criteria	X	X									
Registration/Randomization		X	X								
Hospital Admission	X										
Surgery – Total Knee Arthroplasty			X								
Synovial fluid cytokine concentration			X	X	X						
Infusion of Parecoxib or placebo 40mg BID				X	X	X					
Record Morphine consumption				X							

The Schedule of Activities table provides an overview of the protocol visits and procedures. Refer to Study Procedures (Section 6) and Assessments (Section 7) for detailed information on each procedure and assessment required for compliance with the protocol.											
Protocol Activity	**Screen**	**Baseline Randomization Day-1**	**Surgery Day 0**	**Day 1**	**Day 2**	**Day 3**	**Day 4**	**Week 2**	**Week 4**	**Week 6**	**Week 12**
Celebrex/placebo 200mg BID							X----------X				
Recording the cumulative tramadol consumption					X	X	X	X	X	X	
Adverse Event		X	X	X	X	X	X	X	X	X	X[b]



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SPIRIT 2013 Checklist: Recommended items to address in a clinical trial protocol and related documents*

Section/item	Item No	Description	
Administrative information			
Title	1	Descriptive title identifying the study design, population, interventions, and, if applicable, trial acronym	**Yes, please see the "Title " part**
Trial registration	2a	Trial identifier and registry name. If not yet registered, name of intended registry	**Yes, please see the "Abstract" Part**
	2b	All items from the World Health Organization Trial Registration Data Set	
Protocol version	3	Date and version identifier	**Yes, please see the "Abstract" Part**
Funding	4	Sources and types of financial, material, and other support	**Yes, please see the "Funding" part**
Roles and responsibilities	5a	Names, affiliations, and roles of protocol contributors	**Yes, please see the "Contributors" part**
	5b	Name and contact information for the trial sponsor	**Yes, please see the "Funding" part**
	5c	Role of study sponsor and funders, if any, in study design; collection, management, analysis, and interpretation of data; writing of the report; and the decision to submit the report for publication, including whether they will have ultimate authority over any of these activities	**Yes, please see the "Funding" part**
	5d	Composition, roles, and responsibilities of the coordinating centre, steering committee, endpoint adjudication committee, data management team, and other individuals or groups overseeing the trial, if applicable (see Item 21a for data monitoring committee)	**Yes, please see the "Contributors" part**
Introduction			

Background and rationale	6a	Description of research question and justification for undertaking the trial, including summary of relevant studies (published and unpublished) examining benefits and harms for each intervention	**Yes, Please see the "Introduction" Part**
	6b	Explanation for choice of comparators	**Yes, Please see the "Introduction" Part**
Objectives	7	Specific objectives or hypotheses	**Yes, Please see the "Introduction" Part**
Trial design	8	Description of trial design including type of trial (eg, parallel group, crossover, factorial, single group), allocation ratio, and framework (eg, superiority, equivalence, noninferiority, exploratory)	**Yes, Please see the "Introduction" Part**
Methods: Participants, interventions, and outcomes			
Study setting	9	Description of study settings (eg, community clinic, academic hospital) and list of countries where data will be collected. Reference to where list of study sites can be obtained	**Yes, please see the "3.2 Study setting"**
Eligibility criteria	10	Inclusion and exclusion criteria for participants. If applicable, eligibility criteria for study centres and individuals who will perform the interventions (eg, surgeons, psychotherapists)	**Yes, please see the "3.3 Study Participants"**
Interventions	11a	Interventions for each group with sufficient detail to allow replication, including how and when they will be administered	**Yes, please see the "3.4 Intervention measures**
	11b	Criteria for discontinuing or modifying allocated interventions for a given trial participant (eg, drug dose change in response to harms, participant request, or improving/worsening disease)	**Yes, please see the "3.3.3 withdrawal criteria**
	11c	Strategies to improve adherence to intervention protocols, and any procedures for monitoring adherence (eg, drug tablet return, laboratory tests)	**Yes, please see the "3.4 Intervention measures**
	11d	Relevant concomitant care and interventions that are permitted or prohibited during the trial	**Yes, please see the "3.4 Intervention measures**

Outcomes	12	Primary, secondary, and other outcomes, including the specific measurement variable (eg, systolic blood pressure), analysis metric (eg, change from baseline, final value, time to event), method of aggregation (eg, median, proportion), and time point for each outcome. Explanation of the clinical relevance of chosen efficacy and harm outcomes is strongly recommended	**Yes, please see the "3.5 Outcome measures"**
Participant timeline	13	Time schedule of enrollment, interventions (including any run-ins and washouts), assessments, and visits for participants. A schematic diagram is highly recommended (see Figure)	**Yes, please see the "3.7 Study procedures" and Figure 1(Flowchart of the trial design)**
Sample size	14	Estimated number of participants needed to achieve study objectives and how it was determined, including clinical and statistical assumptions supporting any sample size calculations	**Yes, please see the "3.11 Sample Size Determination"**
Recruitment	15	Strategies for achieving adequate participant enrolment to reach target sample size	**Yes, please see the "3. Design and Methods"**
Methods: Assignment of interventions (for controlled trials)			
Allocation:			
Sequence generation	16a	Method of generating the allocation sequence (eg, computer-generated random numbers), and list of any factors for stratification. To reduce predictability of a random sequence, details of any planned restriction (eg, blocking) should be provided in a separate document that is unavailable to those who enrol participants or assign interventions	**Yes, please see the "3.4.1 Allocation to treatment"**
Allocation concealment mechanism	16b	Mechanism of implementing the allocation sequence (eg, central telephone; sequentially numbered, opaque, sealed envelopes), describing any steps to conceal the sequence until interventions are assigned	**Yes, please see the "3.4.1 Allocation to treatment"**
Implementation	16c	Who will generate the allocation sequence, who will enrol participants, and who will assign participants to interventions	**Yes, please see the "3.4.1 Allocation to treatment"**
Blinding (masking)	17a	Who will be blinded after assignment to interventions (eg, trial participants, care providers, outcome assessors, data analysts), and how	**Yes, please see the "3.4.1 Allocation to treatment"**

	17b	If blinded, circumstances under which unblinding is permissible, and procedure for revealing a participant's allocated intervention during the trial	**Yes, please see the "3.4.1 Allocation to treatment"**
Methods: Data collection, management, and analysis			
Data collection methods	18a	Plans for assessment and collection of outcome, baseline, and other trial data, including any related processes to promote data quality (eg, duplicate measurements, training of assessors) and a description of study instruments (eg, questionnaires, laboratory tests) along with their reliability and validity, if known. Reference to where data collection forms can be found, if not in the protocol	**Yes, please see the "3.12. Data collection, management, and statistical analysis"**
	18b	Plans to promote participant retention and complete follow-up, including list of any outcome data to be collected for participants who discontinue or deviate from intervention protocols	**Yes, please see the "3.12. Data collection, management, and statistical analysis"**
Data management	19	Plans for data entry, coding, security, and storage, including any related processes to promote data quality (eg, double data entry; range checks for data values). Reference to where details of data management procedures can be found, if not in the protocol	**Yes, please see the "3.12. Data collection, management, and statistical analysis"**
Statistical methods	20a	Statistical methods for analysing primary and secondary outcomes. Reference to where other details of the statistical analysis plan can be found, if not in the protocol	**Yes, please see the "3.12. Data collection, management, and statistical analysis"**
	20b	Methods for any additional analyses (eg, subgroup and adjusted analyses)	**Yes, please see the "3.12. Data collection, management, and statistical analysis"**
	20c	Definition of analysis population relating to protocol non-adherence (eg, as randomised analysis), and any statistical methods to handle missing data (eg, multiple imputation)	**Yes, please see the "3.12. Data collection, management, and statistical analysis"**
Methods: Monitoring			

Data monitoring	21a	Composition of data monitoring committee (DMC); summary of its role and reporting structure; statement of whether it is independent from the sponsor and competing interests; and reference to where further details about its charter can be found, if not in the protocol. Alternatively, an explanation of why a DMC is not needed	**Yes, please see the "3.12. Data collection, management, and statistical analysis"**
	21b	Description of any interim analyses and stopping guidelines, including who will have access to these interim results and make the final decision to terminate the trial	**Yes, please see the "3.12. Data collection, management, and statistical analysis"**
Harms	22	Plans for collecting, assessing, reporting, and managing solicited and spontaneously reported adverse events and other unintended effects of trial interventions or trial conduct	**Yes, please see the "3.6 Adverse Events Reporting**
Auditing	23	Frequency and procedures for auditing trial conduct, if any, and whether the process will be independent from investigators and the sponsor	**Yes, please see the "3.13 Quality control and quality assurance**
Ethics and dissemination			
Research ethics approval	24	Plans for seeking research ethics committee/institutional review board (REC/IRB) approval	**Yes, please see the supplemental ethics approval certificate**
Protocol amendments	25	Plans for communicating important protocol modifications (eg, changes to eligibility criteria, outcomes, analyses) to relevant parties (eg, investigators, REC/IRBs, trial participants, trial registries, journals, regulators)	**Yes, please see the "Ethics and dissemination"**
Consent or assent	26a	Who will obtain informed consent or assent from potential trial participants or authorised surrogates, and how (see Item 32)	**Yes, please see the supplemental consent inform**
	26b	Additional consent provisions for collection and use of participant data and biological specimens in ancillary studies, if applicable	**Yes, please see the supplemental consent inform**
Confidentiality	27	How personal information about potential and enrolled participants will be collected, shared, and maintained in order to protect confidentiality before, during, and after the trial	**Yes, please see the supplemental consent inform**
Declaration of interests	28	Financial and other competing interests for principal investigators for the overall trial and each study site	**Yes, please see the "Competing interests"**

Access to data	29	Statement of who will have access to the final trial dataset, and disclosure of contractual agreements that limit such access for investigators	**Yes, please see the "3.12. Data collection, management, and statistical analysis"**
Ancillary and post-trial care	30	Provisions, if any, for ancillary and post-trial care, and for compensation to those who suffer harm from trial participation	**Yes, please see the supplemental consent inform**
Disseminatio n policy	31a	Plans for investigators and sponsor to communicate trial results to participants, healthcare professionals, the public, and other relevant groups (eg, via publication, reporting in results databases, or other data sharing arrangements), including any publication restrictions	**Yes, please see the "Ethics and dissemination"**
	31b	Authorship eligibility guidelines and any intended use of professional writers	**Yes, please see the "Ethics and dissemination"**
	31c	Plans, if any, for granting public access to the full protocol, participant-level dataset, and statistical code	**Yes, please see the "Ethics and dissemination"**
Appendices			
Informed consent materials	32	Model consent form and other related documentation given to participants and authorised surrogates	**Yes, please see the supplemental consent inform**
Biological specimens	33	Plans for collection, laboratory evaluation, and storage of biological specimens for genetic or molecular analysis in the current trial and for future use in ancillary studies, if applicable	**Yes, please see the supplemental consent inform**

*It is strongly recommended that this checklist be read in conjunction with the SPIRIT 2013 Explanation & Elaboration for important clarification on the items. Amendments to the protocol should be tracked and dated. The SPIRIT checklist is copyrighted by the SPIRIT Group under the Creative Commons "Attribution-NonCommercial-NoDerivs 3.0 Unported" license.