Author's response to reviews

Title: Evaluation of etoricoxib in patients undergoing total knee replacement surgery in a double-blind, randomized controlled trial

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Author's response to reviews: see over
Reviewer's report

Reviewer 1

Comment 1: This is an interesting, well conducted RCT that shows safety and efficacy of etoricoxib, that it reduces post-op morphine requirement and it is at least as effective as ibuprofen. It would have been interesting if they could compare the efficacy of etoricoxib and morphine instead of ibuprofen, since rarely ibuprofen is used on a regular bases after total knee replacement. It is worth publishing with following considerations.

Response 1: We thank the reviewer for the time dedicated to the review. The design of the trial examined background use of patient controlled analgesia with morphine or oral oxycodone and placebo to etoricoxib for 7 days, versus morphine or oral oxycodone plus etoricoxib (90 or 120 mg daily) for 7 days versus morphine or oral oxycodone and ibuprofen 1800 mg a day for 7 days. We do have data the examines the comparison of morphine alone (etoricoxib placebo) versus etoricoxib plus morphine, and the results demonstrate that the use of etoricoxib leads to better pain control, reduced use of morphine and less morphine side effects reported by the patients. We understand the point that not all surgeons/anaesthesiologists would use ibuprofen post operatively, but we also felt it was important to have some positive control to benchmark the effects of etoricoxib in this trial. Ibuprofen was added as a positive control in this study on the recommendations of an advisory board.

Comment 2: I would add that the indications for total knee replacement are expanding in younger and more active patients with various intra-articular pathologies. The aims of the study should be numbered.

Response 2: We agree with the reviewer that the role of TKR is not limited to the population we studied. Rather we wished to provide some uniformity in the study population to aid in interpretation of the study results.

We have numbered the objectives in the methods section:

Methods, Page 10: The objectives of this study was to 1) demonstrate that the analgesic effect of etoricoxib 90 mg or 120 mg, administered once daily, is superior to placebo for the treatment of pain following total knee replacement orthopedic surgery (primary objective); 2) to demonstrate that the analgesic effect of etoricoxib 90 mg or 120 mg, administered once daily, is non-inferior to ibuprofen 1800 mg; and 3) to assess the safety and tolerability of repeated doses of etoricoxib administered over a total 7-day time period in patients treated for pain following total knee replacement orthopedic surgery.

Comment 3: Very long, should be more condense and to the point if possible. In “patients” section, why morbidly obese pts were excluded? Basically all pts with ASA class III/IV were excluded?
Response 3: The methods were revised to reduce the length and to eliminate redundant passages. Morbidly obese patients were excluded to reduce unrelated health factors that would confound the interpretation of the results. Morbidly obese patients may be at higher risk of a variety of complications, including post op infections, cardiovascular events and DVT.

Comment 4: **Surgical procedure:** The use of tourniquet is a potential confounder of the post-op complications and it should be included.

Response 4: Use of a tourniquet post operatively was not specifically proscribed against by the protocol and further we did not capture its use or non-use.

Comment 5: **Please provide a reference for the Recovery Index.**

Response 5: The Recovery Index-49 (RI-49) was developed to assess the quality of recovery across many different types of surgeries. It also includes an opioid side effect subscale. A reference has been added.

Comment 6: **What degree of knee flexion? Active or passive? In the immediate post-op period, extreme knee flexion obviously causes more pain.**

Response 6: As the reviewer notes, the intent of the knee pain flexion manoeuver was to elicit functionally relevant knee pain and the pain reports were higher with flexion than at rest. Knee flexion was performed passively, to 90 degrees and the procedure for doing so was specified in the protocol. This information has been added to the Methods section on Page 11.

Comment 7: **The first paragraph of discussion should focus on details of etoricoxib then describe the goals of the study.**

Response 7: We have modified the first paragraph of the discussion to incorporate the reviewer’s suggestion.

Comment 8: **Page 24, second paragraph:** “Etoricoxib 90 mg was evaluated using the third-molar extraction dental pain model and in patients who underwent total abdominal hysterectomy surgery [19,20]” is confusion, please clarify and separate the references.

Response 8: We have revised the text.

**Discussion, Page 25:** Etoricoxib 90 mg has been compared to etoricoxib 120 mg in two other prior post-operative pain settings. It was evaluated in the post-operative pain setting using third-molar extraction over a 3-day treatment period [19]. These two doses were also evaluated in patients undergoing total abdominal hysterectomy surgery over a treatment period of 5 days that included pre-operative dosing [20].
Comment 9: Page 26, second paragraph: cardiovascular complications, DVT, PE are also dependent on patients’ factors, tourniquet time (if used), surgical time, technique (cementation, intramedullary instrumentation), and modes of post-op DVT prophylaxis.

Response 9: We agree with the reviewer that post-operative complications are also associated with patient factors and technical factors associated with the surgery as well as choice of post-operative medications. The goal in providing the incidence of these events was more to remind readers that these events do occur. We note that the study investigators did not think that the events were related to study therapy, but we did not capture what they expressly thought that the events were related to.
Reviewer 2

Comment 1: Methods section: Several critical flaws can be found. In addition, the method section looks redundant.

Response 1: We have eliminated the redundant passages in the methods section.

Comment 2: The major flaw of this study is in enrollment of patients from too many hospitals (63 sites) in about 17 different countries and consequent heterogeneous nature of the patients. Although the authors enrolled relatively a large number of patients (776 for randomization with 9.5% loss till completion of the study), due to involvement of too many sites the allocated number of patients in each site would be small, about 12 patients on average in each site. Pain perception after major surgeries can vary between the patients with different conditions including differences in gender, ethnicities, contributory diseases, surgical techniques, and health care environment in each country. Thus, to overcome these variations, the number (proportion) of patients allocated in each study group should be evenly distributed in each site. However, the number of placebo group, i.e. 98 subjects in 63 sites at the time of randomization, indicates that proper distribution of the study subjects in each site would not be made. The authors should mention the precise information on randomization method and the way of allocation of the study subjects.

Response 2: Studies using the total knee replacement model for the evaluation of analgesia have been previously published. A unique aspect of our trial is that this is a truly global trial. As far as we are aware, this is the largest post-operative pain study in the total knee replacement setting, and in fact larger than a recent metaanalysis of all prior trials combined. We regard the size of the trial as a real strength.

However, we acknowledge that there is always a trade-off between the internal validity of a trial (sometimes called efficacy results), which we maximize by minimizing sites, and the external generalizability of the findings of the study (sometimes called effectiveness), which we maximize by including more sites. We have paid strict attention to training investigators and following up carefully on study results reported in real time – to maintain as high a quality trial methodology as possible. In addition we have produced results that are more relevant for more regions of the globe, which we think is a strength. We do acknowledge that having multiple sites and multiple countries could introduce greater potential variability in the study results. These concerns have been acknowledged in the discussion section. However, our results for pain and opioid use are well in line with the results from the recent metaanalysis on these issues.

Discussion, Page 28: This was a multicenter study conducted in several countries; research has recently shown increasing the number of countries and sites increases the study variability, leading to different estimates of treatment effectiveness in osteoarthritis patients [26]. In the total knee replacement acute pain setting, an increase in study variability could occur due to different operation procedures, different anesthesia, and different
post-operative care depending on standard procedures at individual sites and countries, which could confound results.

Comment 3: Did the entire patients undergo TKA due to primary knee OA? If other contributory diseases, such as RA, Traumatic OA, osteonecrosis, or neuropathic joint, were included, were there any differences in the proportion of the diseases between the groups?

Response 3: The patients in this study underwent TKA due to primary knee OA.

Comment 4: The authors designed the study that the first dose of study medicine (oral form) was given in the recovery room. Was it possible for all study patients and accepted by all investigators involved in this study? Many patients received general anesthesia in this study. Although there is controversy, generally a considerable amount of complete fasting time is still applied to the patients undergoing TKAs under general and even spinal anesthesia. The authors need to mention the applied protocols regarding this issue.

Response 5: The Authors Respond

1. Due to the fact that ibuprofen interferes with platelet function, we did not want to provide the ibuprofen pre-operatively. All patients had to be able to tolerate oral therapy and have a pain score of 5 or higher out of a possible 10 within 6 hours of cessation of surgery. In order to help patients tolerate oral therapy, we administered 4 mg of ondansetron by IV to all patients during induction. We acknowledge that some practices do not allow patients any oral intake for 24 hours post operatively. This was a feature that was extensively discussed with sites prior to their commitment to participate. We did have a small number of sites who were unwilling to participate for this reason. However all sites providing data in this study did agree to orally dose patients with placebo, etoricoxib or ibuprofen within 6 hours of completing surgery.

Comment 6: Did the authors evaluate use of MIS technique and/or tourniquet in each site and in each group? Although controversial, these two can influence on the pain levels during the immediate postoperative period.

Response 6: The protocol for the study states the following: “Patient is scheduled to have major orthopedic surgery defined as unilateral total knee replacement. (Note: patients scheduled for bilateral total knee replacement or revision of total knee replacement are not eligible for the study).” MIS technique was not reported by the investigators and we believe it was not used. Use of tourniquets was not proscribed in the protocol and data was not collected on this.

Comment 7: Were any other pain management methods, such as periarticular injection, not used for all patients?

Response 7: We attempted to standardize the use of intra-operative induction and anaesthesia as well as post-operative pain management, by protocol. So we did
specify that the use of intra-articular injections, intra-wound injections and femoral nerve blocks were prohibited.

Comment 8: I can easily expect that statistical specialists fully involved in this study and thus the statistical method seems to be perfect. However, it also seems to be complex. In particular, too many statistical analyses were performed for pain level per se. Considering the limitation of patient enrollment in this study, it would be better to simplify the statistical methods, especially for pain level analysis.

Response 8: The design and analysis of this study was done by PhD-level statisticians. Because of the large nature of this study, particularly for this type of pain model, we felt that this was an opportunity to extract clinically important information. Our goal was to try to bridge the gap between mean scores and actual response, which was the reason that we presented responder curves. Additionally, the duration of the trial is longer than similar trials using this pain model. Further, we wanted to present the full safety profile from the trial. We therefore believe that the methods chosen for the conduct and analysis of this study were appropriate and gave us an opportunity to present a complete profile of the efficacy and safety of etoricoxib in the post-operative total knee replacement setting.

Comment 9: Due to too high power for pain level in this study, small difference in the pain levels between the groups (placebo vs. other group) may be considered as significant difference. To overcome this problem, assessment of patient satisfaction in each group would be helpful. Dis the authors evaluate patient satisfaction in this study? If not, should be mentioned as a limitation of this study.

Response 9: We acknowledge that there was no patient satisfaction endpoint in this trial. However, our evaluation of the RI-49 endpoint provides important information on tolerability in this trial, and further, our inclusion of responder curves were meant to address the reviewer’s point with regard to small differences in mean values inappropriately being interpreted as clinically important.

Comment 10: I believe that the authors can make results section more simple and clear by adjusting the statistical analyses in this study.

Response 10: There are 4 treatment groups, two doses of etoricoxib, a superiority test to placebo and a non-inferiority test to ibuprofen and co-primary hypotheses. We understand the reviewers concern that the trial is complicated. However, we feel that, for the sake of transparency, it wouldn’t be appropriate to not include the full analysis that was prespecified in our protocol. We also shared the reviewers concern regarding the large sample leading to small differences in mean values being interpreted as clinically meaningful, as addressed in the previous comment; therefore, we believe that it is important to include the responder analyses to provide clinicians additional information that is clinically meaningful to patients.
Comment 11: *Introduction (Background) section: Should remove one of the duplicated periods just after the citation [6].

Response 11: This has been corrected.

Comment 12: *Introduction (Background) section: Information on etoricoxib and study purposes intermingled in the last paragraph of the introduction. It would be better to describe the information on the etoricoxib and the study purpose separately and more clearly for better understanding of this study by readers.

Response 12: This has been re-written consistent with this suggestion.

Comment 13: *Method section: It would be better to move the sentence for hypothesis to end of introduction.

Response 13: The primary hypothesis of the study has been added at the end of the introduction.