Author's response to reviews

Title: A Multinational Randomized, Controlled, Clinical Trial of Etoricoxib in the Treatment of Rheumatoid Arthritis

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PDF covering letter
Author’s Reply to Reviewer’s Comments

Reviewer 1

Comment 1: (a) What was the time difference between recruiting the first patient and the last patient in this study? (b) Were the numbers of patients in each centre equal? (c) Did the authors assess treatment effect for each centre? I do appreciate that results from individual centres maybe not of interest, however if particular results can be attributed to certain centres than a common factor can be identified. I also appreciate that the precision of centre-specific treatment estimates maybe very low, however it is necessary to investigate treatment by centre interaction. (d) I would recommend the use of Bayesian or mixed model approach, as the use of fixed effect approach may produce unstable or inefficient estimates of the regression coefficients. This method utilizes all the data and can be used to investigate treatment effects. It may also produce better parameter estimates then the time-weighted average change method.

Response:

(a) The time difference was 8 months (the enrollment period dates have been added in the Methods section).

(b) The numbers of patients in each center were not equal (range = 1 to 79).

(c) The Data Analysis Plan for the study pre-specified that the treatment-by-center interaction would not be formally assessed, and the ANCOVA model would not include a term for center. The rationale stems from the expectation that some centers would contribute only 1 patient (or even no patients), to a given treatment group, in the test for interaction. Final data revealed that 7 out of the total 67 centers (10%) had no patients for some treatments, and 19 centers (28%) had only 1 patient for some treatments. Nevertheless, we have tabulated the mean differences from placebo for each center on the primary end points. The majority of centers (33 to 43 centers, depending on the endpoint, among 53 that had at least 2 patients in each of placebo and etoricoxib 90 mg groups) showed the efficacy advantage of etoricoxib 90 mg over placebo for all primary endpoints.

(d) The time-weighted average change method was suggested by the FDA and pre-specified in the Data Analysis Plan for the study. Since the treatment effects of etoricoxib and naproxen occurred by the first assessment, at 2 weeks, and became relatively flat thereafter, the time-weighted average change method is an appropriate approach for assessing the overall treatment response over the 12 weeks. Although the mixed model or Bayesian approach may have a better precision on parameter estimates, the results and conclusions would remain the same due to the flat pattern of treatment effects and the large sample size in this study.
Comment 2: The statistical test may not be appropriate to investigate centre effects and treatment by centre interaction.

Response: See response to Comment 1 above.

Comment 3: The tables are adequate but the graphs are poorly drawn. I was unable to see the error bars.

Response: We have re-drawn the figures to make the error bars clearer and will liaise with the journal editorial staff to ensure that the figures are as legible as possible in the final version. It should be noted that the error bars are quite small.

Comment 4: Competing interests - None declared.

Response: Competing interests (disclosed after the Discussion section) have been revised as follows:
SP Curtis, A Melian, PL Zhao, DB Rodgers, CL McCormick, M Lee, CR Lines, and BJ Gertz are employees of Merck & Co., Inc. and have held Merck stocks or shares. E Collantes, KW Lee, N Casas, and T McCarthy have received funding from the following pharmaceutical companies to perform studies, act as a consultant, or be a speaker at company-sponsored symposia: E Collantes (Merck, Novartis, Lilly, Roche, Aventis, Pfizer, AstraZeneca), KW Lee (Merck, Aventis), N Casas (Merck), T McCarthy (Merck, Pharmacia, Novartis, Immunex, Isotechnika, Janssen-Ortho, AstraZeneca, Knoll and Abbott).

Reviewer 2

Comment 1: The major puzzle from this manuscript is the safety data and how they are presented. The significant increase in overall drug-related adverse events with etoricoxib as compared to placebo cannot be explained by the breakdown of adverse events in table 3b. The almost 8% increase in adverse events seen in patients with etoricoxib (i.e., table 3a) cannot be explained by the ~3% increase in headache and hypertension in patients with etoricoxib as compared to placebo in table 3b. The breakdown of adverse events, particularly the serious ones, should be more transparent.

Response: The numbers in Table 3b are not directly comparable with those in Table 3a because Table 3b shows adverse events regardless of drug-relatedness, a conservative approach. There was no specific individual drug-related adverse which was predominantly responsible for the difference between etoricoxib and placebo – no individual adverse event had an incidence ≥4%. The increase was due to small differences (usually only 1 or 2 patients) on a number of individual adverse events (overall, there were 91 different types of drug-related adverse events in the study). We have re-written the Results section to explain this point and to try to clarify the overall presentation. We have also added details of the serious adverse events as a footnote to Table 3a and added some text about serious adverse events in the Results section.

Comment 2: Was low dose aspirin use permitted in the study?

Response: Yes, but not many patients took it (<3%). We have added this information in the Methods section.
Comment 3: In the introduction, it is stated the study was performed “at sites throughout the world.” Is Japan included in this statement? Is it possible to list the 28 countries involved somewhere in the publication?

Response: Japan was not included. We have added the countries involved to the list of participating investigators in the Acknowledgments section. We also added the word “Multinational” to the title.