Reviewer's report

**Title:** Safety and efficacy of long-term esomeprazole 20 mg in Japanese patients with a history of peptic ulcer receiving daily non-steroidal anti-inflammatory drugs

**Version:** 1  **Date:** 17 October 2012

**Reviewer:** Sander Veldhuyzen van Zanten

**Reviewer's report:**

This group of Japanese authors is to be congratulated on conducting a study on the usefulness of esomeprazole in high-risk Japanese patients requiring chronic NSAIDs. This study question is important, as it is necessary to document that PPI co-therapy indeed is also effective in Asian populations.

Overall, the manuscript is well-written and the study is clearly laid out, and I will make my comments as I go through the manuscript. First of all, the study design is not the strongest, but this was obviously by choice. All patients received the intervention with esomeprazole, and therefore this makes it hard to make definitive statements about efficacy, although the one-year risk of endoscopically diagnosed ulcers at 4% was low. A somewhat unusual inclusion criterion was chosen; that is, the patient needed to have an ulcer scar but could not have an active ulcer. Although in general terms, it is clear what the endoscopists were looking for. For the purpose of this study report it would be helpful if the authors further defined their criteria for what constituted an ulcer scar. In this reviewer’s opinion, the authors could have considered letting patients who had ulcers continue on their NSAIDs while giving PPI, as studies, for example, with omeprazole have shown this to be generally safe. More than 40% of patients were infected by Helicobacter pylori but nothing is said about whether such patients received treatment for Helicobacter during the study or whether they were going to be offered treatment after the one-year study period; this needs to be clarified. The authors also do not mention at all the concomitant use of anti-platelet agents such as aspirin or clopidogrel, which would increase the risk of ulcers.

The reviewer had difficulty with the choice and reporting of the primary endpoint. This was a combination of safety, tolerability, blood tests and vital signs. However, it is unclear how this translates into a measureable primary outcome. I believe the secondary outcome, the proportion of patients free of ulcers at the end of the study, is much more meaningful and a better primary outcome. The reviewer also had some difficulty following the numbers in the results section. It was stated that 130 patients met the inclusion criteria but that 116 patients completed the study. The number of discontinued patients 6, 5 and 4, which is a total of 15, should have added up to 14. It is also unclear if patients dropped out during the study. How can the one-year ulcer event rate be reported as 96.2% at one year for all patients. Perhaps the authors used the method of carrying the last observation, in this case the endoscopy result, forward. If so, this should be
more clearly stated in the results section.

With regard to reporting of the primary endpoint, the manuscript is not clear in what actually is considered to be the primary endpoint. Is this 83.1% that is the proportion of patients not reporting an adverse event related to treatment? This does not seem to be logical as the stated primary endpoint was a combination of several factors, a comment I made before. Finally, in the result section, I am not sure whether fracture and pneumonia risk need to be mentioned, as in my view in the literature the association with PPI use overall is not that strong. Furthermore, even if there was a relationship between PPIs and fracture risk or pneumonia, the average risk is small, and a trial of 130 patients would not be able to detect a signal for PPIs for these outcomes.

Comments to the Editor:

**Level of interest:** An article of limited interest

**Quality of written English:** Acceptable

**Statistical review:** No, the manuscript does not need to be seen by a statistician.

**Declaration of competing interests:**

I have received research support, speaking fees and served on advisory boards of AstraZeneca, sponsor of the study.