Author's response to reviews

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

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Version: 2 Date: 4 December 2012

Author's response to reviews: see over
Response to Editor’s comments

Please revise your manuscript to provide the name of the ethics committee that approved your study. This information should be added to the Methods section of your manuscript.

Authors’ response: For a multicentre study in Japan (and in accordance with local regulatory requirements) it is necessary to seek approval from the corresponding ethics committee of each study centre. As such, it is not feasible to list details for every ethics committee, given the number of centres involved. The Editor is directed to the Methods section, where it is noted that the protocol was approved by an independent institutional review board or research ethics committee of each participating centre.
Response to reviewer comments

Reviewer #1 (Sander Veldhuyzen van Zanten)

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.

Authors’ response: We appreciate the reviewer’s positive evaluation on this study. We are aware of the limitations of this study, which are already acknowledged in the Discussion.

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.

Authors’ response: The reviewer raises a good point, and we had covered this in the Discussion in terms of discussing the results relative to similar studies.

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.

Authors’ response: Study investigators evaluated ulcer scarring according to the Sakita/Miwa classification (Miyake et al. Dig Dig Sci 1980). Further information has been added to the Methods section, along with the supporting reference.

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.

Authors’ response: It was not possible to recruit patients with active ulcers for the purposes of this study, because Japanese regulatory requirements prohibit the use of NSAIDs if active ulcer is present. The inclusion criterion for ulcer scarring and no active ulcer is consistent with the previous Sugano et al. study (AP&T 2012).

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.

Authors’ response: The reviewer raises a relevant point. We have clarified in the Methods section that eradication therapy was not permitted after enrolment, to avoid the potential confounding effect on ulcer recurrence rates. Unfortunately no information is available as to whether patients were to be offered such therapy after study completion, and therefore we are unable to comment further.
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.

**Authors’ response:** Please refer to the Methods section, where it states that continuous use of pre-specified concomitant medications including anticoagulant/antiplatelet therapy (including aspirin <325 mg/day) was not permitted.

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 measurable 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.

**Authors’ response:** The study was designed to specifically evaluate the long-term safety and tolerability of esomeprazole in at-risk NSAID users (for which there is limited information in Japan), while ulcer recurrence was a secondary endpoint. In view of this, and the open, non-comparative design, we do not consider that it would be appropriate to revise the paper such that ulcer recurrence became the primary endpoint. Our previous randomised, placebo-controlled study (Sugano et al. AP&T 2012) has already reported on this aspect.

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.

**Authors’ response:** Reference to Figure 1 (patient flow) shows that 14 patients failed to complete the study, because of adverse events (n=6), voluntary withdrawal (n=4) or other reasons (including severe non-compliance, n=4). The confusion may have arisen as the 5 patients who developed ulcer were deemed to have completed the study (as per the protocol), whereas the reviewer may be counting these patients as drop-outs.

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.

**Authors’ response:** As described in the Statistical Analyses section, peptic ulcer-free rates (and 95% CIs) were estimated using the Kaplan-Meier method. For the purposes of this analysis, an event was defined as endoscopy-confirmed peptic ulcer; time-to-event comprised the time between the date of initial administration and the date of event occurrence. The LOCF (Last Observation Carried Forward) approach was not used in this study, which is now clarified in Methods.

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.

**Authors’ response:** The reviewer raises a good point, because the primary ‘endpoint’ was actually a combination of several factors consistent with the study objective to evaluate the long-term safety and tolerability of esomeprazole. In order to improve clarity we have changed the corresponding description in the manuscript from primary ‘endpoint’ to ‘objective’ (and similarly for secondary ‘endpoints’).
Finally, in the Results 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.

Authors’ response: The reviewer’s comment is well taken, although the manuscript text already alludes to the limitations of drawing conclusions from such data given a relatively small patient sample. Generally speaking, there has been concern about the moderately elevated risk of fracture (hip, spine and wrist) with PPI therapy based on a recent meta-analysis of observational studies. Concerns have also been raised about the increased risk of pneumonia with long-term PPI therapy (in some, but not all, studies). These issues of PPI long-term safety are of timely concern in Japan, and therefore warranted brief discussion. Given that only 3 patients experienced a fracture (hand finger, rib and upper arm), and 1 patient experienced pneumonia, we therefore decided to report these findings in the Discussion section where the limitations of drawing any conclusions from these findings are noted.
Reviewer #2 (Akinori Yanaka)

Since the efficacy of PPI is influenced by genotype of CYP2C19, it seems also important to show the data on the adverse events of esomeprazole among three different genotypes of CYP2C19.

Authors’ response: In fact, CYP2C19 genotype did not impact on the gastroprotective efficacy of esomeprazole in the present study, as the estimated ulcer-free rates were similar for all CYP2C19 genotypes (see Results). As such, presenting AE data according to genotype (while of general interest) is probably not necessary or relevant. We also have to consider that such findings would be limited by the small patient numbers for the subgroups.

There are 5 cases of ulcer relapse, despite the treatment of esomeprazole for 1-year period. It seems useful to show clinical characteristic of the 5 cases by Table, in order to give us information about what kinds of risk factors are related to NSAIDs-related ulcer relapse among patients taking with esomeprazole.

Authors’ response: The Results section has been briefly expanded to provide further details on the 5 patients with ulcer recurrence.
Sugano and colleagues submit a manuscript considering the efficacy and safety of once-daily omeprazole [sic] in patients with prior GI ulcer concomitantly treated with NSAIDs. An open-label design is used, and 130 patients are included and followed for 12 months. The authors conclude that omeprazole [sic] 20 mg once daily is well tolerated and effective in preventing adverse events (including recurrent ulcer). I congratulate the authors with a well-designed and meticulously conducted study. The manuscript is well written. The following issues must be addressed.

About one quarter of the patients received concomitant corticosteroid treatment. Corticosteroids likely increase the risk of abdominal complications due to a reduced ulcer healing and increased bleeding tendency. This deserves a mention. Despite the fact that the study seems underpowered for subgroup analyses, the authors may want to include “+/- corticosteroid treatment” in Table 4.

Authors’ response: The reviewer makes a good point. Use of corticosteroids (yes/no) was included in the subgroup analysis for ulcer recurrence, and relevant data are now included in Table 4.

Compliance is measured by pill counting and NSAID diaries. These are not very strong compliance parameters, although I acknowledge that they are the only feasible options in the current study. I think the compliance issue deserves a mention under Limitations.

Authors’ response: We agree with the reviewer, and a comment to this effect is now included under limitations.

I do not find any information on the duration of NSAID treatment prior to study start. The risk of NSAID-induced GI complications (including ulcer) must depend on how long NSAID treatment has been ongoing. A patient that starts taking NSAID very shortly prior to being included in the study has another a-priori risk of GI complications than a patient who has been treated with NSAIDs for years. Would the authors please try to address this issue?

Authors’ response: This is a good point, as patients who are new to NSAID therapy do have an increased risk of upper GI complications such as ulcer; however, whether this is relevant in the context of ulcer recurrence (i.e. present study population) remains unclear. Unfortunately, information on duration of NSAID therapy was not collected as part of the baseline assessment, and therefore we could not explore this further. We accept this as a limitation, which is now mentioned in the Discussion section.

I appreciate the inclusion of CYP2C19 genotyping. However, there are no details on what specific SNPs the authors looked for. Was it the *2 polymorphism? Please elaborate a little in the Methods section.

Authors’ response: For the purposes of clarification, the Methods section has been revised to note that poor metabolisers were defined as those with *2 and *3 variant alleles.

Regarding Figure 1: The figure would benefit from a little more detail: some words to describe the main reasons for ineligibility in the 247 patients being excluded. This is important, because some extent of selection bias is likely to be found here.

Authors’ response: Almost all ineligible patients had no evidence of ulcer scarring during endoscopic assessment at screening. This is now highlighted in the Results text.
Regarding Table 3: The authors report the most frequent adverse events. I have a problem with the mix of subjective symptoms (e.g. headache and pruritus), objective signs (e.g. hypertension and eczema) and biochemical measurements (e.g. GGT levels and platelet count) under the heading “Adverse events”. For instance, in my view elevated GGT levels are not an adverse event per se, but they reflect liver damage caused by whatever reason. Such damage may be due to true adverse events like infectious hepatitis, toxic hepatitis, and autoimmune hepatic disease and so on. I suggest dividing the content of Table 3 by use of subheadings to distinguish between symptoms, objective signs and biochemistry.

**Authors’ response:** We agree with the reviewer’s comments. However, it is important to consider that information on AEs was collected according to standard regulatory requirements:

“An AE is the development of an undesirable medical condition or the deterioration of a pre-existing medical condition following or during exposure to a pharmaceutical product, whether or not considered causally related to the product. An undesirable medical condition can be symptoms (e.g., nausea, chest pain), signs (e.g., tachycardia, enlarged liver) or the abnormal results of an investigation (e.g., laboratory findings, electrocardiogram).”

We have provided clarification on this point within Methods and as a footnote to Tables 2 and 3.

The reference list should be extended to include up to 30 authors before using “et al”.

**Authors’ response:** The reference list has been updated accordingly.

The use of LANZA scoring (and the frequent endoscopies) is an obvious strength. Although the LANZA score is well-known, for the sake of the readers of the journal you may want to expand your description of this scoring system in Methods. A single sentence describing the content of the LANZA score would be helpful to many readers.

**Authors’ response:** The Methods section has been expanded to include further information on the LANZA scoring system. An explanatory footnote has also been added to Table 5.