Author's response to reviews

Title: Palonosetron versus ondansetron as rescue medication for postoperative nausea and vomiting: a randomized, multicenter, open-label study

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Author's response to reviews: see over
I am pleased to submit for your consideration our revised manuscript “Palonosetron versus ondansetron as rescue medication for postoperative nausea and vomiting: a randomized, multicenter, open-label study.”

We are grateful to you and the reviewers for your helpful comments on our manuscript. We have detailed our response to each reviewer comment below and highlighted revisions in the manuscript.

Thank you for your consideration of our revised submission.

Sincerely,

Keith A. Candiotti, MD

Response to reviewers:

Title: Palonosetron versus ondansetron as rescue medication for postoperative nausea and vomiting: a randomized, multicenter, open-label study

Version: 2 Date: 26 January 2014

Reviewer: Piotr Janicki

Reviewer's report:

Major Compulsory Revisions

1. For the study with basically negative results the power analysis is necessary to ascertain the statistical power of results. The authors justify the lack of the formal statistical power analysis by the statement that the study was 'descriptive'. I am not sure how the study is classified as 'descriptive', when in fact it was prospective, randomized design. In fact, in the discussion part, they claim that the study was underpowered - how they now this without statistical analysis. I believe that at least post hoc power estimation should be included (despite all its drawbacks).

   Changed from description of study from “descriptive” to “proof of concept.” Post hoc analysis added in Discussion.
2. Not sure why only females were enrolled. It should be significant bias in the interpretation of results and the limitation of the study. It is my understanding the study was open for both genders. This limitation should be stated and discussed.

*Females have a higher incidence of PONV. Although the study was open to both male and female patients, we were not able to recruit any male patients. This has been added to the limitations in the Discussion.*

3. The timing of administration of ondansetron is in according to old FDA guidelines but contrary to the most recent PONV Guidelines just published in A&A by some of the authors. Why this discrepancy?

*The study is sponsored by Eisai; therefore, drugs had to be given per FDA-approved labeling. This limitation is already stated, but discussed further. SAMBA guidelines also have been updated to 2014.*

4. I am a bit puzzled by the aim of the study. The authors declare in this paper (and also in mentioned before guidelines) that the PONV rescue should be from different group of medication that used in prophylaxis. In this respect the results are not unexpected at all. If they wanted to have some type of positive control, they should rather use, instead of ondansetron (not effective by definition) some other antiemetic from different group.

*Because palonosetron has several pharmacologic properties that are distinct from other 5-HT₃ RAs, the goal of this study was to show that it would be useful when these other agents had failed. Wording was adjusted to elaborate further on this goal and rationale and to affirm the SAMBA guidelines in light of this study’s findings.*
Reviewer's report:

I have serious concerns about this manuscript, because it appears to be over-reaching to find something positive to say about palonosetron, especially given the potential for bias with two of the four authors having currently or previously worked for Eisai. This is of a particular concern given the open-label design of this trial.

Major compulsory revision:

Although neither the primary nor secondary endpoints showed any advantage to the use of palonosetron, the conclusions in the abstract and manuscript are trying to massage any possible advantage to the use of palonosetron, by referring to trends in emesis reduction that favour palonosetron, but are not statistically significant.

Why not comment that this work appears to confirm the earlier work of Candioti showing no efficacy with rescue administration of 5-HT3 RA's after earlier prophylaxis for PONV with these same type of agents? Also, there should be more commentary in the discussion about the study design choosing to administer prophylactic ondansetron at the beginning of the case, rather than at the end of the case as per SAMBA PONV Guidelines. Giving ondansetron at the beginning of the case would potentially bias study results to favor palonosetron.

A statement about the earlier Candioti study has been added, as well as elaboration on dosing as per labeling (not as per SAMBA guidelines) as a limitation. We do not feel that giving ondansetron at the beginning of the case would have biased the study towards palonosetron since all patients received the same preoperative dose at the same time point and both groups were rescued based on the same clinical criteria.

There needs to be more discussion about how the study was powered. Although I did not review their calculation, they indicate that the study was powered for descriptive purposes, but later on claim that it could have been underpowered and that's why there was no detectable difference in the primary or secondary endpoints. And yet the authors achieved the total number of patients treated with either palonosetron or ondansetron that they were trying to recruit (98 vs 100), which leads me to believe that the study was adequately powered for the primary endpoint.

Post hoc analysis was added to the Discussion. Contrary to our initial estimate that 100 patients per treatment group would be adequate to show differences, the post hoc analysis showed that 540 patients per arm actually would be needed to show a statistically significant difference in the primary endpoint.

What could further studies add to this topic? There appears to be no advantage in using palonosetron vs ondansetron for rescue anti-emetic therapy, after prophylactic treatment with a 5-HT3 RA. Even if a small, statistical difference could be eventually be proven, the clinical relevance is negligible, given the 300X cost differential, not to mention the availability of other cheaper pharmacologic alternatives that work via different receptor antagonists or mechanisms, and are efficacious. Furthermore, these data are almost 5 years old. Why has it taken them so long to submit their work? But most seriously, the only
piece of data that would potentially show any advantage to the use of palonosetron does not appear to be credible. Everything in their argument hinges in table 3 (secondary end points).

Looking down the columns for palonosetron and ondansetron, and across the rows, "no-emesis," "0-72 hr," and "0-24 hr," the number of patients who received ondansetron and had no episodes of emesis was lower over the 0-72 hr time period than it was over the 0-24 hr time period. That simply does not make sense, and this is the only reason why the 0-72hr time period "approaches statistical significance," while the 0-24hr time periods, and 24-72hr time periods show no difference.

*Statements added that further studies are unlikely to show clinically relevant differences in outcomes and wording generally toned down about the trend for a potential difference. Also, reference added about differing half-lives possibly contributing to the trend seen for emesis.*

*The publication delay largely was due to the fact that the company that was introducing palonosetron in the US sold the US rights to Eisai.*

*Regarding the specific data from Table 3, the number of ondansetron patients experiencing emesis over the entire 0-72 h period was greater than over the first 0-24 h. That is, those having that symptom increased over the greater time period (ie, those having “no emesis” decreased). Therefore, the numbers and p value (approaching statistical significance) are correct.*
This trial compares the newer 5HT3 antagonist palonosetron with the classical HT3 antagonist ondansetron in the treatment of postoperative nausea and vomiting (PONV). Results show no difference in the percentage of complete control of PONV (primary end-point) between the drugs. Also, no difference was reported in relation to secondary end-points (complete response and change from baseline nausea scoring).

1) Abstract: in the ‘conclusion’ paragraph of the abstract, the authors reported they found a trend for emesis. However, they did not specify the drug for which the trend was observed. Please, specify. This has been clarified.

2) ‘Background’ paragraph: Ref 12 refers to Guidelines for the treatment of PONV published by SAMBA in 2007. However, in February 2014, New Guidelines for surgical patients with post-operative nausea and vomiting have been published by the same Society. Thus, this reference should be updated. The updated guidelines have been substituted.

3) ‘Methods’ paragraph: the authors affirm that Guidelines for PONV treatment recommend the use of a drug from a different class (i.e. with a different mechanism of action) from that used for the antiemetic prophylaxis. Thus, the authors should better explain in the text why they used not only a drug from the same class (i.e. palonosetron group underwent ondansetron as prophylaxis followed by palonosetron as medication rescue) but also the same drug in both treatments (i.e. ondansetron group underwent ondansetron as prophylaxis followed by ondansetron as medication rescue).

See explanation in Background as to why palonosetron was hypothesized to work in this setting (ie, different pharmacology from ondansetron). Ondansetron rescue of ondansetron prophylaxis served as an active drug comparator with previously known results. The authors acknowledge that we could potentially learn more from a study designed with a different comparator than ondansetron (eg, an antiemetic with a different mechanism of action relative to the 5-HT3 RAs). This has been added to the Discussion section.

4) ‘Patient selection’ paragraph: in this kind of studies, among the exclusion criteria the body weight (i.e. obesity) is usually considered. The authors should indicate if they considered it and if available, they should insert this data in table 1. BMI data have been added to exclusion criteria and to Table 1.

5) ‘Discussion’ paragraph: the authors wrote that the study could have been underpowered and this could be the reason for which not statistically significant difference between treatments was observed. However, some considerations must be done: first, results indicate a trend for emesis in favour of palonosetron at later time points. An explanation could be the different pharmacokinetic profile of palonosetron compared to that of ondansetron (see for example the different half-lives). This, but also
other hypotheses should be suggested. Second, if no statistically significant difference has been found this is not necessarily due to the limited number of patients. In fact, sometimes a limited case series may be representative of a larger case series. It is clear that this must be verified but it cannot be excluded a priori. Thus, the authors should try to better discuss their findings and to suggest some other hypothesis for their results (for instance, what about concomitant medications, etc.?).

Reference to differing half-lives has been added. Post hoc analysis added to the Discussion.

Third, the authors should better contextualize their results with those of other available recent studies in which palonosetron and ondansetron are compared.

Reference to 5 studies from 2011 to 2013 has been added to both the Background and Discussion that compare palonosetron with ondansetron for prevention of PONV. However, to our knowledge, these two drugs have not been compared in the rescue setting.

Minor Essential Revisions

1) ‘Background’ paragraph: Ref 17 and 18 are indicated as ‘recent’ studies. However, the year of publication is 2008. The sentence should be modified. In addition, more recent studies (e.g. Moon et al, 2012; Kim et al., 2013; Baisakhi et al, 2013) should be added and commented.

“Recent” has been deleted. Five studies from 2011-2013 have been added to both the Background and Discussion that compare palonosetron with ondansetron for the prevention of PONV. However, to our knowledge, these two drugs have not been compared before in the rescue setting.

2) Table 1: please delete the line indicating the IV level of physical status according to ASA. It is not due since according to the inclusion criteria, patients with IV ASA were excluded.

This has been deleted.