Reviewer's report

Title: Safety and efficacy analysis of posaconazole as oral antifungal prophylaxis in pediatric patients under 12 years of age following allogeneic stem cell transplantation

Version: 2 Date: 10 June 2012

Reviewer: Ronen Ben-Ami

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Major compulsory revisions

1. Posaconazole is currently unlicensed for use in children and the age of 12 years. The authors should clearly state this fact. Furthermore, there is currently no reliable pharmacokinetic data on posaconazole in children. Simple extrapolation from adult pharmacokinetics is generally not sufficiently accurate. Why did the authors choose posaconazole over antifungals that have been studied in this age group? As this is a retrospective review, were these 60 patients given posaconazole because they were intolerant to other antifungals?

2. Page 12, paragraph 1: If patients were readmitted for reasons other than IFI and received IV antifungals they were excluded from the analysis. This decision may bias the analysis because readmission could be related to posaconazole adverse effects, and therefore intolerance may be under-appreciated. How many patients started on posaconazole were excluded based on this criterion? Are these the 4 patients mentioned on pages 5 and 6?

3. Unlike adult patients in the Ullman study, only ~10% of the patients in this study had GVH grade 3 or 4 (Table 1). This may be related to the difficulty in ensuring oral intake in these patients. Moreover, none of the patients that underwent therapeutic drug level monitoring had GVH 3 or 4 (Table 3). Thus TDM results may represent an overestimation for patients with GVH which currently represent the main target population for posaconazole prophylaxis in SCT recipients.

4. Although there were no cases of probable-proven IFI, the background risk of IFI may have been low given that most patients did not have significant GVH. Some appreciation of the efficacy of posaconazole may be gained from historical severity-matched controls which would address the background risk of IFI in this patient population.

5. Posaconazole exposure of >700 ng/mL has been shown to correlate with efficacy during prophylactic treatment (Dolton et al. AAC 2012). Thus, most of the patients in this study had low, possibly subtherapeutic posaconazole levels in plasma. The authors discuss some of the reasons for this fact (poor oral intake, concomitant PPI use). This issue should underscore the need for dose finding studies of posaconazole in children aged <12 years.
6. Patients were treated from discharge to day 100 post transplant, and then until T cell function recovery. However the actual duration (median and range) of posaconazole treatment is not clearly stated.

7. The observation period was from the start of posa treatment and until day 200 post SCT. However, the range of observation period was from 12 to 188 days (median 162 days), and 35% of patients were not monitored until day 200. As there were no cases of probable-proven IFI, were these patients taken off of posa because of adverse effects, or because of possible IFI?

Minor essential revisions

8. Page 8. Rantidine is an H2 receptor blocker, not a proton pump inhibitor.

**Level of interest:** An article whose findings are important to those with closely related research interests

**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 served on an advisory board for Pfizer.