Reviewer's report

Title: Anidulafungin compared with fluconazole for treatment of candidemia and other forms of invasive candidiasis caused by Candida albicans: a multivariate analysis of factors associated with improved outcome

Version: 1 Date: 24 May 2011

Reviewer: J Peter Donnelly

Reviewer's report:

Major Compulsory Revisions
1. The manuscript seems to have been written by a medical writer. If so this should be stated clearly.

2. The manuscript should be shorter. For instance showing that the gravimetric difference between the MICs of anidulafungin and fluconazole adds nothing especially as no relationship offered between these and the pharmacokinetics and pharmacodynamics of the two drugs. Nor does the difference necessarily explain the higher response rate of the echinocandin. Besides the authors state this fact in the introduction so it is not germane to the hypothesis. Also I do not believe the study design needs to be so expansively explained since the original study has been published elsewhere. The reader should be treated only to those methods germane to exploring the hypothesis which is clearly stated as being to explore the factors that might explain the better response of infections due to Candida albicans to anidulafungin.

3. Why was the mITT chosen as this reflects only those patients who received at least one dose of study medication and had a positive culture for Candida species within 96 hours before enrolment rather than the more relevant population that had received at least 10 days of intravenous therapy with the allocated drug?

4. Given the number of univariate analysis was there any correction for this?

5. Was a statistician involved in the analysis?

- Minor Essential Revisions
6. Rather than talk about “bloodstream infections” why not simply refer to candidaemia as the yeasts are found in the bloodstream which is not the site of infection but like just a transport system.

7. Using abbreviations is acceptable as long as they are first defined. For instance I do not know what CIC stands for and guess that EIV means end of IV treatment. Also what does AIC stand for?

8. The analysis done was post-hoc a term that is preferred to retrospective.

9. How many centres contributed cases to this analysis and was a centre effect explored?
10. I am not sure that reporting a percentage for small fractions like ¾ or 3/6 is useful.

11. How important is an odds-ratio of 2.65 when the 95%CI varies from 1.19 – 5.9?

12. The lower number of deaths in the anidulafungin arm might be different for the per protocol population. Also given the nature of the mITT I am not sure what, if anything, this means. Could it not simply be the product of a series of chance events given the large number of centres involved (47 in the original study with a single centre contributing 10% of the total number in the mITT).

13. Did the authors confirm that anidulafungin was in fact cidal and that fluconazole was static in vitro against all the strains?

14. The authors suggest that the reason that the better response to anidulafungin did not translate into better long-term survival might be due to underlying diseases other than CIC. This could be addressed in part by comparing the per-protocol population to the mITT could it not?

15. I think eradication of yeast or clearance is more accurate than sterilization of blood cultures.

16. I find the last sentence in the first paragraph of the discussion baffling as it now stands. Do the authors meant that the OR for the study regimens was higher than that of the APACHE II score suggesting a pharmacological benefit for anidulafungin?

17. I do not follow the argument about the release of fragments of beta-d-glucan and the innate response. Might this conjecture not be stretching things a bit too far?

18. The argument about a study with a larger number of patients to show a significant difference may be true but it would still beg the question of how important any survival advantage might be.

19. Is not candidaemia a serious infection irrespective of whether patients are considered moderately or severely ill?

20. Please omit Figure 1 as it is superfluous

21. I do not think figure 4 adds anything and is already stated in the text

Level of interest: An article of importance in its field

Quality of written English: Acceptable

Statistical review: Yes, but I do not feel adequately qualified to assess the statistics.

Declaration of competing interests:

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Speaker’s bureau Gilead, Merck, Pfizer