Reviewer's report

Title: Evaluation of two formulations of adjuvanted RTS,S malaria vaccine in children aged 3 to 5 years living in a malaria-endemic region of Mozambique: a Phase I/II randomized double-blind bridging trial

Version: 3 Date: 28 August 2006

Reviewer: Allan Donner

Reviewer's report:

General

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Major Compulsory Revisions (that the author must respond to before a decision on publication can be reached)

1. What is the principal motivation for the aim of replacing RTS,S/ASO2A with RTS,S,ASO2D? More discussion should also be provided as to the reasons the study was designed as a non-inferiority trial rather than as a superiority trial.

Given the choice of a non-inferiority design, what was the basis for selecting a 3-fold difference in defining the boundary for non-inferiority with respect to immunogenicity?

2. It would be helpful to the reader if a detailed list of inclusion/exclusion criteria for the subjects in this trial was provided.

3. Methods are available for determining the required size of a non-inferiority trial (eg, Jones et al, British Medical Journal, 1996). It is not clear why the authors adopted a significance-testing approach to the sample size assessment for this trial while using a confidence interval approach to assess equivalence in the analysis phase.

4. It would be more informative if in Table 1 95% CI's were computed about the difference in incidence rates attributable to the two vaccines rather than computed separately for each vaccine.

Some of the differences in Table 1 (eg, for pain, local symptoms) appear fairly sizeable, although the authors state that overall "the incidence of symptoms, local and general solicited symptoms was similar in each group". Some comment on this should be provided.

5. There are two figures labelled Figure 1 in the manuscript provided, while Figure 2, referred to in the text as showing comparability of the two groups with respect to age, sex, and race, appears to be missing. In any event, it would be most useful if the authors were to present a table showing the baseline comparability of the two groups with respect to all potential risk factors.

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Minor Essential Revisions (such as missing labels on figures, or the wrong use of a term, which the author can be trusted to correct)

More detail on the method of randomization used in this trial would be useful.

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Discretionary Revisions (which the author can choose to ignore)

What next?: Unable to decide on acceptance or rejection until the authors have responded to the major compulsory revisions

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

Quality of written English: Acceptable
Statistical review: Yes, and I have assessed the statistics in my report.