Reviewer’s report

Title: A randomized, double-blind clinical phase II trial of the efficacy, safety, tolerability and pharmacokinetics of a single dose combination treatment with artefenomel and piperaquine in adults and children with uncomplicated Plasmodium falciparum malaria

Version: 0 Date: 06 Jun 2017

Reviewer: Sam Salman

Reviewer's report:

A negative trial which demonstrates that a single dose ACT combination of artefenomel and piperaquine is not likely to be suitable at any tolerable/safe dose.

Some concerns with regards to the presentation of data, analysis of exposure/response and PK analysis need clarification or correction.

Table 2: The percentages are not consistent with the totals and number - for example n=437 in the total column on the right, in the first row 437 is expressed at 97.5%. It appears the percentage refers to the total randomised patients (437/448) rather than the safety set which the table refers to.

Lines 340-345: The final comment in this section "… despite reported compliance being >95% in all populations." is discordant with the provided information on compliance 65% in the African and 91.5% in the Asian population.

Table 4: When comparing this table to Table 3 it is not clear why the denominator changes from the crude ACPR to the PCR-adjusted ACPR. For example day 42 in table 3 for 800:1440 dose has a crude result of 68/146 and PCR adjusted result of 73/146 while in table 4 it is 67/130 and 72/100 respectively. Although it is understandable that there is a smaller number in the PP analysis set is it not clear why there should be 30 less participants in the PCR adjusted ACPR in this same set. The same pattern exists throughout this table.

Figure 3: Consider presenting the plots as survival free from recrudescence.

Lines 412-413: It would be of benefit to present data to support the comment that "No association between Kelch13 mutation and ACPR28 was identified." This could be included in the text.
Table 6: The reported percentage of Malaria + Pf infection (27.9+5.9=33.8%) is lower than suggested from the efficacy data. For example, crude ACPR 42 days reported as 45.1% (197/437) therefore 54.9% (240) had malaria diagnosis at this time. The reported rate of vomiting here (11.4%) differs from that in the text (line 342 - 28.8%).

Lines 481-482: There is a very high CV in the AUC and Cday7 values (both >100%) the impact of high CV on target concentration attainment, particularly with a single dose therapy, should be discussed.

Lines 513-514: It is not clear if the interaction between region and artefenomel Cday7 was included before or after the assessment of the effect of Kelch13 mutation. Given that the mutation was only present parasites from Asian participants and a higher day 7 concentration was required to achieve the same efficacy in these participants, it would be important to know that the potential interaction of these mutations was investigated completely before incorporating another interaction.

Line 516: The equation was distorted in the pdf for review.

Table 7: This simulation exercise predict a ACPR of 92% (89-95%) for the highest dose in this study, much higher than the observed 84 and 62% in those 2-5 and <2 years, respectively. It may be of greater value to perform simulations with results closer to the observed results. It would be of interest to model 2 or 3 dose regimens.

Line 652: The tolerability is noted as "generally good", it is difficult to marry this comment with the observed rate of vomiting of 28.8%.

PK analysis: A non-linear PK relationship was identified for artefenomel. It would be more common for the nonlinearity to be related to concentration (ie michaelis menten elimination) rather than dose. A justification for using dose to model nonlinear elimination should be provided.
Are the methods appropriate and well described?
If not, please specify what is required in your comments to the authors.

Yes

Does the work include the necessary controls?
If not, please specify which controls are required in your comments to the authors.

Unable to assess

Are the conclusions drawn adequately supported by the data shown?
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No

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