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

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Reviewer: Cor Jesus Fontes

Reviewer's report:

- Macintyre F and colleagues performed 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. The manuscript is quite extensive, but very well written, well analyzed and has its results clearly shown and well discussed.

- The primary objective of the study was to determine whether a single dose combination of 129 artefenomel plus piperaquine is an efficacious treatment for uncomplicated P. falciparum malaria. Secondary and exploratory objectives included determination of the incidence of recurrence, recrudescence and new infection, estimation of parasite clearance kinetics and exploration of the relationship between Kelch13 genotype and parasite clearance half-life (PCt1/2) in Asian patients. An additional key exploratory objective was to characterise the dose/exposure response relationship for the combination for the primary efficacy end point across the patient population. Safety, tolerability and pharmacokinetics (PK) was also assessed in the study.

- Since the study proposes the introduction of a single dose antimalarial regimen, the following points highlight its relevance: poor adherence to the standard malaria treatment in endemic areas impacts malaria morbidity and mortality and contributes to development of parasite resistance; An effective cure obtained by a such single treatment, directly observed if required, would also provide an important tool to support malaria elimination efforts.

- Artefenomel 800mg was administered in loose combination with three doses of PQP (640, 960,1440 mg) to 3 groups of patients. Although none of the treatment arms reached the target efficacy of ≥95% PCR-adjusted ACPR (adequate clinical and parasitological response) at Day 28, the results found in this phase II trial are very promising in the current context of malaria therapy.

- The manuscript is suitable for publication, without revision.
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?
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Yes

Are the conclusions drawn adequately supported by the data shown?
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