Reviewer's report

Title: The effect of the novel phosphodiesterase-4 inhibitor MEM 1414 on the allergen induced responses in mild asthma

Version: 3 Date: 21 July 2014

Reviewer: Alastair Stewart

Reviewer's report:

Other reviewers' comments

Minor essential

2. The authors have not adequately addressed comments made regarding the use of LAR or in vitro LPS responses to justify conclusions regarding an anti-inflammatory mechanism of action.

Discretionary

1. The authors' response lacks clarity in that it is not clear in context what is meant by "there was no significant change in responses"

Dose of MEM1414

The authors have not addressed the question which asked for justification of the dose in relation to the suggested mechanism of action. Why use a dose producing plasma concentrations three orders of magnitude higher than required selectively inhibit PDE4. The authors response suggested that the dosing was geared towards the highest dose previously shown to be well-tolerated. This design and the lack of a dose-response relationship raise the issue of whether the dose used has other effects that explain the impact on LAR. Specifically the new introduction asserts IC50 values in the nanomolar range for a number of the isoforms of PDE4, but IC50s for other PDEs are not provided. The plasma levels of MEM1414 reached in this study are in the order of 30 micromolar. The concentrations of MEM1414 required to inhibit LPS induced TNFa are in the micromolar range. No evidence has been provided by the authors to establish the selectivity of MEM1414 in the micromolar concentration range. Comparisons with roflumilast suggesting similarity do not stand up to scrutiny eg "MEM1414 IC50 12.3 micromolar is slightly higher than roflumilast 85.8 nM". Not slightly higher, but 143 times higher.

Figure 5. Whilst the 8 hour time is annotated as being significant the data as presented are not persuasive. The axis or the figure legend need to carry units (presumably micromolar).

Level of interest: An article of insufficient interest to warrant publication in a scientific/medical journal
Quality of written English: Acceptable

Statistical review: No, the manuscript does not need to be seen by a statistician.

Declaration of competing interests:

peter barnes is on the advisory committee of a centre I am associated with.