Reviewer’s report

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

Version: 2 Date: 30 April 2014

Reviewer: alastair stewart

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The study by Leaker and colleagues is well-conducted and most of the design elements are carefully considered. The major and inescapable limitation in the study is the choice of a dose level of MEM 1414 that generates concentrations 3 orders of magnitude higher than the Ki value for the compound at PDE4 isoforms (unreferred data from Memory Pharmaceutical Corp’s data file).

We are not provided any data on the potency of MEM1414 on other PDEs, nor on other potential targets, as are assessed on commonly available and commonly used receptor-binding screens. It is therefore not possible to gauge whether the activity of MEM1414 is due to selective PDE4 inhibition and it is unclear why such a high dose was chosen, given phase 1 safety data (not cited in the current manuscript and not available from Pubmed search using “MEM 1414”) should have provided guidance to appropriate dosing to achieve selective PDE4 inhibition. It is noted that the compound has an earlier history as a development compound for alzheimers disease having been ascribed nootropic activity.

The study does not add to our understanding of PDE4 inhibitors in the treatment of asthma. The proof-of-concept achieved is that a single dose of an uncharacterized chemical (at least in respect to refereed data) has an effect on LAR, but the relationship of such an action to PDE4 is highly speculative.

Additional major issues

The comment that the nausea, vomiting and diarrhea are self-limiting is not appropriate given a very short period of treatment for a compound being developed for a chronic condition. The abstract, conclusion and discussion should be edited to remove this commentary.

The methodology and discussion of the analysis of the LPS data is confusing/incorrect. It is suggested that the potency of MEM1414 was quantified as EC50 and ECmax, but in fact MEM1414 concentrations are not displayed (and will be different for each donor). The concentration response curve for LPS was actually presented, but the EC50 and EC max were not displayed or stated in the text. Moreover the authors assert that the effect of the MEM1414 treatment was not active until 8 hours but this doesn’t accord with my visual interpretation of the graphical data, as that suggested that the effect of treatment was greatest.
at zero hours.

Given the variance in plasma concentrations it would be useful to demonstrate whether there was any relationship between concentration and effect at a particular time post allergen, regardless of the expected inter-individual differences.

It is important to have data on the impact of MEM1414 concentrations added ex vivo to whole blood to ascertain what impact this direct treatment has on LPS cytokine production.

Methacholine PC20 data is described as showing a trend that did not reach significance (p=0.38), but the arithmetic effect size and the variance clearly do not amount to a trend.

Minor but essential correction
The methods section refers to either a 3 or 2 week period of washout – whichever was the shorter should be use throughout the text.

Line 325 – Altering the pharmacokinetic properties of the formulation of MEM 1414.

**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 a member of the lung health research centre of which i am co-director