Reviewer's report

Title: Safety, tolerability, pharmacokinetics and pharmacodynamics of GSK233633, a CC-chemokine receptor 4 antagonist, in healthy male subjects: results from an open-label and from a randomised study

Version: 2 Date: 21 December 2012

Reviewer: Karl J. Staples

Reviewer's report:

The role of the Th2 cell in atopic asthma has been central to our understanding of the disease for the last 20 years. Previous work has identified that CCR4 is expressed predominantly on the surface of Th2 cells and that inhibiting the function of this receptor preferentially prevents Th2 cell chemotaxis. Thus drugs that inhibit the recruitment of Th2 cells to the asthmatic airway via CCR4 antagonism have been a key goal for some time.

This paper by Cahn et al, provides the first in man testing of the CCR4 inhibitor GSK2239633, demonstrating that whilst this compound had low-to-moderate plasma clearance, when taken orally there was severely restricted bioavailability. Because of this the receptor occupancy rates calculated for this drug was below the 90% threshold desired. Thus this drug is not suitable for oral dosing in its current formulation.

Major Compulsory Revisions:

1. The phrase "determined using an internally validated analytical method" is used more than once in the manuscript which makes it hard to review properly. Either the authors should provide full details of methods used or provide references upon which the methods are based.

2. Please explain the criteria used for the investigator to determine whether an adverse event was related to the study drug.

3. The Ro experiments and data raise a number of issues, not least whether the drug is really binding to the receptor as there appears to be very little change in occupancy as the dose of study drug increases. The authors should show that the drug is actually effective in this assay rather than reporting as unpublished observations in the introduction. It would also be useful for the authors to display the data for the placebo group in Table 5 to give an idea of what the Ro is in this untreated group to allow evaluation of the noise in this system. In addition when comparing the Ro between placebo and treated groups (Figure 1B), the 900 mg dose appears most effective, but there is little discussion of the shifts in EC50 as a result of drug treatment. Was there any difference in the fed cohort?

4. The discussion is largely a reiteration of the results with very little attempt to explain the results in the context of the relevant literature. For example the first
statement after the summary says "The results from the Single Oral Dose Study are consistent with the physicochemical properties of the molecule" but provides no references for this statement. The discussion continues in this vein until the final paragraph.

Minor Essential Revisions:

1. In the methods it states "Subjects completed a screening visit within 28 days of receiving the first dose of study medication" this is confusing as it could be read that the subjects were screened 28 days after the first dose. This should be revised for clarity.

2. Figure 1B is labelled as Figure 2

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

**Quality of written English:** Acceptable

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

**Declaration of competing interests:**

I currently have grant funding from GSK Biologicals in Belgium.

I was previously employed as a postdoctoral scientist on a project funded by GSK Pharma, Stevenage, UK (2006-2008).

I was a co-author on a paper detailing CCR4 inhibitor efficacy in an ex vivo model of disease alongside a different group of employees from GSK Pharma, Stevenage, UK.