Reviewer's report

Title: Randomized study of the safety, pharmacokinetics, and bronchodilatory efficacy of a novel glycopyrrolate metered-dose inhaler in study patients with chronic obstructive pulmonary disease

Version: 1
Date: 11 February 2014
Reviewer: Eric Bateman

Reviewer's report:

Compulsory Revisions:

1. This paper presents results of a randomized double-blind four period, six treatment placebo and active controlled, incomplete cross-over study of glycopyrrolate delivered in a porous particle in patients with COPD. Four doses of Glycopyrrolate were compared with placebo and open-label tiotropium. The authors conclude that a single dose GPMDI of 77 or 144µg was non-inferior to Tiotropium 18µg. The AUC measurement suggested that BID dosing would be preferable, and the authors propose 36 or 72µg administering twice daily for future development. The manuscript is unnecessarily long and the discussion is laboured. It must be considerably shortened.

2. Line 96: It would be helpful to have a description of the size of the particles.

3. Important statements in the introduction are not supported by references (or only abstracts) and in places sounds like marketing. For example, the 2nd sentence of background in the abstract and the paragraph beginning line 92. The statement “allows therapeutic agents to be more easily delivered into the lungs” needs explanation. In what respect is it easier? Higher dose delivered or easier for patient? The sentences 102 – 106 need explanation or should be deleted. What does “favourable engineering properties” mean? That sentence seems to repeat parts of the sentence above and line 105 and 106. The sentence in lines 101, 102 needs an explanation. Is it relevant? And, what are “good in-vitro characteristics”? Either explain or delete, or is it repeating lines 92 to 97?

4. The conclusion of the abstract states “as well as a favourable safety profile”. I suggest the words “no adverse events were recorded”, or similar, as there were only 33 patients in the study, and each was given only a single dose on 3 occasions!

5. Paragraph 117 – 127 describing the purpose of the study contains a number of odd statements. The second sentence can be more simply written. Reference to cardiovascular risk is out of place since this study does not address safety. With such limited exposure of patients to the drug, neither is the data on dry mouth meaningful. These are therefore not the objectives of this study. This was a single dose-ranging study, with tiotropium simply an open label active comparator. This could be stated in one sentence.
Minor Essential Revisions:

6. The method section is too long, in particularly lines 152 – 164. The sentence beginning 191 should be in the analysis section.

7. The first sentence of the discussion is not supported by references and should be deleted.

8. Line 300 – what is meant by “trough FEV1 at 12 hours”? This was not the trough.

9. The meaning of the sentence 301 – 304 is unclear.

10. The paragraphs 312-325 can be deleted. It makes too much of the increase between 10 and 12 hours, which is a well-recognised feature in 24-hour lung function assessments (as confirmed by the placebo). In any event in a single dose study this has less meaning than with steady state dosing.

11. Paragraph 326 – 330 is also needlessly long. Lines 326 – 330 can be deleted.

12. The discussion line 357 considerably simplified.

13. The discussion 369 – 378 is unnecessary and can be stated in one sentence, since it is largely opinion. This drug is in early stages of development, and there will be place in phase 3 studies to consider the pro’s and con’s of twice daily dosing. Preferably in studies designed for that purpose. This one was not.

14. The section on study limitation has some repetition. More important than the sample size is the fact that this is single dose study and provides only the information expected from the study design. The issue of generalizability is not relevant in a dose-ranging study.

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

Quality of written English: Not suitable for publication unless extensively edited

Statistical review: Yes, but I do not feel adequately qualified to assess the statistics.

Declaration of competing interests:

I declare that I have not competing interests.