Author's response to reviews

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

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Author's response to reviews: see over
Dear Editor:

We have reviewed the comments and queries related to our manuscript entitled: “Randomized study of the safety, pharmacokinetics, and bronchodilatory efficacy of a novel glycopyrronium metered-dose inhaler in study patients with chronic obstructive pulmonary disease” that were raised during the peer-review process.

We have incorporated changes to address them. The summary which follows provides the reviewer comments and the revisions that have been made to the manuscript. We are pleased to re-submit our manuscript entitled for further consideration and publication in *BMC Pulmonary Medicine*.

Sincerely yours,

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Reviewer #1

The authors present the primary efficacy, safety and PK results of a four-period, incomplete block, single dose crossover study randomizing 33 patients (18-20 to each treatment) to single doses of a new MDI formulation (with porous particles) of four escalated doses of glycopyrolate 18, 36, 72 and 144ug compared to placebo, and to tiotropium 18ug. Subjects were 40-75 year old COPD patients with post ipratropium FEV1 of 50-85%, all with greater than 12% (150ml) reversibility to Ipratropium. This study, therefore, selected patients likely to benefit with LAMA (GP vs. TIO) treatment to look for dose response characteristics after single doses. All subjects were followed for 24 hours after each dose. Primary endpoint was peak FEV1 (change from baseline) and secondary endpoints were AUC 0-12°, 0-24°, 12-24°, 12 and 24 hour trough FEV1 and other typical endpoints. Safety analyses included AE monitoring, as well as dry mouth and paradoxical bronchospasm monitoring.

The MS does an excellent job of presenting the results of this single dose dose-ranging clinical trial. The essential conclusion evident on Figure 2 is that while all GP doses (18-144ug) were equivalent or superior to TIO at Day 1 peak (2 hours), and doses of 36 and 144ug were comparable or better than TIO during hours 0-12, none of the GP doses were numerically as effective for FEV1 as TIO during hours 16-24, or at the 22-24 hour trough. Therefore, this trial indeed suggests that once daily dosing of GP does not provide as long lasting twenty-four hour effective bronchodilation as the active comparator Tiotropium.

The authors address this point carefully in their Discussion. Interestingly, the two higher doses of GP 72 and 144mcg did show significant improvements over placebo in 24 hour trough FEV1 and in AUC 12-24 of some 120-130ml better than placebo. This suggests GP’s topical effects at airway muscarinic receptors may indeed persist for at least 24 hours (compared to placebo). Moreover, the persistent 24 hour benefit vs. placebo on FEV1 contrasts to the fairly rapid fall off in serum GP levels in PK graph Figure 5. This suggests GP may have a longer effective residence time at airway muscarinic receptors than occurs for serum PK levels. In effect, GP may have a relatively high topical potency and topical effect at airways, with a lower and shorter systemic exposure profile. These may be favorable characteristics for a LAMA, allowing relatively long bronchodilation without much systemic side effect risk. Such prolonged airway effects have also been seen (I believe) for other LAMAs such as Umeclidinium.

In summary, I highly recommend this MS be accepted for publication by BMC Pulmonary Medicine. It provides quite interesting and novel information on the dose-ranging, PK and safety characteristics of a new MDI formulation of glycopyrolate.

Response: We appreciate the reviewers excellent summary and kind remarks.

Minor corrections requested include the following:
- P22 = Non-employee authors (Rennard and Fogarty) should provide fuller, complete
Disclosure statements on any conflicts of interest.

Response: These have been provided

• Authors should list the dates during which the study enrollment and treatment occurred in the Methods section.

Response: These have been provided

• Authors should clarify what percent of patients utilized inhaled corticosteroids during the study.

Response: This information has been provided

• Table 1 should just report means. Medians are duplicative and confusing for readers.

Response: While we believe that medians are more rigorous, we have made the suggested change as we agree it is more conventional.

• Figure 1 includes typographical errors under Sequence 2 and Sequence 4. Presumably four sequences included TIO and four included PLA.

Response: We have made the correction (thanks)

Reviewer #2

Excellent paper, very thorough, clear and novel. While the authors highlight very appropriately the selective nature of their population (bronchodilator responsiveness to antimuscarinic challenge) it would be interesting to know how many patients of the total that were screened failed to meet the reversibility criteria.

Response: This information has been added

Since this was a dose ranging study biased toward patients with reversibility, how might this influence dose selection (if any) for larger efficacy and safety trials?

Response: Drug development strategies generally regard bronchodilators as a physiologic class and have assumed that dose ranging can be accomplished most easily among those with larger responses. In general, those with more modest responses respond similarly, albeit with reduced effect size. In COPD, moreover, response to bronchodilators can vary from day to day. Thus, the general assumption is that dose selection in the current population will be applicable to the COPD (and all other) populations. The discussion has been revised (briefly as reviewer #3 recommended shortening the manuscript) to address these important issues.
### Reviewer #3

1. This paper presents results of a randomized double-blind four period, six treatment placebo and active controlled, incomplete cross-over study of glycopyrollate delivered in a porous particle in patients with COPD. Four doses of Glycopyrollate 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.

**Response:** We have shortened the discussion

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

**Response:** We have provided this information

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?

**Response:** We have revised the manuscript to clarify the sections.

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!

**Response:** We have made the recommended revision.

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.

**Response:** We have revised the manuscript to clarify the section.
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.

Response: We appreciate the reviewer’s desire for brevity. However, we feel that an explicit description of the methods is necessary.

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

Response: We have revised the sentence.

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

Response: We have revised this content to read post-dose FEV₁, and to clarify that GP MDI is twice-daily product.

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

Response: We have edited for clarification and to emphasize twice-daily dosing.

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.

Response: We have made the recommended revision.

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

Response: We have made the recommended revision.

12. The discussion line 357 considerably simplified.

Response: As noted above, we have shortened the discussion.

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.

Response: We have made the recommended revision.

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
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from the study design. The issue of generalizability is not relevant in a dose-ranging study.

Response: We have revised the manuscript to address this point.

Additional Changes:

Globally:
- Visit numbers were capitalized.

Background: Paragraph 2.
- Sentence was rephrased to read: "The particles themselves are comprised of distearoyl-phosphatidylcholine (DSPC), a naturally occurring lung surfactant that is used frequently in approved pharmaceutical preparations, and CaCl₂.”
- The following sentence was deleted: “The potential for co-suspension formulation became apparent with the observation that glycopyrronium, which was also in development as an MDI, was found to crystallize.”

Background: Paragraph 4.
- The first sentence was revised to replace “novel” with “proprietary” and “technology” with “engineering”

Materials and Methods: Paragraph 1.
- The following sentence was added: “To aid in the selection of doses for further development a marketed open-label active comparator was included in this study (TIO DPI).

Statistical Analysis

Paragraph 1.
- The following content was deleted: ” To identify investigational doses likely to demonstrate clinical efficacy that was not substantially less than the active comparator (tiotropium), a non-inferiority assessment was performed where the lower bounds of the 95% two-sided CIs for the (adjusted) group differences in mean peak, AUC₀-₁₂, and AUC₀-₂₄ responses were compared with -100 mL. A Wilcoxon rank sum test was used to assess differences in time-to-onset of effect.”

Paragraph 3:
- GP MDI dose and bronchodilation response (ΔFEV₁ AUC₀-₁₂ and ΔFEV₁ AUC₀-₂₄ data) were fit using various pharmacodynamic (PD) models (eg, linear, sigmoidal, with and without baseline). Dose-response modeling of bronchodilation data was performed using Phoenix NLME 1.0 (Pharsight, St. Louis, Missouri). Statistical criteria such as Akaike Information and Log likelihood were used to assess the goodness-of-fit of the dose-response model as well as other criteria such as visual assessments of fit, absolute residual distribution, and coefficient of variation of PD parameters.
Results and Discussion:

Disposition and Baseline Characteristics: Paragraph 1:
- PD was deleted.

Secondary Efficacy Variables, Paragraph 1:
- The following content was deleted: “The GP MDI 57.6 and 115.2 µg doses were shown to be non-inferior to tiotropium in terms of improvement from baseline in peak FEV$_1$, FEV$_1$ AUC$_{0-12}$, and FEV$_1$ AUC$_{0-24}$ using the a priori defined non-inferiority bound of 100 mL (Figure 4). The GP MDI 115.2 µg dose was also non-inferior to tiotropium for 12-hour tFEV$_1$ and FEV$_1$ AUC$_{12-24}$

PK and PD:
- PD was deleted.

Safety:
- Paragraph 1, Sentence 1: the following content was deleted: , although there did not appear to be a relationship between dry mouth and the dose of GP MDI

Discussion

Paragraph 1.
- “The first sentence was revised to replace “novel” with “proprietary.””

Paragraph 2.
- The following sentence was deleted: “The 14.4 and 28.8 µg doses did not satisfy the non-inferiority bound compared with tiotropium for any parameter.”
- tFEV$_1$ was revised to read post-dose FEV$_1$
- The following content was revised to read: All GP MDI doses demonstrated a rapid onset of action, and the 115.2 µg dose demonstrated a significantly faster onset than TIO 18 µg.
- The following text was revised to read: For all GP MDI doses, the changes from baseline in FEV$_1$ compared to Placebo MDI at 12 hours post-dose were appreciably greater than the changes at 24 hour post-dose, while these values were more consistent for TIO compared to Placebo MDI.
- The following text was revised to read: Similarly, FEV$_1$ AUC$_{0-12}$ was greater than FEV$_1$ AUC$_{12-24}$ for all GP doses compared with Placebo MDI, while for TIO the difference from Placebo MDI in FEV$_1$ AUC maintained close to 1:1 ratio across the 0- to 12- and 12- to 24-hour intervals.
- The following content was deleted: with no apparent relationship to the dose of GP MDI.

Paragraph 3
- The first sentence was revised to read: With regard to the duration of action of GP MDI, several observations confirm that the GP MDI is appropriate appropriateness for twice daily dosing.
Paragraph 4
• on Day 1 was revised to read: “after initial dosing”.
• tFEV\textsubscript{1} was changed to post-dose FEV\textsubscript{1}
• The following content was added: In the GLOW2 study,[18] study patients received either NVA 237 50 µg, tiotropium 18 µg, or placebo QD, the differences from placebo in 24-hr post dose FEV\textsubscript{1} after initial dosing were 91 and 83 mL for NVA 237 and tiotropium, respectively.
• The last sentence was revised to read: It should be noted that in the current study that the screening post-bronchodilator percentage predicted FEV\textsubscript{1} was 60.6% compared with 54% for GLOW1 and 56% for GLOW2. Such patients may be expected to demonstrate a greater post-bronchodilator response. Of further note, since subjects in the current study were required to be reversible, while most groups of COPD patients benefit clinically by typical LAMAs[1], subgroup data for QD umeclidinium suggest that subjects who are more reversible or who are current smokers may demonstrate somewhat greater FEV\textsubscript{1} responses to treatment with LAMA.

Paragraph 5
• The following text was deleted: study patients received either NVA 237 50 µg, tiotropium 18 µg, or placebo QD.
• The following text was added: whereas in the current study the difference from Placebo MDI for GP MDI was 208, 155, 137, and 109 mL for 115.2, 57.6, 28.8, and 14.4 µg, respectively, in comparison to 172 mL for TIO.
• The sentence was revised to read: Also in GLOW2, the Day 1 improvement in peak FEV\textsubscript{1} for NVA 237 compared to placebo was 200 mL, 47 mL greater than tiotropium.
• The sentence was revised to read: Whereas in the current study, the peak change from baseline in Peak FEV\textsubscript{1} for GP MDI compared to Placebo MDI was 248, 180, 158, and 146 mL for 115.2, 57.6, 28.8, and 14.4 µg, respectively, in comparison with 198 mL for TIO.

Paragraph 6
• The following sentence was deleted: Once daily dosing may be preferred by many patients because reduced administration may improve both convenience and adherence.

Conclusions
• The third sentence was revised to read “The overall profile of GP MDI based on 12-hr post dose FEV\textsubscript{1} compared with 24-hr post dose FEV\textsubscript{1}, and AUC\textsubscript{0-12} compared with AUC\textsubscript{12-24} support a BID dosing regimen at all doses evaluated.”

Figure 4: was deleted.