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: 29 January 2014
Reviewer: Edward Kerwin

Reviewer's report:

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 glycopyrrolate 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.

Minor corrections requested include the following:

• P22 = Non-employee authors (Rennard and Fogarty) should provide fuller, complete disclosure statements on any conflicts of interest.
• Authors should list the dates during which the study enrollment and treatment occurred in the Methods section.
• Authors should clarify what percent of patients utilized inhaled corticosteroids during the study.
• Table 1 should just report means. Medians are duplicative and confusing for readers.
• Figure 1 includes typographical errors under Sequence 2 and Sequence 4. Presumably four sequences included TIO and four included PLA.

With these minor corrections, I believe this will be an excellent MS for BMS Pulmonary Medicine.

Thank you for giving me the opportunity to review this MS.

Reviewer #2

Level of interest: An article of importance in its field

Quality of written English: Acceptable

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

Declaration of competing interests:

Reviewer #2 has served on advisory boards, speaker panels, or received travel reimbursement for Astra Zeneca, Forest, Ironwood, Merck, Mylan, Novartis, Pearl, Pfizer, Sanofi Aventis, Sunovion, Targacept and Theravance. He has conducted multicenter clinical research trials for approximately seventy pharmaceutical companies.