LETTER TO THE EDITOR

Reply to: Garcia Arieta A. The efficacy of tiotropium administered via Respimat® Soft Mist™ Inhaler or HandiHaler® in COPD patients

We want to thank Dr Garcia Arieta for his interest in our comparative study of tiotropium administered via Respimat® Soft Mist™ Inhaler (Rmt) or via the HandiHaler® (HH) conducted in COPD patients.1 We agree that an inhalation product comparison is a difficult task and that the present study1 would not suffice as sole evidence to establish comparability in efficacy, safety and systemic exposure and to support a product registration based on therapeutic equivalence to an originator product.

However, this was neither intended nor stated in the article1: Our core conclusions were (1) superiority of all tiotropium doses and formulations over placebo, (2) non-inferiority of both doses of tiotropium Rmt to the HH formulation and (3) similar systemic exposure. (4) We are not aware of general safety comparisons between formulations in the literature that are fully powered. This would be an extremely difficult endeavour. However, our study especially mentions similar and low incidence of dry mouth following Rmt 5 µg and HH 18 µg, which can be regarded a sensitive marker for anticholinergic effects, which is informative also in smaller studies.

To be noted, tiotropium Rmt 5 µg was profiled by a full stand-alone development programme beyond the study discussed here consisting of a chronic dose-ranging study,2 and four Phase III studies of 12–48 weeks duration including more than 3000 patients with COPD. Dose selection for tiotropium Rmt was based on the totality of data, and eventually on comparison of efficacy and safety in two large 48 week placebo controlled studies including two doses of tiotropium Rmt.

Our study provides undisputed evidence that the 5 µg dose of tiotropium Rmt, selected based on Phase III-study evidence, is at least non-inferior to tiotropium HH. The observed difference of 0.029 L in favour of the tiotropium Rmt was statistically significant, but is probably not clinically relevant.

Our study was not designed as a formal bioequivalence study and respected limitations in the number of blood samples that may be taken in a therapeutic trial with patients. Formal bioequivalence criteria are not established for inhalation products anyway. As described,1 the geometric mean renal excretion value, the plasma concentration at 10 min post-dose and the area under the plasma concentration-time curve over 6 h were numerically slightly higher following inhalation of 5 µg via the Rmt inhaler compared to tiotropium 18 µg via the HH, but evaluation of the intra-individual comparison between treatments did not suggest a systematic difference in systemic exposure between the formulations.

In conclusion, our study positions an alternative innovative formulation of tiotropium by Rmt as non-inferior in efficacy and similar in exposure compared to the established HH formulation.

Conflict of interest

None declared.

References


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17 June 2009
Available online 18 August 2009