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Title: Comparison of the pharmacokinetics and pharmacodynamics of once daily tiotropium Respimat® and tiotropium HandiHaler® in COPD patients

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Body: Background/Objective: Primary objective of this study was to characterize the pharmacokinetics of tiotropium Respimat® 5µg (R5) in comparison with tiotropium HandiHaler® 18µg (HH18). Secondary objective was to assess the dose-dependency of bronchodilator efficacy (FEV_1, FVC) by including 2 lower tiotropium Respimat® doses (1.25µg and 2.5µg) and placebo. Methods: Multicentre, placebo-controlled, randomised, double-blind (within Respimat® device), 5-way crossover trial with 4-week treatment periods in 154 patients. Primary endpoints were peak plasma concentration ($C_{max,ss}$) and area under the plasma concentration-time profile ($AUC_{0-6h,ss}$), with first sample 2 min following inhalation. Results: Tiotropium was rapidly absorbed, showing no difference between devices, with a median $t_{max,ss}$ of 5-7 min post-dosing. Pharmacokinetics of tiotropium Respimat® treatments (R5, R2.5 and R1.25) was dose proportional. The bioavailability of R5 was lower than HH18. The gMean ratio of Test/Reference for R5/HH18 was 81% (90% CI 73% to 89%) for $C_{max,ss}$ and 76% (90% CI 70% to 82%) for $AUC_{0-6h,ss}$, indicating that bioequivalence was not established pointing to lower systemic exposure with R5. Dose-ordering for bronchodilation was evident for the Respimat® doses, with R5 showing similar efficacy to HH18. Treatments were safe and well tolerated with no apparent differences between devices. Conclusions: The bioavailability of R5 was lower than HH18. In view of lower systemic exposure and similar bronchodilator efficacy, these results support the currently marketed R5 dose for the once-daily maintenance therapy of COPD patients. Funded by Boehringer Ingelheim.