

At day 0 and appropriate time intervals until the final dose was dispensed and the lock-out mechanism of the inhaler was activated, the following parameters were assessed: water content, degradation products, content per cartridge, delivered dose (DD), fine particle dose (FPD) and microbial growth. All results, notably DD and FPD (Figure 1), were within the expected range and well inside the specifications applied during development. More precisely, the mean results of DD for acclidinium bromide were between 370 µg and 451 µg (specification 320–480 µg) and for FPD between 139 µg and 182 µg (specification $\geq 80\mu\text{g}$), while the mean values of DD for formoterol fumarate dihydrate were between 10.1 µg and 13.1 µg (specification 9.6–14.4 µg) and for FPD between 2.5 µg and 3.7 µg (specification $\geq 1.8\ \mu\text{g}$).

The studies show that stable pharmaceutical quality can be guaranteed under

in-use conditions for a period longer than the allowed 60 days after unpacking the drug product pre-stored even up to the end of shelf life.

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P292 PILOT STUDY TO ASSESS BRONCHODILATOR RESPONSE DURING AN ACUTE EXACERBATION OF COPD USING A VIBRATING MESH NEBULISER VERSUS JET NEBULISER FOR BRONCHODILATOR DELIVERY

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Introduction Recovery from COPD exacerbation is associated with increases in respirable lung volume. Accelerating these changes through improved bronchodilator delivery could hasten recovery.

Hypothesis Vibrating mesh nebuliser (Aerogen® Ultra) results in greater change in lung physiology compared to standard small volume jet nebuliser.

Methods Patients with an exacerbation of COPD were randomised to receive combined salbutamol 2.5 mg/ipratropium bromide 0.5mg via vibrating mesh (Active group) or standard hospital jet nebuliser (Control) on one occasion between day 2–7 of hospitalisation. Spirometry, body plethysmography and impulse oscillometry were performed pre-bronchodilator and at 1 hour post. Borg breathlessness score was measured.

Results Thirty-one patients have been recruited to date, 16 to the active group and 15 control group. Mean FEV₁ was $48 \pm 18\%$ predicted. Baseline demographics were comparable between groups. Both groups had significant improvements in FEV₁ and Inspiratory Capacity post-bronchodilator, with greater increases in FVC in the active group ($0.40 \pm 0.39\ \text{L}$ vs $0.19 \pm 0.19\ \text{L}$, $p = 0.06$). Significant changes in operating lung volumes and airway impedance were seen in both groups. There was no significant difference in Borg score.

Conclusion Bronchodilator administration, during a COPD exacerbation, results in significant improvements in spirometry, lung volume and airway impedance. Drug delivery by vibrating mesh nebuliser results in greater absolute increases in FVC. Further studies will assess whether this translates into accelerated exacerbation recovery.

P293 DRUG DELIVERY PERFORMANCE OF BUDESONIDE (BD), GLYCOPYRRONIUM (GP) AND FORMOTEROL (FF) TRIPLE COMBINATION (BGF) CO-SUSPENSION™ DELIVERY TECHNOLOGY MDIS

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Introduction To assure consistency of clinical outcomes, orally inhaled products must have consistent *in vitro* delivered dose and aerosol properties. Achieving this consistency has been challenging with MDIs, particularly those that combine multiple drugs. Co-Suspension™ delivery technology has been developed for *in vitro* drug-drug interaction-free delivery of multiple drugs from fixed-dose MDI combinations. This versatile technology suspends the micronised drugs with spray-dried phospholipid porous particles in hydrofluoroalkane propellant. The objective of this study was to determine whether BGF MDI, the triple Co-Suspension delivery technology formulation of BD/GP/FF, displays *in vitro* drug delivery comparable to its constituent single and dual drug formulations.

Methods Single, dual and triple therapy MDIs of BD, GP and FF were prepared by suspending each drug's microcrystals with phospholipid porous particles in HFA propellant. *In vitro* drug delivery was assessed by comparing delivered dose uniformity and aerodynamic particle size distribution.

Results BD, GP and FF formed stable suspensions in the presence of phospholipid porous particles, despite differences in drug physicochemical properties and doses. A consistent and comparable delivered dose and aerodynamic particle size distribution was observed whether emitted from a single, dual or triple therapy MDI.

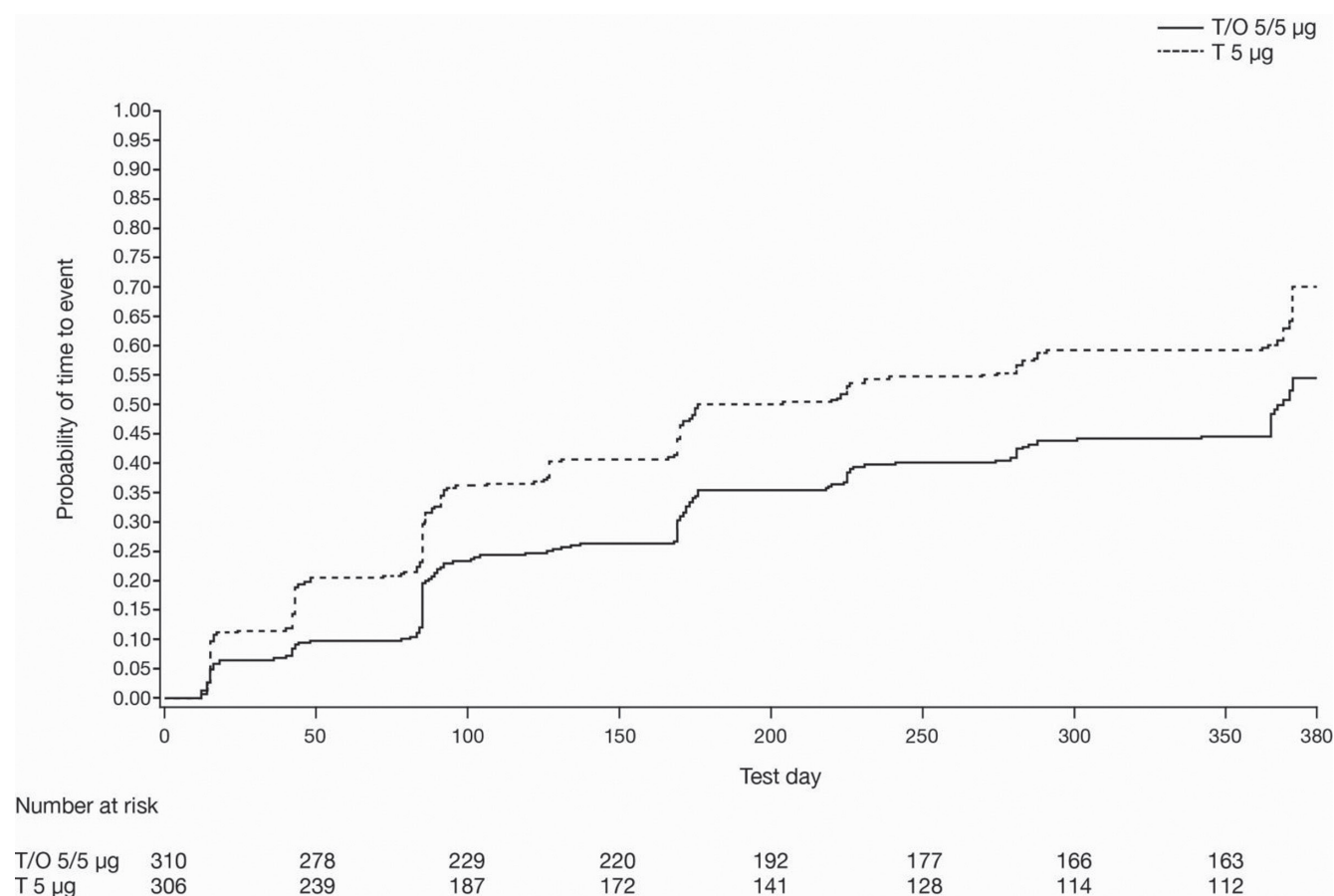
Conclusion The single, dual and triple drug MDI formulations demonstrated comparable aerosol characteristics which should enable patients to transition across the continuum of these MDI therapies without *in vitro* drug-drug interaction impacting drug delivery and clinical outcomes.

P294 BENEFITS OF TIOTROPIUM/OLODATEROL OVER TIOTROPIUM AT DELAYING CLINICALLY SIGNIFICANT EVENTS IN PATIENTS WITH COPD CLASSIFIED AS GOLD B

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Rationale The once-daily combination of tiotropium (T), a long-acting muscarinic antagonist, and olodaterol (O), a long-acting β_2 -agonist, has demonstrated efficacy and safety in COPD. Two large clinical studies (TONADO® 1 + 2) have also demonstrated the benefits of T/O compared to the monocomponents in patients with moderate to very severe COPD. This *post hoc* analysis investigated whether T/O is more effective than T at delaying



Abstract P294 Figure 1 Kaplan-Meier estimates of time to clinically significant event (decline from baseline FEV₁ of ≥ 100 mL; increase from baseline of ≥ 4 units SGRQ total score; severe exacerbation; death) in patients with GOLD stage B COPD

clinically significant events in patients with GOLD stage B COPD.

Methods A total of 5162 patients were randomised to O 5 µg, T 2.5 µg, T 5 µg, T/O 2.5/5 µg or T/O 5/5 µg (delivered via Respimat[®] inhaler) in two 52-week, parallel-group, double-blind studies (NCT01431274; NCT01431287). In this *post hoc* analysis of the combined TONADO[®] data, clinical deterioration was defined according to a composite end point: time to first decrease in trough forced expiratory volume in 1 second (FEV₁) from baseline of ≥ 100 mL; increase in St George's Respiratory Questionnaire (SGRQ) total score from baseline of ≥ 4 units; severe (hospitalised) exacerbation; or death. Only patients classified as GOLD stage B were included. Data are presented for comparisons of the licensed doses of T 5 µg and T/O 5/5 µg.

Results 306 and 310 patients were included in this analysis in the T 5 µg and T/O 5/5 µg treatment groups, respectively. Time to clinical deterioration was significantly longer with T/O 5/5 µg than T 5 µg (25th percentile 128 versus 85 days; HR 0.650; 95% CI: 0.524, 0.805; $p < 0.0001$) (Figure). Times to trough FEV₁ decline and SGRQ increase were significantly longer with T/O 5/5 µg than T 5 µg (226 versus 91 days and 369 versus 175 days, respectively). 25th percentiles for time to severe exacerbation and time to death were not estimable due to low event rates.

Conclusions In the TONADO[®] studies, T/O increased time to clinical deterioration compared to T alone in patients with GOLD stage B disease. This suggests that, in this patient population, T/O is more effective than T in preventing these significant

events. Further studies are warranted to prospectively study this effect.

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Please refer to page A272 for declarations of interest in relation to abstract P294.

P295 EFFICACY AND SAFETY OF TIOTROPIUM/OLODATEROL IN PATIENTS WITH COPD BY ATS CATEGORY

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Rationale The once-daily combination of tiotropium (T), a long-acting muscarinic antagonist, and olodaterol (O), a long-acting β_2 -agonist, has demonstrated efficacy and safety in chronic obstructive pulmonary disease (COPD).¹ Recently, it has been demonstrated that patients with milder disease (GOLD 2) have better bronchodilator responses compared to those with more severe disease. This *post hoc* analysis investigated whether the response to T/O and to T alone is influenced by forced expiratory volume in 1 second (FEV₁) American Thoracic Society (ATS) category (mild, moderate or severe).