Abstract P295 Table 1 Lung-function responses at 24 weeks according to baseline ATS category

Trough FEV ₁ , L			FEV ₁ AUC ₀₋₃ , L	
µg	n	Adjusted mean (SE)	n	Adjusted mean (SE)
Mild	351	0.058 (0.011)	353	0.152 (0.011)
T 5	338	0.141 (0.012)*	340	0.275 (0.011)*
T/O 5/5				
Moderate	320	0.097 (0.011)	322	0.174 (0.011)
T 5	338	0.156 (0.011)**	339	0.282 (0.011)*
T/O 5/5				
Severe	347	0.088 (0.009)	351	0.131 (0.009)
T 5	341	0.123 (0.009)***	344	0.227 (0.009)*
T/O 5/5				

*p<0.0001 vs T 5 µg; **p<0.001 vs T 5 µg; ***p<0.01 vs T 5 µg
SE, standard error

Methods In total, 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 (via Respimat[®] inhaler) in two 52-week, parallel-group, double-blind studies (TONADO[®] 1 and 2: NCT01431274; NCT01431287). This *post hoc* analysis focuses on the T 5 µg and T/O 5/5 µg analyses. Primary efficacy end points were trough FEV₁ response (ie, change from baseline) and FEV₁ area under the curve from 0–3 hours (AUC₀₋₃) response. Data are presented for patients by ATS category subgroups: mild (predicted FEV₁ ≥50%), moderate (35 ≤ 50%) and severe (<35%), using data pooled from both of the TONADO[®] studies.

Results In all disease-severity categories, the improvements in trough FEV₁ and FEV₁ AUC₀₋₃ were larger with T/O compared to T alone. However, trough FEV₁ and FEV₁ AUC₀₋₃ responses were generally greater in patients with mild (T/O versus T: both p < 0.0001) or moderate (T/O versus T: p < 0.001 and p < 0.0001, respectively) COPD versus those with severe COPD (T/O versus T: p < 0.01 and p < 0.0001, respectively) at baseline (Table). Treatments were well tolerated across all ATS categories and similar responses were observed in both of the studies individually.

Conclusions These data build on the analysis of the GOLD 2 population from TONADO[®] and confirm that patients with mild to moderate disease derive greater benefits with T/O than with T. There was an overall trend towards greater lung-function improvement with T/O or T alone in patients with mild/moderate versus severe airflow obstruction.

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REFERENCE

1 Buhl R, et al. *Eur Respir J* 2015;**45**:969–979.

Please refer to page A273 for declarations of interest in relation to abstract P295.

P296

EFFECT OF TIOTROPIUM/OLODATEROL THERAPY ON COPD EXACERBATIONS IN THE TONADO[®] STUDIES

¹E Derom, ²M Fležar, ³L Grönke, ³F Voß, ⁴R Buhl. ¹Ghent University Hospital, Ghent, Belgium; ²University Clinic of Respiratory and Allergic Diseases, Golnik, Slovenia; ³Boehringer Ingelheim Pharma GmbH and Co. KG, Ingelheim, Germany; ⁴Pulmonary Department, Mainz University Hospital, Mainz, Germany

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Rationale The lung-function efficacy, symptomatic benefits and safety of combined tiotropium (T), a long-acting muscarinic antagonist, and olodaterol (O), a long-acting β₂-agonist, for the treatment of COPD, was established in the year-long TONADO[®] studies (NCT01431274; NCT01431287). It is unknown if these benefits of T/O translate into a reduction in COPD exacerbation rate.

Methods Two replicate, randomised, double-blind, parallel-group trials assessed T/O 2.5/5 µg and T/O 5/5 µg compared to the monocomponents T 5 µg, T 2.5 µg and O 5 µg (all delivered via Respimat[®] inhaler) in patients with moderate to very severe COPD. Primary end points included lung function (forced expiratory volume in 1 second [FEV₁] area under the curve from 0–3 hours response, trough FEV₁ response) and quality of life (SGRQ). Analysis of the number of exacerbations and time to exacerbation was pre-specified using data from the combined TONADO[®] studies. We present data from the T/O and T treatment arms.

Results 4124 patients were evaluable for the T/O and T treatment arms. Moderate or severe exacerbations occurred in 27.7% of patients with T/O 5/5 µg, 25.8% of patients with T/O 2.5/5 µg, 28.8% with T 5 µg and 29.6% with T 2.5 µg. Severe exacerbations occurred in 5.9% of patients receiving T/O 5/5 µg, 4.5% receiving T/O 2.5/5 µg, 4.5% receiving T 5 µg and 5.2% receiving T 2.5 µg. The treatment comparisons for any exacerbation and moderate/severe exacerbations were generally consistent between the two studies, except for a higher number of severe exacerbations with T/O 5/5 µg in TONADO[®] 1 only (Table).

Conclusions Although there were fewer exacerbations overall with T/O 2.5/5 µg or 5/5 µg compared to T 2.5 µg or 5 µg, and a numerically longer time to first moderate/severe exacerbation,

Abstract P296 Table 1 Treatment comparisons of time to first COPD exacerbation and first moderate/severe COPD exacerbation

Treatment comparison, µg	Time to first COPD exacerbation	Time to first moderate/severe COPD exacerbation	Time to first severe COPD exacerbation
T/O 5/5 –	0.938	0.931	1.279
T 5	(0.801, 1.099)	(0.791, 1.095)	(0.874, 1.871)
T/O 5/5 –	0.897	0.901	1.105
T 2.5	(0.767, 1.049)	(0.767, 1.059)	(0.766, 1.593)
T/O 2.5/5 –	0.819	0.822	0.817
T 2.5	(0.698, 0.960)*	(0.697, 0.969)*	(0.551, 1.210)
T/O 2.5/5 –	0.857	0.850	0.948
T 5	(0.730, 1.007)	(0.720, 1.003)	(0.632, 1.424)
T/O 5/5 –	1.095	1.096	1.352
T/O 2.5/5	(0.931, 1.288)	(0.927, 1.295)	(0.922, 1.983)

Hazard ratio (95% confidence interval) p<0.05

the TONADO® studies did not show a significant difference in the hazard ratios for time to exacerbation end points. These findings are partially attributable to a higher number of severe exacerbations with T/O 5/5 µg in TONADO® 1. TONADO® was not designed for formal comparison of exacerbations with T/O versus T; however, a study powered to assess this is ongoing.

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P297 LUNG-FUNCTION PROFILE BEFORE AND AFTER THE FIRST MODERATE TO SEVERE EXACERBATION DURING THE WISDOM STUDY

¹E Wouters, ²H Magnussen, ³R Rodriguez-Roisin, ⁴K Tetzlaff, ⁵S Bell, ⁶PM A Calverley.

¹Department of Respiratory Medicine, University of Maastricht, Maastricht, the Netherlands;

²Pulmonary Research Institute at Lung Clinic Grosshansdorf, Airway Research Centre North,

German Centre for Lung Research, Grosshansdorf, Germany; ³Servei de Pneumologia,

Hospital Clínic IDIBAPS-CIBERES, Universitat de Barcelona, Barcelona, Spain; ⁴Boehringer

Ingelheim Pharma GmbH and Co. KG, Ingelheim, Germany; ⁵Department of Biometry and

Data Management, Boehringer Ingelheim, Bracknell, UK; ⁶Institute of Ageing and Chronic

Disease, Aintree University Hospital, Liverpool, UK

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Rationale The WISDOM study (NCT00975195) showed no increased risk of exacerbation when inhaled corticosteroid (ICS) was withdrawn stepwise in patients with severe COPD on LAMA+LABA maintenance therapy versus continued LAMA+LABA+ICS.¹ Daily home spirometry measured the time course of lung-function changes throughout the study. The aim of this *post hoc*

analysis was to address the lung-function profile leading up to, during and following the first moderate-to-severe exacerbation.

Methods WISDOM was a multinational, randomised, double-blind study.¹ Patients with severe to very severe COPD entered a 6-week run-in with LAMA+LABA+ICS (tiotropium 18 µg once daily; salmeterol 50 µg twice daily; fluticasone propionate 500 µg twice daily), and were randomised to continue LAMA+LABA+ICS or salmeterol/tiotropium for 52 weeks while discontinuing ICS in a stepwise manner over 12 weeks. On-treatment daily forced expiratory volume in 1 second (FEV₁) change from baseline was calculated before and after the first moderate-to-severe exacerbation. In this *post hoc* analysis, we included patients who experienced a moderate-to-severe exacerbation after the ICS-withdrawal visit, did not have an exacerbation in the 8 weeks before or after the exacerbation, and had daily home-measured FEV₁ data available for every week analysed.

Results Of 2488 patients, 262 experienced a moderate-to-severe exacerbation after the ICS-withdrawal visit and had lung-function data for every week. For all patients combined (ICS and ICS withdrawal), change in FEV₁ remained relatively stable 56–14 days before the first moderate-to-severe exacerbation (mean FEV₁ change from baseline values: –0.04 to –0.07 L) (Figure). There was a decline in lung function starting 2–3 weeks before exacerbation (FEV₁ change value of –0.12 L from baseline), followed by a moderate improvement over ~14 days. Post-exacerbation lung function did not reach pre-exacerbation levels.

Conclusions Lung function was relatively stable in both treatment groups. Home spirometry measurements showed a marked decline in FEV₁ prior to moderate-to-severe exacerbation with improvements seen post-exacerbation, although not to pre-exacerbation levels. These findings support the usefulness of home

Plot includes patients whose first moderate to severe exacerbation after the ICS-withdrawal visit was neither preceded by an exacerbation of any severity in 8 weeks prior nor followed by a further exacerbation of any severity within 8 weeks (56 days) after
Note that Day 0 is the day of the exacerbation

Abstract P297 Figure 1 Mean change from baseline in on-treatment daily FEV₁ before and after first moderate to severe exacerbation for both treatment combined.