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Tiotropium and olodaterol fixed-dose combination versus mono-components in COPD (GOLD 2–4)

Roland Buhl1, François Maltais2, Roger Abrahams3, Leif Bjerner4, Eric Derom5, Gary Ferguson6, Matjaž Fležar7, Jacques Hébert8, Lorcan McGarvey9, Emilio Pizzichini10, Jim Reid11, Antony Veale12, Lars Grönke13, Alan Hamilton14, Lawrence Korducki15, Kay Tetzlaff13,16, Stella Waitere-Wijker17, Henrik Watz18 and Eric Bateman19

Affiliations: 1Pulmonary Department, Mainz University Hospital, Mainz, Germany. 2Département de Médecine, Centre de Recherche, Institut Universitaire de Cardiologie et de Pneumologie de Québec, Québec, Canada. 3Department of Clinical Research, Morgantown Pulmonary Associates, Morgantown, WV, USA. 4Department of Respiratory Medicine and Allergology, Lund University, Lund, Sweden. 5Department of Respiratory Medicine, Ghent University Hospital, Ghent, Belgium. 6Pulmonary Research Institute of Southeast Michigan, Livonia, MI, USA. 7Klinika Golnık, Golnik, Slovenia. 8Department of Medicine, Centre de Recherche Appliquée en Allergie de Québec (CRAAQ), Québec, Canada. 9Department of Medicine, Centre for Infection and Immunity, School of Medicine, Dentistry and Biomedical Sciences, Queen’s University Belfast, Belfast, UK. 10Department of Pulmonology, NUPAWA (Asthma Research Centre), Universidade Federal de Santa Catarina, Santa Catarina, Brazil. 11Dunedin School of Medicine, University of Otago, Dunedin, New Zealand. 12Department of Respiratory Medicine, The Queen Elizabeth Hospital, Adelaide, Australia. 13Department of Medical Affairs Respiratory, Boehringer Ingelheim Pharma GmbH & Co. KG, Ingelheim, Germany. 14Medical Department, Boehringer Ingelheim, Burlington, Ontario, Canada. 15Department of Biostatistics, Boehringer Ingelheim Pharmaceuticals Inc., Ridgefield, CT, USA. 16Department of Sports Medicine, Medical Clinic V, University of Tübingen, Tübingen, Germany. 17Medical Department, Boehringer Ingelheim B.V., Alkmaar, The Netherlands. 18Pulmonary Research Institute at Lung Clinic Grosshansdorf, Airway Research Center North, Member of the German Center for Lung Research, Grosshansdorf, Germany. 19Division of Pulmonology, Department of Medicine, University of Cape Town Lung Institute, Cape Town, South Africa.

Correspondence: Roland Buhl, Pulmonary Department, Mainz University Hospital, Langenbeckstraße 1, D-55131 Mainz, Germany. E-mail: r.buhl@3-med.klinik.uni-mainz.de

ABSTRACT Efficacy and safety of tiotropium+olodaterol fixed-dose combination (FDC) compared with the mono-components was evaluated in patients with moderate to very severe chronic obstructive pulmonary disease (COPD) in two replicate, randomised, double-blind, parallel-group, multicentre, phase III trials.

Patients received tiotropium+olodaterol FDC 2.5/5 μg or 5/5 μg, tiotropium 2.5 μg or 5 μg, or olodaterol 5 μg delivered once-daily via Respimat inhaler over 52 weeks. Primary end points were forced expiratory volume in 1 s (FEV1) area under the curve from 0 to 3 h (AUC0–3) response, trough FEV1 response and St George’s Respiratory Questionnaire (SGRQ) total score at 24 weeks.

In total, 5162 patients (2624 in Study 1237.5 and 2538 in Study 1237.6) received treatment. Both FDCs significantly improved FEV1 AUC0–3 and trough FEV1 response versus the mono-components in both studies. Statistically significant improvements in SGRQ total score versus the mono-components were only seen for tiotropium+olodaterol FDC 5/5 μg. Incidence of adverse events was comparable between the FDCs and the mono-components.

These studies demonstrated significant improvements in lung function and health-related quality of life with once-daily tiotropium+olodaterol FDC versus mono-components over 1 year in patients with moderate to very severe COPD.

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Introduction
Long-acting bronchodilators, such as long-acting muscarinic antagonists (LAMAs), are the cornerstone of maintenance therapy for patients with moderate to very severe chronic obstructive pulmonary disease (COPD) whose symptoms are not adequately controlled by short-acting bronchodilators alone [1, 2].

Tiotropium is an established once-daily LAMA that improves the main functional and patient-orientated outcomes of COPD [3–8]. Tiotropium has also been demonstrated to moderate disease progression, even in the early stages of COPD (e.g. patients not receiving maintenance therapy [9] or those with Global initiative for chronic Obstructive Lung Disease (GOLD) stage 2 disease [10]).

The novel once-daily long-acting $\beta_2$-agonist (LABA) olodaterol is a highly selective and nearly full $\beta_2$ agonist [11, 12] that provides 24-h bronchodilation in patients with COPD [13–16]. Olodaterol is also associated with symptomatic benefit [17] and enhanced exercise capacity [18].

An option recommended by GOLD for patients not adequately controlled on a single long-acting bronchodilator is to combine a LAMA with a LABA [2]. This has prompted the development of combining LAMA+LABA as fixed-dose combinations (FDCs) [1]. The complementary modes of action of tiotropium and olodaterol have previously been demonstrated in animal models and phase II clinical trials [19–22].

We hypothesised that combination therapy with tiotropium+olodaterol FDC would provide improvements in lung function, health-related quality of life and other COPD disease parameters compared to monotherapy with either component alone, with a comparable safety profile. These two replicate, global, phase III trials (TONado 1 and 2) aimed to assess the efficacy and safety of once-daily treatment with orally inhaled tiotropium+olodaterol FDC 5/5 µg or 2.5/5 µg delivered via the Respimat Soft Mist Inhaler (Boehringer Ingelheim, Ingelheim am Rhein, Germany) compared with their individual mono-components in patients with moderate to very severe COPD (GOLD stage 2–4) over 52 weeks.

Methods
Study design
These were multinational, replicate, phase III, multicentre, randomised, double-blind, active-controlled, five-arm, parallel-group studies, registered with ClinicalTrials.gov (Study 1237.5: NCT01431274; Study 1237.6: NCT01431287) (fig. 1). Three primary end points were evaluated after 24 weeks of treatment: forced expiratory volume in 1 s (FEV1) area under the curve from 0 to 3 h (AUC0–3) response (in each individual trial), trough FEV1 response in each individual trial (response defined as change from baseline; mean of the values of 1 h and 10 min prior to the first dose of study medication); and St George’s Respiratory Questionnaire (SGRQ) total score (SGRQ was analysed in a pre-specified combined analysis of data from both studies). Pulmonary function tests (PFTs) were performed on day 1 and at weeks 2, 6, 12, 18, 24, 32, 40 and 52. SGRQ was completed on day 1 and after 12, 24 and 52 weeks, prior to PFTs and all other procedures. Details of the study design, assessments performed and statistical methodology are provided in table S1 of the online supplementary material.

Patients continued to receive treatment with inhaled corticosteroids as required and were provided with salbutamol/albuterol metered-dose inhaler (100 µg per actuation) as rescue medication to be used as necessary at any point during the trial. Temporary increases in the dose or addition of oral steroids or theophylline preparations were allowed during the treatment portion of the study; PFTs were not performed within 7 days of the last administered dose.

Patients
Patients were randomised if they met the following main inclusion criteria: outpatients aged $\geq 40$ years with a history of moderate to very severe COPD (GOLD stage 2–4) [23]; post-bronchodilator FEV1 <80% of predicted normal; post-bronchodilator FEV1/forced vital capacity (FVC) <70%; current or ex-smokers with a smoking history of $>10$ pack–years.

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Patients with a significant disease other than COPD were excluded from the trials. Other exclusion criteria included: clinically relevant abnormal baseline laboratory parameters or a history of asthma; myocardial infarction within 1 year of screening; unstable or life-threatening cardiac arrhythmia; known active tuberculosis; clinically evident bronchiectasis; cystic fibrosis or life-threatening pulmonary obstruction; hospitalised for heart failure within the past year; diagnosed thyrotoxicosis or paroxysmal tachycardia; previous thoracotomy with pulmonary resection; regular use of daytime oxygen if patients were unable to abstain during clinic visits; or currently enrolled in a pulmonary rehabilitation programme (or completed in the 6 weeks before screening).

Patients with moderate or severe renal impairment (creatinine clearance $\leq 50 \text{ mL/min}$) were not excluded from the study but were closely monitored by the investigator.

Both studies were performed in accordance with the Declaration of Helsinki, International Conference on Harmonisation Harmonised Tripartite Guideline for Good Clinical Practice and local regulations. The protocols were approved by the authorities and the ethics committees of the respective institutions, and signed informed consent was obtained from all patients.

Results

Patient disposition and baseline characteristics

A total of 5163 patients (2624 Study 1237.5; 2539 Study 1237.6) were randomised to receive treatment in 25 countries; 5162 patients were treated (2624 Study 1237.5; 2538 Study 1237.6). Overall, 84.6% of patients (86.2% Study 1237.5; 83.0% Study 1237.6) completed the studies. The discontinuation rate was higher in the monotherapy than the combination treatment groups in both studies (fig. 2). The data for the individual studies are presented in the online supplementary material.

Baseline demographics were generally similar across treatment groups. The majority of patients were male (72.9% total) and approximately one-third were current smokers. Most patients were classified as GOLD stage 2/3 (88.6%); the remaining patients (11.3%) were classified as GOLD stage 4. Overall, 86.4% of patients had diagnosed co-morbidities at baseline; 1107 (21.4%) had cardiac disorders and 2481 (48.1%) had vascular disorders including hypertension (table 1, and table S2 in the online supplementary material for individual study data).

Efficacy

Lung function

FEV1 AUCo-3 responses for tiotropium+olodaterol FDC 2.5/5 µg, 5/5 µg, tiotropium 2.5 µg, 5 µg and olodaterol 5 µg were 241, 256, 148, 139 and 133 mL, respectively, in Study 1237.5, and 256, 268, 125, 165 and 136 mL, respectively, in Study 1237.6. Improvements in adjusted mean FEV1 AUCo-3 with tiotropium+olodaterol FDC 5/5 µg and 2.5/5 µg over the corresponding individual components in the individual studies and the combined analysis were statistically significant (p<0.0001 for all comparisons) (table 2, and table S3 in the online supplementary material). The comparison of tiotropium+olodaterol FDC 2.5/5 µg with tiotropium 5 µg (performed to compare the combination with the licensed tiotropium dose) was p<0.0001 for all analyses.

Trough FEV1 responses after 24 weeks for tiotropium+olodaterol FDC 2.5/5 µg, 5/5 µg, tiotropium 2.5 µg, 5 µg and olodaterol 5 µg were 111, 136, 83, 65 and 54 mL, respectively, in Study 1237.5, and 125, 145, 62, 96 and 57 mL, respectively, in Study 1237.6. Improvements in the adjusted mean trough FEV1 with
tiotropium+olodaterol FDC 5/5 µg and 2.5/5 µg over the corresponding individual components in both the individual studies and the combined data were statistically significant (p<0.05 for all comparisons) (table 2, and table S3 in the online supplementary material).
There was no influence of sex on either FEV1 AUC0–3 or trough FEV1 response. An analysis of FEV1 AUC0–3 and trough FEV1 response according to baseline disease severity showed that responses were lower in patients with more severe disease (table S4 in the online supplementary material).

An analysis of FEV1 AUC0–3 and trough FEV1 according to inhaled corticosteroid use is presented in table 3. This confirms that tiotropium+olodaterol improves lung function whether patients were receiving inhaled corticosteroid or not.

Improvements were observed for FEV1 values on all test days over each of the 52-week studies (fig. 3a and b, and fig. S1 in the online supplementary material). Responses in trough FVC and FVC AUC0–3 over 24 weeks of treatment were in line with the primary end points (table S5 in the online supplementary material).

**Health status and symptomatic benefit**

After 24 weeks, the pre-specified analysis of the adjusted mean SGRQ total score (table 4) revealed statistically significant improvements for tiotropium+olodaterol FDC 5/5 µg over corresponding individual components (versus olodaterol 5 µg: −1.693 (0.553), p<0.01; versus tiotropium 5 µg: −1.233 (0.551), p<0.05) but not for tiotropium+olodaterol FDC 2.5/5 µg versus the individual components (table 5).

Responder rates for SGRQ total scores after 24 weeks for the combined data set (responders defined as decrease in SGRQ total score ≥4.0 units, minimum clinically important difference) were: tiotropium...
Both tiotropium+olodaterol FDC 5/5 µg and 2.5/5 µg provided reductions in adjusted weekly mean daily (24-h) rescue medication use compared to the monotherapy components throughout the 52-week treatment period (fig. S2 in the online supplementary material).

Exacerbations

Figure S3 in the online supplementary material shows Kaplan–Meier estimates of probability of moderate/severe COPD exacerbation. There was a trend for improvement in exacerbations with both FDCs versus the monotherapy components.

Safety

Table 6 shows a summary of adverse events for the combined data set (for Studies 1237.5 and 1237.6, see table S7 in the online supplementary material). Adverse event incidence was generally balanced across all treatment groups, with the majority being mild to moderate in severity. The proportion of patients who
reported at least one adverse event while on treatment was 74.4%. Overall, 6.4% of adverse events were
deemed treatment related; rates of serious adverse events were broadly similar across treatment arms. Rates
of serious adverse events were 16.4%, with fatality rates of 1.5%. The majority of treatment-emergent
adverse events (incidence of >3%) were respiratory events, in particular COPD exacerbations and
infections according to Medical Dictionary for Regulatory Activities (MedDRA) classi-
cfications. A higher
proportion of patients in the tiotropium+olodaterol FDC 2.5/5 µg arm experienced upper respiratory
infections while on treatment compared with the other arms. Respiratory events (including COPD
exacerbations) were more frequent among patients treated with monotherapies. No signifi-
ccant abnormalities in vital signs or laboratory parameters were observed in either study.

| Treatment comparison | Yes | ICS usage | No |
|----------------------|-----|-----------|----|
|                      | Adjusted mean±SE (95% CI) | p-value | Adjusted mean±SE (95% CI) | p-value |
| FEV1: AUC0–3 | | | |
| Common study baseline | 1.073±0.009 | | 1.226±0.010 | |
| Tiotropium+olodaterol 5/5 µg versus olodaterol 5 µg | 0.131±0.012 [0.107–0.156] | <0.0001 | 0.125±0.012 [0.101–0.148] | <0.0001 |
| Tiotropium+olodaterol 5/5 µg versus tiotropium 5 µg | 0.113±0.012 [0.089–0.137] | <0.0001 | 0.108±0.012 [0.085–0.132] | <0.0001 |
| Tiotropium+olodaterol 2.5/5 µg versus olodaterol 5 µg | 0.117±0.012 [0.093–0.141] | <0.0001 | 0.113±0.012 [0.090–0.137] | <0.0001 |
| Tiotropium+olodaterol 2.5/5 µg versus tiotropium 2.5 µg | 0.104±0.012 [0.080–0.128] | <0.0001 | 0.120±0.012 [0.096–0.143] | <0.0001 |
| Tiotropium+olodaterol 2.5/5 µg versus tiotropium 5 µg | 0.099±0.012 [0.075–0.123] | <0.0001 | 0.097±0.012 [0.074–0.120] | <0.0001 |
| Tiotropium+olodaterol 5/5 µg versus tiotropium+olodaterol 2.5/5 µg | 0.014±0.012 [−0.010–0.037] | 0.2533 | 0.012±0.012 [−0.012–0.035] | 0.3342 |
| Trough FEV1 | | | |
| Common study baseline | 1.075±0.009 | | 1.227±0.010 | |
| Tiotropium+olodaterol 5/5 µg versus olodaterol 5 µg | 0.087±0.012 [0.063–0.111] | <0.0001 | 0.082±0.013 [0.057–0.107] | <0.0001 |
| Tiotropium+olodaterol 5/5 µg versus tiotropium 5 µg | 0.045±0.012 [0.021–0.070] | 0.0003 | 0.076±0.012 [0.052–0.100] | <0.0001 |
| Tiotropium+olodaterol 2.5/5 µg versus olodaterol 5 µg | 0.068±0.012 [0.044–0.092] | <0.0001 | 0.056±0.013 [0.031–0.080] | <0.0001 |
| Tiotropium+olodaterol 2.5/5 µg versus tiotropium 2.5 µg | 0.030±0.012 [0.006–0.055] | 0.0155 | 0.060±0.012 [0.036–0.084] | <0.0001 |
| Tiotropium+olodaterol 2.5/5 µg versus tiotropium 5 µg | 0.026±0.013 [0.001–0.050] | 0.0385 | 0.050±0.012 [0.025–0.074] | <0.0001 |
| Tiotropium+olodaterol 5/5 µg versus tiotropium+olodaterol 2.5/5 µg | 0.019±0.012 [−0.005–0.043] | 0.1134 | 0.026±0.013 [0.002–0.051] | 0.0369 |

FEV1: forced expiratory volume in 1 s; AUC0–3: area under the curve from 0 to 3 h; ICS: inhaled corticosteroid.

FIGURE 3 Lung function end points (combined data set) over 52 weeks: full analysis set. a) adjusted mean trough
forced expiratory volume in 1 s (FEV1); all comparisons of Tio+Olo 5/5 µg and 2.5/5 µg versus the monotherapies were
statistically significant (p<0.05) with the exception of Tio+Olo 2.5/5 µg versus Tio 2.5 µg at day 43. b) FEV1 area under
the curve from 0 to 3 h (AUC0–3); all comparisons of Tio+Olo 5/5 µg and 2.5/5 µg versus the monotherapies were
statistically significant (p<0.01). Tio: tiotropium; Olo: olodaterol.
A combination of bronchodilators with different modes of action has not been commonly prescribed in COPD maintenance therapy. Long-acting bronchodilators remain the cornerstone of COPD maintenance therapy. However, the selection of optimum doses and dosing frequency is important.

Data are presented as adjusted mean±SE or n/N (%). Data were obtained from fitting a mixed model for repeated measurements including fixed effects of treatment, planned test day, treatment-by-test-day interaction, baseline and baseline-by-test-day interaction; patient as a random effect; spatial power covariance structure for within-patient errors and Kenward–Roger approximation of denominator degrees of freedom. #: number of patients contributing to the mixed model for repeated measurements for adjusted mean SGRQ across both studies: tiotropium+olodaterol 5/5 µg n=979; tiotropium+olodaterol 2.5/5 µg n=990; tiotropium 5 µg n=954; tiotropium 2.5 µg n=960; olodaterol 5 µg n=954; ¶: defined as having an SGRQ total score at week 24 ⩾4.0-times better than baseline SGRQ total score.

Overall incidence of adverse events in the subset of patients with cardiac history was broadly comparable (78.1%, 75.8%, 79.0%, 80.6% and 79.7% in the tiotropium+olodaterol FDC 5/5 µg, tiotropium+olodaterol 2.5/5 µg and olodaterol 5 µg groups, respectively). Rate ratios for major adverse cardiac events (MACE) and “cardiac disorders” System Organ Class (SOC) are presented in table S8 of the online supplementary material, which demonstrates that the incidences of these events were similar with the FDCs and individual components.

Discussion
This pair of replicate, 52-week studies of the effects of once-daily combination of tiotropium+olodaterol administered via the Respimat Soft Mist Inhaler in patients with moderate to very severe COPD confirm statistically significant increases for the primary lung-function end points of trough FEV1 and FEV1 4.0-times better than baseline SGRQ total score. These results are supported by a range of secondary lung-function end points over 52 weeks. FEV1 AUC0–3 and trough FEV1 reflect bronchodilator benefit at the beginning and end of a 24-h cycle and are important measures in the selection of optimum doses and dosing frequency.

Long-acting bronchodilators remain the cornerstone of COPD maintenance therapy. However, the combination of bronchodilators with different modes of action has not been commonly prescribed in...

### TABLE 4 St George’s Respiratory Questionnaire (SGRQ) score at 24 weeks (full analysis set)

| Studies 1237.5+1237.6 common study baseline | SGRQ total score | SGRQ responders |
|--------------------------------------------|-----------------|----------------|
| Olodaterol 5 µg                            | 43.512±0.259    | 427/954 (44.8) |
| Tiotropium 2.5 µg                          | 38.36±0.396     | 476/940 (49.6) |
| Tiotropium 5 µg                            | 37.907±0.393    | 465/955 (48.7) |
| Tiotropium+olodaterol 2.5/5 µg             | 37.335±0.385    | 527/990 (53.2) |
| Tiotropium+olodaterol 5/5 µg               | 36.674±0.386    | 563/979 (57.5) |

Overall incidence of adverse events in the subset of patients with cardiac history was broadly comparable (78.1%, 75.8%, 79.0%, 80.6% and 79.7% in the tiotropium+olodaterol FDC 5/5 µg, tiotropium+olodaterol FDC 2.5/5 µg, tiotropium 2.5 µg and olodaterol 5 µg groups, respectively). Rate ratios for major adverse cardiac events (MACE) and “cardiac disorders” System Organ Class (SOC) are presented in table S8 of the online supplementary material, which demonstrates that the incidences of these events were similar with the FDCs and individual components.

### TABLE 5 St George’s Respiratory Questionnaire (SGRQ) score at 24 weeks (full analysis set): treatment comparisons

| Treatment comparison | SGRQ total score | p-value | Responder analysis | odds ratio | p-value |
|----------------------|-----------------|---------|-------------------|-----------|---------|
| Tiotropium+olodaterol 5/5 µg | -1.59±0.555 [-2.50--0.68] | 0.0022 | 1.67±0.153 [1.29--1.99] | <0.0001 |
| versus olodaterol 5 µg | -1.13±0.551 [-2.13--0.15] | 0.0252 | 1.42±0.131 [1.19--1.70] | 0.0001 |
| Tiotropium+olodaterol 2.5/5 µg | -0.45±0.548 [-1.53--0.18] | 0.0451 | 1.15±0.150 [0.97--1.38] | 0.1071 |
| versus olodaterol 5 µg | 0.57±0.550 [-1.65--0.57] | 0.2988 | 1.19±0.109 [1.00--1.43] | 0.0453 |
| versus tiotropium 5 µg | -1.03±0.552 [-2.11--0.05] | 0.0620 | 1.40±0.128 [1.17--1.47] | 0.0002 |
| Tiotropium+olodaterol 5/5 µg | -0.66±0.545 [-1.74--0.42] | 0.2249 | 1.18±0.108 [0.99--1.42] | 0.0565 |

Data are presented as adjusted mean±SE or n/N (%). Data were obtained from fitting a mixed model for repeated measurements including fixed effects of treatment, planned test day, treatment-by-test-day interaction, baseline and baseline-by-test-day interaction; patient as a random effect; spatial power covariance structure for within-patient errors and Kenward–Roger approximation of denominator degrees of freedom. #: number of patients contributing to the mixed model for repeated measurements for adjusted mean SGRQ across both studies: tiotropium+olodaterol 5/5 µg n=979; tiotropium+olodaterol 2.5/5 µg n=990; tiotropium 5 µg n=954; tiotropium 2.5 µg n=960; olodaterol 5 µg n=954; ¶: defined as having an SGRQ total score at week 24 ⩾4.0-times better than baseline SGRQ total score; responder analysis results are from fitting a logistic-regression model with treatment as covariate and a logit link function; §: number of patients contributing to SGRQ responder analysis across both studies: tiotropium+olodaterol 5/5 µg n=979; tiotropium+olodaterol 2.5/5 µg n=990; tiotropium 5 µg n=954; tiotropium 2.5 µg n=960; olodaterol 5 µg n=954.
clinical practice [1] due, in part, to the lack, until recently, of available FDCs of LAMA+LABA. Olodaterol is a novel once-daily LABA that has been designed as a combination partner for tiotropium, with matching pharmacokinetic and pharmacodynamic profiles [11]. Initial results have indicated that olodaterol may augment the beneficial effects of tiotropium in patients with COPD [21, 22]. The results of our trial are broadly similar with those reported for other LAMA+LAMA FDCs [24–26]. However, comparisons between trials are inadvisable owing to differences in study design, including duration and patient population. Compared with those performed with indacaterol/glycopyrronium [24, 25], our studies included a higher proportion of patients with severe or very severe COPD; the fact that, in general, patients with lower lung function show smaller responses to treatment in clinical trials may explain why the increases with dual bronchodilator treatment were slightly lower. An earlier study with the FDC of tiotropium+olodaterol that included fewer patients with very severe disease showed larger effect sizes than the current studies [27].

Symptomatic benefit of the FDC was demonstrated by statistically significant improvements in mean SGRQ total score; compared with monotherapy, this was observed with tiotropium+olodaterol FDC 5/5 μg but not with 2.5/5 μg. Improvements in SGRQ that exceeded the minimum clinically important difference of 4 units for this measure were seen in all treatment arms, but the difference between the FDCs and the monotherapies did not meet this threshold [28]. Since there was no placebo arm, further analysis of the relevance of these improvements is limited. Responder analyses have been proposed as an additional approach to assessing efficacy of treatments in COPD, particularly for studies in which second and third

### Table 6: Summary of adverse events: combined analysis (treated set)

|                        | Olodaterol 5 μg | Tiotropium 2.5 μg | Tiotropium 5 μg | Tiotropium+olodaterol 2.5/5 μg | Tiotropium+olodaterol 5/5 μg |
|------------------------|----------------|-------------------|----------------|--------------------------------|-----------------------------|
| **Patients n**         | 1038           | 1032              | 1033           | 1030                           | 1029                        |
| **All adverse events** |                |                   |                |                                |                             |
| Treatment-related adverse events | 69 [6.6] | 62 [6.0] | 63 [6.1] | 62 [6.0] | 73 [7.1] |
| Adverse events leading to discontinuation | 103 [9.9] | 90 [8.7] | 93 [9.0] | 57 [5.5] | 76 [7.4] |
| Serious adverse events | 181 [17.4] | 156 [15.1] | 172 [16.7] | 168 [16.3] | 169 [16.4] |
| Fatal                  | 14 [1.3]      | 12 [1.2]          | 17 [1.6]      | 14 [1.4]                       | 18 [1.7]                   |
| Life-threatening       | 3 [0.3]       | 5 [0.5]           | 2 [0.2]       | 5 [0.5]                        | 5 [0.5]                    |
| Disabling/incapacitating | 1 [0.1]     | 3 [0.3]           | 2 [0.2]       | 0 [0.0]                        | 3 [0.3]                    |
| Requiring hospitalisation | 162 [15.6] | 144 [14.0] | 155 [15.0] | 149 [14.5] | 153 [14.9] |
| Prolonging hospitalisation | 12 [1.2]  | 10 [1.0]          | 3 [0.3]       | 7 [0.7]                        | 6 [0.6]                    |
| Other                  | 20 [1.9]      | 16 [1.6]          | 18 [1.7]      | 18 [1.7]                       | 12 [1.2]                   |
| **Specific adverse events with an incidence >3%** | | | | | |
| Respiratory, thoracic and mediastinal disorders | 470 [45.3] | 453 [43.9] | 441 [42.7] | 393 [38.2] | 405 [39.4] |
| COPD                   | 370 [35.6]    | 352 [34.1]        | 340 [32.9]    | 301 [29.2]                     | 332 [32.3]                 |
| Cough                  | 31 [3.0]      | 46 [4.5]          | 45 [4.4]      | 43 [4.2]                       | 40 [3.9]                   |
| Dyspnoea               | 38 [3.7]      | 44 [4.3]          | 51 [4.9]      | 37 [3.6]                       | 39 [3.8]                   |
| Infections and infestations | 393 [37.9] | 363 [35.2] | 348 [33.7] | 394 [38.3] | 374 [36.3] |
| Nasopharyngitis        | 131 [12.6]    | 123 [11.9]        | 121 [11.7]    | 134 [13.0]                     | 128 [12.4]                 |
| Upper respiratory tract infection | 56 [5.4]   | 61 [5.9]          | 57 [5.5]      | 69 [6.7]                       | 54 [5.2]                   |
| Pneumonia              | 36 [3.5]      | 24 [2.3]          | 26 [2.5]      | 31 [3.0]                       | 34 [3.3]                   |
| Bronchitis             | 33 [3.2]      | 23 [2.2]          | 23 [2.2]      | 28 [2.7]                       | 31 [3.0]                   |
| Gastrointestinal disorders | 165 [15.9] | 152 [14.7] | 154 [14.9] | 146 [14.2] | 143 [13.9] |
| Diarrhoea              | 33 [3.2]      | 23 [2.2]          | 27 [2.6]      | 29 [2.8]                       | 24 [2.3]                   |
| Musculoskeletal and connective tissue disorders | 124 [11.9] | 119 [11.5] | 117 [11.3] | 155 [15.0] | 156 [15.2] |
| Back pain              | 35 [3.4]      | 23 [2.2]          | 19 [1.8]      | 40 [3.9]                       | 37 [3.6]                   |
| Nervous system disorders | 87 [8.4]   | 93 [9.0]          | 101 [9.8]     | 100 [9.7]                      | 84 [8.2]                   |
| Headache               | 31 [3.0]      | 23 [2.2]          | 41 [4.0]      | 30 [2.9]                       | 27 [2.6]                   |
| Vascular disorders     | 72 [6.9]      | 54 [5.2]          | 50 [4.8]      | 58 [5.6]                       | 62 [6.0]                   |
| Hypertension           | 48 [4.6]      | 28 [2.7]          | 30 [2.9]      | 35 [3.4]                       | 30 [2.9]                   |

Data are presented as n (%), unless otherwise stated. COPD: chronic obstructive pulmonary disease.

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treatments are added to current therapy [28]. In our studies, responder rates, defined as a reduction in SGRQ total score of ≥ 4 units from baseline, were significantly greater for tiotropium+olodaterol FDC 5/5 µg compared with its monotherapy components and for 2.5/5 µg compared with olodaterol 5 µg.

The doses of tiotropium and olodaterol used in these studies were based on previously published dose–response studies of this drug combination [21, 22]. In the latter, although a dose response for lung function was observed with increasing doses of tiotropium added to a fixed dose of olodaterol, the increase with tiotropium 2.5 µg when added to olodaterol was smaller than the increase with 5 µg when added to olodaterol [21, 22]. Overall, based on the results of the current studies and TIOSPIR, the optimum dose of tiotropium is considered to be 5 µg, both as monotherapy and in combination with olodaterol.

The assessment of safety in our studies yielded no specific concerns in spite of the inclusion of a relatively large proportion of patients with GOLD stage 4 disease and a substantial proportion with co-morbidities. The number of adverse events in the arms with tiotropium+olodaterol FDCs were not higher than in those receiving the individual components; there was also no difference in incidence of adverse events with the higher and lower doses of tiotropium.

“Dry mouth” (typically associated with LAMAs) was reported as a side effect in <2% of patients, possibly attributable to the fact that the majority of patients included in these trials had previously received tiotropium. Additionally, there appears to be no increase in risk of experiencing either a MedDRA SOC “cardiac” or MACE with tiotropium+olodaterol FDC versus the mono-components, and no imbalances between treatment groups were seen in the subgroup of patients with a history of cardiac disease.

Our studies have several limitations. Firstly, there was no placebo group; it was considered inappropriate to deny patients with symptomatic COPD the use of even one long-acting bronchodilator in a study lasting 1 year. Furthermore, these studies were not designed to assess the impact of tiotropium+olodaterol on COPD exacerbations. However, the limited exacerbation data from these studies are encouraging and in line with results for other LAMA+LABA combinations [25]. Further studies powered to examine this end point are planned.

Conclusions

These replicate studies confirm the efficacy and safety of once-daily dosing with tiotropium+olodaterol FDC as maintenance therapy in patients with moderate to very severe COPD (GOLD stage 2–4). The fixed dose of 5 µg of each appears to be optimal in the combination, providing significant improvement in all three primary end points (trough FEV1, FEV1 AUC0–3 and health status) compared to tiotropium or olodaterol administered alone.

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References

1 Tashkin DP, Ferguson GT. Combination bronchodilator therapy in the management of chronic obstructive pulmonary disease. Respir Res 2013; 14: 49.
2 Global Initiative for Chronic Obstructive Lung Disease. Global strategy for the diagnosis, management, and prevention of chronic obstructive pulmonary disease. Updated 2014. www.goldcopd.org/uploads/users/files/GOLD_Report2014_Feb07.pdf Date last updated: 2014. Date last accessed: 2 June 2014.
3 Tashkin DP, Celli B, Senn S, et al., for the UPLIFT Study Investigators. A 4-year trial of tiotropium in chronic obstructive pulmonary disease. N Engl J Med 2008; 359: 1543–1554.
4 Bateman ED, Tashkin D, Siafakas N, et al. A one-year trial of tiotropium Respimat® plus usual therapy in COPD patients. Respir Med 2010; 104: 1460–1472.
5 Cooper CB, Celli BR, Jardim JR, et al. Treadmill endurance during 2-year treatment with tiotropium in patients with COPD: a randomized trial. Chest 2013; 144: 490–497.
6 Yohannes AM, Willgoss TG, Vestbo J. Tiotropium for treatment of stable COPD: a meta-analysis of clinically relevant outcomes. Respir Care 2011; 56: 477–487.
7 Vogelmeier C, Hederer B, Glaab T, et al., for the POET-COPD Investigators. Tiotropium versus salmeterol for the prevention of exacerbations of COPD. N Engl J Med 2011; 364: 1093–1103.
8 Wise RA, Anzueto A, Cotton D, et al., for the TIOSPIR Investigators. Tiotropium Respimat Inhaler and the risk of death in COPD. N Engl J Med 2013; 369: 1491–1501.
9 Troosters T, Celli B, Lystig T, et al., on behalf of the UPLIFT® investigators. Tiotropium as a first maintenance drug in COPD: secondary analysis of the UPLIFT® trial. Eur Respir J 2010; 36: 65–73.

DOI: 10.1183/09031936.00136014
Decramer M, Celli B, Kesten S, et al., for the UPLIFT investigators. Effect of tiotropium on outcomes in patients with moderate chronic obstructive pulmonary disease (UPLIFT): a prespecified subgroup analysis of a randomised controlled trial. *Lancet* 2009; 374: 1171–1178.

Bouyssou T, Casarosa P, Naline E, et al. Pharmacological characterization of olodaterol, a novel inhaled β2-adrenoceptor agonist exerting a 24-hour-long duration of action in preclinical models. *J Pharmacol Exp Ther* 2010; 334: 53–62.

Casarosa P, Kollak I, Kiechle T, et al. Functional and biochemical rationales for the 24-hour-long duration of action of olodaterol. *J Pharmacol Exp Ther* 2011; 337: 600–609.

Lange P, Aumann J-L, Derom E, et al. The 24-h FEV1 time profile of olodaterol QD delivered via Respimat® in COPD: Results from two 6-week studies. *Eur Respir J* 2013; 42: Suppl 57, 982s.

Feldman G, Bernstein JA, Hamilton A, et al. The 24-hour FEV1 time profile of olodaterol once daily (QD) via Respimat® and formoterol twice daily (BID) via Aerolizer® in patients with COPD: Results from two 6-week studies. *Chest* 2013; 144: 749A.

Ferguson G, Feldman G, Hofbauer P, et al. Lung function efficacy of olodaterol QD delivered via Respimat® in COPD patients: Results from two 48-week studies. *Eur Respir J* 2013; 42: Suppl 57, 5s.

Koch A, Pizzichini E, Hamilton A, et al. Lung function efficacy of olodaterol QD delivered via Respimat® versus placebo and formoterol BID in patients with COPD: Two 48-week studies. *Eur Respir J* 2013; 42: Suppl 57, 146s.

Koch A, Paggiaro P, Hamilton A, et al. Symptomatic benefit of olodaterol QD delivered via Respimat® versus placebo and formoterol BID in patients with COPD: Combined analysis from two 48-week studies. *Eur Respir J* 2013; 42: Suppl 57, 145s.

Maltais F, Kirsten A-M, Hamilton A, et al. Evaluation of the effects of olodaterol on exercise endurance in patients with COPD: results from two 6-week studies. *Chest* 2013; 144: 748A.

Bouyssou T, Schnapp A, Casarosa P, et al. Addition of the new once-daily LABA BI 1744 to tiotropium results in superior bronchoprotection in pre-clinical models. *Am J Respir Crit Care Med* 2010; 181: abs 4445.

Bouyssou T, Casarosa P, Pieper M, et al. Synergistic bronchoprotective activity of the long-acting β2-agonist olodaterol with tiotropium (long-acting M3 antagonist) and ciclesonide (inhaled steroid) on the ovalbumin-induced bronchoconstriction in anaesthetized guinea pigs. *Eur Respir J* 2011; 38: Suppl 55, 613s.

Maltais F, Beck E, Webster D, et al. Four weeks once daily treatment with tiotropium+olodaterol (BI 1744) fixed dose combination compared with tiotropium in COPD patients. *Eur Respir J* 2010; 36: Suppl 54, 1014s.

Aalbers R, Maleki-Yazdi MR, Hamilton A, et al. Dose-finding study for tiotropium and olodaterol when administered in combination via the Respimat® inhaler in patients with COPD. *Eur Respir J* 2012; 40: Suppl 56, 525s–526s.

Global Initiative for Chronic Obstructive Lung Disease. Global strategy for the diagnosis, management, and prevention of chronic obstructive pulmonary disease. www.who.int/respiratory/copd/GOLD_WR_06.pdf Date last updated: 2006. Date last accessed: 5 March 2014.

Bateman ED, Ferguson GT, Barnes N, et al. Dual bronchodilation with QVA149 versus single bronchodilator therapy: the SHINE study. *Eur Respir J* 2013; 42: 1484–1494.

Wedzicha JA, Decramer M, Ficker J, et al. Efficacy and safety of QVA149 versus glycopyrronium and tiotropium in severe to very severe COPD: the SPARK study. *Am J Respir Crit Care Med* 2013; 187: abs A2429.

Celli B, Crater G, Kilbride S, et al. A 24-week randomized, double-blind, placebo-controlled study of the efficacy and safety of once-daily umeclidinium/vilanterol 125/25 mcg in COPD. *Am J Respir Crit Care Med* 2013; 187: abs A2435.

Derom E, Westerman J, Groenke L, et al. The 24-hour lung function profile of once-daily tiotropium and olodaterol fixed-dose combination compared with placebo and monotherapies in chronic obstructive pulmonary disease. *Am J Respir Crit Care Med* 2014; 189: abs 6727.

Jones PW. Estimation and application of the minimum clinically important difference in COPD. *Lancet Respir Med* 2014; 2: 167–169.