



Efficacy of Tiotropium/Olodaterol Compared with Tiotropium as a First-Line Maintenance Treatment in Patients with COPD Who Are Naïve to LAMA, LABA and ICS: Pooled Analysis of Four Clinical Trials

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Received: March 27, 2020 / Published online: July 15, 2020
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ABSTRACT

Introduction: The efficacy of tiotropium/olodaterol compared with tiotropium in patients with chronic obstructive pulmonary disease (COPD) has been demonstrated in a large clinical programme. Currently, randomised controlled trial (RCT) data on dual bronchodilation as first-line maintenance therapy are limited. In this post hoc analysis of pooled data from four RCTs, we compared the efficacy of tiotropium/olodaterol versus tiotropium as maintenance therapy in patients with COPD who were not

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receiving maintenance treatment with long-acting muscarinic antagonists (LAMAs), long-acting β_2 -agonists (LABAs) or inhaled corticosteroids (ICS) (“maintenance naïve”) at study entry.

Methods: TONADO[®] 1/2 (52 weeks) and OTEMTO[®] 1/2 (12 weeks) were phase III RCTs in patients with COPD. TONADO 1/2 and OTEMTO 1/2 enrolled patients with post-bronchodilator forced expiratory volume in 1 s (FEV₁) < 80% predicted (lower limit FEV₁ \geq 30% in OTEMTO 1/2 only). We examined the effect of tiotropium/olodaterol 5/5 μ g versus tiotropium 5 μ g on trough FEV₁ response, St. George’s Respiratory Questionnaire (SGRQ) total score and Transition Dyspnoea Index (TDI) focal score at 12 weeks in four pooled studies.

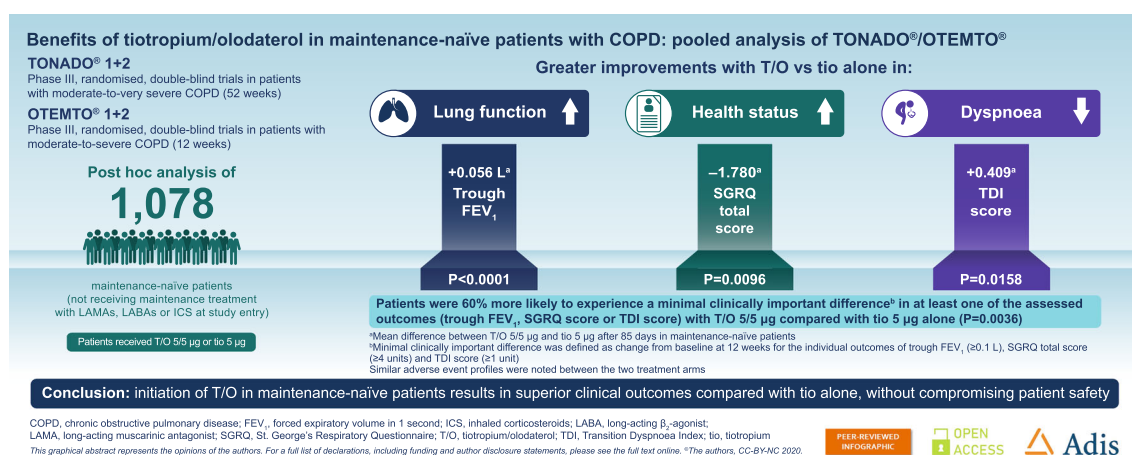
Results: The pooled analysis included 1078 maintenance-naïve patients. There were significant improvements with tiotropium/olodaterol versus tiotropium in trough FEV₁ [0.056 L; 95% confidence interval (CI) 0.033, 0.079; $P < 0.0001$], SGRQ score (– 1.780; 95% CI – 3.126 to – 0.434; $P = 0.0096$) and TDI score (0.409; 95% CI 0.077, 0.741; $P = 0.0158$) at week 12. For patients receiving tiotropium/olodaterol, the odds of achieving a minimal clinically important difference from baseline in any of the analysed outcomes (FEV₁ \geq 0.1 L, SGRQ \geq 4.0 points or TDI \geq 1.0 point) were higher versus tiotropium.

Conclusions: In patients who were maintenance naïve at baseline, treatment initiation with tiotropium/olodaterol resulted in greater

improvements in lung function, health status and dyspnoea severity compared with tiotropium alone, without compromising patient safety. These results support the use of dual bronchodilation with tiotropium/olodaterol as first-line maintenance treatment in patients with COPD.

Trial Registration: ClinicalTrials.gov: TONADO[®] 1 and 2 (NCT01431274 and NCT01431287, registered 8 September 2011) and OTEMTO[®] 1 and 2 (NCT01964352 and NCT02006732, registered 14 October 2013).

Graphic Abstract:



PLAIN LANGUAGE SUMMARY

People with chronic obstructive pulmonary disease (COPD) often have problems breathing, which can make it difficult to carry out daily physical tasks. Bronchodilators are a type of medication that relax the muscles in the lungs and widen airways, making it easier to breathe. Evidence suggests that using a combination of two different bronchodilators is more effective than using one bronchodilator on its own.

In this article, we look at four large studies that compared the effects of at least 12 weeks of treatment with two bronchodilators (tiotropium/olodaterol) with tiotropium on its own

in people who had not received any previous medication for their COPD. The results suggest that people who were treated with tiotropium and olodaterol together had significantly better improvements in lung function, quality of life and breathlessness after 12 weeks than those taking tiotropium alone, without compromising safety. Overall, people treated with tiotropium/olodaterol were 60% more likely to experience a meaningful improvement in at least one of these areas compared with those on

tiotropium alone. These results support the use of tiotropium and olodaterol together as a first medication for COPD.

Keywords: Chronic obstructive pulmonary disease; Dual bronchodilation; Dyspnoea; Health status; Lung function; Olodaterol; Tiotropium; Treatment-naïve

Key Summary Points

Why carry out this study?

There is currently a lack of evidence on the use of dual bronchodilation as first-line maintenance therapy in patients with chronic obstructive pulmonary disease (COPD).

In this pooled analysis, we compared the efficacy of tiotropium/olodaterol with tiotropium in patients with COPD who were not receiving maintenance treatment with long-acting muscarinic antagonists (LAMAs), long-acting β_2 -agonists (LABAs) or inhaled corticosteroids (ICS) at baseline.

What was learned from the study?

In patients who were not receiving LAMA, LABA or ICS treatment at baseline, we showed that treatment with tiotropium/olodaterol compared with tiotropium alone resulted in greater improvements in lung function, health status and dyspnoea without compromising safety.

After 12 weeks of treatment, patients treated with tiotropium/olodaterol were 60% more likely to experience a minimal clinically important difference in lung function, health status or dyspnoea compared with tiotropium alone.

This study shows that initiation of tiotropium/olodaterol in treatment-naïve patients results in superior clinical outcomes compared with tiotropium alone.

abnormalities usually caused by significant exposure to noxious particles or gases [1]. The Global Initiative for Chronic Obstructive Lung Disease (GOLD) recommends that patients with COPD are grouped according to symptom severity and exacerbation history to determine appropriate first-line therapy, with bronchodilators central to the management of the disease [1]. At the point of diagnosis with COPD, a large proportion of patients already have moderate (50%) or severe/very severe (31%) airflow obstruction [2]. First-line therapy for all patients with COPD includes bronchodilator treatment in order to optimise lung function and thereby improve symptom control, exercise capacity and overall health status [1].

Randomised controlled trials (RCTs) have shown that dual bronchodilators are generally more effective than monotherapies in the treatment of COPD [3, 4]. In the GOLD 2020 strategy report, long-acting muscarinic antagonist (LAMA)/long-acting β_2 -agonist (LABA) combination therapy is only recommended as first-line treatment in patients who are highly symptomatic and classified as being in GOLD group D [≥ 2 moderate exacerbations or ≥ 1 leading to hospitalisation, modified British Medical Research Council questionnaire (mMRC) grade ≥ 2 and COPD Assessment Test (CAT) ≥ 10] or for patients in GOLD group B (≤ 1 moderate exacerbation, mMRC grade ≥ 2 and CAT ≥ 10) with severe breathlessness, and as a second-line or step-up treatment in patients whose disease is not adequately controlled by a single bronchodilator [1]. The recent guidelines from the American Thoracic Society (ATS) go further, and strongly recommend dual LAMA/LABA therapy over LAMA or LABA monotherapy for patients with COPD with dyspnoea or exercise intolerance [5]. It is important to note that GOLD recommendations on initial therapy and the recent guidelines from ATS are derived from randomised clinical trial evidence where most patients were already receiving inhaled treatment [1, 5]. However, there is currently a lack of evidence as to the optimal approach to initiation of therapy in maintenance-naïve patients. A better understanding of how to optimise symptom management from the start

INTRODUCTION

Chronic obstructive pulmonary disease (COPD) is a heterogeneous disease characterised by persistent respiratory symptoms and airflow limitation due to airway and/or alveolar

of treatment could allow patients to remain active and in a more stable disease state for longer; this is an important goal, especially when considering that half of patients with COPD are still in their productive, working years [6].

Treatment with the dual bronchodilator tiotropium/olodaterol has been shown to improve lung function and symptoms to a greater extent than monotherapy across different severities and subgroups, including in less severe disease [7]. The long-term efficacy and safety of tiotropium/olodaterol treatment versus the monocomponents tiotropium and olodaterol over 52 weeks were demonstrated in two pivotal phase III trials: TONADO[®] 1 and 2 [8]. In the OTEMTO[®] trials, tiotropium/olodaterol showed improvements in lung function and quality of life versus tiotropium and placebo [9]. In addition, in a recent post hoc analysis of patients from the TONADO and OTEMTO trials who were receiving only LAMA monotherapy at study entry, treatment escalation to tiotropium/olodaterol resulted in significant improvements in lung function, health status and breathlessness compared with tiotropium alone [10].

In this post hoc analysis of pooled data from the four studies, we compared the efficacy of tiotropium/olodaterol with tiotropium in patients with COPD who were not receiving maintenance treatment with LAMAs, LABAs or inhaled corticosteroids (ICS) (“maintenance naïve”) at study entry.

METHODS

Study Design

Detailed methodologies of the phase III TONADO (study 1237.5: NCT01431274; study 1237.6: NCT01431287) and OTEMTO (study 1237.25: NCT01964352; study 1237.26: NCT02006732) trials have been previously published [8, 9]. The TONADO trials were two replicate, double-blind, randomised, parallel-group, 52-week trials that compared tiotropium/olodaterol with the monocomponents tiotropium and olodaterol in patients with

moderate-to-very severe COPD (GOLD stages 2–4).

The OTEMTO trials were two replicate, multinational, double-blind, randomised, parallel-group, 12-week, placebo-controlled trials that compared tiotropium/olodaterol with tiotropium or placebo in patients with moderate-to-severe COPD (GOLD stages 1–3).

The trials 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.

Inclusion and Exclusion Criteria

More detailed inclusion and exclusion criteria have been published previously [8, 9]. The main inclusion criteria were patients with COPD aged ≥ 40 years with post-bronchodilator forced expiratory volume in 1 s (FEV_1) $< 80\%$ of predicted normal (lower limit $\geq 30\%$ in OTEMTO; no lower limit in TONADO); post-bronchodilator FEV_1 /forced vital capacity $< 70\%$; and current or ex-smokers with a smoking history of > 10 pack-years. Hence, most patients selected were from GOLD stages 2–4. A small proportion of the total number of patients recruited were GOLD 1 patients, which may reflect enrolling errors.

The main exclusion criteria were presence of a significant disease other than COPD, clinically relevant abnormal baseline laboratory parameters or a history of asthma.

Maintenance-Naïve Patient Analysis

We examined the effect of tiotropium/olodaterol 5/5 μg or tiotropium 5 μg on lung function (through FEV_1 response and responder rates), health status [St. George’s Respiratory Questionnaire (SGRQ) total score change from baseline and SGRQ responder rates] and dyspnoea severity [Transition Dyspnoea Index (TDI) focal score and TDI responder rates] at 12 weeks. We included patients who were not receiving

LAMAs, LABAs or ICS, either as monotherapy or combination therapy, at study entry (i.e. when they signed the informed consent) in all four studies. These criteria were applied for this post hoc analysis only and not for the original trials; therefore, it is unlikely that any maintenance-naïve patients included here had their treatment stepped down prior to study entry. Responders for trough FEV₁ (an increase of ≥ 0.1 L), SGRQ score (a decrease of ≥ 4.0 points) and TDI score (an increase of ≥ 1.0 point) were defined based on the suggested minimal clinically important difference (MCID) for active treatment compared with placebo [8, 11–13]. Three subgroup analyses were performed, in which patients were stratified by GOLD stage 2 and 3, Baseline Dyspnoea Index (BDI) score or baseline SGRQ total score.

Statistical Analysis

Adjusted means were obtained from fitting a mixed-effect model for repeated measures including treatment, study, planned test day, treatment-by-test day interaction, baseline and baseline-by-test day interaction as fixed effects; and patient as a random effect. The responder analysis used a logistic regression model with treatment and study as covariates.

RESULTS

Baseline Demographics

In the pooled analysis, there were 1078 patients in the tiotropium/olodaterol and tiotropium arms who were not receiving LAMA, LABA or ICS treatment at trial enrolment. Baseline characteristics were generally well balanced across the two treatment arms (tiotropium/olodaterol vs. tiotropium) (Table 1). The majority of patients were male (67–70%) and the mean age was approximately 63 years in both treatment arms (Table 1). FEV₁ per cent predicted was similar for both treatments, and over half of patients were ex-smokers and 46–49% smokers (Table 1). The majority of the maintenance-naïve patients were classed as

GOLD stage 2 (58–59%), followed by GOLD stage 3 (33–34%) (Table 1).

Efficacy

Trough FEV₁

A significantly greater increase in trough FEV₁ from baseline was observed with tiotropium/olodaterol (mean \pm SE, 0.138 ± 0.009 L) compared with tiotropium (0.082 ± 0.008 L) at week 12 [mean treatment difference \pm SE, 0.056 ± 0.012 L; 95% confidence interval (CI) 0.033, 0.079; $P < 0.0001$] (Fig. 1). Tiotropium/olodaterol caused significantly greater improvements in trough FEV₁ compared with tiotropium alone in patients with both moderate (GOLD 2) and severe (GOLD 3) COPD, and regardless of SGRQ or BDI scores at baseline (Fig. 1 and Table 2).

SGRQ Total Score

Both treatments provided clinically relevant improvements in health status from baseline after 12 weeks; SGRQ total score improved by 6.660 ± 0.506 units with tiotropium/olodaterol and 4.880 ± 0.492 units with tiotropium (Fig. 2). The mean treatment difference was -1.780 ± 0.686 (95% CI -3.126 to -0.434 ; $P = 0.0096$) (Fig. 2). In subgroup analyses, use of tiotropium/olodaterol caused a larger improvement in SGRQ total score compared with tiotropium in all subpopulations (Table 3). This reached statistical significance in patients with moderate (GOLD 2) disease and those with low BDI score (BDI ≤ 6) (Fig. 2 and Table 3).

TDI Score

In the pooled analysis for the TDI score, both treatments provided clinically relevant improvements after 12 weeks; the mean TDI score was improved by 2.343 ± 0.121 units with tiotropium/olodaterol and 1.934 ± 0.118 units with tiotropium (Fig. 3). The improvement with tiotropium/olodaterol was significantly greater compared with tiotropium (treatment difference 0.409 ± 0.169 ; 95% CI 0.077, 0.741; $P = 0.0158$) (Fig. 3). In subgroup analyses, use of tiotropium/olodaterol was associated with a larger improvement in TDI focal score

Table 1 Patient demographics and baseline characteristics

Characteristic	Tiotropium 5 µg (<i>n</i> = 560)	T/O 5/5 µg (<i>n</i> = 518)
Male, <i>n</i> (%)	394 (70.4)	347 (67.0)
Age, years	62.8 ± 8.6	62.9 ± 8.5
Smoking status		
Ex-smoker, <i>n</i> (%)	304 (54.3)	264 (51.0)
Current smoker, <i>n</i> (%)	256 (45.7)	254 (49.0)
Pre-bronchodilator spirometry		
FEV ₁ , L	1.323 ± 0.526	1.297 ± 0.514
FEV ₁ % predicted, %	46.797 ± 15.224	46.589 ± 15.195
FVC, L	2.762 ± 0.829	2.732 ± 0.844
FEV ₁ /FVC, %	47.980 ± 12.216	47.505 ± 11.567
Post-bronchodilator spirometry		
FEV ₁ , L	1.489 ± 0.534	1.464 ± 0.526
FEV ₁ % predicted, %	52.754 ± 15.118	52.603 ± 14.939
FVC, L	3.051 ± 0.827	3.010 ± 0.872
FEV ₁ /FVC, %	49.102 ± 12.212	49.042 ± 11.602
GOLD stage, <i>n</i> (%)		
GOLD 1/2: ≥ 80%/50–< 80% ^a	331 (59.1)	301 (58.1)
GOLD 3: 30–< 50%	187 (33.4)	177 (34.2)
GOLD 4: < 30%	42 (7.5)	40 (7.7)
SGRQ score	43.4 ± 18.4	43.1 ± 17.4
BDI score	6.5 ± 2.2	6.5 ± 2.2

Data are mean ± SD unless stated otherwise

BDI Baseline Dyspnoea Index, *COPD* chronic obstructive pulmonary disease, *FEV₁* forced expiratory volume in 1 s, *FVC* forced vital capacity, *GOLD* Global Initiative for Chronic Obstructive Lung Disease, *SD* standard deviation, *SGRQ* St. George's Respiratory Questionnaire, *T/O* tiotropium/olodaterol

^a There were two patients with GOLD 1 COPD in the tiotropium 5 µg treatment group

compared with tiotropium in all subpopulations (Fig. 3 and Table 4). These improvements reached statistical significance in patients with moderate (GOLD 2) disease, those with a higher SGRQ score at baseline and those with a higher BDI score at baseline.

Responder Analysis

Overall, the proportion of patients classed as FEV₁ responders (> 0.1-L improvement), SGRQ responders (≥ 4-unit improvement) or TDI responders (≥ 1-unit improvement) was 55.8%, 59.6% and 63.3% with tiotropium/olodaterol and 41.1%, 48.8% and 55.0% with tiotropium, respectively (Fig. 4). Treatment with

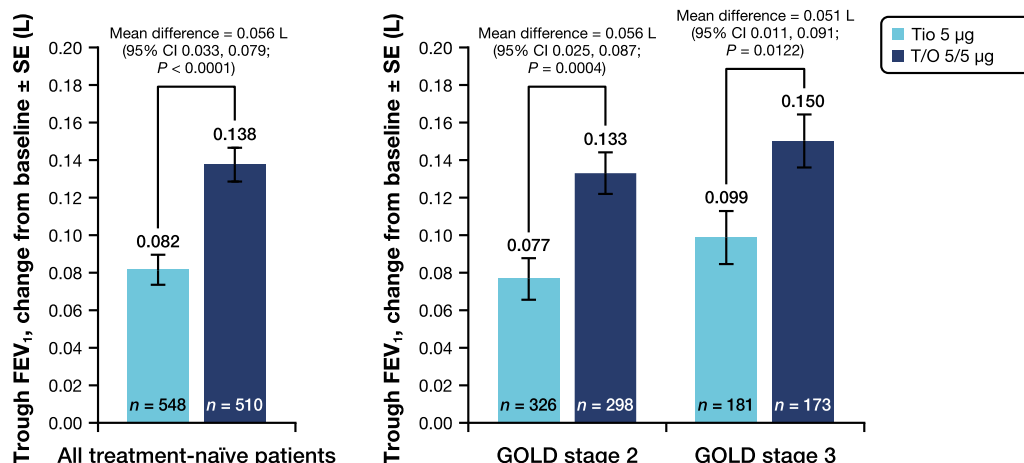


Fig. 1 Change from baseline in trough FEV₁ (L) after 12 weeks. *CI* confidence interval, *FEV₁* forced expiratory volume in 1 s, *GOLD* Global Initiative for Chronic Obstructive Lung Disease, *SE* standard error, *T/O* tiotropium/olodaterol, *Tio* tiotropium

Table 2 Subgroup analyses of FEV₁ trough response (L) at 12 weeks

Subgroup at baseline	Therapy	Number	FEV ₁ trough response, adjusted mean (SE)	Treatment difference, adjusted mean (SE)	<i>p</i> value	95% CI
GOLD 2	Tio	326	0.077 (0.011)	0.056 (0.016)	0.0004	0.025, 0.087
	T/O	298	0.133 (0.011)			
GOLD 3	Tio	181	0.099 (0.014)	0.051 (0.020)	0.0122	0.011, 0.091
	T/O	173	0.150 (0.014)			
BDI ≤ 6	Tio	277	0.074 (0.012)	0.062 (0.017)	0.0002	0.029, 0.095
	T/O	267	0.137 (0.012)			
BDI > 6	Tio	257	0.090 (0.011)	0.054 (0.017)	0.0012	0.021, 0.086
	T/O	240	0.144 (0.012)			
SGRQ < median	Tio	265	0.106 (0.012)	0.041 (0.017)	0.0138	0.008, 0.074
	T/O	263	0.147 (0.012)			
SGRQ ≥ median	Tio	279	0.060 (0.011)	0.068 (0.017)	< 0.0001	0.035, 0.101
	T/O	243	0.128 (0.012)			

BDI Baseline Dyspnoea Index, *CI* confidence interval, *FEV₁* forced expiratory volume in 1 s, *GOLD* Global Initiative for Chronic Obstructive Lung Disease, *SE* standard error, *SGRQ* St. George’s Respiratory Questionnaire, *T/O* tiotropium/olodaterol, *Tio* tiotropium

tiotropium/olodaterol increased the odds of achieving an MCID in trough FEV₁ response by 80.7% compared with tiotropium [odds ratio (OR) 1.81 ± 0.22; 95% CI 1.42, 2.30;

P < 0.0001]. For SGRQ total score, the odds of achieving an MCID were 54.4% higher when comparing tiotropium/olodaterol with tiotropium (OR 1.54 ± 0.20; 95% CI 1.20, 1.99;

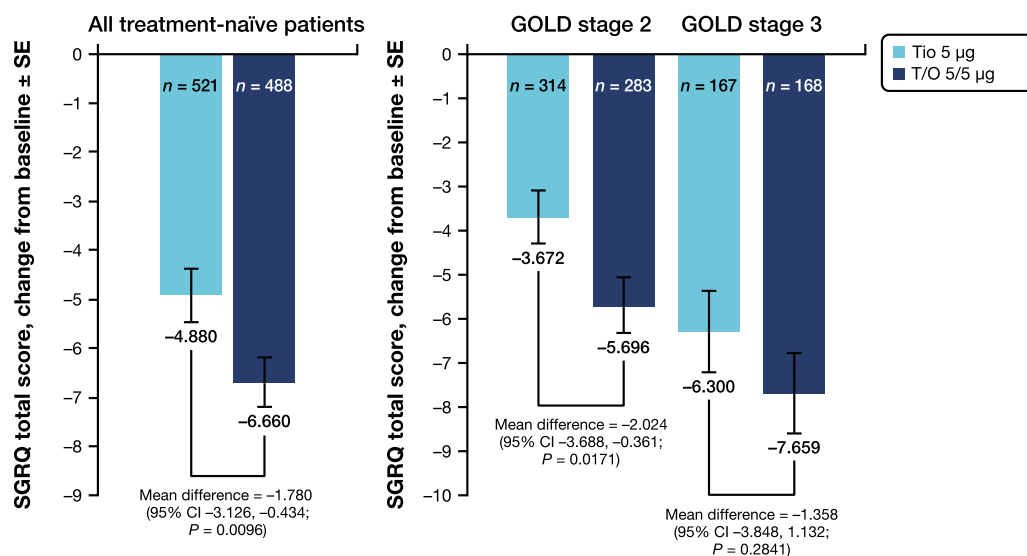


Fig. 2 Change from baseline in SGRQ total score after 12 weeks. CI confidence interval, GOLD Global Initiative for Chronic Obstructive Lung Disease, SE standard error,

SGRQ St. George's Respiratory Questionnaire, T/O tiotropium/olodaterol, Tio tiotropium

Table 3 Subgroup analyses of SGRQ total score change from baseline at 12 weeks

Subgroup at baseline	Therapy	Number	SGRQ total score change from baseline, adjusted mean (SE)	Treatment difference, adjusted mean (SE)	p value	95% CI
GOLD 2	Tio	314	- 3.672 (0.602)	- 2.024 (0.847)	0.0171	- 3.688, - 0.361
	T/O	283	- 5.696 (0.631)			
GOLD 3	Tio	167	- 6.300 (0.924)	- 1.358 (1.266)	0.2841	- 3.848, 1.132
	T/O	168	- 7.659 (0.912)			
BDI ≤ 6	Tio	260	- 5.349 (0.732)	- 2.407 (1.017)	0.0183	- 4.404, - 0.409
	T/O	258	- 7.756 (0.747)			
BDI > 6	Tio	249	- 3.864 (0.654)	- 1.701 (0.909)	0.0617	- 3.486, 0.084
	T/O	228	- 5.565 (0.668)			
SGRQ < median	Tio	260	- 1.906 (0.588)	- 1.5551 (0.811)	0.0562	- 3.143, 0.041
	T/O	252	- 3.457 (0.590)			
SGRQ ≥ median	Tio	261	- 8.120 (0.793)	- 1.974 (1.120)	0.0786	- 4.174, 0.227
	T/O	236	- 10.09 (0.837)			

BDI Baseline Dyspnoea Index, CI confidence interval, GOLD Global Initiative for Chronic Obstructive Lung Disease, SE standard error, SGRQ St. George's Respiratory Questionnaire, T/O tiotropium/olodaterol, Tio tiotropium

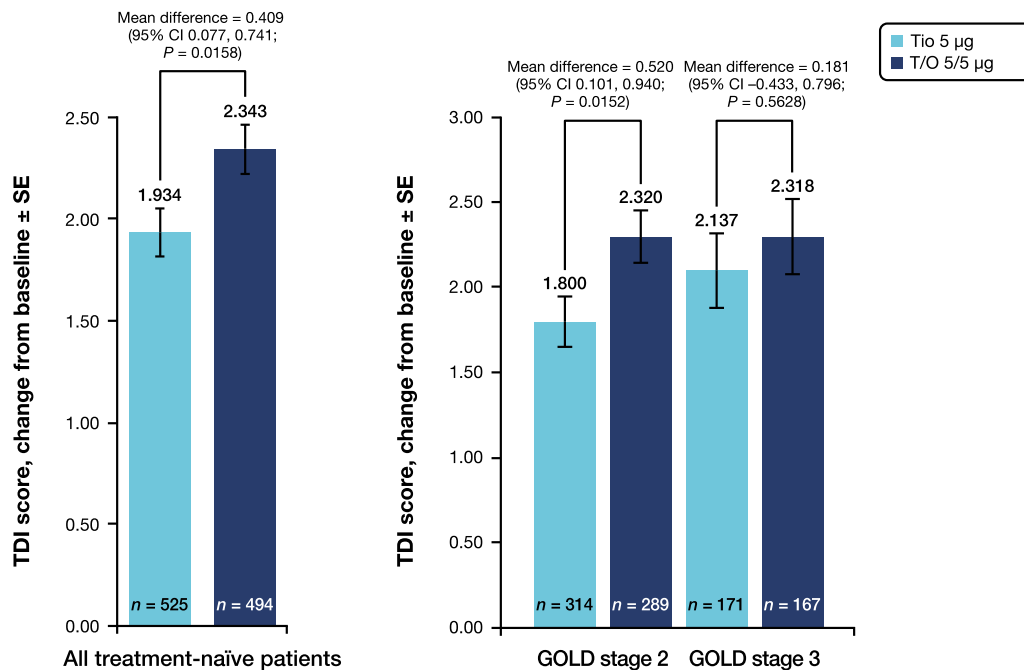


Fig. 3 Change from baseline in TDI focal score after 12 weeks. CI confidence interval, GOLD Global Initiative for Chronic Obstructive Lung Disease, SE standard error,

T/O tiotropium/olodaterol, TDI Transition Dyspnoea Index, Tio tiotropium

$P = 0.0007$) (Fig. 4). The odds of achieving an MCID in TDI focal score with tiotropium/olodaterol were increased by 43.3% compared with those with tiotropium alone (OR 1.43 ± 0.19 ; 95% CI 1.11, 1.85; $P = 0.0057$) (Fig. 4).

FEV₁, SGRQ or TDI Responders

After 12 weeks of treatment, patients treated with tiotropium/olodaterol were 60% more likely to experience an MCID in trough FEV₁, SGRQ score or TDI score compared with tiotropium alone (OR 1.60 ± 0.26 ; 95% CI 1.17, 2.19; $P = 0.0036$) (Table 5).

In subgroup analyses, more patients achieved an MCID in at least one of the analysed outcomes with tiotropium/olodaterol compared with tiotropium in all subpopulations (Table 6). The improvements reached statistical significance in patients with severe (GOLD 3) disease, a lower BDI score and those with greater symptom burden at baseline (Table 6).

Safety

Overall, 60.4% of patients receiving tiotropium/olodaterol and 60.4% receiving tiotropium alone reported adverse events (AEs); 9.7% of patients receiving tiotropium/olodaterol and 11.8% of patients receiving tiotropium reported serious AEs. AEs leading to discontinuation of trial drugs were reported for 3.9% of patients receiving tiotropium/olodaterol and 6.4% receiving tiotropium. In the tiotropium/olodaterol arm, 7.1% of patients had investigator-defined drug-related AEs, compared with 6.4% in the tiotropium arm.

DISCUSSION

This post hoc analysis showed that dual bronchodilation with tiotropium/olodaterol at the initiation of therapy in maintenance-naïve patients with COPD results in greater improvements in lung function, health status and dyspnoea than treatment with tiotropium alone, without any increased safety risk. These

Table 4 Subgroup analyses of TDI focal score at 12 weeks

Subgroup at baseline	Therapy	Number	TDI focal score, adjusted mean (SE)	Treatment difference, adjusted mean (SE)	<i>p</i> value	95% CI
GOLD 2	Tio	314	1.800 (0.148)	0.520 (0.214)	0.0152	0.101, 0.940
	T/O	289	2.320 (0.154)			
GOLD 3	Tio	171	2.137 (0.219)	0.181 (0.313)	0.5628	− 0.433, 0.796
	T/O	167	2.318 (0.221)			
BDI ≤ 6	Tio	272	1.729 (0.165)	0.371 (0.235)	0.1152	− 0.091, 0.833
	T/O	264	2.101 (0.168)			
BDI > 6	Tio	253	2.139 (0.168)	0.498 (0.244)	0.0415	0.019, 0.976
	T/O	230	2.637 (0.176)			
SGRQ < median	Tio	260	2.051 (0.162)	0.314 (0.231)	0.1732	− 0.138, 0.767
	T/O	253	2.366 (0.164)			
SGRQ ≥ median	Tio	262	1.822 (0.172)	0.543 (0.249)	0.0295	0.054, 1.032
	T/O	238	2.365 (0.180)			

BDI Baseline Dyspnoea Index, *CI* confidence interval, *GOLD* Global Initiative for Chronic Obstructive Lung Disease, *SE* standard error, *SGRQ* St. George's Respiratory Questionnaire, *T/O* tiotropium/olodaterol, *TDI* Transition Dyspnoea Index, *Tio* tiotropium

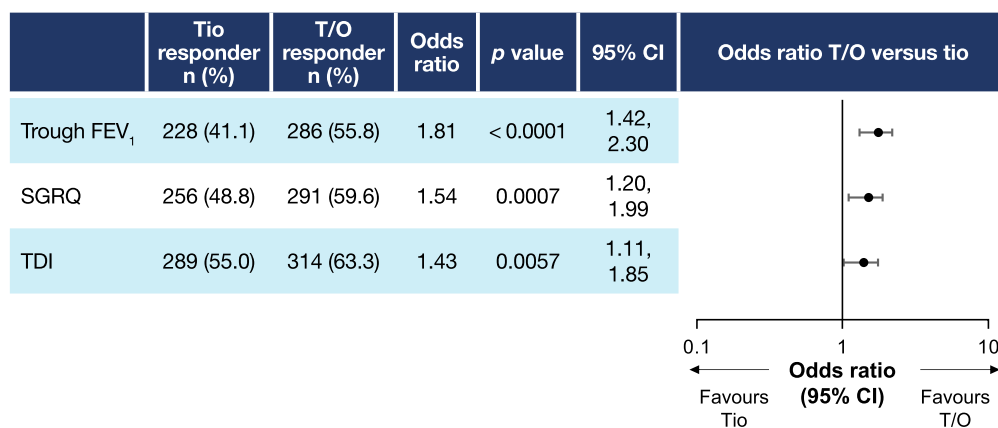


Fig. 4 Responder rates for FEV₁ (> 0.1-L improvement), SGRQ (≥ 4-unit improvement) and TDI (≥ 1-unit improvement) at week 12: pooled data. CI confidence

interval, FEV₁ forced expiratory volume in 1 s, SGRQ St. George's Respiratory Questionnaire, T/O tiotropium/olodaterol, TDI Transition Dyspnoea Index, Tio tiotropium

combined data from the TONADO and OTEMTO trials enabled a large population of maintenance-naïve patients with a range of disease severities to be analysed. As there is a

lack of RCT data in this population, these data provide clinically important information regarding the optimal initial treatment approach for these individuals and support the

Table 5 Responder analysis of MCID in at least one of the assessed outcomes ($FEV_1 \geq 0.1$ L, $SGRQ \geq 4.0$ points or $TDI \geq 1.0$ point) at 12 weeks

Therapy	Number	Responder, <i>n</i> (%)	Treatment difference, odds ratio (SE)	<i>p</i> value	95% CI
Tio	557	436 (78.3)	1.60 (0.26)	0.0036	1.17, 2.19
T/O	514	438 (85.2)			

CI confidence interval, *FEV₁* forced expiratory volume in 1 s, *MCID* minimal clinically important difference, *SE* standard error, *SGRQ* St. George's Respiratory Questionnaire, *T/O* tiotropium/olodaterol, *TDI* Transition Dyspnoea Index, *Tio* tiotropium

Table 6 Subgroup analysis of MCID in at least one of the assessed outcomes ($FEV_1 \geq 0.1$ L, $SGRQ \geq 4.0$ points or $TDI \geq 1.0$ point) at 12 weeks

Subgroup at baseline	Therapy	Number	Responder, <i>n</i> (%)	Treatment difference, odds ratio (SE)	<i>p</i> value	95% CI
GOLD 2	Tio	329	257 (78.1)	1.47 (0.30)	0.0643	0.98, 2.20
	T/O	299	251 (83.9)			
GOLD 3	Tio	184	142 (77.2)	1.95 (0.56)	0.0185	1.12, 3.41
	T/O	175	152 (86.9)			
$BDI \leq 6$	Tio	281	220 (78.3)	1.64 (0.37)	0.0279	1.06, 2.56
	T/O	270	231 (85.6)			
$BDI > 6$	Tio	262	206 (78.6)	1.55 (0.36)	0.0633	0.98, 2.46
	T/O	241	205 (85.1)			
$SGRQ < \text{median}$	Tio	266	214 (80.5)	1.38 (0.32)	0.1629	0.88, 2.18
	T/O	261	222 (85.1)			
$SGRQ \geq \text{median}$	Tio	287	220 (76.7)	2.06 (0.48)	0.0022	1.30, 3.26
	T/O	248	216 (87.1)			

BDI Baseline Dyspnoea Index, *CI* confidence interval, *GOLD* Global Initiative for Chronic Obstructive Lung Disease, *MCID* minimal clinically important difference, *SE* standard error, *SGRQ* St. George's Respiratory Questionnaire, *T/O* tiotropium/olodaterol, *Tio* tiotropium

use of LAMA/LABA treatment as initial pharmacotherapy.

In maintenance-naïve patients, the mean treatment differences observed with tiotropium/olodaterol versus tiotropium were generally in line with previously published results for the overall TONADO and OTEMTO study populations [8, 9]. In the TONADO trials, for example, significant improvements in trough FEV_1 , $SGRQ$ and TDI were observed with tiotropium/olodaterol versus tiotropium [8].

In the current study, clinically relevant improvements from baseline were observed for both tiotropium/olodaterol and tiotropium in maintenance-naïve patients, but these were significantly greater in patients treated with tiotropium/olodaterol versus tiotropium alone. In patients with GOLD 2 COPD (characterised by moderate airflow obstruction) or GOLD 3 COPD (more severe COPD), the change from baseline was also beyond that of the thresholds for an MCID in trough FEV_1 (> 0.1 L), $SGRQ$

score (≥ 4 units) and TDI score (≥ 1 unit) in patients receiving tiotropium/olodaterol. However, this was not the case for all the endpoints in GOLD 2/3 patients treated with tiotropium. In patients with GOLD 2 COPD, tiotropium/olodaterol provided significant improvements compared with tiotropium alone. Hence, combination therapy could be beneficial in patients at this earlier stage of COPD, as well as in patients with more severe COPD (GOLD 3).

It is worth noting that the validated thresholds used to assess clinically relevant improvements have largely been established for comparisons of active treatment against placebo, whereas this analysis compares two active treatments [14]. The mean differences between active treatments are therefore unlikely to exceed thresholds for an MCID, as was the case here. The responder analysis is, however, a valuable alternative approach to compare the two active treatments [14]. In maintenance-naïve patients, the likelihood of achieving an MCID in trough FEV₁ (> 0.1 L), quality of life (SGRQ score ≥ 4 units) or dyspnoea severity (TDI score ≥ 1 unit) was increased by 81%, 54% and 43%, respectively, with tiotropium/olodaterol versus tiotropium. When the data were combined, patients treated with tiotropium/olodaterol were 60% more likely to experience an MCID in at least one of the three assessed outcomes compared with tiotropium alone. In agreement with the current analysis, previous studies have demonstrated the benefits of alternative LAMA/LABA combinations, including umeclidinium/vilanterol and indacaterol/glycopyrronium, as well as tiotropium/olodaterol, in bronchodilator-naïve patients [15–17]. For example, in a post hoc analysis of umeclidinium/vilanterol versus tiotropium, dual therapy resulted in superior lung function and a reduction in short-term deterioration [15]. Similarly, in a pooled analysis of the ARISE, SHINE and SPARK trials, indacaterol/glycopyrronium demonstrated greater improvements in lung function and patient-reported outcomes versus tiotropium or glycopyrronium monotherapy [16]. This finding has been supported more recently by preliminary data from a 24-week RCT that reported a potential benefit of umeclidinium/vilanterol as

initial maintenance therapy versus LAMA and LABA monotherapy with umeclidinium and salmeterol, respectively [17].

The symptoms of COPD can pose a major challenge for patients. The burden of symptoms makes it difficult to complete daily activities, and is associated with poor quality of life, declining health status and poor prognosis [18, 19]. COPD is underdiagnosed, with patients often not being diagnosed until their COPD has progressed to more advanced stages of the disease [2]. The fastest decline in lung function is seen in the initial stages of COPD [20]; as such, treating patients at earlier stages of the disease could help them achieve control of respiratory symptoms sooner [21]. In addition, use of dual bronchodilators has been shown to improve symptoms during physical activity [22, 23]; therefore, treatment of patients while they have more preserved lung function (i.e. at earlier GOLD stages) may allow patients to improve their health status and remain active so they are able to continue their daily activities for longer [24]. Taking all these arguments into account, our results support first-line use of tiotropium/olodaterol in treatment-naïve patients with COPD.

It is worth noting that there is wide variability in how individual patients respond to treatment with long-acting bronchodilators [25]. Not all patients will benefit from dual bronchodilator therapy, and clinical trial data, such as those presented here, cannot predict the response of every individual patient [25]. Different approaches exist regarding whether patients should be treated according to group mean results or whether a more personalised approach, to identify responders versus non-responders, should be used [25]. Nevertheless, our results suggest that tiotropium/olodaterol can provide additional benefits versus tiotropium monotherapy for most patients, without compromising safety.

The key strength of this analysis was the large size of the TONADO and OTEMTO trials, which permitted analysis of the maintenance-naïve subpopulations. This is one of the largest analyses to be conducted in treatment-naïve patients with COPD and, to our knowledge, is the largest analysis of treatment-naïve patients

initiating dual bronchodilation therapy. Restricted options in the collection of patients' medical history are a potential limitation of this analysis—the TONADO and OTEMTO trials only recorded whether patients were receiving LAMA, LABA or ICS treatment at study entry (i.e. when they signed the informed consent); hence, it is possible that some of the patients may have received maintenance treatment at some point previously. In addition, in the TONADO and OTEMTO studies, CAT and mMRC data were not collected; therefore, stratification of patients into GOLD A–D groups was not possible. This may be helpful in future studies to better establish the utility of the data in the real-world clinical setting. Also, given the 12-week duration of the OTEMTO trial, exacerbations were not a primary or secondary outcome. As the current analysis is also performed at 12 weeks, there were too few events to investigate any effect of exacerbations, although this could be of interest for future research.

CONCLUSION

Overall, treatment with tiotropium/olodaterol, compared with tiotropium alone, in patients who were not receiving LAMA, LABA or ICS treatment at baseline, results in superior clinical outcomes, with greater improvements in lung function, health status and dyspnoea without compromising safety. This study supports the benefits of treatment optimisation with tiotropium/olodaterol from the start of maintenance treatment in patients with COPD.

ACKNOWLEDGEMENTS

We thank the participants included in these studies. DS is supported by the National Institute for Health Research (NIHR) Manchester Biomedical Research Centre (BRC).

Funding. Support for this project and rapid service and open access fees were funded by Boehringer Ingelheim International GmbH.

Authorship. All named authors meet the International Committee of Medical Journal Editors (ICMJE) criteria for authorship for this article, take responsibility for the integrity of the work as a whole, and have given their approval for this version to be published.

Medical Writing, Editorial, and Other Assistance. Medical writing assistance, in the form of the preparation and revision of the manuscript, was supported financially by Boehringer Ingelheim and provided by Vicki Cronin of MediTech Media (Manchester, UK), based on a draft provided by the authors, their feedback and under their conceptual direction.

Disclosures. Roland Buhl reports grants and personal fees from AstraZeneca, Boehringer Ingelheim, Chiesi, Cipla, GlaxoSmithKline, Novartis, Roche and Teva. Alberto de la Hoz and Wenqiong Xue are employees of Boehringer Ingelheim. Dave Singh reports personal fees from Apellis, Cipla, Genentech, Peptinnovate, and Vectura (formerly Skyepharma), and grants and personal fees from AstraZeneca, Boehringer Ingelheim, Chiesi, Glenmark, Merck, Mundipharma, Novartis, Pfizer, Pulmatrix, Teva, Theravance, and Verona. Gary T. Ferguson reports consulting and advisory board fees from Boehringer Ingelheim, AstraZeneca, Pearl Therapeutics, Novartis, Forest, Sunovion, and Verona, consulting fees from Receptos, speaker fees from Boehringer Ingelheim, GlaxoSmithKline, AstraZeneca, Pearl Therapeutics, Forest, and Sunovion, and research grants from Boehringer Ingelheim, AstraZeneca, Pearl Therapeutics, Sunovion, Novartis, Theravance, Sanofi, Forest, and GlaxoSmithKline. The authors report no other conflicts of interest in this work.

Compliance with Ethics Guidelines. The trials 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.

Data Availability. Data are available from the corresponding author upon reasonable request.

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