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CLINICAL TRIAL REPORT

Improvement In Self-Reported Physical Functioning With Tiotropium/Olodaterol In Central And Eastern European COPD Patients

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Background: Reduced physical activity is associated with increased morbidity and mortality in patients with COPD. Studies suggest that treatment with the long-acting muscarinic antagonist tiotropium and the long-acting β_2-agonist olodaterol increases exercise capacity. This study assessed the effects of a fixed-dose combination (FDC) of tiotropium/olodaterol (delivered via Respimat®) on physical functioning in patients with stable COPD in a "real-world setting".

Methods: An international, open-label, single-arm, non-interventional study conducted in nine countries measuring changes in self-reported physical functioning in COPD patients treated with tiotropium/olodaterol 5/5 µg FDC for approximately 6 weeks. The primary endpoint was therapeutic success, defined as a minimum 10-point increase in the 10-question Physical Functioning Questionnaire (PF-10) score. Secondary endpoints included absolute change in PF-10 from Visit 1 to Visit 2, patient general condition (measured by Physician's Global Evaluation score) and patient satisfaction with the treatment and device (assessed by Patient Satisfaction Questionnaire at the end of the study period).

Results: Therapeutic success was observed in 67.8% of 7218 patients (95% CI 66.7, 68.8) in the final analysis set after approximately 6 weeks of treatment with tiotropium/olodaterol. Mean change in PF-10 score between Visit 1 and Visit 2 was 16.6 points (95% CI 16.2, 17.0). Therapeutic success was 64.3% (95% CI 63.0–65.6%) in patients with infrequent (≤1) and 76.1% (95% CI 74.3–77.9%) in patients with frequent (≥2) exacerbations ($p<0.0001$). Patient general condition improved as indicated by an improvement in Physician's Global Evaluation scores between visits. Most patients were very satisfied or satisfied with tiotropium/olodaterol treatment in general (81%), reported inhalation satisfaction (85%), and satisfactory handling of the device (84%). 1.3% of patients reported an investigator-defined drug-related adverse event.

Conclusion: Treatment with tiotropium/olodaterol led to an improvement in self-reported physical functioning in patients with COPD.

Keywords: tiotropium, olodaterol, chronic obstructive pulmonary disease, COPD, physical functioning, non-interventional study

Plain language summary

Patients with COPD are less active. This can cause a patient's quality of life to decrease, and they may need more visits to hospital. However, treatment with drugs that open the airways can help people do more exercise and improve their level of physical activity. We tested if using a combination of two of these drugs, called tiotropium and olodaterol, could help increase patients' activity levels. We also studied people's general condition and if they were

happy with the inhaler device. We found that most patients improved their activity levels. Patients' general condition also improved, and most were satisfied with the treatment and inhaler. These results may mean that these drugs could help keep patients active and help them to stay well for longer.

Introduction

COPD affects approximately 251 million people globally.[1,2] It is characterized by airflow obstruction and hyperinflation, resulting in dyspnea and exercise limitation.[3] Exercise-induced breathlessness prevents many patients from carrying out physical activity.[4,5] Household chores and other daily activities are often limited, take longer to complete or are avoided altogether.[6,7] Reduced physical activity in turn has been associated with muscle deconditioning,[8] causing a downward spiral of exercise impairment and clinical worsening, with increased exacerbation risk and hospital admissions.[9] Patients with impairments in physical activity also experience an increased healthcare resource use and costs,[10] depression, and anxiety,[11,12] which may further contribute to the disease burden. Furthermore, the level of deconditioning and disability has proven to be a strong predictor of mortality in patients with COPD.[9,13]

Inhaler therapy with bronchodilators, such as long-acting muscarinic antagonists (LAMAs) or long-acting β_2-agonists (LABAs), plays a central role in COPD treatment. COPD guidelines recommend LAMAs and/or LABAs as the primary maintenance treatment for COPD.[14] Due to the complementary modes of action of these therapies, LAMA/LABA combination therapy can enhance the bronchodilator effect by reducing airway resistance and lung hyperinflation, and improving ventilatory muscle performance,[15–17] allowing patients to exercise for longer before being limited by symptoms.[17,18] This is reflected in clinical studies where patients with COPD treated with tiotropium/olodaterol dual bronchodilator therapy have shown significant improvements in exercise capacity and endurance time compared with placebo.[15,19,20] While randomized controlled trials have confirmed the benefits of tiotropium/olodaterol combination therapy on exercise capacity, real-world data on physical activity are scarce. Recently, observational studies conducted in Germany demonstrated improvements in physical functioning (the ability of an individual to undertake daily tasks)[21] in patients with moderate to very severe COPD using tiotropium and olodaterol.[22,23]

In this observational study, we aimed to measure changes in physical functioning, serving as a surrogate for physical activity and exercise capacity, in patients with COPD treated with tiotropium/olodaterol fixed-dose combination (FDC) in a real-world setting in Central and Eastern Europe. Physician-based assessment of patients' general condition, as well as patient satisfaction with tiotropium/olodaterol inhaler therapy via the Respimat® Soft Mist™ inhaler were also assessed. In contrast to these previous, country-specific studies, this is an international study across nine countries, with varying standards of care. This study was carried out to determine whether the previously observed results were applicable to a broader patient population across different countries, healthcare settings and standards of care.

Methods

Study Population

This was an international, open-label, non-interventional study conducted in nine countries (Austria, Czech Republic, Hungary, Israel, Romania, Russian Federation, Slovakia, Slovenia, and Switzerland) between April 11, 2016 and May 4, 2017 (NCT02720757). This study was approved by the Magistrat der Stadt Wien ethics committee (EK16013VKNIS) on March 15, 2016. The study was carried out in compliance with the protocol, the principles laid down in the Declaration of Helsinki, and as close as possible to the standards of the International Conference of Harmonization Tripartite Guideline for Good Clinical Practice, Guidelines for Good Epidemiological Practice and Good Pharmacoepidemiology Practice. The sponsor of the OTIVACTO® Trial (Boehringer Ingelheim) is committed to responsible sharing of clinical study reports, related clinical documents, and patient-level clinical study data. Researchers are invited to submit inquiries via the Clinical Study Data Request website (https://www.clinicalstudydatarequest.com).

The inclusion criteria for this study were patients aged ≥40 years, with a diagnosis of COPD and requiring long-acting dual bronchodilation (LAMA+LABA) treatment (according to physician-based indication and within the approved tiotropium/olodaterol label)[24] and had provided written informed consent prior to participation in the study. The exclusion criteria included treatment with any LAMA/LABA combination (free- and fixed-dose) up to 6 months prior to the study or contraindications according to the approved Spiolto® label.[24] To avoid double-dosing of a LABA, patients who intended to continue LABA/inhaled corticosteroid (ICS) FDC treatment were not included in

this study. Other exclusion criteria included patients for whom further follow-up was not possible at the enrolling site during the planned study period of approximately 6 weeks; pregnancy and lactation; patients currently listed for lung transplantation; and those participating in any clinical trial or any other non-interventional study of a drug or device.

Study Design

Patients were enrolled consecutively and followed over an observational period of approximately 6 weeks, to minimize the risk of recall bias and increase patient recall accuracy.[25,26] Treatment with tiotropium/olodaterol was delivered via the inhaler device as specified by the approved Spiolto® label. Several questionnaires were used during the study; the mMRC scale (grade 0 [breathless only when I exercise] to 4 [too breathless to leave the house]) was used to assess the degree of breathlessness of the patients before treatment at baseline (Visit 1), as well as the exacerbation history and post-bronchodilator FEV_1 to automatically calculate the GOLD stage in the electronic case report form. Patients were asked to complete the 10-question Physical Functioning Questionnaire (PF-10) to evaluate their physical functioning at baseline (Visit 1) and after approximately 6 weeks' treatment (Visit 2). The PF-10 is a subdomain of the validated 36-item Short Form Health Survey (SF-36) quality-of-life questionnaire.[27] It consists of 10 questions evaluating the extent of experienced restrictions while conducting everyday physical activity. Each question in the PF-10 may be answered with either "yes, limited a lot", "yes, limited a little" or "no, not limited at all", recorded on a 3-point Likert scale. Patient level of restriction is reported in the following activities: vigorous activities (eg, running, lifting heavy objects), moderate activities (eg, moving a table, swimming, pushing a vacuum cleaner or riding a bicycle), lifting or carrying groceries, climbing several flights of stairs, climbing one flight of stairs, bending, kneeling or stooping, walking more than 1 km, walking several hundred meters, walking 100 m, bathing or dressing yourself. The final scores from the 10 questions were summed up and standardized on a scale of 0 to 100 using the formula 100×(sum-10)/20; a higher score represented better physical functioning.[27] A threshold score of a 10-point change in minimal important difference was selected based on a distribution-based method by Cohen.[28] Patient satisfaction with the treatment, inhalation, and handling of the inhaler device was assessed at the end of the study via a patient satisfaction questionnaire on a 7-point ordinal scale, with divisions from "very satisfied" to "very dissatisfied" (Visit 2).[29]

Patient general condition was assessed by the Physician's Global Evaluation (PGE), an 8-point scale in which the treating physician evaluated the patient's general condition as poor (1–2), satisfactory (3–4), good (5–6), or excellent (7–8),[22] both at Visit 1 and Visit 2. This was used to assess changes in patient condition from baseline to study end.

Visits

Variables were collected at both Visit 1 (baseline) and Visit 2 (after approximately 6 weeks of treatment). The following variables were recorded: demographics; history of COPD, last record of spirometric COPD severity of airflow obstruction according to GOLD (I–IV); number of overall exacerbations and number of exacerbations leading to hospitalization in the previous 12 months; history of smoking; past and present concomitant pulmonary medication; other concurrent diagnoses; other concomitant medication; breathlessness (assessed by mMRC) and tiotropium/olodaterol soft mist inhaler administration history (ie, date of first administration, training of device handling provided). The decision as to whether patients continued with tiotropium/olodaterol after the study was noted at Visit 2. Drug-related adverse events (AEs) were recorded during the time between signing of the informed consent and the end of the study.

Endpoints And Assessments

The primary endpoint was the occurrence of therapeutic success, defined as a 10-point increase in the PF-10 score, between Visit 1 (baseline) and Visit 2 (approximately 6 weeks after starting treatment).[30] The secondary endpoints were changes in PF-10 score from Visit 1 (baseline) to Visit 2; patient general condition, evaluated by the physician (PGE score) at Visit 1 (baseline) and Visit 2; and patient satisfaction with therapy, assessing overall satisfaction, inhalation satisfaction and device handling at Visit 2.

Statistical Analysis

Any patient who received at least one dose of tiotropium/olodaterol was included in the treated set (TS). Safety endpoints and demographic/baseline data were analyzed in the TS. Patients in the TS who had a PF-10 score at Visit 1 and Visit 2 comprised the full analysis set (FAS). All analyses for primary and secondary endpoints are descriptive and were performed on the FAS. For the primary endpoint, the percentage of patients with therapeutic success is presented

together with the 95% CI. For the secondary endpoints (ie, the general condition of patients and patients' satisfaction with tiotropium/olodaterol), the number and percentage of patients within each category (according to the scale used) is displayed. For changes in PF-10 score, summary statistics (mean, standard deviation, minimum, median, maximum) are provided. For all efficacy measures, results were also analyzed in several patient subgroups (ie, GOLD ABCD groups based on mMRC dyspnea scale and history of COPD exacerbations,[31] maintenance therapy-naïve patients versus those previously treated, and baseline use of ICS vs no use of ICS). Patients were also stratified by number of exacerbations experienced in the previous 12 months (infrequent [≤1 exacerbation] and frequent [≥2 exacerbations]).

For subgroups, PGE and patient satisfaction were compared by Chi-squared test. If the Chi-squared test was not valid, Fisher's exact test was used, or the PGE and patient satisfaction were treated as continuous outcomes and then compared by Wilcoxon rank-sum test (Mann–Whitney *U*-test) or Kruskal–Wallis test. For subgroups, changes from baseline in PF-10 were compared by Wilcoxon rank-sum test (Mann–Whitney *U*-test) or Kruskal–Wallis test. For change from baseline in PF-10, 95% CIs were calculated. P-values ≤0.05 were considered statistically significant and are to be interpreted nominally.

Results

Patient Characteristics

Overall, 7477 patients were screened, of which 7443 were included in the TS and 7218 in the FAS (Figure 1). Patients in the TS had a mean age of 65.1 years, 68.4% were male and 41.4% were current smokers. Based on GOLD 2017, 48.9% were classified GOLD B, 24.2% GOLD D, 21.8% GOLD A and 5.1% GOLD C (Table 1). Over two-thirds of patients (72.1%) had recorded comorbidities (Tables 1 and 2).

At baseline, mMRC scores revealed that patients were predominantly suffering from grade 2 (42.4%) and grade 3 (25.2%) dyspnea severity (Table 1), had a mean PF-10 score of 46.1 ± 23.3 (Table 3), and a PGE score of predominantly 3 (26.4%) or 4 (29.9%), corresponding to a satisfactory general condition (Figure 2). A total of 2384 patients (32.0%) were treatment naïve (no COPD

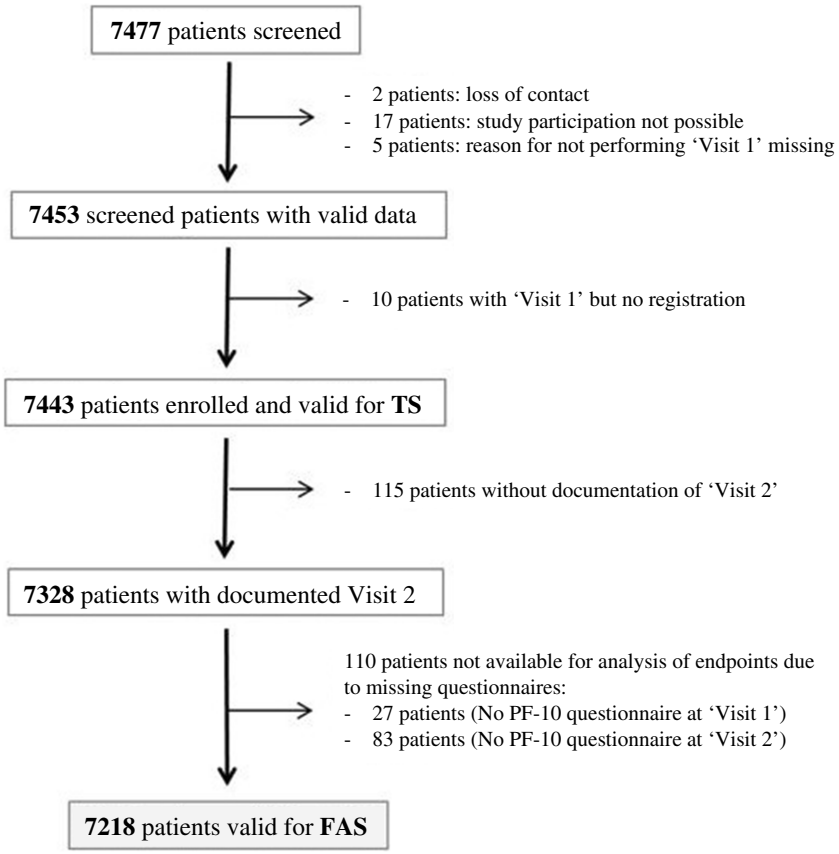

Figure 1 Patient flow chart.
Abbreviations: FAS, full analysis set; PF-10, 10-question Physical Functioning Questionnaire; TS, treated set.

Table 1 Demographic And Baseline Data Of Patients In The Treated Set (N=7443)

Variable	
Age at registration	
Mean, years (SD)	65.1 (9.3)
≤65 years, n (%)	3783 (50.8)
>65–<75 years, n (%)	2438 (32.8)
≥75 years, n (%)	1222 (16.4)
Sex	
Male, n (%)	5094 (68.4)
Patients with concomitant diseases	
n (%)	5366 (72.1)
Patients taking concomitant medication (except respiratory therapeutics)	
n (%)	4482 (60.2)
Smoking status	
Smoker, n (%)	3080 (41.4)
Ex-smoker, n (%)	3325 (44.7)
Never smoked, n (%)	1038 (14.0)
Pack-years	
Mean (SD)	35.1 (19.8)
Duration between initial diagnosis and baseline visit	
Years, mean (SD)	4.8 (5.86)
COPD degree of severity, spirometric	
Patients in stage GOLD 1, n (%)	119 (1.60)
Patients in stage GOLD 2, n (%)	3379 (45.40)
Patients in stage GOLD 3, n (%)	3111 (41.80)
Patients in stage GOLD 4, n (%)	744 (10.00)
mMRC Questionnaire	
Patients with grade 0, n (%)	238 (3.2)
Patients with grade 1, n (%)	1763 (23.7)
Patients with grade 2, n (%)	3157 (42.4)
Patients with grade 3, n (%)	1874 (25.2)
Patients with grade 4, n (%)	411 (5.5)
GOLD group, based on symptoms and exacerbations only (version 2017)	
Patients in group A, n (%)	1625 (21.8)
Patients in group B, n (%)	3639 (48.9)
Patients in group C, n (%)	376 (5.1)
Patients in group D, n (%)	1803 (24.2)
Exacerbations in the 12 months prior to the study	
Number of exacerbations	8014
Patients with at least one event, n (%)	4831 (64.9)
Mean (SD)	1.1 (1.1)

treatment within the 6 months prior to study treatment). Of the 68% of patients who were treated with respiratory

Table 2 Concomitant Diseases And Medication Use At Baseline In The Treated Set

Concomitant diseases	Number (%) of patients[a]
Allergic disease	153 (2.1)
Cardiac	3162 (42.5)
Gastrointestinal/hepatobiliary	914 (12.3)
Metabolic/endocrine	1799 (24.2)
Musculoskeletal/dermatologic	488 (6.6)
Neurologic	307 (4.1)
Pulmonary (except COPD)	439 (5.9)
Psychiatric	274 (3.7)
Renal/urogenital	367 (4.9)
Vascular	2174 (29.2)
Other	424 (5.7)
COPD therapies taken 6 months prior to study start	
ICS monotherapy	326 (4.4)
LABA	1100 (14.8)
LAMA	1999 (26.9)
SABA	1056 (14.2)
SAMA	513 (6.9)
SAMA+SABA in fixed-dose combination	1071 (14.4)
LABA+ICS	859 (11.5)
LAMA+LABA in fixed-dose combination	50 (0.7)
Systemic corticosteroid	45 (0.6)
Theophylline	719 (9.7)
Roflumilast	36 (0.5)
Other	192 (2.6)

Notes: [a]"Multiple answers possible", meaning that patients might have more than one concomitant disease.

Abbreviations: ICS, inhaled corticosteroid; LABA, long-acting β_2-agonist; LAMA, long-acting muscarinic antagonist; SABA, short-acting β_2-agonist; SAMA, short-acting muscarinic antagonist.

therapeutics, 26.9% received LAMAs, 14.8% received LABAs, 14.2% received short-acting β_2-agonists, and 11.5% of the patients were pre-treated with LABA+ICS (Table 2).

Physical Functioning

Therapeutic success was achieved in 67.8% (95% CI: 66.7, 68.8) of patients (FAS) (Table 3). A mean improvement in PF-10 score from baseline of 16.6 points was observed (95% CI: 16.2, 17.0). The highest therapeutic success rates were observed in GOLD D (79.7%; 95% CI: 77.7, 81.6) and GOLD B patients (70.9%; 95% CI: 69.4, 72.4) followed by GOLD C (58.5%; 95% CI: 5302, 63.7) and GOLD A (49.3%; 95% CI: 46.8, 51.8) (P<0.0001) (Table 3). This difference by GOLD group is also highlighted when assessed by absolute change in PF-10 score (Supplementary Figure 1). Similarly,

Table 3 Ten-question Physical Functioning Questionnaire Scores At Visits 1 And 2, And Change From Baseline (full Analysis Set) (N=7218)

PF-10 score	
Visit 1 (baseline)	
Mean (SD)	46.1 (23.3)
Median (min–max)	45.0 (0–100)
95% CI	45.6, 46.7
Visit 2 (after approximately 6 weeks)	
Mean (SD)	62.7 (21.5)
Median (min–max)	65.0 (0–100)
95% CI	62.2, 63.2
Therapeutic success (proportion of patients with a ≥10-point increase in PF-10 after approx. 6 weeks)	
Overall	
n (%)	4891 (67.8)
95% CI	66.7, 68.8
GOLD A[a]	
n (%)	766 (49.3)
95% CI	46.8, 51.8
GOLD B[a]	
n (%)	2515 (70.9)
95% CI	69.4, 72.4
GOLD C[a]	
n (%)	209 (58.5)
95% CI	53.2, 63.7
GOLD D[a]	
n (%)	1401 (79.7)
95% CI	77.7, 81.6

Notes: [a]GOLD subgroup according to 2017 classification, based on symptoms and exacerbations only.
Abbreviation: PF-10, 10-question Physical Functioning Questionnaire.

there was a statistically significant difference in therapeutic success rates between patients with mild and moderate airflow obstruction when compared with patients with more severe airflow obstruction (64% therapeutic success rate for GOLD 1 and 2 vs 70.9% therapeutic success rate for GOLD 3 and 4) (P<0.0001) (Supplementary Table 1). A higher proportion of patients with frequent (≥2) exacerbations reported therapeutic success, compared with patients with infrequent exacerbations, 76.1% (95% CI: 74.3, 77.9) vs 64.3% (95% CI: 63.0, 65.6), respectively (P<0.0001). There was no significant difference (P=0.4534) in the proportion of patients with therapeutic success between maintenance-naïve (68.0%; 95% CI: 66.74, 69.24) and pre-treated (67.1%; 95% CI: 64.84, 69.21) patients. This was also true for patients who received previous therapy with ICS at baseline (66.9%; 95% CI: 64.0, 69.7) compared with those with no prior ICS therapy (67.9%; 95% CI: 66.7, 69.1) (P=0.5127).

Patient General Condition And Self-Reported Treatment Satisfaction

A shift towards an improvement in patient general condition was seen from baseline (11.8% scored PGE 1–2 corresponding to "poor" condition, 56.3% scored PGE 3–4, corresponding to "satisfactory" condition; 31.9% scored PGE 5–8, corresponding to "good/excellent" condition) to study end (0.7% scored 1–2, 16.0% scored 3–4, 83.3% scored 5–8) (post hoc grouping and analysis, P<0.0001) (Figure 2). Eighty-one percent of patients were satisfied/very satisfied with tiotropium/olodaterol treatment overall, 85% with inhaling from the soft mist inhaler device and 84% with device

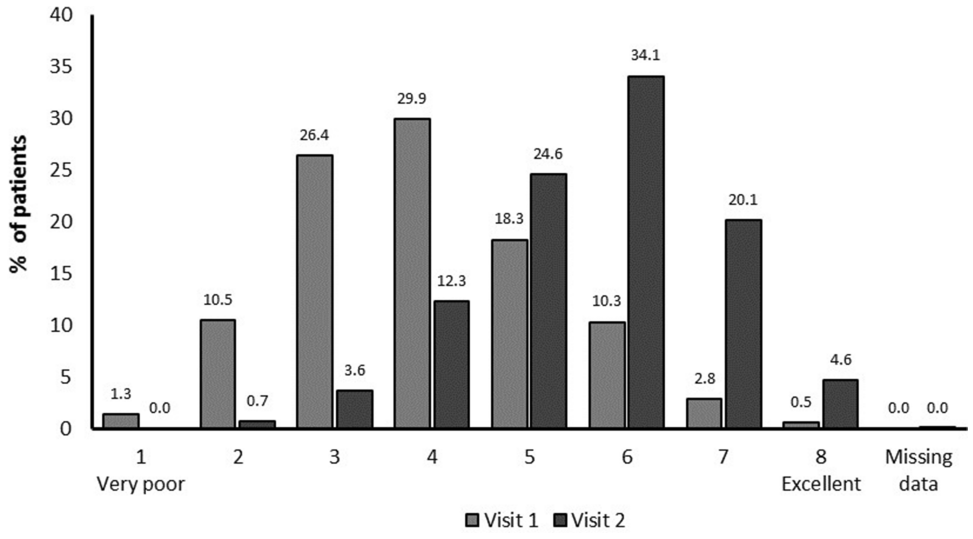

Figure 2 General patient condition: Physician's Global Evaluation score.

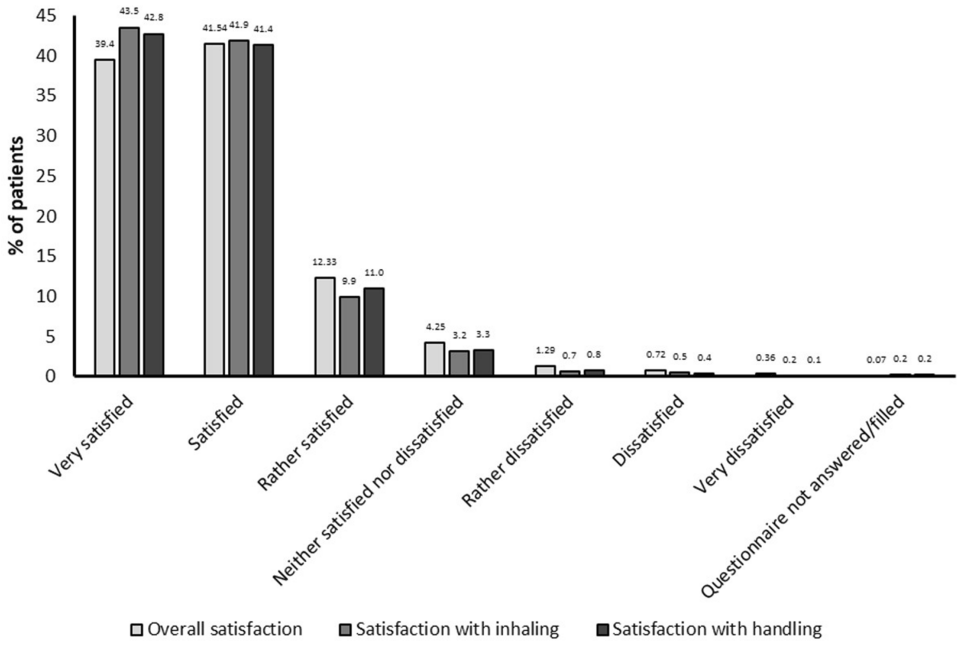

Figure 3 Patient overall satisfaction with treatment.

handling (Figure 3). Patient satisfaction was also reflected by a high proportion of patients continuing tiotropium/olodaterol treatment at the end of the observational period (95%).

Safety

Overall, 110 drug-related AEs were reported by 1.3% (96/7443) of the TS population. The most common drug-related AEs included cough (30 events), dry mouth (23 events), and COPD worsening (exacerbations; 10 events). Forty-seven patients discontinued treatment, predominantly due to cough (10 patients), worsening of COPD (exacerbations; 9 patients) and dry mouth (8 patients). A total of five serious AEs (atrial fibrillation, pneumonia, sepsis, neoplasm, and neoplasm progression), including one serious drug-related AE (atrial fibrillation) (Table 4), were documented in five patients, four of which were fatal and one required hospitalization.

Table 4 Summary Of Drug-related Adverse Events In The Treated Set (N=7443)

AE category	Number (%) of patients
All AEs	96 (1.3)
Serious AEs	5 (0.07)
AEs leading to discontinuation	47 (0.63)
Fatal AEs	4 (0.05)

Abbreviation: AE, adverse event.

Discussion

This observational study investigated the effect of tiotropium/olodaterol FDC on self-reported physical functioning in a large population of patients with a wide range of COPD severity in Central and Eastern Europe. The majority of patients in this study reported clinically meaningful improvements in physical functioning, as measured by an increase in PF-10 score of at least 10 points, in response to dual bronchodilator therapy. We did not observe a statistically significant difference in the proportion of patients with therapeutic success between pre-treated and maintenance-naïve groups, or between patients with or without ICS use. Patients were also found to be in better general condition after the treatment period and reported a high rate of overall treatment and inhaler device satisfaction.

Physical activity is an independent predictor of health-related quality of life,[32] hospital admissions,[9] as well as all-cause and disease-specific morbidity and mortality.[33] Inhaled bronchodilator therapy may exert a positive impact on physical activity on the basis of a variety of mechanisms, such as improvements in breathlessness,[34] static and dynamic hyperinflation,[35,36] breathing effort,[17,37] cardiovascular function,[38] and/or exercise capacity.[15,20,39]

Data from randomized controlled clinical trials have shown an increase in exercise endurance with dual bronchodilator therapy compared with monotherapy.[15] Nevertheless, it is still not clear whether the observed

effects on exercise capacity translate to true changes in daily physical activity in patients.[40,41]

Physical activity is affected by many factors including patient behavior.[20] Although bronchodilation treatment in patients with COPD has been found to increase exercise tolerance,[42] this does not always translate to a more active lifestyle in patients. This may be due to negative patient experiences during physical activity or a lack of motivational and behavioral factors in pulmonary rehabilitation programs.[43] Previous studies have demonstrated that there are significant differences in the perception of how COPD affects daily activities in patients and the understanding that physicians have of their patients' perception.[44,45] In order to prescribe the optimal treatment strategy to improve symptoms and quality of life, awareness of the impact of patient perception is essential. The current study reinforces this theory using self-reported questionnaires and demonstrates that a large proportion of the trial population felt improvements in their ability to carry out daily activities resulted in high patient satisfaction with the treatment.

Furthermore, assessment of self-reported physical activity may serve as an important alternative to objective assessments of physical activity.[32] Physical activity and physical capacity are integral components of patient-reported outcome assessments, such as the St. George's Respiratory Questionnaire (SGRQ), one of the most frequently used health-related quality of life tools in clinical trials in COPD. Previous studies using either free-dose or FDCs of tiotropium and olodaterol delivered via soft mist inhaler device demonstrated improved SGRQ scores in patients with moderate to severe COPD when compared with mono-components.[34,46] The SGRQ, however, is of limited use in day-to-day clinical practice. In contrast, the PF-10 can be easily completed within few minutes in a physicians' office.[47] It is a validated subdomain of the SF-36 score, designed to examine a person's perceived limitation with physical functioning, in which subjects are asked if their condition limits not only physical activity, but also basic mobility, and basic activities of daily living.[27] Self-reported functional limitations are common in COPD among persons with a broad range of disease severity, and accompanied by muscle weakness and impaired exercise tolerance.[48]

Our data corroborate two previous observational studies using the PF-10 in patients with COPD and comparable disease characteristics.[22,30] Both studies, conducted by German pulmonologists, reported improvements in PF-10 score after 6 weeks of tiotropium mono or tiotropium/olodaterol free-dose combination therapy, respectively.[22,30] The magnitude of PF-10 score improvement (16.6 points) and the proportion of patients categorized to be in good or excellent general condition in the present study may suggest a higher treatment response to tiotropium/olodaterol FDC than reported in previous studies with monotherapy or free-dose combination therapy of the bronchodilators, with a 13.4 points and 10.2 points PF-10 score treatment difference at 6 weeks, respectively.[22,30] Importantly, the overall safety profile in these studies was similar.[29]

In contrast to the above reports we had a relatively high proportion of GOLD A patients who received tiotropium/olodaterol FDC from their treating physicians, a therapeutic approach currently not recommended by treatment strategy.[14] This may, in part, be explained by the method used to categorize patients into the GOLD risk groups. In fact, mMRC- and CAT-based approaches to estimate symptoms have provided contradictory results and can result in underestimation of patient severity by physicians.[49,50] Thus, it may be possible that a proportion of our patients would indeed qualify for GOLD B, if CAT were used. In that case, the use of LAMA/LABA treatment would be considered consistent with the GOLD treatment recommendations, in patients with a high symptom load. On the other hand, our findings may confirm previous studies showing discordance in inhaler COPD management between treatment recommendations and clinical practice, on both a primary and secondary care level.[51] Factors responsible for this phenomenon may include lack of awareness of recommendations,[51] difficulties in distinguishing between asthma and COPD in clinical practice,[52] and/or reimbursement-related factors.[53] There may also be a shift towards early intervention with LAMA/LABA FDC in COPD in clinical practice, based on the cumulating scientific evidence of their ability to improve lung function and measures of disease worsening, when compared with mono-bronchodilator or LABA/ICS therapy.[54–57] In this context, further studies are required to investigate physician treatment behavior in real-life clinical studies.

Furthermore, we observed a higher PF-10 responder rate in frequent exacerbators (≥2 exacerbations in 12 months) compared with infrequent exacerbators (≤1 in 12 months). This is of particular importance, as both moderate[58] and severe exacerbations[59] have been shown to impact physical activity. Improvements in physical functioning and general condition through dual bronchodilation, as seen in this study, could encourage patients to adopt a more active lifestyle, resulting in an improved

quality of life and lower risk of COPD-related hospitalizations.[60,61] Additionally, there is evidence of a direct impact of dual bronchodilator therapy on exacerbation rates in COPD.[62–65]

We should acknowledge a number of limitations in this study. First and foremost, the current study is a real-world observational study and not a randomized controlled clinical trial lacking a control group with which to compare the intervention. The differential treatment response observed in patients with differing disease stage, however, may suggest a true therapeutic intervention rather than a mere placebo effect. Second, we used a questionnaire to establish the level of physical activity rather than a direct measure. While questionnaires on physical activity only have a moderate level of concordance with objective assessments of physical activity, they have a tendency towards overestimation rather than underestimation compared with objective methods.[66,67] While the threshold of 10 points for clinically relevant changes in the PF−10 has been selected on the basis of statistical rationale, we need to acknowledge that this cut-off has not been validated in terms of its clinical impact beyond daily physical activity or its correlation with other patient-reported outcomes. Similarly, we did not perform lung function measurements during follow-up to correlate any potential improvements in airway physiology with the benefits observed in physical activity. Despite these limitations, self-reported levels of physical activity, such as time patients spent walking during their leisure time, have been reported as important independent predictors of health-related quality of life in COPD.[32] Third, we must acknowledge the rather short duration of the observational period. As this study relied on patient self-reported data there was a risk of recall bias, which could affect the validity of the data collected, the shorter study duration was the best approach to minimize this risk.[25] Participants can inaccurately recall a past event, which can influence their responses. Should this effect be underestimated, the true effect or association of the treatment could be incorrectly recorded. Recall bias has been associated with multiple factors, including the length of recall period.[26] Previous studies have demonstrated that short recall periods are better than longer periods, especially when asking patients to recall routine or frequent events.[25,26] Further studies to evaluate alignment between gold-standard data collection sources and self-reported methods are needed to clearly define appropriate timelines to reduce the risk of such bias. Finally, patient use of concomitant medications and patient adherence to the treatment regimen was self-controlled and there was no treatment diary; patient use and adherence to tiotropium/olodaterol was therefore dependent on physician inquiry and could not be verified or controlled. As such, the effect these variables may have had on efficacy and safety is unknown.

Strengths of this non-interventional study include a large, international patient population, with varying disease severity and a spectrum of comorbidities, treated for COPD in clinical practice, allowing these data to be more readily generalized to a real-life setting.[68] Thus, the efficacy and safety data observed here complement findings from previous randomized controlled clinical trials of LAMA/LABA FDC therapy in patients with COPD.

Conclusion

Treatment with tiotropium/olodaterol via soft mist inhaler device under real-life conditions led to an improvement in self-reported physical functioning and PGE scores, as well as in patient satisfaction with treatment via the inhaler device across a wide range of COPD severities.

Abbreviations

AE, adverse event; FAS, full analysis set; FDC, fixed-dose combination; ICS, inhaled corticosteroid; LABA, long-acting β_2-agonist; LAMA, long-acting muscarinic antagonist; PF-10, 10-question Physical Functioning Questionnaire; PGE, Physician's Global Evaluation; SF-36, 36-item Short Form Health Survey; SGRQ, St. George's Respiratory Questionnaire; TS, treated set.

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Author contributions

The authors meet criteria for authorship as recommended by the International Committee of Medical Journal Editors. They take full responsibility for the scope, direction, content of, and editorial decisions relating to, the manuscript, were

involved at all stages of development, and have approved the submitted manuscript. All authors contributed to data analysis, drafting and revising the article, gave final approval of the version to be published, and agree to be accountable for all aspects of the work.

Disclosure

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