Health and functional status of tiotropium/olodaterol-treated patients with COPD: results from the AERIAL® non-interventional study

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Shareable abstract (@ERSpublications)
The AERIAL non-interventional study demonstrated that patients with COPD treated with tiotropium/olodaterol *via* Respimat in routine clinical practice had high product satisfaction and clinically relevant improvements in health and functional status https://bit.ly/3jf6hIf

Cite this article as: Gillissen A, Marseille A, Skowasch D, *et al*. Health and functional status of tiotropium/olodaterol-treated patients with COPD: results from the AERIAL® non-interventional study. *ERJ Open Res* 2021; 7: 00004-2021 [DOI: 10.1183/23120541.00004-2021].

This article has supplementary material available from openres.ersjournals.com

Received: 4 Jan 2021
Accepted: 21 June 2021

Abstract

Patients with COPD often have reduced physical activity, which can impair health status. Real-world data can provide valuable information on the health and functional status of patients with COPD treated with tiotropium/olodaterol.

AERIAL® (ClinicalTrials.gov NCT03165045) was a German, non-interventional study of patients with COPD receiving treatment with tiotropium/olodaterol under real-world conditions for ∼6 weeks. The primary end-point was the proportion of patients achieving a decrease of ⩾0.4 points in Clinical COPD Questionnaire (CCQ) score. The CCQ-4 subdomain was used to assess functional status, and the Physician's Global Evaluation (PGE) scale was used to assess the patients' general condition. Safety was assessed, as well as patient satisfaction and willingness to continue treatment.

Out of 1351 screened patients, 1322 were treated and 1140 comprised the full analysis set. The primary end-point was met: 66.3% of patients achieved a ⩾0.4-point decrease in overall CCQ score (mean±SD decrease 0.78±0.95). Mean±SD decreases in CCQ symptoms and functional state subdomains were 0.84±1.06 and 0.75±1.05 points, respectively. PGE scores improved. One fatality (not treatment-related) and 23 drug-related adverse events were recorded, most commonly nausea and vertigo. >85% of patients were satisfied/very satisfied with tiotropium/olodaterol overall and with the Respimat® device, both in terms of inhalation and handling. Most patients (95.2%) expressed willingness to continue treatment.

Patients with COPD treated with tiotropium/olodaterol *via* Respimat® in routine clinical practice had clinically relevant improvements in health and functional status compared with baseline.

Introduction

COPD is a common and treatable disease that is characterised by airflow limitation and persistent respiratory symptoms [1]. Patients with COPD often have reduced physical activity [2, 3], which results in impaired health status and reduced health-related quality of life (HRQoL), and may contribute to hospitalisations and increased mortality [4–6].

Pharmacological therapy for COPD can reduce symptoms, decrease the frequency and severity of exacerbations, and improve health status and exercise tolerance [1]. Combination treatment with a

long-acting muscarinic antagonist (LAMA) and long-acting β_2-agonist (LABA) increases forced expiratory volume in 1 s and reduces symptoms and exacerbations compared with monotherapy [1].

Tiotropium/olodaterol (Spiolto®) is a fixed-dose LAMA/LABA combination, administered *via* a soft-mist inhaler (SMI; Respimat® Soft Mist™ inhaler), which has demonstrated greater improvements in lung function, symptoms, HRQoL and exercise capacity among patients with COPD than its monocomponents (tiotropium or olodaterol) or placebo in clinical studies [7–11]. Real-world evidence shows treatment effects in a broader patient population, as seen in routine clinical practice, thus providing valuable additional information.

At the time of planning this observational study, only one non-interventional study had reported on the health status and physical activity/functional status of patients with COPD treated with tiotropium/olodaterol in routine clinical practice [12]. This study was the first to provide evidence of improved physical functioning, measured by the self-reported 10-item Physical Functioning Questionnaire (PF-10), which translated into an overall improvement in the general condition of patients with COPD receiving tiotropium and olodaterol (in separate inhalers) [12].

The current study (AERIAL®; ClinicalTrials.gov registration number NCT03165045) was conducted to generate real-world data regarding the effect of tiotropium/olodaterol on the health and functional status of patients with COPD. The Clinical COPD Questionnaire (CCQ) was used to assess changes in the health and functional status of patients with COPD who were treated for ∼6 weeks with tiotropium/olodaterol *via* the Respimat® SMI in routine clinical practice in Germany.

Methods

This was an open-label non-interventional study enrolling consenting patients with COPD, who received treatment with tiotropium/olodaterol according to the approved summary of product characteristics (SmPC) [13]. Patients were observed for ∼6 weeks under real-world conditions. Site selection was performed to reflect routine COPD care in Germany and ensure representativeness of the COPD population; therefore, the study included physicians who routinely treat COPD patients in an outpatient setting. Sites were selected randomly *via* phonebook research (general practitioners and specialists alike), as well as on the basis of physicians participating in a prior non-interventional study, SPIRIT.

The feasibility form covered estimated number of patients in Global Initiative for Chronic Obstructive Lung Disease (GOLD) group B–D within the past 12 months, within the upcoming 12 months, and a question regarding conflicting study projects. To minimise patient selection bias, consecutive enrolment was employed.

European Commission approval was obtained for the study and the German Federal Institute for Drugs and Medical Devices was notified. The study has been registered with both the European Network of Centres for Pharmacoepidemiology and Pharmacovigilance and www.clinicaltrials.gov.

The study included patients meeting all of the following criteria: 1) written informed consent prior to participation; 2) aged ⩾40 years; 3) diagnosed with COPD and having an indication for treatment with a combination of two long-acting bronchodilators (LAMA/LABA) according to approved SmPC [13] and GOLD strategy report 2017 (GOLD COPD groups B–D) [14]; and 4) treatment with tiotropium/olodaterol according to SmPC at the discretion of the physician. Patients were excluded if any of the following conditions were met: 1) contraindications according to the tiotropium/olodaterol SmPC; 2) already on a LAMA/LABA combination (free or fixed dose) in the 6 weeks prior to study entry; 3) continuing LABA/inhaled corticosteroid (ICS) treatment in parallel with tiotropium/olodaterol (to avoid double-dosing of LABA); 4) pregnant or lactating; or 5) current participation in any clinical trial or any other non-interventional study of a drug or device.

As per the statistical analysis plan, patients violating any inclusion or exclusion criterion were retained in all analyses (treated set and full analysis set) and listed accordingly in the final statistical report and in the final study report.

The primary end-point was the proportion of patients achieving “therapeutic success”, pre-defined as a ⩾0.4-point decrease in the CCQ score between visit 1 (baseline visit) and visit 2 (final visit, ∼6 weeks after visit 1). The secondary end-points were 1) changes in total CCQ score and CCQ-4 (functional status domain) score from visit 1 to visit 2; 2) patients’ general condition at visit 1 and 2; and 3) patient satisfaction and willingness to continue treatment with tiotropium/olodaterol at visit 2. The CCQ includes

10 questions relating to symptoms, and functional and mental status. Each question was scored by the patients on a 7-point scale from 0 to 6; the sum of the scores divided by 10 provides the CCQ score, with a higher score indicative of worse status. Functional status (CCQ-4), calculated as the sum of questions 7–10 divided by four, assesses limitations in moderate and strenuous physical, daily and social activities. A change of 0.4 points is considered to be the minimal clinically important difference for both the total CCQ and CCQ-4 score [15, 16].

The treating physician completed the Physician's Global Evaluation (PGE) to evaluate patients' general condition, on an 8-point ordinal scale (from 1 (very poor) to 8 (excellent)). A patient satisfaction survey was completed at visit 2, using a 7-point ordinal scale (very dissatisfied to very satisfied). Willingness to continue treatment was assessed by a yes/no question at visit 2.

Subgroup analyses were performed to assess therapeutic success according to prior use of COPD maintenance therapy (LABA only, LAMA only, or LABA/ICS) and GOLD ABCD classification. Patients who had not received COPD maintenance therapy in the 6 weeks prior to the study were considered maintenance-naïve. Adverse drug reactions (serious and nonserious) and fatal adverse events were assessed; all adverse events occurring after signing of informed consent and up to visit 2 were considered treatment-emergent.

Data were collected from patients enrolled between March 2017 and November 2018. AERIAL® was completed in adherence with the International Conference on Harmonization good clinical practice guidelines, with ethical approval received from the state medical council of Baden-Württemberg, Germany.

Sample size calculation

A CCQ therapeutic success rate similar to the St George's Respiratory Questionnaire (SGRQ) responder rate was assumed. In the TONADO studies, patients with COPD treated with tiotropium/olodaterol had a 57.5% SGRQ responder rate [7]. A more diverse, real-world population would probably show a lower value than the selected trial population in the TONADO studies. Therefore, a 50% CCQ therapeutic success rate was considered a reasonable assumption. Assuming this and a sample size of ∼1170 patients, the 95% confidence interval for the therapeutic success rate would be between 47.1% (lower limit) and 52.9% (upper limit).

Subgroups treated with long-acting bronchodilators at visit 1 (*i.e.* LABA only, LAMA only, LABA/ICS) were analysed only if they included >20% of all patients. In the smallest subgroup (with ⩾234 patients), assuming a 50% therapeutic success rate, the 95% CI would be between 43.6% and 56.4%. To account for a 10% dropout rate, the sample size was increased to 1300 patients.

Statistical analysis

Primary and secondary end-points were analysed on the full analysis set, defined as patients with at least one documented administration of tiotropium/olodaterol (this was documented in the patient file and information was taken over into the electronic case report form), available CCQ scores at both visits and written informed consent. Safety end-points and demographic/baseline data were analysed on the treated set, comprising all patients with at least one documented administration of tiotropium/olodaterol and written informed consent.

For the primary end-point, the percentage of patients with therapeutic success is presented together with the 95% CI. For comparison of subgroups, Chi-squared test or Fisher's exact test (if Chi-squared test was not valid) was used and p-values were interpreted nominally. For the secondary end-points, all analyses were descriptive. Missing observations (*i.e.* missing values or missing subgroup outcomes) were not considered for comparisons. No formal hypothesis testing was performed due to the self-controlled nature of the study. Analyses were carried out using SAS® 9.3 software, and were performed by Alcedis GmbH, Germany.

Results

Patient disposition and baseline characteristics

A total of 1351 patients were recruited from 114 sites in Germany (figure 1). These included general and specialty practice sites (general medicine n=28; internal medicine n=22; pneumology n=4; internal medicine and pneumology n=59; internal medicine and general medicine n=1). 29 patients were excluded, resulting in 1322 patients in the treated set (figure 1). A further 182 patients had missing total CCQ scores at visit 1 and/or visit 2, resulting in a full analysis set comprising 1140 patients.

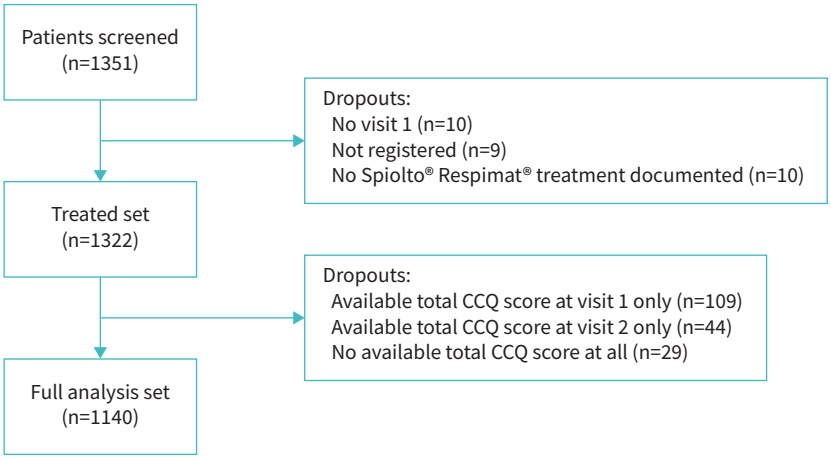

FIGURE 1 Patient disposition. Of the nine patients who were not registered, the reasons were violation of inclusion criterion 2 (n=2), allocation to Global Initiative for Chronic Obstructive Lung Disease COPD group A (n=3), meeting an exclusion criterion (unspecified, n=1), ongoing combined long-acting β_2-agonist (LABA) + inhaled corticosteroid therapy (n=1) or LABA/long-acting muscarinic antagonist therapy (n=2). There were no protocol violations due to informed consent. CCQ: Clinical COPD Questionnaire.

The median (range) age of patients in the treated set was 65 (40–104) years; 50.5% of patients were aged ⩽65 years (table 1). There were 760 (57.5%) male patients; 612 (46.3%) patients were current smokers, and 548 (41.5%) were ex-smokers. 831 (62.9%) patients were classified as GOLD group B, 321 (24.3%) were classified as GOLD group D, 153 (11.6%) as GOLD group C and one (0.1%; a protocol violation) as GOLD group A (table 1). The majority of patients had either GOLD stage 2 (43.0%) or GOLD stage 3 (38.1%) airflow limitation; 48.0% of patients had grade 2 breathlessness, as per the modified UK Medical Research Council questionnaire. More than half (61.3%) of patients had at least one exacerbation within the previous 12 months, and 12.2% had at least one exacerbation leading to hospitalisation during this period (table 1). Concomitant diseases were reported in 923 (69.8%) patients, the most frequent of which was cardiac disease (48.0%).

In the 6 weeks before the study, 258 (19.5%) patients were treated with short-acting β_2-agonists, 228 (17.3%) with a LAMA, 131 (9.9%) with a LABA, and 45 (3.4%) with ICS only. More than half (n=718, 54.3%) of the patients had no COPD treatment in the 6 weeks before the study (table 1). Most patients (98.4%) were trained on how to correctly inhale tiotropium/olodaterol before treatment started.

From the full analysis set population, 959 patients (84.1%) were maintenance-naïve at study enrolment. The mean total CCQ score at visit 1 was 3.12 (mean symptom score 3.42; mean functional state score 3.05; mean mental state score 2.69).

Efficacy

Therapeutic success was achieved in 66.3% of patients (95% CI 63.49–69.06) (figure 2). When stratified by prior COPD maintenance therapy, a higher proportion of patients who were previously maintenance-naïve achieved therapeutic success (68.5%) compared with those who were pre-treated with LABA only, LAMA only or LABA/ICS (54.7%; figure 2). When stratified by GOLD groups, the proportion of patients with therapeutic success was highest in GOLD group D (75.5%), followed by C (74.2%) and B (61.5%) (figure 2). When stratified by exacerbation history, the proportion of patients with therapeutic success increased with increasing exacerbation history (exacerbations in prior year: 0 (therapeutic success 56.8%); 1 (67.4%); ⩾2 (77.1%)) (supplementary table 1). The proportion of patients with therapeutic success stratified by exacerbation frequency, GOLD spirometric classification and baseline ICS use is provided in supplementary tables 1–3.

The mean±SD absolute change in CCQ total score from visit 1 to visit 2 was 0.78±0.95 (figure 3). Regarding the CCQ subdomains, the largest mean absolute changes were observed in the symptoms subdomain (0.84±1.06) and functional state subdomain (0.75±1.05) (figure 3). Patients who were maintenance-naïve before study enrolment achieved greater absolute changes in total CCQ score, and in

TABLE 1 Patient demographics and baseline characteristics

Total number of patients	1322 (100.00)
Age ⩽65 years	668 (50.53)
Male	760 (57.49)
Smoking status	
Current smoker	612 (46.29)
Ex-smoker	548 (41.45)
Never-smoker	162 (12.25)
COPD severity (GOLD groups)	
A	1 (0.08)
B	831 (62.86)
C	153 (11.57)
D	321 (24.28)
Missing	16 (1.21)
GOLD spirometric classification	
1	29 (2.19)
2	569 (43.04)
3	503 (38.05)
4	134 (10.14)
No preliminary examination result	87 (6.58)
mMRC questionnaire classification	
Grade 0	51 (3.86)
Grade 1	103 (7.79)
Grade 2	635 (48.03)
Grade 3	279 (21.10)
Grade 4	238 (18.00)
Missing	16 (1.21)
Exacerbations in the past 12 months	
0	512 (38.73)
1	405 (30.64)
⩾2	405 (30.64)
⩾1 exacerbation leading to hospitalisation	161 (12.18)
Patients with concomitant diseases	923 (69.82)
Cardiac disease	634 (47.96)
Allergic disease	17 (1.29)
Patient trained to use Respimat inhaler	
No	21 (1.59)
Yes	1301 (98.41)
Pharmacologically treated for COPD in the 6 weeks prior to start of study treatment	
No	718 (54.31)
Yes	604 (45.69)
Type of treatment for COPD in the 6 weeks prior to start of study treatment	
Short-acting β_2-agonist	258 (19.52)
LABA	131 (9.91)
Short-acting anticholinergic	9 (0.68)
Long-acting anticholinergic	228 (17.25)
Long-acting anticholinergic+LABA in fixed combination	6 (0.45)
Short-acting anticholinergic+short-acting β_2-agonist in fixed combination	69 (5.22)
LABA+ICS[#]	49 (3.71)
ICS	45 (3.40)
Systemic corticosteroid	5 (0.38)
Theophylline	6 (0.45)
Roflumilast	12 (0.91)
Other	5 (0.38)
Missing	2 (0.15)

Data are presented as n (%). GOLD: Global Initiative for Chronic Obstructive Lung Disease; mMRC: modified UK Medical Research Council; LABA: long-acting β_2-agonist; ICS: inhaled corticosteroid. [#]: none of the 49 patients who were on LABA+ICS prior to the study continued ICS treatment or received a new prescription for ICS treatment during the study.

symptoms and functional state subdomain scores, compared with those who were pre-treated (supplementary table 4). Patients in GOLD groups C and D achieved greater absolute changes in total CCQ and subdomain scores compared with patients in GOLD group B (supplementary table 4).

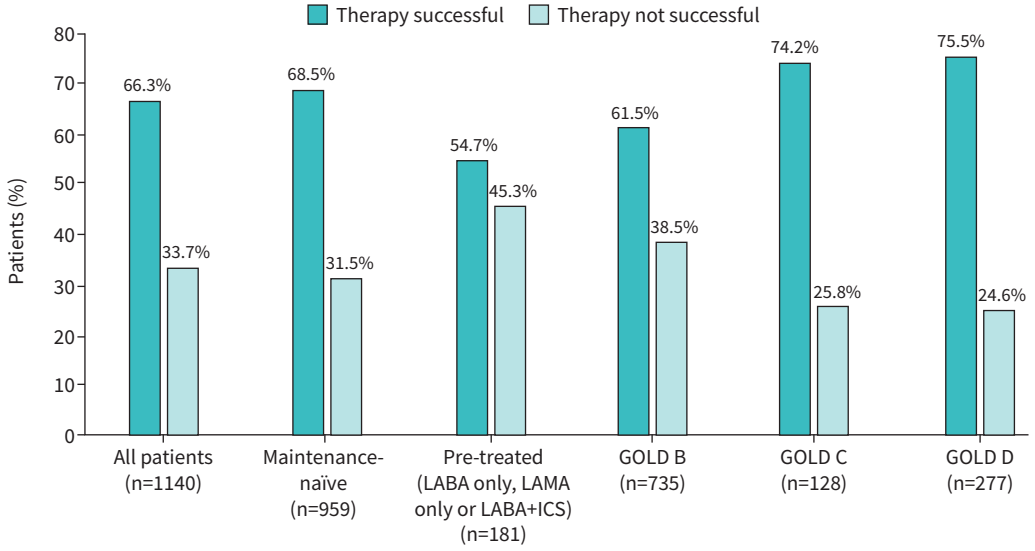

FIGURE 2 Proportion of patients achieving therapeutic success at visit 2. Therapeutic success was defined as a 0.4-point decrease in Clinical COPD Questionnaire score between visit 1 and visit 2. LABA: long-acting β_2-agonist; LAMA: long-acting muscarinic antagonist; ICS: inhaled corticosteroid; GOLD: Global Initiative for Chronic Obstructive Lung Disease.

Patients' general condition improved during the treatment period. At visit 1, most patients had a PGE score of 4 (n=378, 33.2%), followed by those with scores of 3 (n=281, 24.7%) and 5 (n=195, 17.1%) (where PGE score 1–2 is poor, 3–4 is satisfactory, 5–6 is good, and 7–8 is excellent). At visit 2, most patients had a PGE score of 5 (n=350, 33.7%), followed by those with scores of 6 (n=325, 28.5%) and 4 (n=223, 19.6%) (figure 4). PGE scores were significantly lower in maintenance-naïve patients than in pre-treated patients at visit 1; however, there was no statistically significant difference between the groups at visit 2; improvements in PGE scores were observed in both groups from visit 1 to visit 2. Stratification according to GOLD groups revealed that GOLD group D patients had lower PGE scores at both study visits (but also improved from visit 1 to visit 2).

Regarding patient satisfaction, 971 (85.2%) patients were "very satisfied" or "satisfied" with tiotropium/olodaterol overall; when asked specifically about inhalation and handling, 1008 (88.4%) and 979 (85.9%) of patients were "very satisfied" or "satisfied", respectively, with the Respimat® device (figure 5). Of the

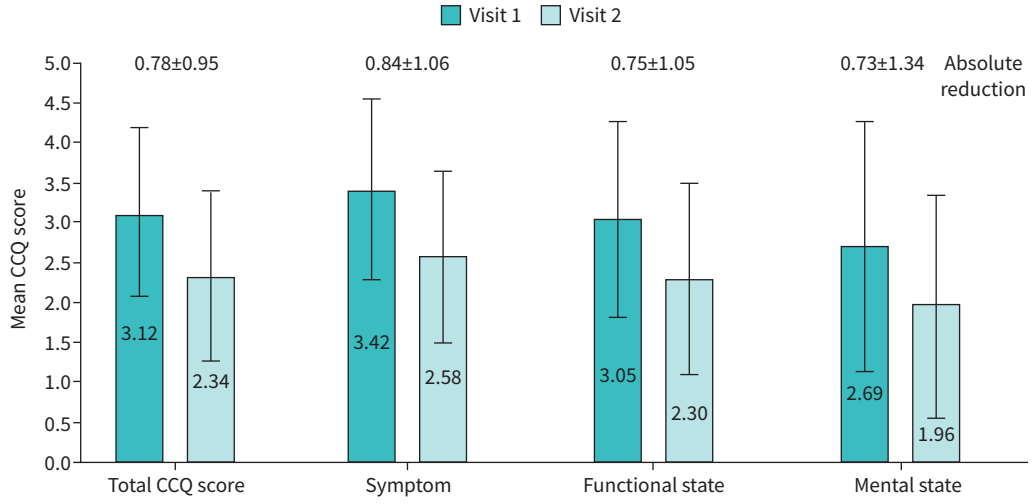

FIGURE 3 Absolute change in Clinical COPD Questionnaire (CCQ) score from visit 1 to visit 2. Data are presented as mean±SD.

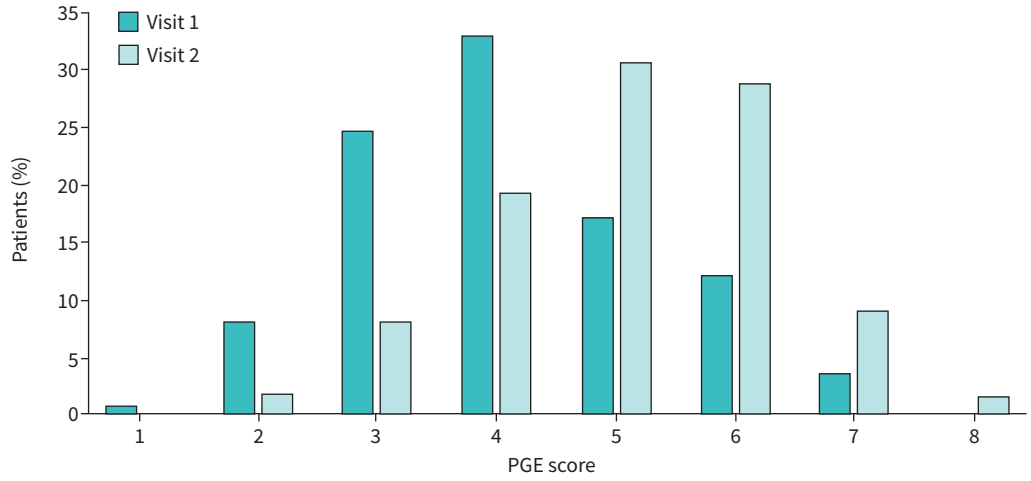

FIGURE 4 Patients' general condition (Physician's Global Evaluation (PGE) score) at visits 1 and 2. PGE score 1–2=poor, 3–4=satisfactory, 5–6=good, 7–8=excellent.

1254 patients attending visit 2, 1194 (95.2%) expressed willingness to continue tiotropium/olodaterol treatment. Among the remaining 60 (4.8%) patients, the most frequent reasons for therapy discontinuation were "patient's wish" (n=38, 3%) and "adverse events" (n=13, 1%) (table 2).

Requirement for additional medication

Changes of COPD therapy were observed in 27 (2.2%) patients between visits 1 and 2. For example, patients received additional short-acting β_2-agonists (n=8, 0.6%), ICS alone (n=4, 0.3%) and LABA, alone or in combination with a LAMA or ICS (n=8, 0.6%).

Safety

Overall, 17 (1.3%) patients experienced at least one investigator-defined drug-related adverse event, which led to treatment discontinuation in 13 (1.0%) patients. None of the drug-related adverse events were serious. In total, 23 drug-related adverse events were documented. The most frequent of these were vertigo and nausea (three events each; 13% of all drug-related adverse events each), followed by dry mouth, peripheral oedema, paraesthesia and hypertension (two events each; 8.7% of all drug-related adverse events each).

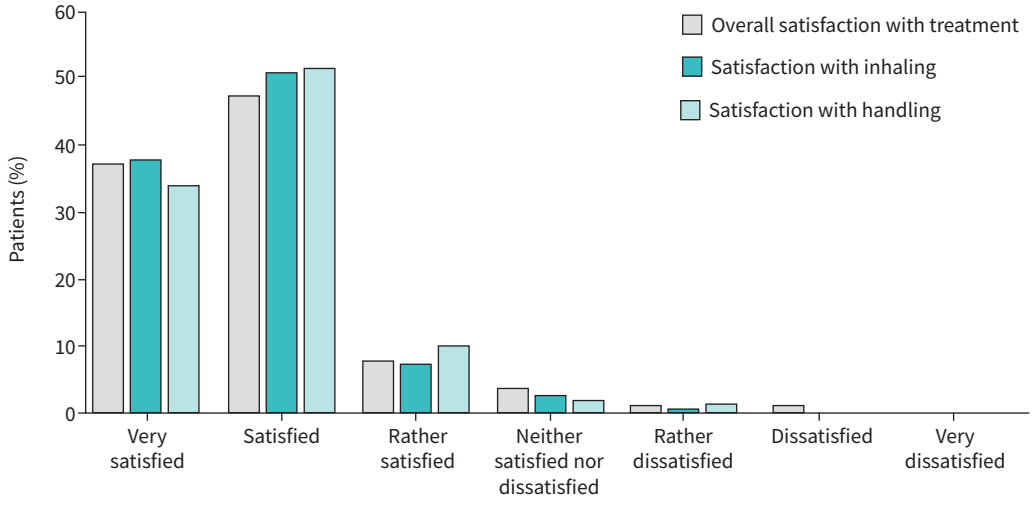

FIGURE 5 Patient satisfaction with tiotropium/olodaterol treatment overall, and in terms of inhaling from, and handling of the device at visit 2. Visit 2 was ~6 weeks after visit 1 (baseline).

TABLE 2 Patient willingness to continue treatment with tiotropium/olodaterol after visit 2

Patients with data at visit 2	1254 (100.00)
Patients willing to continue treatment	
Yes	1194 (95.22)
No	60 (4.78)
Reason for treatment discontinuation	
Adverse events	13 (1.04)
Patient's wish	38 (3.03)
Loss of contact	1 (0.08)
Other	8 (0.64)

Data are presented as n (%).

Only one serious adverse event (pulmonary embolism, one patient (0.1% of all patients from the treated set)) was documented during the study, which led to hospitalisation and ultimately death. As assessed by the treating physician, there was no causal relationship between the event and study treatment.

Discussion

AERIAL® was a non-interventional study assessing changes in the health and functional status of patients with COPD treated with tiotropium/olodaterol for ∼6 weeks in routine clinical practice. Therapeutic success was achieved by the majority of patients (66.3%), so the primary end-point of the study was met. The mean total and subdomain CCQ scores decreased during the study, with greatest improvements seen in the symptom subdomain. Mean reductions in both the total and subdomain CCQ scores exceeded the minimal clinically important difference of 0.4 points, thus demonstrating clinical relevance.

A larger proportion of patients who were maintenance-naïve prior to the study achieved therapeutic success compared with patients who were pre-treated. In addition, maintenance-naïve patients showed larger absolute changes in total and subdomain CCQ scores (except for the mental state subdomain) *versus* patients who were pre-treated. This may be attributable to a greater capacity to benefit from bronchodilator therapy in patients not previously receiving maintenance COPD therapy compared with those who had already been treated. Other studies indicate that initiation of dual bronchodilation from the start of maintenance treatment onwards may result in greater improvements in lung function [17, 18], health status [18], dyspnoea severity [18] and use of rescue medication [17], as well as a reduced risk of short-term clinical deterioration [17], when compared with a single bronchodilator. However, this is not in line with the GOLD 2021 strategy report, which recommends dual bronchodilation with LAMA/LABA as initial therapy only for GOLD D patients with more severe symptoms (COPD Assessment Test™ score ⩾20) and GOLD B patients with severe breathlessness [1]. In contrast, recent guidelines from the American Thoracic Society and the National Institute for Health and Care Excellence recommend the use of LAMA/LABA as first-line therapy in a wider range of patients [19, 20].

Of note, 84.1% of patients in this study were maintenance-naïve. This study included GOLD groups B, C and D patients, who, according to the GOLD 2021 strategy report, should be treated with a long-acting bronchodilator at a minimum [1]. This indicates a high rate of undertreatment and a lack of guideline adherence in real-world practice, which is consistent with other studies [21, 22]. More patients in GOLD groups C and D achieved therapeutic success than patients in GOLD group B, supporting the results of another observational study with tiotropium/olodaterol, which evaluated therapeutic success using PF-10 score [23].

PGE scores improved in all patients over the period assessed; improvements were larger in maintenance-naïve patients than in patients who were pre-treated, in line with the CCQ results. The improvements in PGE scores observed in our study provide further support for the benefits of treating symptomatic patients with LAMA/LABA therapy in accordance with the GOLD recommendations [1]. However, it is important to note that our study was not designed to analyse the superiority of tiotropium/olodaterol in maintenance-naïve *versus* pre-treated patients.

Improvements in PGE scores were also seen in three other non-interventional studies with tiotropium/olodaterol, supporting the finding that tiotropium/olodaterol therapy improves patients' general condition [12, 23, 24].

Most patients were very satisfied or satisfied with tiotropium/olodaterol treatment overall, as well as with inhaling from and handling the Respimat® device. Only ∼2% of patients expressed dissatisfaction. Patient satisfaction with inhalers and treatment is an important patient-reported outcome and can impact patient

treatment adherence [25]. >95% of patients reported willingness to continue tiotropium/olodaterol treatment beyond the study, although dropouts may have introduced bias here.

The results of this study are similar to those from two recently published open-label non-interventional studies evaluating COPD patients who received tiotropium/olodaterol for ∼6 weeks in Germany. Treatment with tiotropium/olodaterol led to therapeutic success (defined as a 10-point increase in PF-10 score) in ∼50% of patients, and to improvements in the patients' general condition; moreover, the majority of patients were very satisfied or satisfied with the Respimat® inhaler [12, 23]. In contrast to these studies, the current study used the CCQ to measure health and functional status. This is a strength of the AERIAL® study since the CCQ was developed and validated especially for COPD patients and is widely used to monitor COPD health status [26–28]. In addition, unlike the PF-10, the CCQ contains separate domains for symptoms and mental and functional state [15]. In terms of patient population, the AERIAL® study was similar to the studies by Steinmetz *et al*. [23] and Sauer *et al*. [12] with respect to the proportion of males (57% and 59%, respectively), current smokers (40% and 35%, respectively) and prevalence of cardiac disease (51% and 53%, respectively). However, distribution of GOLD ABCD groups varied, with a predominance of GOLD A patients in the study by Steinmetz *et al*. [23] (42%) compared with 0.1% of patients in the AERIAL® study and 0% in the study by Sauer *et al*. [12]; the AERIAL® study had the highest proportion of GOLD B patients. The proportion of treatment-naïve patients also varied between studies and was highest in the AERIAL® study (54% (with 84% maintenance-naïve) *versus* 31% and 46% in the Sauer *et al*. [12] and Steinmetz *et al*. [23] studies, respectively). The proportion of patients receiving LABA/ICS prior to study entry was lower in our study (3.7% *versus* 9–21%) compared with other observational studies evaluating tiotropium/olodaterol [12, 23, 29]. Similarly, the DACCORD study, a non-interventional study recruiting patients following COPD maintenance treatment change or initiation in Germany enrolled a greater proportion of patients on LABA/ICS at baseline (22%) [30]. The lower proportion of patients in our study may be due to compliance with GOLD 2017 recommendations, which advise prescribing LABA/ICS to only some patients with GOLD group D COPD [14]. Hence, this low number may reflect guideline-recommended patient management, which might be more apparent in our study due to differences in recruitment compared with the other studies.

The number of patients with drug-related adverse events in the AERIAL® study (1.3%) was lower than those observed in clinical trials [7, 10]. This may be because drug-related adverse events in clinical trials are more actively screened by investigators because all adverse events have to be documented; the investigators are therefore more aware of adverse events in general than in an observational study, in which "only" drug-related adverse events (and fatal adverse events) need to be recorded. The reported drug-related adverse events are mostly in line with the adverse reactions listed in the SmPC for tiotropium/olodaterol [13].

This study had some limitations. The duration (∼6 weeks) was short, preventing an assessment of long-term therapeutic effects. However, this duration corresponds to the usual treatment period before assessing the efficacy of a new COPD treatment. This was a non-interventional study and therefore did not include a comparator group; hence, data focusing on subjective parameters have to be considered cautiously. In addition, the non-interventional nature of the study prohibited monitoring of patient treatment adherence using a medication diary. In some subgroup analyses, there were imbalances in the number of patients in the subgroups. For example, there were considerably more maintenance-naïve than pre-treated patients (959 *versus* 181 patients) and more patients in GOLD group B *versus* GOLD groups C and D (735 *versus* 128 and 277, respectively). Therefore, the results of these subanalyses should be interpreted with caution. Another limitation was that the survey used to assess patient satisfaction at visit 2 was not a validated instrument.

This study has several strengths. Firstly, the study was performed under routine medical practice conditions, and therefore results can be transferred to a more heterogeneous patient population with COPD in real-world clinical settings. For example, 48% of patients in AERIAL® had cardiac disease at baseline, compared with a lower proportion in randomised clinical trials (RCTs) of tiotropium/olodaterol (*e.g.* 29% had a cardiovascular history in a pooled analysis of TONADO 1 and 2 and DYNAGITO [31]). There was a lower proportion of males in our study (57%) compared with the pooled analysis of tiotropium/olodaterol RCTs (71%) and a higher proportion of current smokers (46% *versus* 37%); however, the average ages of the populations were similar (65–66 years) [31]. Secondly, since a great number of sites throughout Germany enrolled patients, we consider the results to be representative of COPD patients in this country.

The AERIAL® non-interventional study provides further real-world evidence to support the use of tiotropium/olodaterol *via* Respimat® in patients with COPD. Treatment with tiotropium/olodaterol under

routine medical care conditions was effective and well tolerated, even in a patient population suffering from a variety of concomitant diseases, including almost half with cardiac disease.

Conclusion

Patients with COPD who were treated with tiotropium/olodaterol *via* Respimat® in routine clinical practice in Germany had clinically relevant improvements in health status and functional status compared with baseline. The majority of patients participating in the study were very satisfied or satisfied with the drug treatment and device.

Acknowledgements: Medical writing assistance was provided by Vicki Cronin (MediTech Media, Manchester, UK), which was funded by Boehringer Ingelheim Pharma GmbH & Co. KG.

Provenance: Submitted article, peer reviewed.

This study is registered at www.clinicaltrials.gov with identifier number NCT03165045.

Conflict of interest: A. Gillissen reports nonfinancial support from Boehringer Ingelheim during the conduct of the study. A. Marseille is an employee of Boehringer Ingelheim. D. Skowasch reports personal fees from Boehringer Ingelheim, AstraZeneca, Berlin-Chemie, GSK, Grifols and Novartis, outside the submitted work. J. Ritz is an employee of Boehringer Ingelheim. M. Mattiucci-Guehlke is an employee of Boehringer Ingelheim. S. Pabst has nothing to disclose. T. Greulich reports personal fees from AstraZeneca, Berlin-Chemie, Boehringer Ingelheim, GSK, Novartis, Roche and Chiesi, and grants and personal fees from CSL Behring and Grifols, outside the submitted work. R. Koczulla has nothing to disclose.

Support statement: This study was funded by Boehringer Ingelheim Pharma GmbH & Co. KG. Funding information for this article has been deposited with the Crossref Funder Registry.

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