

SOSPES: SPIRIVA[®] observational study measuring SGRQ score in routine medical practice in Central and Eastern Europe

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Purpose: The long-acting inhaled anticholinergic agent, tiotropium, is recommended as first-line maintenance therapy for moderate to very severe Chronic Obstructive Pulmonary Disease (COPD) to improve symptoms, exercise tolerance, health status, and to reduce exacerbations. Few studies have evaluated the therapeutic efficacy of tiotropium in patients in routine clinical conditions. The current study was designed to investigate the therapeutic efficacy of tiotropium delivered via the HandiHaler[®] device on the health status of patients with COPD with Global initiative for chronic Obstructive Lung Disease (GOLD) disease classification 2–4 in six central and eastern European countries in a real-life clinical setting.

Methods: The study was an open-label, prospective, uncontrolled, and single-arm surveillance study with three clinic visits during a 6-month observation period (baseline, and months 3 and 6). Health status was measured using the disease-specific St George's Respiratory Questionnaire (SGRQ). The primary efficacy endpoint was the mean change from baseline in SGRQ total score at the end of the 6-month observational period.

Results: Patients treated with tiotropium 18 µg once daily showed statistically significant and clinically meaningful reduction (improvement) of 21.7 units in the SGRQ total score, regardless of smoking status or cardiac comorbidities at enrollment ($P < 0.0001$). The analysis also showed that age, treatment compliance, and GOLD disease classification were significant factors that impact the health status of patients with COPD differently.

Conclusion: These results provide further support for the use of the tiotropium HandiHaler[®] as first-line maintenance treatment of patients with COPD with a clinician-assessed disease.

Keywords: tiotropium, HandiHaler[®], chronic obstructive pulmonary disease, health-related quality of life

Introduction

Chronic Obstructive Pulmonary Disease (COPD) is a respiratory disease characterized by persistent and progressive airflow limitation and is a major cause of morbidity and mortality.¹ In Europe, COPD mortality ranges between 200,000 and 300,000 each year, with an annual treatment burden estimated at €102 billion.^{2,3}

The clinical manifestations of COPD include dyspnea and impaired activity levels, which impact negatively on health-related quality of life (HRQoL).⁴ Improving HRQoL is, therefore, an important treatment goal in COPD, and health status measurements now form an established assessment of treatment efficacy, especially as health status is often poorly correlated with forced expiratory volume in 1 second (FEV₁). HRQoL can be measured using disease-specific questionnaires such as the St George's Respiratory Questionnaire (SGRQ), a validated and widely accepted instrument that

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aims to provide an overall measure of impairment, and one that has often been used in recent COPD randomized clinical trials.^{5,6} The SGRQ score ranges from 0–100, and a reduction of ≥ 4 units is considered to be a clinically relevant improvement in health status.⁷

The 2006 Global initiative for chronic Obstructive Lung Disease (GOLD) treatment guidelines recommend the use of long-acting inhaled anticholinergics as a first-choice maintenance therapy for patients with stage 2 COPD (FEV_1 /forced vital capacity [FVC] < 0.70 ; $50\% \leq FEV_1 < 80\%$ predicted), stage 3 (FEV_1 /FVC < 0.70 ; $30\% \leq FEV_1 < 50\%$ predicted), and stage 4 (FEV_1 /FVC < 0.70 ; $FEV_1 < 30\%$ predicted [or as defined in the 2011 GOLD guidelines, risk groups B, C, and D]), to improve symptoms, exercise tolerance, and health status, as well as to reduce exacerbations.^{8,9} Using data compiled from 6 months to 4 years of treatment, clinical trials of patients with COPD have demonstrated that the long-acting inhaled anticholinergic agent, tiotropium (Spiriva[®]; Boehringer Ingelheim Pharma and Co, KG, Ingelheim, Germany), significantly improves HRQoL compared with either placebo,^{7,9–11} or with the long-acting β_2 -agonist (LABA), salmeterol.¹² The effect of tiotropium on HRQoL has been confirmed in the 4-year Understanding Potential Long-term Impacts on Function with Tiotropium (UPLIFT[®]) study, which showed long-term, tiotropium-mediated improvements in HRQoL.¹⁰ In these studies, patients were often recruited from secondary care centers. However, the effect of tiotropium on HRQoL has not been investigated under routine clinical conditions in the community respiratory and primary care centers within Central and Eastern European countries (CEE). In this region, many COPD patients seen in routine clinical practice have severe or very severe disease,¹³ yet management of their COPD might not always be in accordance with international guideline recommendations because the community pneumologists and primary care physicians may have differing interpretations of guidelines or a limited understanding of COPD.¹⁴

Suboptimal treatment is likely to worsen the already significant impact of COPD on HRQoL, particularly if a patient's lung function is poor. It is challenging to assess HRQoL in COPD patients from CEE countries, as there is no established procedure for its objective evaluation in daily practice, and the use of the SGRQ is almost exclusively reserved for clinical trials.

The SPIRIVA[®] Observational Study measuring SGRQ in Routine Medical Practice in Central and Eastern European Region (SOSPES) was conducted to assess the therapeutic effect of tiotropium administered with the HandiHaler[®]

device on the HRQoL of patients with COPD. The study was conducted in six CEE countries within a real-life clinical setting. We also sought to evaluate the real-world applicability of the evidence of tiotropium's efficacy in COPD, derived largely through randomized COPD trials, to study patients and conditions not typically included or studied in these trials.

Methods

Study objective

The objective of the SOSPES observational study was to evaluate the therapeutic effect of tiotropium 18 μ g once daily given via the HandiHaler[®] device on the HRQoL of patients with COPD in CEE countries in a real-life clinical setting over 6 months. The study was performed in accordance with the Declaration of Helsinki and the International Conference on Harmonisation/Good Clinical Practice standards. It was approved by the relevant local ethics board and/or Institutional Review Board in accordance with the local regulations in each country. Written informed consent was obtained from subjects prior to initiation of the studies, if required by the national regulations.

Study design

SOSPES was an open-label, prospective, uncontrolled and single-arm, postmarketing, surveillance study conducted with the involvement of 897 study centers based in Croatia, Poland, Romania, Russian Federation, Slovakia, and Slovenia. The study consisted of three clinic visits during a 6-month observation period (baseline, month 3, and month 6). Only patients who had undergone regular medical assessments and previously discussed the introduction of the HandiHaler[®] as part of their treatment regimen during regular visits to their physicians were considered eligible to take part in the study. Inclusion criterion was adult outpatients aged ≥ 40 years with a clinical diagnosis of COPD (GOLD stage 2–4; FEV_1 /FVC < 0.7 and $FEV_1 < 80\%$ predicted, as defined in the 2006 GOLD guidelines), who were attending a participating physician's office for routine care. Patients were required to: have stable disease (no COPD exacerbation for ≥ 1 month before the study); have had no prior treatment with tiotropium within the previous 4 weeks; be suitable for this therapy as described in the product label; be fluent in the language of the questionnaire; and to have the cognitive and functional abilities required to complete it without help. There were no restrictions on concomitant, rescue, and additional medications required by study participants. However, all treatment decisions for regimen remained with the patient's physician.

Patients were excluded from participation if they were considered unlikely to be able to cooperate with the requirements of the study, had any condition that might decrease the chance of obtaining satisfactory data, were ineligible for treatment with tiotropium HandiHaler® according to the country-specific approval of this agent, and/or were currently enrolled in another clinical trial that required a change in medication for respiratory problems. Due to the noninterventive character of the study, violations in the planned schedule of the study were not considered as important protocol deviations and these patients were included into analyses as well as those patients with COPD GOLD stage 1 ($FEV_1/FVC < 0.7$ and $FEV_1 > 80\%$ predicted, as defined in the 2006 GOLD guidelines).¹

The primary efficacy endpoint was the mean change from baseline in SGRQ total score at the end of the 6-month observational period. Secondary endpoints included mean change in SGRQ total score by domains; the use of concomitant COPD therapy; and compliance with tiotropium HandiHaler® (<10 capsules' difference between the number of days, and the actual number of capsules taken during these days, assessed between study visits).

Statistical analysis

Data were analyzed descriptively with calculation of 95% confidence intervals (CIs). The statistical significance of SGRQ score changes was assessed using the nonparametric signed-rank test and Kruskal–Wallis test for post hoc analysis comparing GOLD stages. The analysis was undertaken using SAS® Version 9.2 (SAS Institute, Inc, Cary, NC, USA). In addition to the treated set (TS) (all patients with documented evidence of tiotropium treatment during the observation period), the full analysis set (FAS) (all patients with documented SGRQ scores at months 3 and 6), the per-protocol set (PPS) (all patients from the FAS without important protocol violations), and a subgroup of PPS with compliance between 80% and 120% (inclusive) were defined. The primary and secondary endpoints have been presented for the FAS population. No attempt was made to impute missing data. Values for which no clarification with the investigator was possible were excluded from analyses.

A series of post hoc analyses were undertaken to explore changes in SGRQ scores among clinically relevant subgroups of patients. In addition, adjusted changes in SGRQ scores were calculated using a mixed-effect model, the standard technique for analysis of longitudinal data,¹⁵ with patients nested within country as random effect and gender, age, stage of COPD, occurrence of cardiac comorbidities, compliance,

and smoking status as fixed effect (ie, covariates). Further, the proportion of patients with a minimal clinically important difference (MCID) of 4 units in SGRQ score was analyzed.¹⁶ Patients were classified as improved, worsened and unchanged if the difference from baseline in SGRQ score was <4 units, >4 units, and within range ± 4 units, respectively.

The association between improvement by 4 units of the SGRQ score and patients' characteristics was analyzed using generalized estimating equations for the logistic model (implemented in PROC GENMOD), which enabled calculation of robust estimates controlling within-country correlations.¹⁷ Relative improvement (improvement ratio, similar to a risk ratio) and its 95% CIs based on multivariate analysis are presented. The characteristics of patients (gender, age, weight, stage of COPD disease, compliance, occurrence of cardiac comorbidities and smoking status) were included in the model as covariates.

Adverse events (AEs) were evaluated in the TS and are presented descriptively. An AE was defined as any untoward medical occurrence in a patient administered the study drug regardless of whether or not it was considered to be related to the study drug. An AE was considered serious if it was either immediately life threatening or resulted in persistent or significant disability, prolonged hospitalization, or death.

Results

In all, 4854 COPD patients participated in SOSPEs and were evaluated from October 2009 to June 2011. Of these, 4852 were included in the TS, 4435 were included in the FAS, 4280 were included in the PPS, and 3891 were included in a subgroup of the PPS (Figure 1). The majority of the patients in the FAS were male (70.9%), current or exsmokers (85.8%), with a mean age of 62.6 (standard deviation: 9.8) years (Table 1). Almost all patients were classified by their physicians as being GOLD stage 2 or 3 (89%) with 50% of the population classified as having severe (stage 3) or very severe (stage 4) disease. At baseline, 67.4% of patients in the TS were receiving COPD medication, the most common of which were LABAs (24.5%), SABAs (22.9%), theophylline (20.1%), LABA/inhaled corticosteroid (ICS) combinations (20.0%), and ICS (15.4%). Most patients had at least one concomitant disease (75.1%), the most common of which either were cardiac (41.6%) or peripheral vascular and cerebrovascular (37.4%) in nature.

Change in SGRQ score

Patients in the FAS population treated with tiotropium 18 μ g once daily via the HandiHaler® device showed a statistically

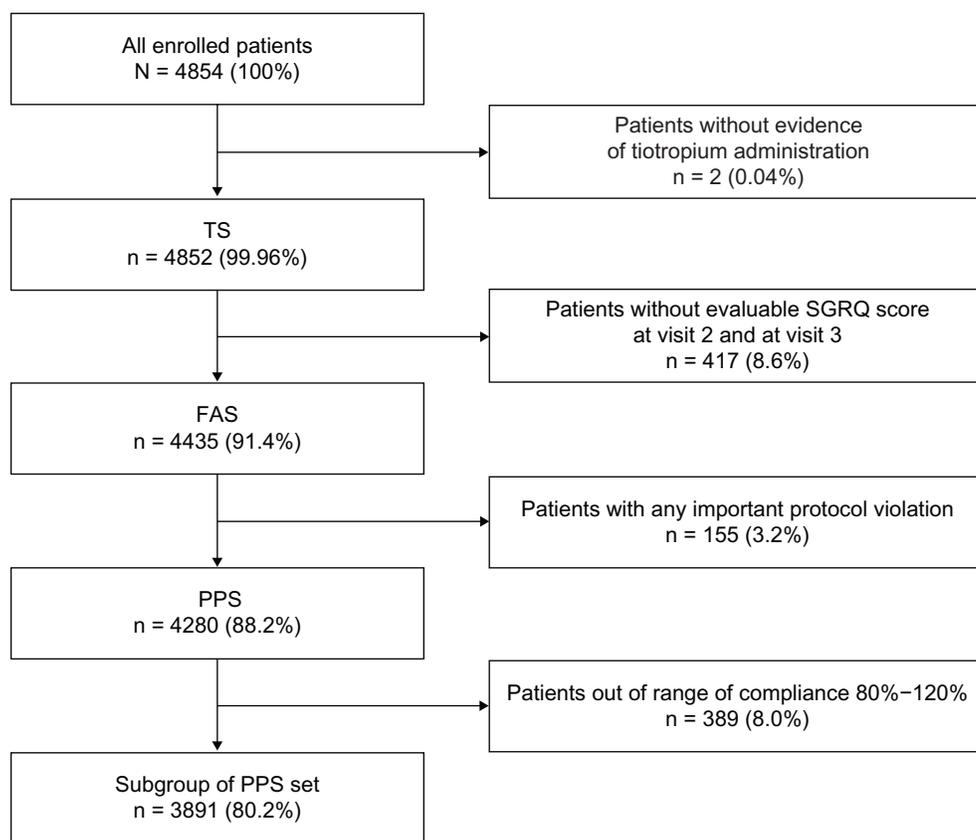


Figure 1 Disposition of study patients.

Abbreviations: FAS, full analysis set; N, total number; n, sample number; PPS, per-protocol set; SGRQ, St George’s Respiratory Questionnaire; TS, treated set.

Table 1 Patient baseline demography and disease characteristics (FAS population; N = 4435)

Variable	N	Baseline value
Mean age, years (SD) [†]	4364	62.6 (9.8)
Mean height, cm (SD)	4367	170.0 (8.3)
Mean weight, kg (SD)	4371	79.0 (15.6)
Mean BMI, kg/m ² (SD) [†]	4360	27.3 (4.9)
Males, % [†]	3145	70.9
Current smokers, % [†]	1935	43.6
Exsmokers, % [†]	1873	42.2
Never smoked, % [†]	594	13.4
GOLD 1 (FEV ₁ >80% predicted), % [‡]	32	0.7
GOLD 2 (50% ≤ FEV ₁ , <80% predicted), % [‡]	2140	48.3
GOLD 3 (30% ≤ FEV ₁ , <50% predicted), % [‡]	1818	41.0
GOLD 4 (FEV ₁ <30% predicted), % [‡]	386	8.7
Any concomitant medication, %	1146	25.8
Mean SGRQ total score (SD)	4435	56.3 (20.3)
Mean SGRQ activity domain score (SD)	4435	62.3 (21.2)
Mean SGRQ impact domain score (SD)	4435	49.5 (23.2)
Mean SGRQ symptom domain score (SD)	4435	66.8 (21.6)

Notes: [†]Data on age, height, weight, BMI, gender, smoking habits, and GOLD stage were not available for 1.6%, 1.5%, 1.4%, 1.7%, 0.6%, 0.7%, and 1.3% of patients, respectively; [‡]GOLD stage was determined by the physician.

Abbreviations: BMI, body mass index; FAS, full analysis set; FEV₁, forced expiratory volume in 1 second; GOLD, Global Initiative for Chronic Obstructive Lung Disease; N, number; SD, standard deviation; SGRQ, St George’s Respiratory Questionnaire.

significant and clinically relevant improvement from baseline in SGRQ total score, with a reduction of 21.7 units (95% CI: 22.3–21.2; *P* < 0.0001) after 6 months’ observation (Figure 2). A statistically significant and clinically relevant reduction in SGRQ total score of 14.6 units (95% CI: 15.1–14.2; *P* < 0.0001) was also observed after 3 months’ treatment. The greatest improvement in SGRQ score after 6 months was seen in the symptoms domain (reduction of 27.2 units; 95% CI: 27.9–26.5), followed by the impact domain score (reduction of 22.0 units; 95% CI: 22.6–21.3) and the activity domain score (reduction of 18.2 units; 95% CI: 18.8–17.6) (all *P* < 0.0001 versus baseline) (Figure 2).

Mean change in SGRQ total score by country

Statistically significant reductions from baseline to month 6 in the mean total SGRQ score was observed for the FAS population in each of the six participating countries (*P* < 0.0001 for each country). The mean reduction in SGRQ total score among the six CEE countries ranged from 13.7–32.7 units, with the smallest change observed in patients from Slovenia and the largest change observed in patients from Romania (Figure 3A).

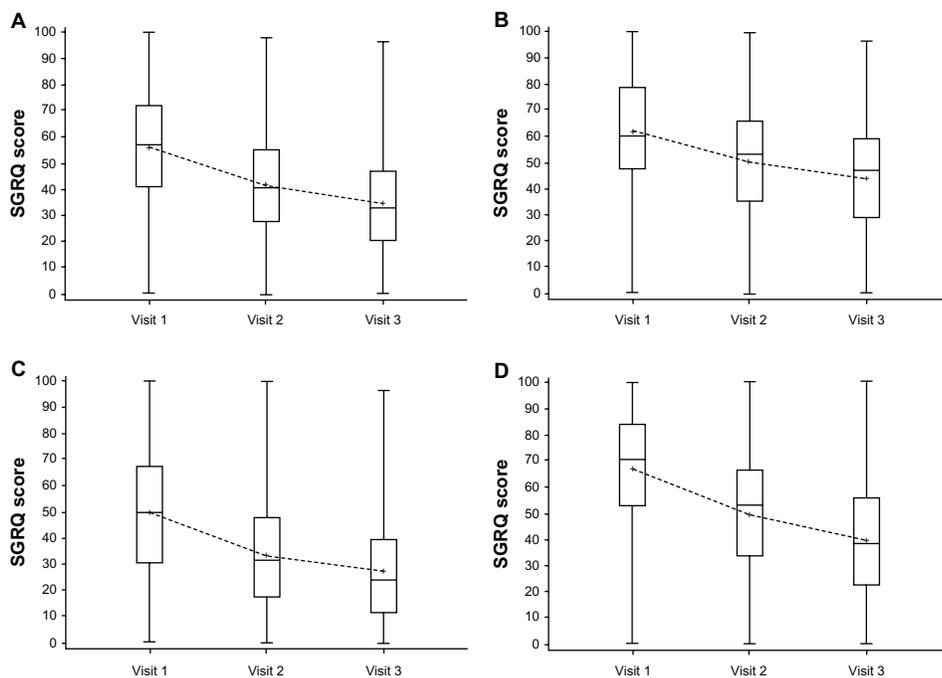


Figure 2 Summary change from baseline in SGRQ total scores, activity domain, impact domain, and symptom domain (FAS population).
Notes: Summary change from baseline in (A) SGRQ total scores, (B) activity domain, (C) impact domain, and (D) symptom domain (FAS population).
Abbreviations: FAS, full analysis set; SGRQ, St George’s Respiratory Questionnaire.

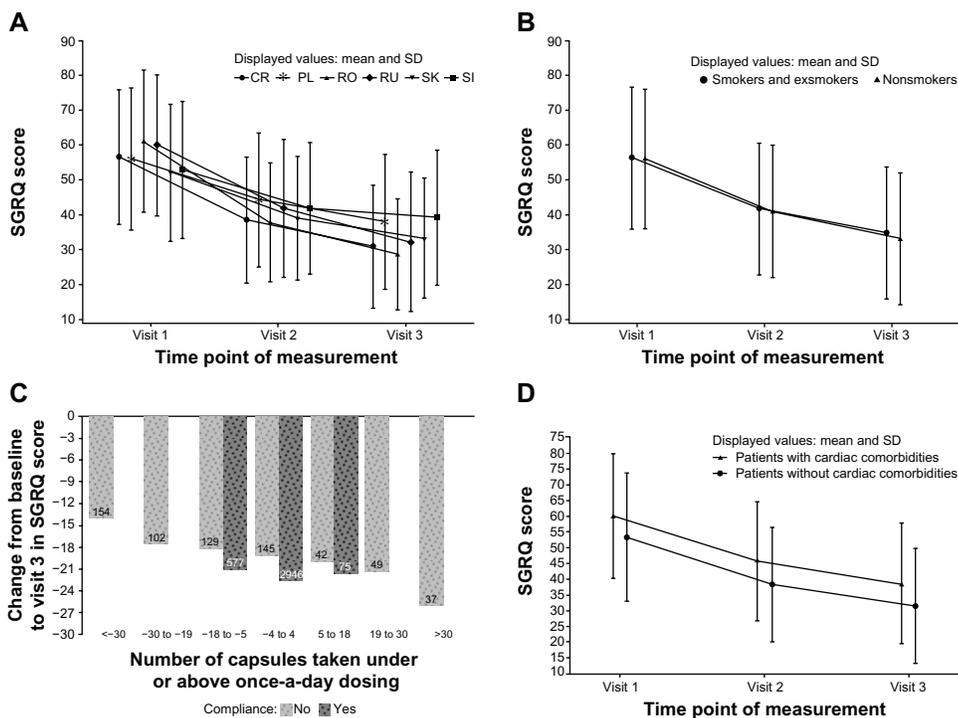


Figure 3 Summary change from baseline in SGRQ total scores among COPD patients.
Notes: Summary change from baseline in SGRQ total scores in (A) participating countries, (B) current or exsmokers and nonsmokers, (C) compliant or noncompliant, and (D) with and without cardiac comorbidities. Bars show mean values of SGRQ scores. Number of patients is shown on bottom of bars. The negative number of capsules means that the patient had taken less capsules and vice versa. The patient is considered as noncompliant if the difference between the number of days and actual number of capsules taken between visit 1 and visit 2 or visit 2 and visit 3 is ≥ 10 capsules.
Abbreviations: COPD, chronic obstructive pulmonary disease; CR, Croatia; PL, Poland; RO, Romania; RU, Russian Federation; SD, standard deviation; SGRQ, St George’s Respiratory Questionnaire; SI, Slovenia; SK, Slovakia.

Mean change in SGRQ total score by smoking status

Statistically significant reductions from baseline to month 6 were noted, regardless of smoking status. Among current or exsmokers, the mean reduction in the SGRQ total score was 21.6 units (95% CI: 22.2–21.0; $P < 0.0001$); among never-smokers, the mean reduction was 23.1 units (95% CI: 24.7–21.5; $P < 0.0001$) (Figure 3B). The difference in mean reduction in SGRQ total score between current or exsmokers and nonsmokers was not significant ($P = 0.2$).

Mean change in SGRQ total score by age

There were statistically significant reductions in SGRQ total score from baseline to month 6, regardless of age (either ≤ 65 or > 65 years). Among patients who were aged ≤ 65 years, the mean reduction was 22.3 units (95% CI: 23.1–21.6; $P < 0.0001$); among patients aged > 65 years, the mean reduction was 20.6 units (95% CI: 21.5–19.7; $P < 0.0001$) (Figure 3C). The difference in mean reduction in SGRQ total score between patients aged ≤ 65 years or > 65 years was statistically significant ($P = 0.002$).

Mean change in SGRQ total score by the presence of cardiac comorbidities

Statistically significant reductions in SGRQ total score from baseline to month 6 were noted, regardless of the presence of cardiac comorbidities. There was a mean reduction of 21.7 units (95% CI: 22.6–20.8; $P < 0.0001$) and 21.7 units (95% CI: 22.5–21.0; $P < 0.0001$) (Figure 3D) for patients with and without recorded comorbid cardiac conditions, respectively, so there was no difference between these two groups of patients ($P = 0.9693$).

Mean change in SGRQ total score by documented compliance

The mean reduction from baseline to month 6 in the mean SGRQ total score was greater among patients classed as compliant during the observation period (22.4 units; 95% CI: 23.0–21.8; $P < 0.0001$) than among those patients receiving more than or less than once-daily dosing, classed as noncompliant (18.3 units; 95% CI: 19.7–17.0; $P < 0.0001$) (Figure 3C). For those patients classed as noncompliant because of receiving more than or less than once-daily dosing, the mean reduction in SGRQ total score was 20.3 units (95% CI: 17.7–22.9; $P < 0.0001$) and 17.5 units (95% CI: 16.0–19.1; $P < 0.0001$), respectively.

There is a greater mean reduction in the SGRQ total score between patients who were compliant with the prescribed treatment regimen and those who were classed

as noncompliant. However, this difference was statistically significant ($P < 0.0001$) for all noncompliant patients and for noncompliant patients on less than once-daily dosing, but not statistically significant for those on more than once-daily dosing ($P = 0.08$).

Mean change in SGRQ total score by GOLD stage 1–4

The mean reduction from baseline to month 6 in the mean SGRQ total score was independent of GOLD disease classification. Patients having GOLD stage 1, 2, 3, or 4 disease classification (as defined by the 2006 GOLD guidelines) had mean reductions in SGRQ total score of 17.4 units (95% CI: 21.8–13.1), 20.3 units (95% CI: 21.1–19.5), 23.2 units (95% CI: 24.1–22.3), and 22.8 units (95% CI: 25.0–20.6), respectively. The mean reduction in SGRQ total score from baseline to visit 3 was statistically significant ($P < 0.0001$) for patients with GOLD stage 1, 2, 3, or 4 disease. Between GOLD stages, significant differences in the mean reduction in SGRQ total score from baseline to visit 3 were observed between GOLD stage 2 and stage 3 ($P < 0.0001$) only.

Minimum clinically important difference (MCID) in SGRQ scores overall and by patient characteristics

The majority of patients enrolled in SOSPEs showed improvement in their SGRQ score within 3 months. This improvement persisted for the study duration. After 6 months, 83.5% of patients showed an improvement in their SGRQ score, whereas 12.5% and 4% of patients showed either no change or worsening in their SGRQ score, respectively.

Older patients with COPD enrolled in SOSPEs were significantly less likely to achieve a clinically important change. An increment of 5 years of age decreased the probability of the improvement by 1% (Table 2). Furthermore, patient compliance increased the probability of improvement by 9%. Other factors examined such as weight, body mass index, disease severity, presence of cardiac comorbidities, and smoking status did not have a significant effect on the likelihood of the patient showing a relative improvement in their SGRQ score (Table 2).

Requirement for additional COPD medications

Of the 4435 patients in the FAS population, 3289 (74.2%) did not require COPD medication in addition to that prescribed at the baseline visit. Among those patients who did require additional medication, 293 were treated with combination LABA/ICS and 363 required treatment with SABAs.

Table 2 Summary of patients SGRQ status and the association between characteristic of patients and relative improvement in SGRQ score within 6 months – FAS

Variable	Patient status, N (%)			P
	Improvement*	No change	Worsening*	
Change from baseline to visit 3, N = 4335	3621 (83.5)	541 (12.5)	173 (4.0)	
Change from baseline to visit 2, N = 4367	3257 (74.6)	907 (20.8)	203 (4.6)	
Change from visit 2 to visit 3, N = 4267	2473 (58.0)	1468 (43.4)	326 (7.6)	
	Improvement N = 3621	Worsening or no change, N = 714	RI (95% CI)	P
Males, %	71.8	69.7	1.02 (0.99, 1.06)	0.18
Mean age, years, SD	62.6 (9.8)	63.5 (9.8)	0.99 (0.987, 0.996)	<0.001
Patient aged >65 years	38.0	40.8	0.98 (0.97, 1.00)	0.06
Mean weight, kg, SD	79.0 (15.5)	79.4 (16.0)	0.99 (0.99, 1.00)	0.62
Mean BMI, kg/m ² , SD	27.3 (4.9)	27.5 (5.1)	1.00 (1.00, 1.00)	0.60
GOLD Stages 3 and 4, %	51.0	47.0	1.03 (0.99, 1.07)	0.16
Compliance, %	84.3	76.5	1.09 (1.04, 1.14)	<0.001
Patient with cardiac comorbidities	41.7	42.6	1.00 (0.99, 1.01)	0.70
Smokers and exsmokers, %	86.4	87.3	0.98 (0.89, 1.08)	0.70

Notes: *Patients with increasing/decreasing of SGRQ score by 4 points or more were considered as improved/worsened. RI and its 95% CI based on multivariate analysis (ie, each other adjusted) controlling within-country correlations are presented.

Abbreviations: BMI, body mass index; CI, confidence interval; FAS, full analysis set; GOLD, Global Initiative for Chronic Obstructive Lung Disease; N, number; RI, relative improvement; SD, standard deviation; SGRQ, St George's Respiratory Questionnaire.

Adherence to treatment regimen during the observation period

In the FAS patient population, 3636 (82.0%) were compliant with the treatment regimen (treatment compliance of $\geq 80\%$ and $\leq 120\%$). Overall, noncompliance among the FAS patient population was 18%. There were 537 patients (12%) who were noncompliant due to undertreatment (noncompliant patients receiving less than once-daily dosing) and 262 patients (6%) were noncompliant due to overtreatment (noncompliant patients receiving more than once-daily dosing). The median number of inhaled capsules used during the 6 months of the SOSPEs study was 180 (interquartile range, 178–182).

Exposure to study treatment, safety, and tolerability

The mean exposure to tiotropium was 25.7 weeks and the majority of patients (4208 [86.7%]) were exposed between ≥ 25 and 30 weeks. In all, 306 AEs were reported by 182 patients from the TS population during the 6-month study (Table 3). Of the reported AEs, 90 were determined by the investigator to be related to the study drug. The most common AE considered by physicians to be related to the study drug was dry mouth (51 cases). In all, 14 patients (0.3%) reported a total of 23 AEs and discontinued treatment (Table 3). The most common AEs leading to treatment discontinuation were dry mouth (four patients reporting four cases), cough (two patients reporting two cases), and urinary retention (two patients reporting two cases).

In all, 15 patients (0.3%) reported 26 serious AEs (SAEs) (Table 3). Four patients reported 10 SAEs and discontinued treatment. However, all of the SAEs were determined to be unrelated to the study drug by the investigators and sponsor. During the 6-month observation period, there were seven SAEs with fatal outcomes reported. None of these deaths were considered to be related to the study drug.

Discussion

The SOSPEs study recruited a population of patients who were treated with tiotropium as per the usual, day-to-day

Table 3 Summary of reported AEs (TS population; N = 4852)

	Number of AEs	Number (%) of patients
Any AE	306	182 (3.8)
Respiratory, thoracic, and mediastinal disorders	136	83 (1.71)
Gastrointestinal	67	56 (1.15)
Nervous system	38	26 (0.54)
Severe AEs	38	23 (0.5)
Study drug-related AEs	90	68 (1.4)
AEs leading to treatment discontinuation	23	14 (0.3)
Other significant AEs ^a	15	12 (0.2)
Any SAE	26	15 (0.3)
Hospitalizations	16	9 (0.2)
Fatal AEs	10	7 (0.1)

Note: ^aAEs classified as "other significant" includes those nonserious and nonsignificant AEs with "action taken = discontinuation" or "action taken = reduced."

Abbreviations: AE, adverse event; N, number; SAE, serious adverse event; TS, treated set.

practice in CEE. In the SOSPEs countries, the recruited patient population was treated routinely in day-to-day clinical practice: there were no strict enrollment criteria imposed. This differs from controlled clinical trials where disease severity and comorbidities within the study population are strictly determined.¹⁸ Observational studies such as SOSPEs tend to have broader inclusion criteria, fewer exclusion criteria, and are able to capture patients across the full spectrum of COPD disease severity. These patients are therefore more representative of day-to-day practice. Since tiotropium is recommended as the first-line maintenance treatment of choice in COPD patients with disease classification GOLD stages 2–4, or risk groups B, C, and D (as defined in the 2011 GOLD guidelines),⁸ the inclusion of COPD patients of different GOLD stages/groups and the prescription of tiotropium was acceptable to physicians involved in SOSPEs.

The hypothesis that our study included patients with suboptimal management of the disease at enrollment is supported by baseline observations; these showed that the patient population in SOSPEs had a worse mean SGRQ total score at baseline (56.3) compared with COPD patients in the clinical trials that assessed this endpoint, such as the UPLIFT® (score of 45.7)⁹ and the Tiotropium: Influence sur la Perception de l'amélioration des activités Habituelles Objectivée par une échelle Numérique (TIPHON) trial (score of 45.8).⁷

We have shown that, in a population of patients with COPD treated in day-to-day clinical practice within six countries of the CEE region, tiotropium HandiHaler® maintenance therapy was associated with a statistically significant and clinically relevant improvement in HRQoL over a 6-month period, with statistically significant improvements observed across all three domains of the SGRQ (symptoms, impact, and activity). The magnitude of improvement was greatest in the symptoms domain (27.2 units) and smallest in the activity domain (18.2 units). However, two studies by Casaburi et al¹⁹ and Kesten et al²⁰ have suggested that tiotropium, together with encouraging patients to get involved in a regular rehabilitation or activity plan, may increase the impact on the activity domain by enhancing exercise endurance. Patients who enrolled in the SOSPEs study achieved a statistically significant reduction of 21.7 units (95% CI: 22.3–21.2; $P < 0.0001$) in SGRQ total score after 6 months of maintenance treatment with tiotropium. Statistically significant improvements in the SGRQ total score were noted at the month 3 assessment, with patients continuing to experience improvements through to the month 6 assessment.

Post hoc analyses of the change in SGRQ total score among clinically relevant subgroups of patients showed that

patients experienced improvements in HRQoL, regardless of smoking status (current and exsmoker, and those who have never smoked) and presence of comorbidities. Age (≤ 65 years and > 65 years) and disease severity (GOLD stages 1–4, as defined in the 2006 GOLD guidelines) were significant factors in the magnitude of the improvement in SGRQ total score. Patients aged ≤ 65 years achieved better improvement in health status compared to those patients aged > 65 years. This is most likely because patients who are aged ≤ 65 years are more physically active and more likely to present with fewer comorbidities. Furthermore, patients who complied with their treatment regimen showed statistically significant improvement in health status as well as a significantly higher probability to achieve clinically important improvement in comparison with patients who did not use, or used less than, the recommended treatment. The change in SGRQ score over time was not reduced by controlling gender, age, stage of COPD, occurrence of cardiac comorbidities, compliance, smoking status, and within-country correlation effect; this provides evidence that the robust treatment effect observed with tiotropium was independent of patient characteristics.

Marked differences in the mean SGRQ improvement were noted between the patient populations from the six participating countries. This suggests that country-specific differences in the approach to treating COPD might impact clinical outcomes resulting from treatment with tiotropium. What these country-specific differences might be requires further investigation. Regardless, the mean SGRQ total score improved significantly from baseline in the patient populations for each country. This latter observation suggests that considerable undertreatment of COPD patients at entry in this observational study was common to all six participating countries. It is unknown whether this undertreatment is the result of underdosing, lack of compliance with treatment, differences in the interpretation of international clinical guidelines, or use of inappropriate medication. Regardless, our results show that many of the patients recruited in SOSPEs would have benefited from earlier intervention with tiotropium. One-third of COPD patients included in the SOSPEs analysis commenced tiotropium treatment at the initiation of the study; this also raises the possibility that the effect of being regularly monitored within this observational trial, in addition to the effect of the study drug, might have contributed to improved measures of HRQoL in these patients.

The improvement in the mean SGRQ total score reported here was greater than that reported in the Towards

a Revolution in COPD Health (TORCH) study,²¹ in which a change in SGRQ total score of -2.2 was recorded for patients from Eastern Europe treated with a salmeterol/fluticasone propionate combination. The magnitude of our result was also unexpected; most clinical trials with active treatment struggled to achieve the minimum clinically important difference in SGRQ score of four units compared to placebo.^{7,10} In the TIPHON study,⁷ for example, a clinically important improvement in SGRQ score of up to 8.5 units versus baseline was achieved, but that was still significantly less than that achieved in SOSPEs. Considering the absolute scores achieved in this study, compared to the 6-month data from the UPLIFT® study⁹ and the 9-month data from the TIPHON study,⁷ the mean SGRQ scores of 39.4 and 37.3, respectively, were comparable to the SGRQ score of 34.6 achieved in this study at month 6. Not only is this SGRQ score comparable to the data from other clinical trials, it was consistent across all six participating countries.

Compliance with the once-daily tiotropium HandiHaler® was high and suggests that when patients with COPD saw major improvements in their disease condition with good tolerability, they were highly motivated to continue with their tiotropium HandiHaler®. Similarly, it may be that patient preference for a particular device might be a motivating factor in compliance.

Reported AEs and their frequency were in accordance with the known safety profile of the tiotropium HandiHaler®, although the overall number of reported deaths or AEs was lower than that seen in randomized clinical trials;^{7,10} this is consistent with the real-life setting and with the reporting of these incidents by primary care physicians in everyday practice.¹⁸ The most frequently reported AE (dry mouth) is a known class effect and other frequently reported AEs (such as dyspnea and cough) are common within COPD patient groups.

When reviewing the results presented here, it is important to consider the limitations inherent in the design of an observational study such as the present one. As the study did not utilize a randomized, double-blind, placebo-controlled design, potential bias could have been introduced as a result of country-specific climate conditions during the 6-month follow-up period. However, since the period from first patient in to last patient out was around 1 year for all the SOSPEs countries, any potential seasonal impact would be minimal. Additionally, no attempt was made to impute missing data.

Real-life studies such as SOSPEs provide valuable information about patient populations encountered in clinical

practice and their response to interventions outside the clinical trial setting. The high percentage of never-smokers (14%) in the study population is also worthy of note because it raises the possibility that a proportion of patients may not have been appropriately diagnosed with COPD and instead may have been more appropriately diagnosed with bronchiolitis or asthma with remodeling. Among the patient population who were smokers or exsmokers with ≥ 10 pack/years, the SOSPEs study population is similar to the patient population in randomized clinical trials. The burden of nonsmoking COPD is also much higher than previously thought.²²

In addition, disease severity (GOLD stage) was not formally defined in terms of lung function and relied on physician assessment only. However, a recent report of a cross-sectional study among primary care physicians managing patients in five European countries showed that they were successfully able to grade COPD severity clinically and that their rating of disease severity was closely related to the patients' HRQoL.²³ This observation is mirrored in the updated GOLD 2011 recommendations, which emphasize assessment of COPD based on the patient's level of symptoms, future risk of exacerbations, the severity of the spirometry abnormality, and identification of comorbidities instead of spirometry alone.⁸

Conclusion

Despite the limitations discussed previously, the results of this observational, real-world trial show that patients with COPD experience considerable and clinically relevant improvements in HRQoL, improving the SGRQ total score and all three domains, during extended treatment with tiotropium delivered via the HandiHaler® device. The results reported here provide further support for the use of the tiotropium for first-line maintenance treatment of patients with COPD with a clinician-assessed disease severity ranging from Groups B, C, and D (as defined in the 2011 GOLD guidelines). The reported AEs and their frequency were in accordance to the known safety profile of tiotropium HandiHaler®.

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Gloria Enache and Pavla Kadlecová have no conflicts of interest to declare.

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References

- Global Initiative for Chronic Obstructive Lung Disease. 2013 Global Strategy for the Diagnosis, Management, and Prevention of Chronic Obstructive Pulmonary Disease. 2013. Available at <http://www.goldcopd.org/guidelines-global-strategy-for-diagnosis-management.html>. Accessed June 21, 2013.
- European Lung Foundation. [homepage on the Internet]. Available at <http://www.european-lung-foundation.org/63-european-lung-foundation-elf-burden-in-europe.htm>. Accessed June 21, 2013.
- Organisation for Economic Cooperation and Development (OECD). Health at a Glance, Europe 2012. Available at <http://www.oecd.org/els/health-systems/HealthAtAGlanceEurope2012.pdf>. Accessed June 21, 2013.
- Shavro SA, Ezhilarasu P, Augustine J, Bechtel JJ, Christopher DJ. Correlation of health-related quality of life with other disease severity indices in Indian chronic obstructive pulmonary disease patients. *Int J Chron Obstruct Pulmon Dis*. 2012;7:291–296.
- Jones PW. Quality of life measurement for patients with diseases of the airways. *Thorax*. 1991;46(9):676–682.
- Jones PW. Health status measurement in chronic obstructive pulmonary disease. *Thorax*. 2001;56(11):880–887.
- Tonnel AB, Perez T, Grosbois JM, Verkindre C, Bravo ML, Brun M; for TIPHON study group. Effect of tiotropium on health-related quality of life as a primary efficacy endpoint in COPD. *Int J Chron Obstruct Pulmon Dis*. 2008;3(2):301–310.
- Global Initiative for Chronic Obstructive Lung Disease. 2011. Global strategy for the diagnosis, management, and prevention of chronic obstructive pulmonary disease. 2011. Available at http://www.goldcopd.org/uploads/users/files/GOLD2011_Summary.pdf. Accessed June 21, 2013.
- Decramer M, Celli B, Kesten S, Lystig T, Mehra S, Tashkin DP; for UPLIFT investigators. Effect of tiotropium on outcomes in patients with moderate chronic obstructive pulmonary disease (UPLIFT): a prespecified subgroup analysis of a randomised controlled trial. *Lancet*. 2009;374(9696):1171–1178.
- Tashkin DP, Celli B, Senn S, Kesten S, Menjoge S, Decramer M; for UPLIFT Study Investigators. A 4-year trial of tiotropium in chronic obstructive pulmonary disease. *N Engl J Med*. 2008;359(15):1543–1554.
- Troosters T, Celli B, Lystig T, et al; for Uplift Investigators. Tiotropium as a first maintenance drug in COPD: secondary analysis of the UPLIFT trial. *Eur Respir J*. 2010;36(1):65–73.
- Brusasco V, Hodder R, Miravittles M, Korducki L, Towse L, Kesten S. Health outcomes following treatment for six months with once daily tiotropium compared with twice daily salmeterol in patients with COPD. *Thorax*. 2003;58(5):399–404.
- Stepanian IE, Khmel'kova NG, Belin-Atarac B. The efficacy of tiotropium bromide (spiriva) in the treatment of patients with chronic obstructive pulmonary disease of varying severity: results of the Russian trial. *Ter Arkh*. 2010;82(10):46–51. Russian.
- Aisanov Z, Bai C, Bauerle O, et al. Primary care physician perceptions on the diagnosis and management of chronic obstructive pulmonary disease in diverse regions of the world. *Int J Chron Obstruct Pulmon Dis*. 2012;7:271–282.
- Verbeke G, Molenberghs G. *Linear Mixed Models for Longitudinal Data*. New York, NY: Springer; 2009.
- Jones PW. St George's Respiratory Questionnaire: MCID. *COPD*. 2005;2(1):75–79.
- Carter RE, Zhang X, Woolson RF, Apfel CC. Statistical analysis of correlated relative risks. *J Data Sci*. 2009;7:397–407.
- Freeman D, Lee A, Price D. Efficacy and safety of tiotropium in COPD patients in primary care – the SPiRiva Usual CarE (SPRUCE) study. *Respir Res*. 2007;8:45.
- Casaburi R, Kukafka D, Cooper CB, Witek TJ Jr, Kesten S. Improvement in exercise tolerance with the combination of tiotropium and pulmonary rehabilitation in patients with COPD. *Chest*. 2005;127(3):809–817.
- Kesten S, Casaburi R, Kukafka D, Cooper CB. Improvement in self-reported exercise participation with the combination of tiotropium and rehabilitative exercise training in COPD patients. *Int J Chron Obstruct Pulmon Dis*. 2008;3(1):127–136.
- Jones PW, Anderson JA, Calverley PM, et al; for TORCH investigators. Health status in the TORCH study of COPD: treatment efficacy and other determinants of change. *Respir Res*. 2011;12:71.
- Salvi SS, Barnes PJ. Chronic obstructive pulmonary disease in non-smokers. *Lancet*. 2009;374(9691):733–743.
- Jones PW, Brusselle G, Negro RW, et al. Patient-centred assessment of COPD in primary care: experience from a cross-sectional study of health-related quality of life in Europe. *Prim Care Respir J*. 2012;21(3):329–336.

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