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Consistent improvement in health-related quality of life with tiotropium in patients with chronic obstructive pulmonary disease: Novel and conventional responder analyses

Donald P. Tashkin [a, *], Eric D. Bateman [b], Paul Jones [c], Valentina B. Zubek [d], Norbert Metzdorf [e], Dacheng Liu [d], Thomas Leonard [d], Emmanuelle Clerisme-Beaty [d], Robert A. Wise [f]

[a] David Geffen School of Medicine at UCLA, 10833 Le Conte Avenue, Los Angeles, CA 90095, USA
[b] Division of Pulmonology, Department of Medicine, University of Cape Town, George Street, Mowbray 7700, Cape Town, South Africa
[c] St George's, University of London, Cranmer Terrace, London SW17 0RE, UK
[d] Boehringer Ingelheim Pharmaceuticals Inc., 900 Ridgebury Road, Ridgefield, CT 06877, USA
[e] Boehringer Ingelheim Pharma GmbH & Co. KG, Ingelheim, Binger Strasse 173, 55216 Ingelheim am Rhein, Germany
[f] Johns Hopkins University School of Medicine, 5501 Hopkins Bayview Circle, Baltimore, MD 21224, USA

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ABSTRACT

Introduction: Improving health-related quality of life (HRQoL) in COPD patients is an important pharmacotherapeutic objective. This study investigated the extent, consistency, and durability of tiotropium maintenance therapy impact on HRQoL in moderate-to-very severe COPD.

Methods: Patients received once-daily tiotropium 18 μg (n = 5244) or placebo (n = 4799) via HandiHaler® (10 trials), or once-daily tiotropium 5 μg (n = 2622) or placebo (n = 2618) via Respimat® inhaler (3 trials). St George's Respiratory Questionnaire (SGRQ) total scores were measured at baseline, and 6 months (13 trials) and 1 year (9 trials) from treatment start. Adjusted mean differences between treatments for change from baseline in total scores were calculated at each time-point for each trial. Responder and deteriorator rates (decrease or increase in score ≥4 units from baseline, respectively), net benefit (responder rate increase plus deteriorator rate decrease), and cumulative improvement and deterioration were determined.

Results: Adjusted mean total score differences between treatments for change from baseline were significant ($p < 0.05$) in favor of tiotropium in 10/13 trials at 6 months and in 8/9 trials at 1 year. In all trials, estimated differences in responder rates between treatments favored tiotropium (significant [$p < 0.05$]: 5/13 trials at 6 months; 8/9 trials at 1 year). Net benefit favored tiotropium and cumulative improvement rates were consistently greater and deterioration rates consistently lower for tiotropium versus placebo.

Conclusions: Tiotropium maintenance therapy significantly and consistently improved HRQoL in moderate-to-very severe COPD patients in a durable manner. These results may provide a benchmark for assessing benefits on HRQoL of other COPD treatments.

Abbreviations: COPD, chronic obstructive pulmonary disease; EXACTT, Exercise Endurance and COPD Patients Treated with Tiotropium; FEV_1, forced expiratory volume in 1 s; FVC, forced vital capacity; HRQoL, health-related quality of life; ICS, inhaled corticosteroids; LABA, long-acting β-agonist; LAMA, long-acting muscarinic antagonist; MCID, minimal clinically important difference; MMRM, mixed model repeated measures; SAFE, Spiriva Assessment of FEV_1; SGRQ, St George's Respiratory Questionnaire; TIPHON, Tiotropium: Influence sur la Perception de làmélioration des activités Habituelles Objectivée par une échelle Numérique; UPLIFT, Understanding Potential Long-term Impacts on Function with Tiotropium.

* Corresponding author. David Geffen School of Medicine at UCLA, 10833 Le Conte Avenue, Los Angeles, CA 90095, USA. Tel. : +1 310 825 3163, +1 310 825 3163; fax: +1 310 206 5088.

E-mail addresses: dtashkin@mednet.ucla.edu (D.P. Tashkin), eric.bateman@uct.ac.za (E.D. Bateman), pjones@sgul.ac.uk (P. Jones), valentina.zubek@boehringer-ingelheim.com (V.B. Zubek), norbert.metzdorf@boehringer-ingelheim.com (N. Metzdorf), dacheng.liu@boehringer-ingelheim.com (D. Liu), thomas.leonard@boehringer-ingelheim.com (T. Leonard), emmanuelle.clerisme-beaty@boehringer-ingelheim.com (E. Clerisme-Beaty), rwise@jhmi.edu (R.A. Wise).

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1. Introduction

Chronic obstructive pulmonary disease (COPD) is characterized by a progressive decline in lung function, resulting in deleterious effects on patients' exercise tolerance, functional capacity, and overall well-being [1]. With an increase in symptoms patients become less able to work and feel socially isolated, anxious, and depressed [2–4]. These factors, together with COPD exacerbations, have a negative effect on patients' health-related quality of life (HRQoL) [5–7].

Health status instruments, such as the St George's Respiratory Questionnaire (SGRQ), are intended to assess disease impact on patients' perception of their ability to lead a useful and fulfilling life and changes in health status resulting from treatment. In COPD, SGRQ questionnaires have been used in stable disease and during exacerbations [6].

The SGRQ is a self-administered, respiratory disease-specific, health-status questionnaire developed by Jones et al. [8,9], which allows direct comparisons between patient populations and treatment groups to quantify benefits of an intervention. A responder/deteriorator analysis calculates the proportion of patients who decrease (i.e., improve) or increase (i.e., deteriorate) SGRQ total scores by more than the minimal clinically important difference (MCID) of 4 units [10–12]. In treatment comparisons, net response rate, or net benefit, is calculated as the difference in the sum of benefits from the increase in responder rate and decrease in deteriorator rate between treatments.

The long-acting muscarinic antagonist (LAMA), tiotropium, administered by HandiHaler® or Respimat® inhalers, has been confirmed in many clinical trials, performed over 13 years, to improve SGRQ total score, and an overall estimate of its efficacy was reported in a formal meta-analysis of SGRQ total scores in COPD [13]. The magnitude of SGRQ responses achieved with some newly licensed LAMAs has varied, and in most reports improvement (group mean difference from placebo) has not exceeded the MCID [14–21]. We have analyzed the consistency of changes in SGRQ total score observed in patients with COPD receiving tiotropium in 13 previously reported clinical trials [22–31]. We have also expressed our findings as responder and deteriorator rates, net benefit, and cumulative improvement and deterioration rates, which were not reported in the original papers; these analyses may be more clinically useful when evaluating benefits achieved with maintenance treatment in patients with COPD and when comparing different interventions.

2. Methods

2.1. Study trials

All Boehringer Ingelheim-sponsored clinical trials of tiotropium monotherapy in COPD that met the criteria of ≥6 months' duration, placebo controlled, double blind, and in which SGRQ data were collected were included in the analyses. Patients were randomized to receive once-daily tiotropium 18 μg or placebo delivered via HandiHaler® (Boehringer Ingelheim, Ingelheim am Rhein, Germany) in 10 trials and once-daily tiotropium 5 μg or placebo delivered via Respimat® inhaler (Boehringer Ingelheim, Ingelheim am Rhein, Germany) in three trials. Based on past research, tiotropium doses delivered via HandiHaler and Respimat devices were considered comparable in terms of pharmacokinetics, efficacy, and safety [32–34]. In some trials, patients were also randomized to receive tiotropium 10 μg delivered via Respimat® inhaler or an alternative active comparator; data from these treatment arms were not included in the analyses.

With the exception of two trials (one of 2 years' duration and one of 4 years' duration), the trials were 1 year or less in duration from start of treatment. Our analyses, focused on two time-points: 6 months and 1 year.

The primary papers for each trial have been published [22–31] and their designs are summarized in Supplementary Table A1.

2.2. Study participants

Patients in all trials were of either sex, aged ≥40 years, with a smoking history of ≥10 pack-years and moderate-to-very severe COPD. Lung function inclusion criteria for patients (forced expiratory volume in 1 s [FEV_1] % predicted normal [35,36] and FEV_1/forced vital capacity [FVC]) in each trial are provided in Supplementary Table A1.

All patients could remain on their usual COPD medications, with the exception that inhaled anticholinergics, other than study drug, were not permitted in any trial. In addition, in all trials except four (205.235 [UPLIFT], 205.259 [SAFE], 205.368 [EXACTT], and 205.372) long-acting β-agonists (LABAs) were not allowed.

Details of the inclusion and exclusion criteria are provided in the published primary papers for each trial, as cited in Table 1 [22–31].

2.3. St George's Respiratory Questionnaire

The SGRQ focusses on three major HRQoL domains: symptoms; activity; and impacts [8,9]. Scores from the domains are combined into a total score, which is on a scale of 0–100, with higher scores associated with poorer HRQoL. In this study, we have analyzed data for SGRQ total scores, rather than for the separate domains.

For all 13 trials, SGRQ total scores, for patients within each treatment group, were measured at baseline and 6 months from start of treatment. In addition, in nine trials, SGRQ total scores were also measured at 1 year from start of treatment. In all trials, SGRQ data were either a primary or secondary outcome measure (Supplementary Table A1).

Within-treatment changes in SGRQ total score from baseline at 6 months and 1 year from start of treatment were calculated on a trial-by-trial basis. Adjusted mean differences between treatments (tiotropium versus placebo) for change from baseline at each time-point for each trial were calculated. The MCID for SGRQ total score is a difference of 4 units [10–12]. Responder and deteriorator rates at 6 months and 1 year from start of treatment were calculated. A responder was defined as a patient who achieved a reduction of at least 4 units in SGRQ total score from baseline and a deteriorator was defined as a patient who had an increase of at least 4 units in SGRQ total score from baseline.

Net benefit was calculated as the sum of benefits from the increase in responder and decrease in deteriorator rates between treatments, assuming equal weight should be given to both. For the net benefit analysis, two cut-off points were evaluated, based on a change from baseline in SGRQ total score of ≥4 and ≥ 8 units.

For each trial, cumulative improvement and cumulative deterioration were determined. Patients were considered to have improved if their change from baseline in SGRQ total score was negative or to have deteriorated if their SGRQ total score increased from baseline. The cut-off ranges examined were between −12 and 0 units for cumulative improvement and between 0 and 12 units for cumulative deterioration. For the two largest trials, 205.235 (UPLIFT) and 205.372 (representing 64% of the overall study population with baseline scores), the range was extended to −20 to 20 units at 1 year from start of treatment. To explain the cumulative nature of the analysis, as the cut-off increases the number of patients at each cut-off decreases (e.g., the set of patients whose score decreased by 1 point from baseline includes patients whose score decreased by 2 points from baseline).

Table 1
Baseline demographic and clinical characteristics (treated set).

BI trial number (trial name) ClinicalTrials.gov number primary reference	Treatment	N	Males, n (%)	Age, years, mean ± SD (range)	Smoking History, pack-years, mean ± SD	Duration of COPD, years, mean ± SD	Pre-BD FEV_1 % predicted, mean ± SD	Pre-BD FEV_1/FVC (%), mean ± SD	SGRQ Total score, mean ± SD
HandiHaler trials									
205.114/117 Casaburi et al., 2002 [22]	Tiotropium	279	186 (67)	65.0 ± 8.6 (40–85)	64.5 ± 33.1	9.3 ± 8.0	39.2 ± 13.8[a]	46.2 ± 11.8	47.53 ± 15.90 (n = 265)
	Placebo	191	121 (63)	65.5 ± 9.0 (39–81)	60.5 ± 30.2	8.6 ± 6.9	37.7 ± 14.1[a]	46.2 ± 11.5	49.65 ± 16.31 (n = 171)
205.115/128 Casaburi et al., 2002 [22]	Tiotropium	271	180 (66)	65.2 ± 8.5 (41–87)	60.6 ± 27.6	8.0 ± 6.6	39.1 ± 13.6[a]	45.5 ± 11.5	45.68 ± 16.00 (n = 251)
	Placebo	180	112 (62)	65.2 ± 8.8 (41–82)	57.4 ± 30.5	7.7 ± 6.7	38.6 ± 14.0[a]	44.7 ± 11.8	43.90 ± 14.87 (n = 153)
205.130 NCT02172287 Brusasco et al., 2003 [23]	Tiotropium	209	154 (74)	64.5 ± 7.9 (45–84)	46.9 ± 24.7	9.2 ± 7.8	39.2 ± 11.8[b]	43.6 ± 9.8	45.19 ± 16.42 (n = 186)
	Placebo	201	151 (75)	65.6 ± 7.8 (41–83)	45.5 ± 24.3	9.7 ± 7.9	38.1 ± 11.5[b]	41.3 ± 8.7	46.45 ± 16.41 (n = 159)
205.137 NCT02173691 Brusasco et al., 2003 [23]	Tiotropium	193	157 (81)	63.0 ± 8.1 (41–80)	41.1 ± 20.5	8.9 ± 6.7	39.2 ± 11.5[b]	43.7 ± 9.5	44.54 ± 17.33 (n = 170)
	Placebo	199	154 (77)	63.7 ± 9.2 (39–87)	39.2 ± 20.6	9.9 ± 7.0	39.4 ± 12.8[b]	43.2 ± 9.5	43.29 ± 17.48 (n = 167)
205.230 NCT00274521 Casaburi et al., 2005 [24]	Tiotropium	55	30 (55)	65.9 ± 8.8 (42–83)	58.6 ± 34.6	9.7 ± 7.6	32.6 ± 12.4[a]	41.5 ± 10.4	50.41 ± 15.38 (n = 49)
	Placebo	53	31 (58)	67.3 ± 6.9 (52–78)	58.8 ± 31.4	8.9 ± 6.6	36.2 ± 12.2[a]	44.6 ± 11.2	46.58 ± 16.12 (n = 47)
205.235 (UPLIFT) NCT00144339 Tashkin et al., 2008 [25]	Tiotropium	2986	2251 (75)	64.5 ± 8.4 (40–88)	49.0 ± 28.0	9.9 ± 7.6	39.5 ± 12.0[b] (n = 2908)	42.4 ± 10.5 (n = 2908)	44.98 ± 16.97 (n = 2478)
	Placebo	3006	2222 (74)	64.5 ± 8.5 (40–88)	48.4 ± 27.9	9.7 ± 7.4	39.3 ± 11.9[b] (n = 2937)	42.1 ± 10.5 (n = 2937)	45.07 ± 17.17 (n = 2337)
205.247 NCT00157235 Ambrosino et al., 2008 [26]	Tiotropium	117	97 (83)	67.8 ± 7.8 (47–83)	38.3 ± 25.2	10.9 ± 9.8 (n = 116)	42.5 ± 13.3[b]	47.3 ± 11.8	38.30 ± 18.39 (n = 103)
	Placebo	117	99 (85)	66.9 ± 7.3 (50–85)	35.0 ± 22.4	11.3 ± 9.5	40.3 ± 12.6[b] (n = 116)	45.2 ± 10.4 (n = 116)	39.90 ± 19.52 (n = 104)
205.256 TIPHON) NCT00274053 Tonnel et al., 2008 [27]	Tiotropium	266	231 (87)	64.9 ± 9.7 (40–86)	44.4 ± 21.3 (n = 264)	7.9 ± 7.6	47.5 ± 13.3[b] (n = 264)	55.3 ± 11.3	45.92 ± 17.68 (n = 247)
	Placebo	288	246 (85)	63.5 ± 10.1 (38–85)	43.0 ± 22.5 (n = 285)	8.0 ± 7.9 (n = 286)	46.2 ± 12.4[b]	54.6 ± 11.3	48.67 ± 17.89 (n = 245)
205.259 (SAFE) NCT00277264 Chan et al., 2007 [28]	Tiotropium	608	361 (59)	66.8 ± 8.7 (43–92)	50.2 ± 22.6 (n = 607)	9.9 ± 8.1	39.4 ± 13.4[a] (n = 607)	46.4 ± 11.6 (n = 607)	45.85 ± 16.98 (n = 501)
		305	185 (61)	66.9 ± 9.1 (40–90)	51.0 ± 26.3	9.9 ± 7.9	39.3 ± 13.6[a] (n = 303)	46.3 ± 11.8 (n = 303)	47.64 ± 17.00 (n = 233)
205.368 (EXACTT) NCT00525512 Cooper et al., 2013 [29]	Tiotropium	260	199 (77)	64.7 ± 8.2 N/A	52.2 ± 29.0	8.7 ± 6.3	38.3 ± 10.9[b] (n = 259)	45.2 ± 11.0 (n = 259)	42.99 ± 16.98 (n = 220)
	Placebo	259	202 (78)	64.5 ± 8.5 N/A	51.0 ± 26.3	8.8 ± 7.0	38.3 ± 11.5[b] (n = 258)	45.6 ± 10.8 (n = 258)	41.76 ± 17.49 (n = 216)
Respimat trials									
205.254 NCT00168844 Bateman et al., 2010 [30]	Tiotropium	332	243 (73)	65.0 ± 8.2 (42–90)	46.8 ± 28.6	8.6 ± 6.5	38.3 ± 11.0[b]	42.9 ± 10.8	45.44 ± 16.60 (n = 318)
	Placebo	319	252 (79)	64.7 ± 8.9 (40–87)	45.8 ± 25.4	9.9 ± 8.1	37.8 ± 11.5[b]	43.1 ± 10.8	45.28 ± 17.91 (n = 275)
205.255 NCT00168831 Bateman et al., 2010 [30]	Tiotropium	338	248 (73)	64.4 ± 8.9 (38–85)	47.4 ± 25.1	8.1 ± 6.4	39.2 ± 12.0[b] (n = 335)	43.0 ± 11.3 (n = 335)	44.17 ± 16.71 (n = 310)
	Placebo	334	235 (70)	65.7 ± 8.4 (41–87)	49.326.7	9.0 ± 6.8	38.8 ± 11.7[b]	42.4 ± 11.1	45.98 ± 16.13 (n = 276)
205.372 NCT00387088 Bateman et al., 2010 [31]	Tiotropium	1952	1524 (78)	64.8 ± 9.1 N/A	46.0 ± 26.1	8.3 ± 7.0	39.9 ± 12.0[b]	47.2 ± 10.8	42.94 ± 17.99 (n = 1691)
	Placebo	1965	1513 (77)	64.8 ± 9.0 N/A	45.0 ± 26.5	8.1 ± 6.5	39.8 ± 12.0[b]	46.7 ± 10.7	44.12 ± 18.28 (n = 1670)

BD, bronchodilator; EXACTT, Exercise Endurance and COPD Patients Treated with Tiotropium; FEV_1, forced expiratory volume in 1 s; FVC, forced vital capacity; N/A, not available; qd, once daily; SAFE, Spiriva Assessment of FEV_1; SD, standard deviation; TIPHON, Tiotropium: Influence sur la Perception de làmélioration des activités Habituelles Objectivée par une échelle Numérique; UPLIFT, Understanding Potential Long-term Impacts on Function with Tiotropium.
Number of patients is given in column 3 unless specified elsewhere.
[a] % Predicted according to Morris [35].
[b] % Predicted according to European Community for Coal and Steel [36].

2.4. Statistical analyses

The full analysis set (FAS) included all patients with a baseline SGRQ total score and at least one non-missing score post-randomization. The exception to this was for 205.235 (UPLIFT), where the FAS included all patients with a baseline SGRQ total score and at least two non-missing scores after 6 months of treatment. The UPLIFT trial investigated the slope of change in SGRQ as a secondary endpoint, so required two non-missing SGRQ scores. All analyses were performed with SAS software, version 9.2

(SAS Institute, Cary, NC, USA).

For SGRQ total score, adjusted mean differences in treatments (tiotropium versus placebo) for change from baseline were calculated at each time-point using mixed model repeated measures (MMRM). All visits were used in the MMRM models for estimation. Means were adjusted for treatment, visit, baseline SGRQ total score, and interactions treatment × visit and baseline × visit. For calculation of responder rates, deteriorator rates, net benefit, cumulative improvement, and cumulative deterioration, multiple imputation was used to impute missing SGRQ total scores using a regression model based on previously non-missing SGRQ total scores. Imputed data were used for inference. Differences in responder rates, deteriorator rates, and net benefit were compared between treatments using the z-test. There was no control of type I error for the analyses; therefore a p-value <0.05 was considered statistically significant in a nominal manner.

A meta-analysis was performed for SGRQ total score (inverse variance, fixed-effect model); I^2 was used to assess heterogeneity among study results.

3. Results

3.1. Demographic and clinical characteristics

The demographic and clinical characteristics of patients were generally similar across the clinical trials and treatment groups (Table 1). In the HandiHaler trials, 5244 patients received tiotropium and 4799 received placebo, and in the Respimat trials, 2622 patients received tiotropium and 2618 received placebo. The majority of patients were male.

3.2. SGRQ total scores

In total, 12,842 patients had baseline SGRQ total scores; mean ± SD for each trial are provided in Table 1. Estimated mean changes from baseline in total scores at 6 months and 1 year from start of treatment are provided in Supplementary Table A2. Estimated mean differences between treatments in change from baseline in total scores were statistically significant ($p < 0.05$) in favor of tiotropium in 10 of the 13 trials at 6 months and in eight of the nine trials at 1 year (Fig. 1). The MCID of a 4-point decrease (tiotropium versus placebo difference in change from baseline) was exceeded in two HandiHaler trials at 6 months and in one HandiHaler trial at 1 year; the MCID between tiotropium and placebo was not met in the Respimat trials at either time-point.

Estimated mean difference in total score between tiotropium and placebo for change from baseline in the two trials that continued beyond 1 year from start of treatment, the 4-year UPLIFT (205.235) and 2-year EXACTT (205.368) trials, are shown in Supplementary Table A3.

A meta-analysis for mean difference in SGRQ total score (as change from baseline) between tiotropium and placebo at 1 year from start of treatment resulted in a mean of −3.0 SGRQ total score units (95% CI −3.4 to −2.5) with no observed heterogeneity between trials ($\chi^2 = 3.29$, $p = 0.91$, $I^2 = 0\%$; test for overall effect: $z = 12.25$, $p < 0.0001$; Supplementary Fig. A1).

3.3. Responder and deteriorator rates

Estimated SGRQ responder rates at 6 months and 1 year from start of treatment are shown in Supplementary Table A4. At both time-points, all estimated differences in responder rates for tiotropium versus placebo were positive in favor of tiotropium (Fig. 2). At 6 months, statistical significance ($p < 0.05$) in favor of tiotropium for estimated differences in responder rates between treatments was achieved in three out of the 10 HandiHaler trials and two out of three Respimat trials and, at 1 year, it was achieved in five of the six HandiHaler trials and in all three Respimat trials.

Estimated SGRQ deteriorator rates at 6 months and 1 year from start of treatment are given in Supplementary Table A5. In each trial, at both time-points, the estimated difference in deteriorator rates for tiotropium versus placebo was negative in favor of tiotropium (Fig. 3). At 6 months, statistical significance ($p < 0.05$) in favor of tiotropium for deteriorator rates was achieved in six out of the 10 HandiHaler trials and two of the three Respimat trials and, at 1 year, it was achieved in three of the six HandiHaler trials and in all three Respimat trials.

Fig. 4 shows the proportions of patients who responded, deteriorated, and neither responded nor deteriorated as measured by a change in SGRQ total score from baseline of ≥4 units at 1 year from start of treatment (equivalent data for a ≥8-unit change from baseline to 1 year are provided in Supplementary Fig. A2). In each trial, there was a higher responder rate and a lower deteriorator rate with tiotropium compared with placebo. At 1 year, at the ≥4 and ≥ 8 cut-points, there were more responders than deteriorators in the tiotropium groups in all nine trials; whereas, in the placebo groups at these cut-points three out of the nine trials had more deteriorators than responders. The proportion of patients who neither responded nor deteriorated, as measured by a positive or negative change in SGRQ total score from baseline of <4 units at 1 year, accounted for 25–29% in the tiotropium groups and 25–32% in the placebo groups.

SGRQ responder rates for trials continuing beyond 1 year from start of treatment, the 4-year UPLIFT (205.235) and 2-year EXACTT (205.368), are given in Supplementary Table A6.

3.4. Net benefit

In all trials, at 6 months and 1 year from start of treatment, estimated net benefit for tiotropium versus placebo was positive in favor of tiotropium (Fig. 5). At 6 months, statistical significance ($p < 0.05$) in favor of tiotropium was achieved in six out of the 10 HandiHaler trials and two of the three Respimat trials, and, at 1 year, it was achieved in four of the six HandiHaler trials and in all three Respimat trials. At 1 year compared with 6 months, three HandiHaler trials and one Respimat trial showed a net benefit increase and two HandiHaler trials showed a net benefit decrease; in the remaining one HandiHaler and two Respimat trials, net benefits were similar at 6 months and 1 year (Fig. 5).

3.5. Cumulative response analyses

Cumulative improvement and cumulative deterioration curves for SGRQ total score changes from baseline in the range −12 and + 12 units showed consistent trends across trials at 6 months and 1 year from start of treatment (Supplementary Fig. A3 and Fig. 6, respectively). At both time-points, cumulative improvement rates were consistently greater and deterioration rates consistently lower for tiotropium versus placebo. Cumulative improvement and deterioration curves were mostly in parallel between tiotropium and placebo, suggesting a constant treatment effect that is insensitive to the threshold defining a response. Cumulative curves tended to flatten towards the extremes; this was more marked with the cumulative deterioration curves, where the placebo and tiotropium arms tended to converge. This is evident because few patients could achieve very large improvement or deterioration. When cumulative deterioration exceeded 8 units, the relative benefit of tiotropium versus placebo was eroded in about half the trials. This phenomenon was generally not seen with large improvements. This is seen most clearly in the two largest trials,

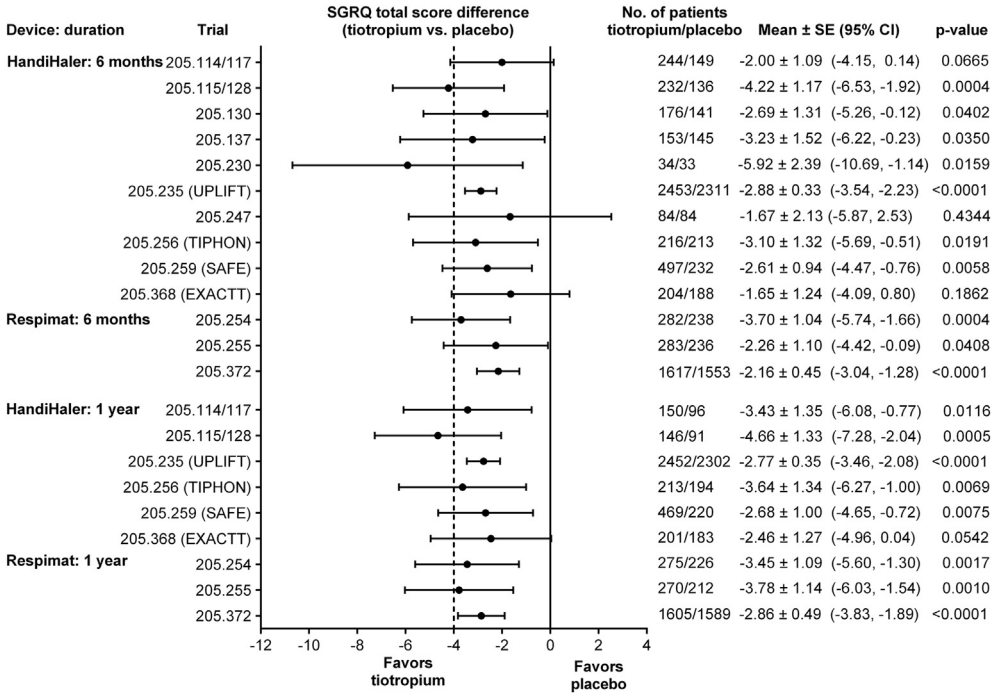

Fig. 1. Estimated mean difference between tiotropium and placebo in SGRQ total score change from baseline at 6 months and 1 year from start of treatment: full analysis set. EXACTT, Exercise Endurance and COPD Patients Treated with Tiotropium; SAFE, Spiriva Assessment of FEV_1; SE, standard error of the mean; TIPHON, Tiotropium: Influence sur la Perception de làmélioration des activités Habituelles Objectivée par une échelle Numérique; UPLIFT, Understanding Potential Long-term Impacts on Function with Tiotropium.

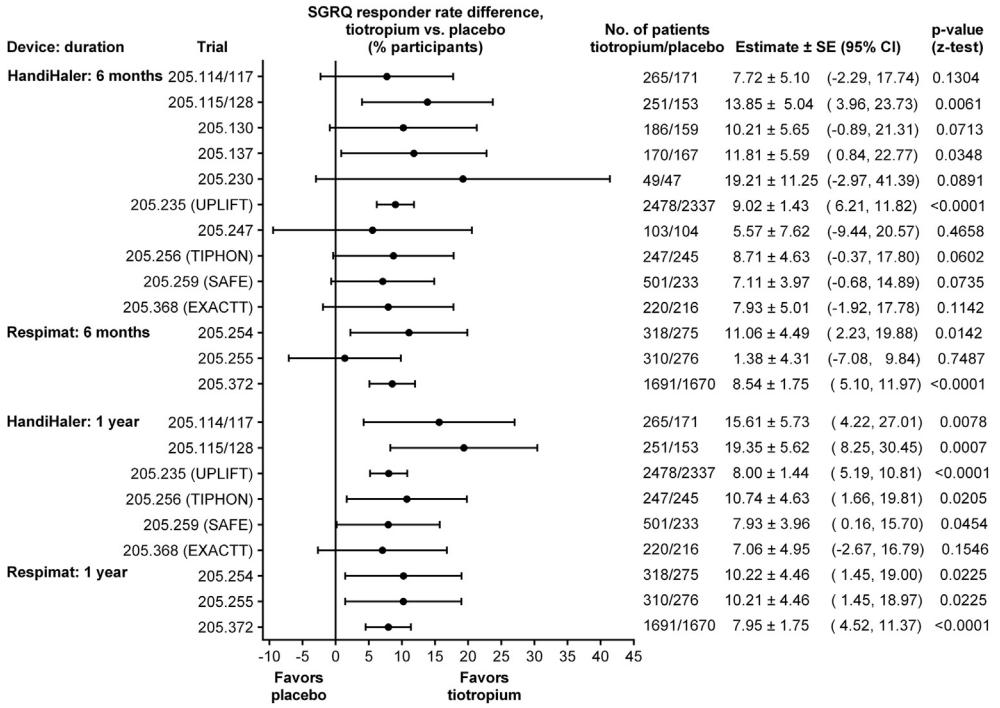

Fig. 2. Estimated difference in SGRQ responder rates (in % participants) between tiotropium and placebo at 6 months and 1 year in each trial: full analysis set.
A responder was defined as a patient who achieved a reduction of at least 4 units in SGRQ total score from baseline. EXACTT, Exercise Endurance and COPD Patients Treated with Tiotropium; SAFE, Spiriva Assessment of FEV_1; SE, standard error of the mean; TIPHON, Tiotropium: Influence sur la Perception de làmélioration des activités Habituelles Objectivée par une échelle Numérique; UPLIFT, Understanding Potential Long-term Impacts on Function with Tiotropium.

205.235 (UPLIFT) and 205.372, where, in Supplementary Fig. A4, the SGRQ total score changes from baseline range has been extended to −20 and + 20 units. The cumulative improvement and cumulative deterioration curves for these two trials were very similar. In 205.235 (UPLIFT), at 1 year from start of treatment, 15% of patients (12% responders and 3% deteriorators) in the tiotropium

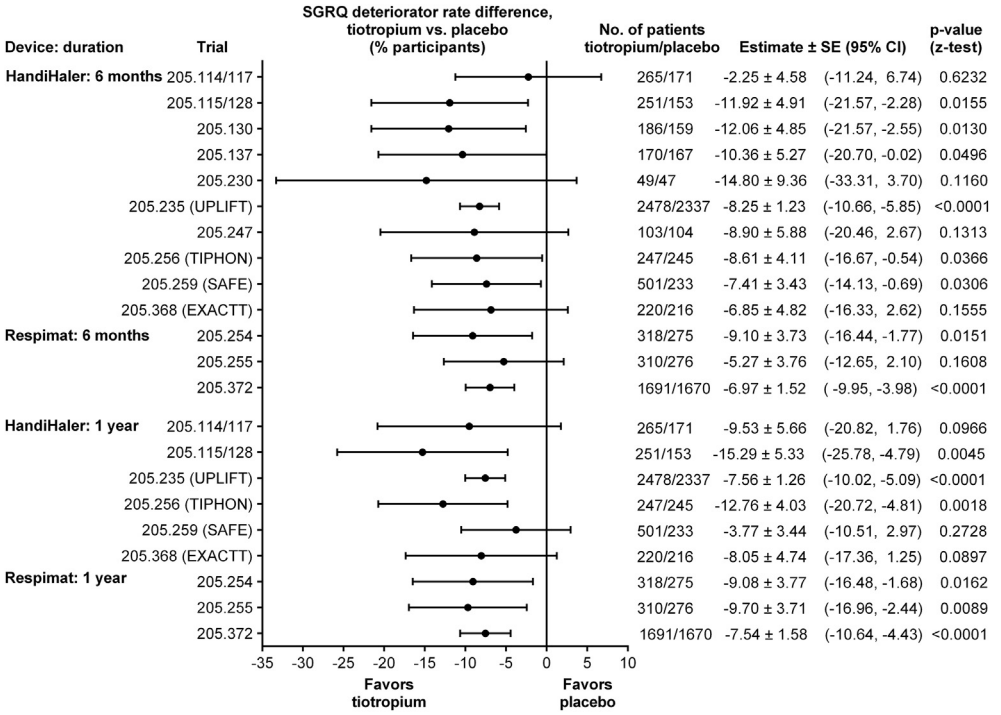

Fig. 3. Estimated difference in SGRQ deteriorator rates (in % participants) between tiotropium and placebo at 6 months and 1 year in each trial: full analysis set. A deteriorator was defined as a patient who had an increase of at least 4 units in SGRQ total score from baseline. EXACTT, Exercise Endurance and COPD Patients Treated with Tiotropium; SAFE, Spiriva Assessment of FEV_1; SE, standard error of the mean; TIPHON, Tiotropium: Influence sur la Perception de làmélioration des activités Habituelles Objectivée par une échelle Numérique; UPLIFT, Understanding Potential Long-term Impacts on Function with Tiotropium.

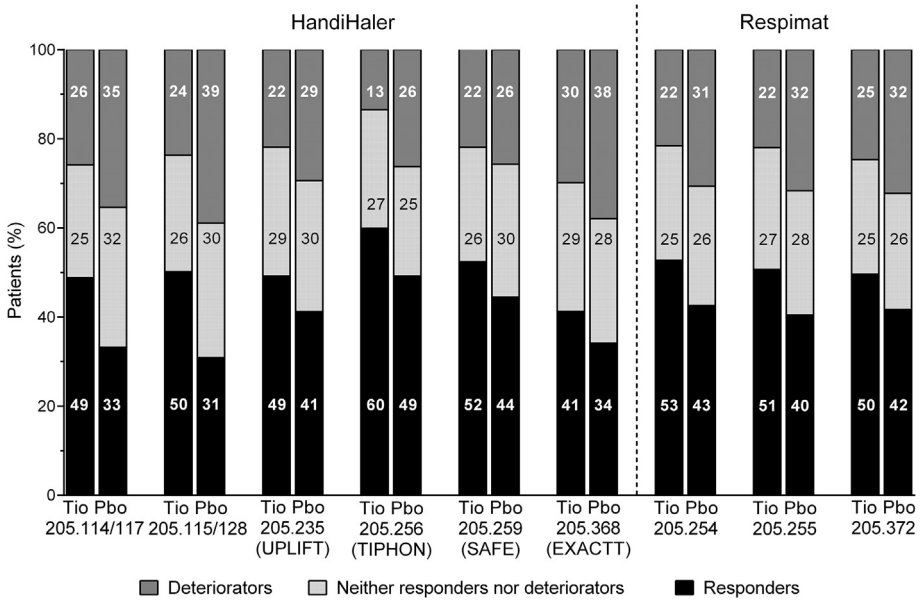

Fig. 4. Proportions of patients who responded, deteriorated, and neither responded nor deteriorated as measured by change in SGRQ total score from baseline at 1 year from start of treatment. A responder was defined as a patient who achieved a reduction of at least 4 units in SGRQ total score from baseline and a deteriorator was defined as a patient who had an increase of at least 4 units in SGRQ total score from baseline. EXACTT, Exercise Endurance and COPD Patients Treated with Tiotropium; Pbo, placebo; SAFE, Spiriva Assessment of FEV_1; Tio, tiotropium; TIPHON, Tiotropium: Influence sur la Perception de làmélioration des activités Habituelles Objectivée par une échelle Numérique; UPLIFT, Understanding Potential Long-term Impacts on Function with Tiotropium.

group had a change in SGRQ total score from baseline at the extremes of, or outside, the range −20 to 20 units and for 205.372 these proportions were 18% of patients (13% responders and 5% deteriorators).

4. Discussion

The aim of these analyses was to assess the effect of tiotropium delivered as maintenance treatment via either HandiHaler or Respimat inhalers on HRQoL, expressed in the conventional

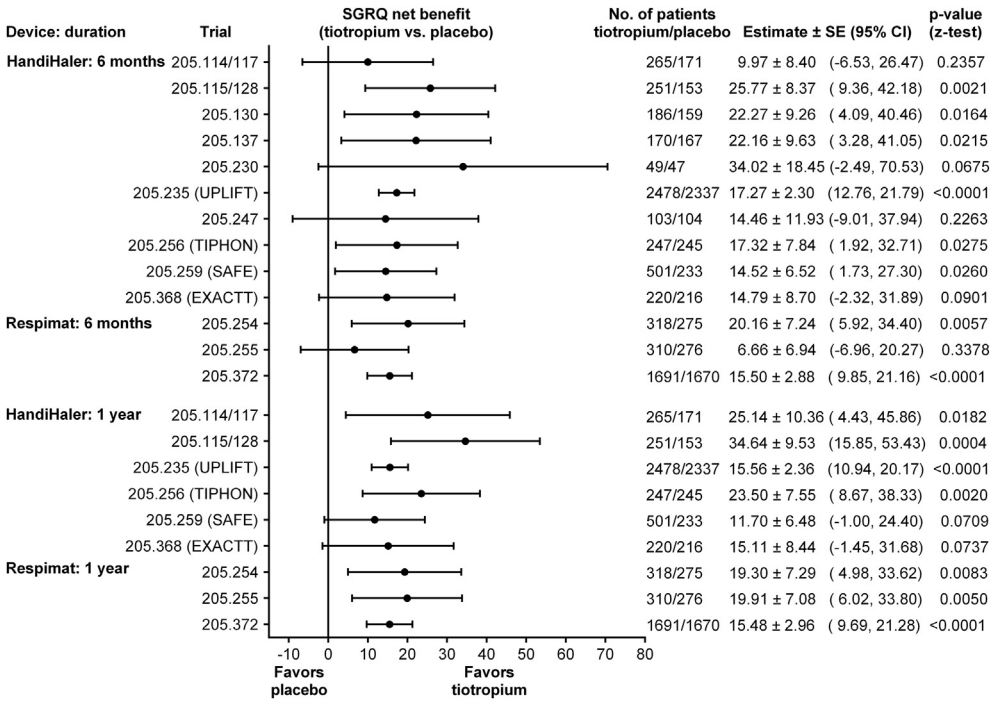

Fig. 5. Estimated SGRQ net benefit between tiotropium and placebo at 6 months and 1 year in each trial: full analysis set. Net benefit was calculated as the difference in responder rate minus the difference in deteriorator rate between the tiotropium and placebo groups. Where a responder was defined as a patient who achieved a reduction of at least 4 units in SGRQ total score from baseline and a deteriorator was defined as a patient who had an increase of at least 4 units in SGRQ total score from baseline. EXACTT, Exercise Endurance and COPD Patients Treated with Tiotropium; SAFE, Spiriva Assessment of FEV_1; SE, standard error of the mean; TIPHON, Tiotropium: Influence sur la Perception de làmélioration des activités Habituelles Objectivée par une échelle Numérique; UPLIFT, Understanding Potential Long-term Impacts on Function with Tiotropium.

manner (SGRQ total score) and in newer forms of SGRQ response (responder and deteriorator rates, net benefit, and cumulative improvement and deterioration rates) in patients with moderate-to-very severe COPD. An additional aim was to assess the consistency of the impact of tiotropium on the SGRQ response when measured using these different methods. Data were derived from 13 clinical trials, which covered a wide geographical range, spanning five continents, and were performed over a period of 13 years (Supplementary Table A1). The results confirm the general consistency in impact of tiotropium versus placebo on HRQoL, as measured by SGRQ total score, between trials, although not uniform in all trials. Possible explanations for variations in results between trials include differing trial designs, patient characteristics, and use of concomitant therapies, and, in some trials, relatively high placebo responses, as discussed below.

Comparable improvements in HRQoL, measured by SGRQ total score, were seen in patients with COPD receiving tiotropium maintenance therapy, whether delivered via HandiHaler or Respimat. In all trials, at 6 months and 1 year from the start of treatment, responder rates were greater and deteriorator rates were lower with tiotropium compared with placebo. As a consequence, net benefit in all trials was also greater with tiotropium compared with placebo. Cumulative improvement was greater and cumulative deterioration lower for tiotropium compared with placebo, with consistent and durable trends across trials at 6 months and 1 year. There was a tendency for the cumulative deterioration curves for tiotropium and placebo to converge at the higher unit scores for change in SGRQ total score from baseline. This may be due to a floor effect, in that patients receiving either tiotropium or placebo had little room for worsening by more than 12 SGRQ units. Convergence of the curves might also be speculated to be the result of factors other than COPD, including comorbidities, contributing to the extreme improvement or deterioration observed.

The magnitude of treatment effects differed slightly between trials, possibly due to variations in study design and participant characteristics. A meta-analysis of adjusted mean difference in SGRQ total score (as change from baseline) between tiotropium and placebo at 1 year from start of treatment showed a −2.97 unit change, indicating HRQoL improvement in patients treated with tiotropium; however, this value was less than the MCID of 4 units. Heterogeneity between trials was not observed in the meta-analysis, but the two largest trials, 205.235 (UPLIFT) and 205.372, dominated, with weightings of 47% and 24%, respectively. Our results are similar to the meta-analysis mean value of −2.89, reported by Karner et al. [13], which included several trials in common with those in our study; our heterogeneity test results were also similar to those of Karner et al. [13]. For a study population to exceed the MCID it would require 50% of patients (assuming a normal distribution) to exceed the MCID, which is a very large effect. This analysis has shown that the net benefit rate across the 13 trials was ≈20%.

Differences in permitted background therapies may have contributed to variations in treatment effects. In all trials, inhaled corticosteroid (ICS) use was permitted at baseline and throughout the treatment period, if at a pre-trial stabilized dose rate. In addition, in four trials, 205.235 (UPLIFT), 205.259 (SAFE), 205.368 (EXACTT), and 205.372, concomitant use of LABAs and/or ICS was permitted, at baseline and during the treatment period. Although ICS only was allowed in all trials, the four permitting LABA/ICS use dominated the overall investigation population, comprising ~80% of all patients at 1 year from start of treatment; this dominance may account for the meta-analysis MCID of 4 units not being reached. The magnitude of SGRQ responses achieved with some newly licensed LAMAs in clinical trials may also have been affected by allowed or non-allowed concomitant background therapies [14–21].

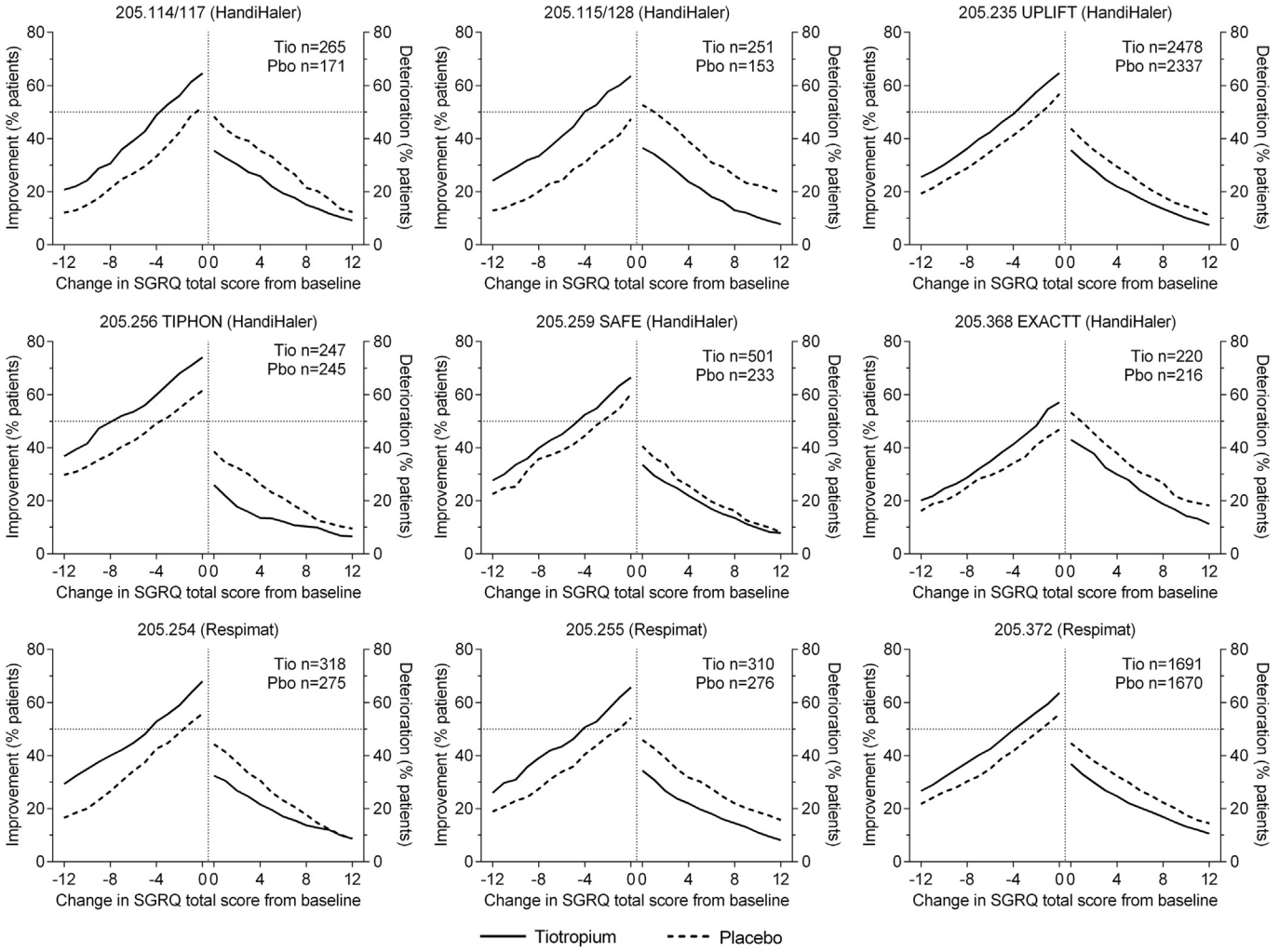

Fig. 6. Cumulative improvement and deterioration curves for tiotropium and placebo at 1 year: full analysis set. Patients were considered to have improved if they had a decrease in SGRQ total score from baseline and to have deteriorated if they had an increase in score from baseline. Change from baseline was examined over the range −12 to 12 units. EXACTT, Exercise Endurance and COPD Patients Treated with Tiotropium; Pbo, placebo; SAFE, Spiriva Assessment of FEV_1; Tio, tiotropium; TIPHON, Tiotropium: Influence sur la Perception de làmélioration des activités Habituelles Objectivée par une échelle Numérique; UPLIFT, Understanding Potential Long-term Impacts on Function with Tiotropium.

At 6 months from start of treatment, in all but one of the 13 trials there was an improvement in SGRQ total score in the placebo group compared with baseline (i.e., any score decrease from baseline); at 1 year, six of the nine trials had an improved placebo SGRQ score. This improvement phenomenon, known as the 'Hawthorne effect', has been noted previously in relation to SGRQ scores in clinical trials with COPD [37,38], and it is thought to arise because patients participating in trials may receive a better standard of care than usual care, and have greater compliance with concomitant therapies. The extent of improvement as a result of the Hawthorne effect is generally thought to be a decrease (improvement) in SGRQ score of around 2–3 units [12]. In the placebo groups, a decrease in score of >3 units, was seen at 6 months from the start of treatment in three trials, and at 1 year in one trial. The improvements in SGRQ score seen in the placebo group may also have contributed to the MCID of a 4-point decrease (tiotropium versus placebo difference in change from baseline) not being met in some of the trials.

Two of the trials included in our analyses, EXACTT (205.368) [29] and UPLIFT (205.235) [25], had treatment periods lasting >1 year, the maximum time covered by our analyses. These trials support our finding of a long-term sustained benefit of maintenance treatment with tiotropium. After 2 years of treatment in the EXACTT trial, SGRQ total scores had improved from baseline in patients treated with tiotropium and worsened in those treated with placebo. Throughout the 4-year UPLIFT trial, a sustained and significant benefit of tiotropium was also observed compared with placebo. After an initial period of improvement, there was an upward trajectory of SGRQ total scores (i.e., deterioration) in both treatment groups beginning 6 months to a year after randomization, which was consistent with age-related worsening of HRQoL. The rate of increase in SGRQ score in the tiotropium group paralleled that in the placebo group, indicating the beneficial effect of tiotropium compared with placebo persisted over time. The proportions of patients with a ≥4-unit improvement (i.e., score decrease) from baseline were significantly higher ($p < 0.001$) for tiotropium compared with placebo at 6 months through 4 years. However, it was reported that annual rates of increase in SGRQ total score (i.e., HRQoL worsening) over the 4 years were not significantly different between the two treatments. In the EXACTT trial, the proportions of patients with a ≥4-unit improvement from baseline were also higher for tiotropium compared with placebo at 6 months through 2 years, but differences were not statistically significant, possibly due to the small sample size or potential impact of formal exercise endurance testing during the trial on

patients' perceptions of HRQoL in this longer (2 year) treadmill endurance exercise trial. In both trials, decline in responder rates versus baseline over time in both treatment groups probably reflects the progressive character of the disease.

Examination of the relative responder and deteriorator results at 1 year reveals a general pattern of more responders than deteriorators in the tiotropium groups for all nine trials (Fig. 4). In contrast, in three of the nine trials, more deteriorators than responders were noted in the placebo groups. These three trials are of note as two of them (205.114/117 and 115/128) are trials conducted as part of the basic registration package with limited background therapy, and it is possible to hypothesize that in the placebo arms this provided an enhanced opportunity to detect a loss of HRQoL over the 1-year trial duration. In the third trial, EXACTT (205.368), exercise testing may have increased the potential for patients to detect changes in HRQoL. These observations support the view that study design should be carefully considered when assessing HRQoL.

Strengths of our analyses lie in the large number of trials and patients included, the geographic diversity of patient populations, standardization of SGRQ instrument administration, and general similarity of baseline characteristics of patients across trials. While one might expect differences in health status perception across different cultures, the consistency of results suggests that such differences did not excessively distort the overall findings. It may be questioned whether 6 months (the duration of four of the 10 HandiHaler trials) is sufficient to assess the maximum effect of tiotropium on SGRQ. However, in the trials of longer duration with both the HandiHaler and Respimat inhalers, adjusted mean difference in SGRQ total score from baseline between treatments at 6 months and 1 year were similar.

The trials considered in these analyses spanned a considerable period of time (1997–2010) during which substantial changes in COPD management occurred [39,40]. Such changes may have altered the pattern of impairment, e.g., death rates [41,42], exacerbation rates, and hospitalizations [43] in patients with COPD, yet the pattern of efficacy regarding SGRQ response appears to have persisted.

A limitation of the analysis is that it is based on data from randomized controlled clinical trials, and may not be generalizable to clinical practice because of the exclusion and inclusion criteria employed. However, a recent comparison of baseline demographics in patients in 35 tiotropium HandiHaler and Respimat studies, which included all the trials in our analysis, found patients' clinical characteristics were quite representative of patients in “real-world” settings [44].

5. Conclusions

Tiotropium maintenance treatment via either HandiHaler or Respimat inhalers improved HRQoL in patients with moderate-to-very severe COPD, expressed in the conventional manner (SGRQ total score) and in alternative forms as different measures of SGRQ response/deterioration. These results may serve as a benchmark for assessments of the beneficial impact of other treatments used in COPD on health status.

Author contributions

The authors meet criteria for authorship as recommended by the International Committee of Medical Journal Editors (ICMJE). All authors were involved in the concept and design of the study, interpretation of the results, drafting and critically reviewing the manuscript for important intellectual content, and approving the final submitted version. In addition, Dacheng Liu and Valentina B. Zubek conducted the statistical analyses.

Conflict of interest statements

Donald P. Tashkin has served as a consultant for AstraZeneca, Pearl Therapeutics, Novartis, Sunovion, Theravance, and Boehringer Ingelheim, as a speaker for AstraZeneca, Novartis, Sunovion, and Boehringer Ingelheim, and has received research grant support from AstraZeneca, Pearl Therapeutics, Pfizer, Boehringer Ingelheim, Sunovion, and the National Heart, Lung and Blood Institute/NIH.

Eric D. Bateman reports personal fees for lectures, consulting and advisory board membership from Boehringer Ingelheim and grants to his institution for participation in clinical trials sponsored by Boehringer Ingelheim; personal fees for advisory board membership or consulting from Almirall, AstraZeneca, Cipla, GlaxoSmithKline, ICON, Medimmune, Novartis, Roche, Takeda, and Vectura; personal fees for lectures from AstraZeneca, Chiesi, Cipla, GlaxoSmithKline, Menarini, Novartis, and Takeda; personal fees for educational materials from PeerVoice; and grants to his institution for participation in clinical trials sponsored by Actelion, Almirall, AstraZeneca, Cephalon, Chiesi, GlaxoSmithKline, Hoffmann La Roche, Merck, Novartis, Roche, Takeda, TEVA, and Sanofi-Aventis outside the submitted work.

Paul Jones is also employed by GlaxoSmithKline as a Global Medical Expert.

Robert A. Wise reports grants and personal fees from Boehringer Ingelheim during the conduct of the study. He reports personal fees AstraZeneca, Boehringer Ingelheim, Bristol-Myers Squibb, ContraFect, GlaxoSmithKline, Janssen, Mylan, Novartis, Pfizer, Pulmonx, Roche, Spiration, Sunovion, Teva, Theravance, Verona, and Vertex, and grants from Boehringer Ingelheim, GlaxoSmithKline, and Pearl Therapeutics outside the submitted work.

Valentina B. Zubek, Dacheng Liu, Thomas Leonard, and Emmanuelle Clerisme-Beaty are employees of Boehringer Ingelheim Pharmaceuticals Inc.

Norbert Metzdorf is an employee of Boehringer Ingelheim Pharma GmbH & Co KG.

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Role of the funding source

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Appendix A. Supplementary data

Supplementary data related to this article can be found at http://dx.doi.org/10.1016/j.rmed.2016.10.002.

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