Dual bronchodilation with QVA149 versus single bronchodilator therapy: the SHINE study

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METHODS (ADDITIONAL DETAILS)

Study design

The study was conducted in academic and clinical research centres in Europe, North America, South America, Asia (Philippines, Japan, India), Australia, China, Taiwan and South Africa.

During washout, patients discontinued long-acting bronchodilator therapy: at least seven days for long-acting muscarinic antagonists and the long-acting β_2-agonist (LABA) indacaterol, and 48 hours for all other LABAs and LABA/inhaled corticosteroid (ICS) combinations.

Concomitant medications permitted during the SHINE study are detailed in appendix table 2.

Screening tests were performed and baseline electronic diary data collected during a 14-day run-in period.

Randomisation and blinding

Eligible patients were assigned a randomisation number via Interactive Response Technology (IRT), linking the patient to a treatment arm and specific unique medication number for the study drug. The randomisation number was not communicated to the investigator contacting the IRT. Patients randomised to open-label tiotropium were not assigned a medication number as this treatment was supplied locally. Randomisation was stratified by baseline smoking status and ICS use.

Blinding of patients, investigator staff, personnel performing assessments and data analysts was maintained by ensuring randomisation data remained strictly confidential and inaccessible to anyone involved in the study until the time of unblinding. In addition, the identity of the treatments was concealed by the use of study drugs that were all identical in packaging, labelling, and schedule of administration, appearance, taste and odour. Unblinding occurred in the case of emergencies and at the conclusion of the study. The bioanalyst of the pharmacokinetic samples was unblinded.

Statistical methods

Statistical power

For the primary endpoint, 1710 evaluable patients gave 87% power for QVA149 versus the mono-components, >99% power for active drugs versus placebo, and 80% power for non-inferiority of QVA149 versus tiotropium. A standard deviation of 245 mL was assumed for trough forced expiratory volume in 1 second (FEV_1) and a treatment difference in trough FEV_1 of 120 mL (minimally clinically important difference [MCID]) was assumed for active versus placebo, 60 mL (1/2 MCID) for QVA149 versus the mono-components and a non-inferiority margin of 40 mL (1/3 MCID) for QVA149 versus tiotropium. This sample size also gave adequate power for the three key secondary endpoints (Transition Dyspnoea Index [TDI] focal score, 92%; St George's Respiratory Questionnaire [SGRQ] total score, 81%; rescue medication use, >99%).

Statistical analyses

Efficacy analyses were conducted on all randomised patients who received at least one dose of study drug (full analysis set [FAS]) according to treatment assignment at randomisation. The safety set comprised all patients receiving at least one dose of study drug; patients were analysed according to the treatment they received.

The primary variable of trough FEV_1 at Week 26 (with missing values imputed with last observation carried forward [LOCF]) was analysed for the FAS using a mixed model with treatment as a fixed effect and covariates of baseline FEV_1, FEV_1 before and after salbutamol and ipratropium inhalation. The model also included baseline smoking status (current/ex-smoker), baseline ICS use (yes/no) and region as fixed effects with centre nested within region as a random effect. Estimated treatment differences are presented as least squares means (LSM) with standard errors, and associated 95% confidence intervals (CI). Superiority of QVA149 versus indacaterol or glycopyrronium was demonstrated if the adjusted one-sided p-value was less than the multiplicity adjusted significance level. Key and important secondary efficacy variables were analysed using the same method as for the analysis of the primary variable, with Baseline Dyspnoea Index, baseline SGRQ or baseline rescue medication use replacing the baseline FEV_1 covariate as appropriate. Superiority of QVA149 and other active treatments versus placebo, and non-inferiority of QVA149 versus tiotropium (for trough FEV_1) was demonstrated if the adjusted one-sided p-value was less than the multiplicity adjusted significance level. Non-inferiority of QVA149 versus tiotropium was evaluated for the per-protocol set (non-inferiority criterion, 40 mL treatment difference); all other treatment comparisons were evaluated for the FAS. Other secondary efficacy variables were analysed using similar methods, with appropriate baseline measurements as covariates and no adjustment for multiplicity was made. For the responder analyses of dyspnoea and health status performed using logistic regression, the estimated adjusted odds ratios are displayed along with the associated 95% CIs and two-sided p-values. Analyses of trough FEV_1 at Week 26 performed in subgroups divided according to age, gender, disease severity, and ICS use, included appropriate interaction terms and additional covariates as appropriate in the analysis model, and no adjustment for multiplicity was made. Adverse events and other safety endpoints are presented using descriptive statistics.

RESULTS (ADDITIONAL DETAILS)

Spirometry

Increase from baseline in trough FEV_1 at Week 26

All active treatments at Week 26 (LOCF) had an increase from baseline in trough FEV_1, the mean increase being highest for the QVA149 group (0.16 L, +15.3%); mean change from baseline for indacaterol was 0.08 L (+7.7%); glycopyrronium 0.07 L (+7.1%), and tiotropium 0.09 L (+9.3%).

Post-hoc analyses of the primary endpoint

Post-hoc analyses indicated that the proportion of patients with an increase of >100 mL in trough FEV_1 at Week 26 (LOCF) from baseline was greater for QVA149 (64.3%) compared with indacaterol (46.2%), glycopyrronium (43.2%), tiotropium (46.6%) and placebo (18.9%), ($p<0.001$ for all treatment comparisons). The proportion of patients with an increase of >200mL from baseline in trough FEV1 at Week 26 (LOCF) from baseline was greater for QVA149 (39.8%) compared with indacaterol (26.2%), glycopyrronium (23.8%), tiotropium (25.1%) and placebo (8.4%), ($p<0.001$ for all treatment comparisons).

Secondary analyses

FEV_1 area under the curve $[AUC]_{0–12\,h}$ was significantly greater in the QVA149 treatment group compared with placebo and the active comparators at Day 1 (all $p<0.001$; table 2). At Week 26, QVA149 provided significant improvements versus placebo and the active comparators in FEV_1 $AUC_{0–24\,h}$ (all $p<0.001$) and FEV_1 $AUC_{12–24\,h}$ (all $p<0.01$; table 2).

QVA149 demonstrated a statistically significant improvement in FEV_1 2 hours post-dose compared with placebo and all active comparators at Week 26 ($p<0.001$; table 2).
Inspiratory capacity was statistically significantly greater in the QVA149 treatment group than in the placebo group at all assessed time points including Day 1 (LSM treatment difference: 0.18 L–0.28 L), Week 12 (LSM treatment difference: 0.24 L–0.32 L) and Week 26 (LSM treatment difference: 0.16 L–0.31 L).
Trough forced vital capacity (FVC) was significantly greater in the QVA149 group at Day 1, Week 12 and Week 26 compared with placebo, indacaterol, glycopyrronium and tiotropium groups (all $p<0.001$; appendix figure 2). Improvements in FVC were statistically significantly greater with QVA149 versus placebo at all assessed timepoints on Day 1 and at Weeks 12 and 26 (all $p<0.001$).

Pre-planned subgroup analyses
Additional analyses of trough FEV_1 at Week 26 demonstrated that data for the subgroups of age, gender, severity of chronic obstructive pulmonary disease (COPD) and baseline ICS use were similar to those of the overall population (appendix figure 3).

Dyspnoea
The proportion of patients achieving a minimal clinically important difference for TDI score (improvement of ≥1 point [1]) at Week 26 was significantly greater in the QVA149 group (68.1%) compared with placebo (57.5%; p=0.004) and tiotropium groups (59.2%; p=0.016; appendix figure 5). Significantly greater proportions of patients receiving QVA149 achieved improvements in TDI score of ≥2 points (p=0.004) and ≥3 points (p=0.019) compared with placebo at Week 26 (appendix figure 5). More than half (56.7%) of the QVA149 patients had major improvements (≥3 points) in TDI focal score (appendix table 4).

Health status
An improvement in SGRQ total score was seen at Week 12 with QVA149 compared with placebo (LSM difference: –3.99; $p<0.001$), glycopyrronium (LSM difference: –1.84; p=0.020) and tiotropium (LSM difference: –2.37; p=0.003). The proportion of patients achieving the MCID for SGRQ total score (≥4-point reduction [2]) at Week 26 was significantly greater in patients receiving QVA149 compared with those receiving tiotropium (p=0.047 [appendix table 5; appendix figure 5]). Additionally, significantly greater proportions of patients receiving QVA149 or indacaterol achieved improvements in SGRQ total score of ≥8 compared with placebo, glycopyrronium and tiotropium at Week 26 ($p<0.05$ [appendix table 5; appendix figure 5]).

REFERENCES

1. Witek TJ, Jr., Mahler DA. Minimal important difference of the transition dyspnoea index in a multinational clinical trial. *Eur Resp J* 2003; 21: 267–272.
2. Jones P, Lareau S, Mahler DA. Measuring the effects of COPD on the patient. *Respir Med* 2005; 99: Suppl. B, S11–S18.

TABLE S1. Inclusion and exclusion criteria – the SHINE study

Inclusion criteria

- Male or female adults aged ≥40 years, who had signed an Informed Consent Form prior to initiation of any study-related procedure.
- Patients with moderate-to-severe stable COPD (Stage II or Stage III) according to the GOLD Guidelines 2008.
- Current or ex-smokers who had a smoking history of at least 10 pack-years (defined as 20 cigarettes a day for 10 years, or 10 cigarettes a day for 20 years etc.).
- Patients with a post-bronchodilator FEV_1 ≥30% and < 80% of the predicted normal, and post-bronchodilator $FEV_1/FVC < 0.7$ at Visit 2 (Day 14).
- Post refers to 1 hour after sequential inhalation of 84 µg (or equivalent dose) of ipratropium bromide and 400 µg of salbutamol.
- Symptomatic patients, according to daily electronic diary data between Visit 2 (Day 14) and Visit 3 (Day 1), with a total score of 1 or more on at least 4 of the last 7 days prior to Visit 3 (the main study diary was used).

Exclusion criteria

General exclusion

- Pregnant women or nursing mothers (pregnancy confirmed by positive urine pregnancy test).
- Women of child-bearing potential.
- Patients contraindicated for treatment with, or having a history of reactions/hypersensitivity to any of the following inhaled drugs, drugs of a similar class or any component thereof:
    - anticholinergic agents
    - long and short acting β_2-agonists
    - sympathomimetic amines
    - lactose or any of the other excipients.
- Patients with a history of long QT syndrome or whose corrected QT measured at Visit 2 (Day 14) (Fridericia method) is prolonged (>450 ms for males and females) as confirmed by the central electrocardiogram assessor.
- Patients who had a clinically significant abnormality on the Visit 2 ECG who in the judgment of the investigator were at potential risk if enrolled into the study (these patients were not re-screened).
- Patients with Type I or uncontrolled Type II diabetes.
- Patients who had not achieved an acceptable spirometry result at Visit 2 in accordance with the American Thoracic Society/European Respiratory Society criteria for acceptability and repeatability.
- Patients with narrow-angle glaucoma, symptomatic prostatic hyperplasia or bladder-neck obstruction or moderate-to-severe renal impairment or urinary retention (patients with a transurethral resection of prostate were excluded from the study; patients who had undergone full re-section of the prostate were considered for the study, as well as patients who were asymptomatic and stable on pharmacological treatment for the condition).
- Patients with a history of malignancy of any organ system (including lung cancer), treated or untreated, within the past 5 years whether or not there is evidence of local recurrence or metastases, with the exception of localised basal cell carcinoma of the skin.
- Patients who, in the judgment of the investigator, had a clinically relevant laboratory abnormality or a clinically significant condition such as (but not limited to):
    - unstable ischemic heart disease, left ventricular failure (New York Heart Association Class III and IV), history of myocardial infarction, arrhythmia (excluding chronic stable atrial fibrillation). Patients with such events not

considered clinically significant by the investigator were considered for inclusion in the study
    - uncontrolled hypo-or hyperthyroidism, hypokalemia or hyperadrenergic state any condition which might compromise patient safety or compliance, interfere with evaluation, or preclude completion of the study.
- Patients unable to use an electronic patient diary.
- Patients who were, in the opinion of the investigator unreliable or non-compliant.

COPD specific exclusion

- Patients requiring long term oxygen therapy (>15 hours a day) on a daily basis for chronic hypoxemia.
- Patients who had a COPD exacerbation that required treatment with antibiotics, systemic steroids (oral or intravenous) or hospitalisation in the 6 weeks prior to Visit 1 or between Visit 1 and Visit 3.
    - Patients who developed a COPD exacerbation during period between Visits 1 and 3 were not eligible but were permitted to be re-screened after a minimum of 6 weeks after the resolution of the COPD exacerbation.
- Patients who had a respiratory tract infection within 4 weeks prior to Visit 1. Patients who developed an upper or lower respiratory tract infection during the screening period (up to Visit 3) were not eligible, but were permitted to be re-screened 4 weeks after the resolution of the respiratory tract infection.
- Patients with concomitant pulmonary disease, e.g. pulmonary tuberculosis (unless confirmed by chest X-ray to be no longer active) or clinically significant bronchiectasis, sarcoidosis, interstitial lung disorder or pulmonary hypertension.
- Patients with lung lobectomy, lung volume reduction, or lung transplantation.
- Patients with any history of asthma indicated by (but not limited to) a blood eosinophil count >600/mm3 (at Visit 2) or onset of symptoms prior to 40 years. Patients without asthma but who had a blood eosinophil count >600/mm3 at Visit 2 were excluded.
- Patients with allergic rhinitis who used a H1 antagonist or intra-nasal corticosteroids intermittently (treatment with a stable dose is permitted).
- Patients with eczema (atopic), known high immunoglobulin E levels, or a known positive skin prick test in the last 5 years.
- Patients with known history and diagnosis of α-1 antitrypsin deficiency.
- Patients who were participating in the active phase of a supervised pulmonary rehabilitation program.

COPD: chronic obstructive pulmonary disease; ECG: electrocardiogram; FEV_1: forced expiratory volume in 1 second; FVC: forced vital capacity.

TABLE S2. Concomitant medication allowed in the SHINE study

Selective serotonin reuptake inhibitors prior to screening	Treatment regimen has been stable for at least one month prior to screening visit and during the study. Screening ECG is normal with no clinical evidence of prior ECG abnormalities
Inactivated vaccine	Not administered within 48 hrs prior to a study visit
Inhaled corticosteroids	In constant doses and dose regimens for at least 1 month
Intranasal corticosteroids	In constant doses and dose regimens for at least 5 days prior to screening
H1 antagonists	In constant doses and dose regimens

ECG: electrocardiogram.

TABLE S3. Dyspnoea, health status, rescue medication use and patient symptoms over the 26-week study

		QVA149 110/50 µg		Indacaterol 150 µg		Glycopyrronium 50 µg		Tiotropium 18 µg	
	Placebo (LSM, SE)	Difference vs placebo (LSM ± 95% CI)	p-values[a]	Difference vs placebo (LSM ± 95% CI)	p-values[a]	Difference vs placebo (LSM ± 95% CI)	p-values[a]	Difference vs placebo (LSM ± 95% CI)	p-values[a]
TDI focal score at Week 26[b]	1.63 (0.230)	1.09 (0.61, 1.57)	*p<0.001 §p=0.007	0.84 (0.36, 1.31)	*p<0.001	0.89 (0.41, 1.36)	*p<0.001	0.58 (0.10, 1.06)	*p=0.017
SGRQ total score[b]	40.02 (0.941)	–3.01 (–5.05, –0.97)	*p<0.002 §p=0.009	–1.92 (–3.97, 0.12)	–	–1.83 (–3.87, 0.21)	–	–0.88 (–2.92, 1.16)	–
Rescue medication use	–0.92 (0.147)	–0.96 (–1.29, –0.62)	*p<0.001 †p=0.027 ‡p<0.001 §p<0.001	–0.65 (–0.99, –0.32)	*p<0.001 ‡p=0.011	–0.30 (–0.63, 0.04)	–	–0.41 (–0.75, –0.08)	*p=0.015
Days with no rescue medication use, %	34.76 (2.437)	12.33 (6.84, 17.82)	*p<0.001 ‡p<0.001 §p<0.001	10.05 (4.55, 15.55)	*p<0.001 ‡p=0.002 §p<0.001	2.98 (–2.52, 8.48)	–	1.75 (–3.73, 7.23)	–
Nights with ‘no nighttime awakenings’, %	53.67 (2.047)	10.01 (5.37, 14.66)	*p<0.001 ‡p=0.008	8.81 (4.16, 13.47)	*p<0.001	4.97 (0.31, 9.62)	*p=0.037	6.33 (1.70, 10.97)	*p=0.007
Days with ‘no daytime symptoms’, %	4.44 (1.294)	3.05 (0.14, 5.96)	*p=0.040	4.73 (1.81, 7.64)	*p=0.001 ‡p=0.021 §p=0.002	1.96 (–0.96, 4.87)	–	1.10 (–1.81, 4.00)	–
‘Days able to perform usual daily activities’, %	34.49 (2.197)	11.48 (6.52, 16.44)	*p<0.001 †p=0.012 ‡p=0.004 §p<0.001	6.44 (1.47, 11.41)	*p=0.011	5.61 (0.63, 10.58)	*p=0.027	3.03 (–1.92, 7.98)	–

[a]p-values presented where p<0.05; [b]Imputed with last observation carried forward; *versus placebo; other symbols denote where significant treatment differences (not shown) occur; [†]versus indacaterol; [‡]versus glycopyrronium; [§]versus tiotropium. CI: confidence interval; LSM: least squares mean; SE: standard error; SGRQ: St George's Respiratory Questionnaire; TDI: Transitional Dyspnoea Index.

TABLE S4. Proportion of patients with minimally clinically important difference in TDI at Week 26 (LOCF, full analysis set)

	TDI improvement					
	≥1 point (mild)		**≥2 points (moderate)**		**≥3 points (major)**	
Treatment	% patients	p-values[a]	% patients	p-values[a]	% patients	p-values[a]
Placebo	57.5	–	51.3	–	46.6	–
QVA149	68.1	*p=0.004 §p=0.016	62.9	*p=0.004 §p=0.019	56.7	*p=0.019 §p=0.019
Indacaterol	64.6	*p=0.020	59.6	*p=0.014	53.6	–
Glycopyrronium	63.7	*p=0.018	59.4	*p=0.005 §p=0.024	53.8	*p=0.019 §p=0.021
Tiotropium	59.2	–	54.2	–	48.8	–

[a]p-values presented where p<0.05; *versus placebo; §versus tiotropium. LOCF: last observation carried forward; TDI: Transitional Dyspnoea Index.

TABLE S5. Proportion of patients with minimally clinically important difference in SGRQ at Week 26 (LOCF, full analysis set)

	SGRQ improvement			
	≥4 points		≥8 points	
Treatment	% patients	p-values[a]	% patients	p-values[a]
Placebo	56.6	–	37.8	–
QVA149	63.7	[§]p=0.047	51.3	*p=0.002 [‡]p=0.002 [§]p=0.001
Indacaterol	63.0	–	49.2	*p=0.006 [‡]p=0.008 [§]p=0.006
Glycopyrronium	60.5	–	41.9	–
Tiotropium	56.4	–	40.2	–

[a]p-values presented where p<0.05; *versus placebo; [§]versus tiotropium; [‡]versus glycopyrronium.
LOCF: last observation carried forward; SGRQ: St George's Respiratory Questionnaire.

FIGURE LEGENDS

FIGURE S1. FEV_1 (L) at 5 min and 30 min after dosing (full analysis set).

***p<0.001; values are LSM ± SE; n = number per treatment group in the full analysis set.

FIGURE S2. Trough FVC (L).

p<0.001 for QVA149 versus placebo, indacaterol, glycopyrronium and tiotropium at the end of Day 1, Weeks 12 and 26. Values are LSM ± SE; n = number per treatment group in the full analysis set.

FIGURE S3. Subgroup analyses of trough FEV_1 (L) with QVA149 versus placebo and active treatments after 26 weeks treatment (LOCF)

a) By baseline ICS use

b) By disease severity (*moderate or less; **severe or worse)

c) By gender

d) By age

N1 = number of patients included in the analysis in the QVA149 arm of the respective subgroup. N2 = number of patients included in the analysis in the comparator arm of the respective subgroup.

FIGURE S4. TDI focal score at a) Week 26 (LOCF) and b) Week 12 (LOCF).

a) ***p<0.001; §p=0.017; †p=0.007; values are LSM ± SE. n = number per treatment group in the full analysis set.

b) ***p<0.001; §p=0.012; †p=0.046; *p=0.030; values are LSM ± SE. n = number per treatment group in the full analysis set.

FIGURE S5. Odds ratios for differences between the active treatments and placebo in the proportion of patients achieving specified improvements in TDI and SGRQ scores at Week 26 (LOCF).

Data are presented as odds ratios ± 95% CIs. *p<0.05, **p<0.01 versus placebo. Other symbols denote where significant differences (not shown) occur: ‡‡p<0.01 versus glycopyrronium 50 µg; §p<0.05, §§p<0.01 versus tiotropium 18 µg. CI: confidence interval; SGRQ: St George's Respiratory Questionnaire; TDI: Transitional Dyspnoea Index.

FIGURE S6. Mean change from baseline in SGRQ total score[a] after 26 weeks of treatment. Negative value signifies improvement. Data presented as mean ± SE. n = number per treatment group in the full analysis set. [a]Imputed from last observation carried forward.

Figure S1

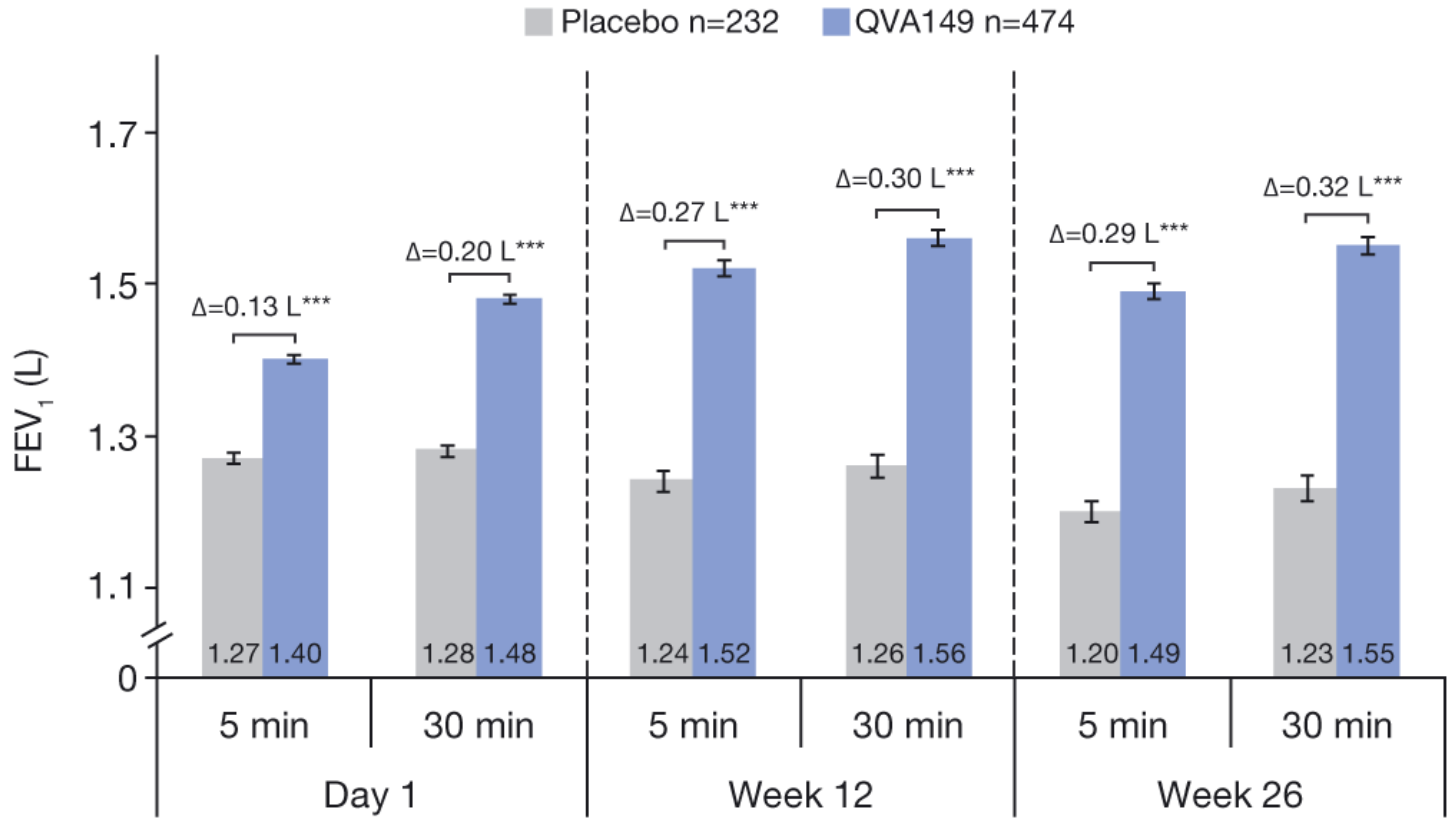

Placebo n=232
QVA149 n=474
FEV1 (L)
1.7
1.5
1.3
1.1
0
Δ=0.13 L***
Δ=0.20 L***
Δ=0.27 L***
Δ=0.30 L***
Δ=0.29 L***
Δ=0.32 L***
1.27 1.40
1.28 1.48
1.24 1.52
1.26 1.56
1.20 1.49
1.23 1.55
5 min
30 min
5 min
30 min
5 min
30 min
Day 1
Week 12
Week 26

Figure S2

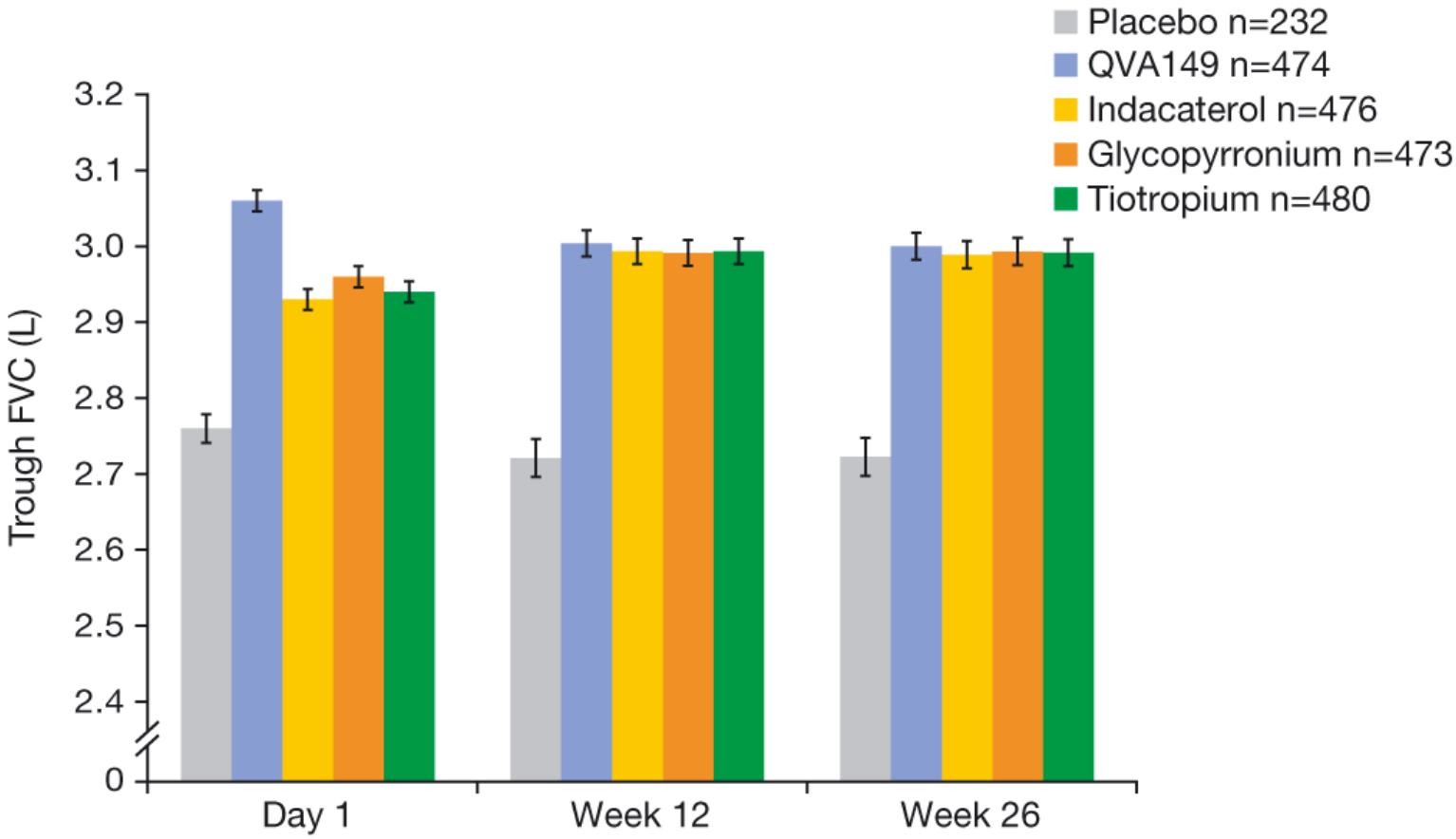
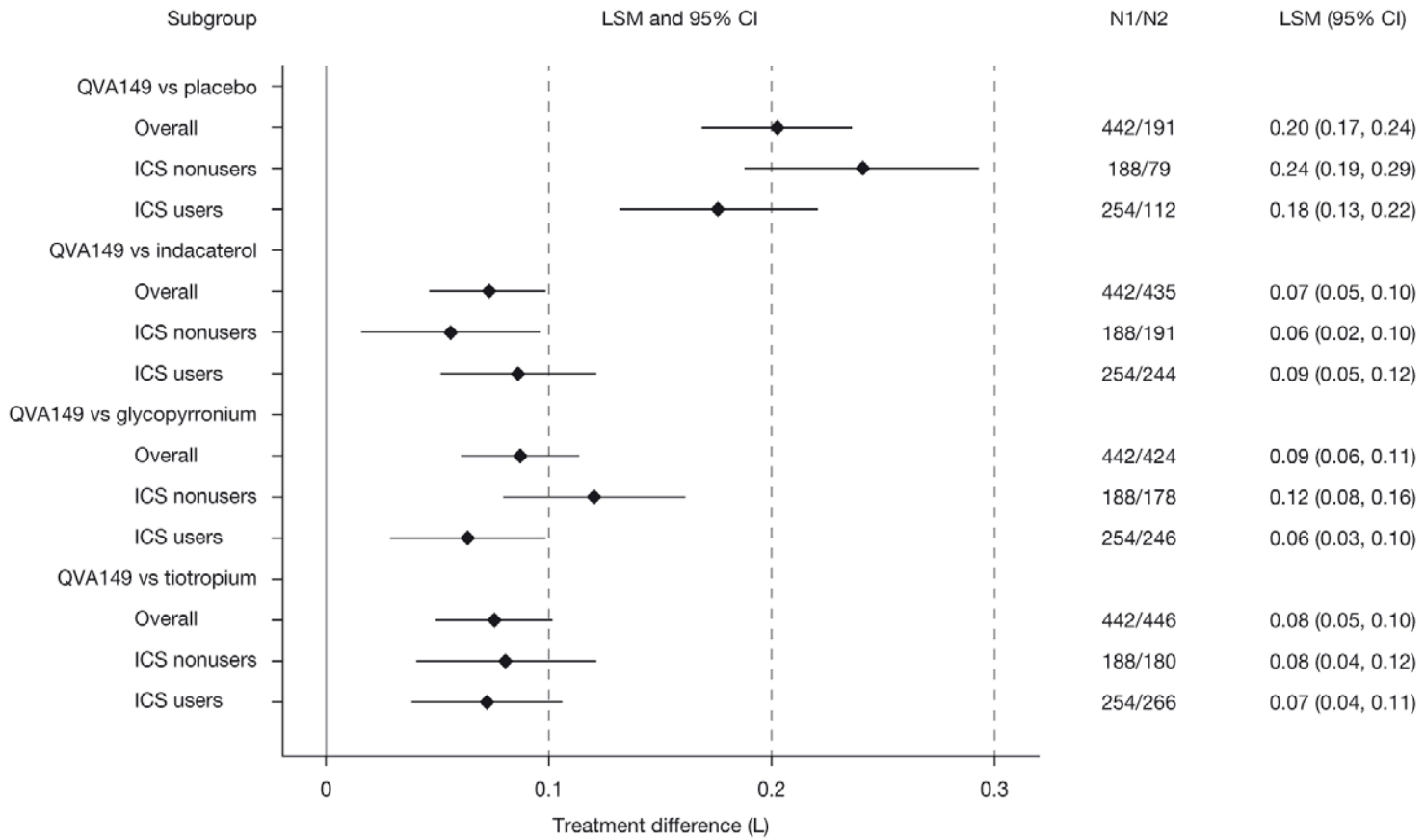
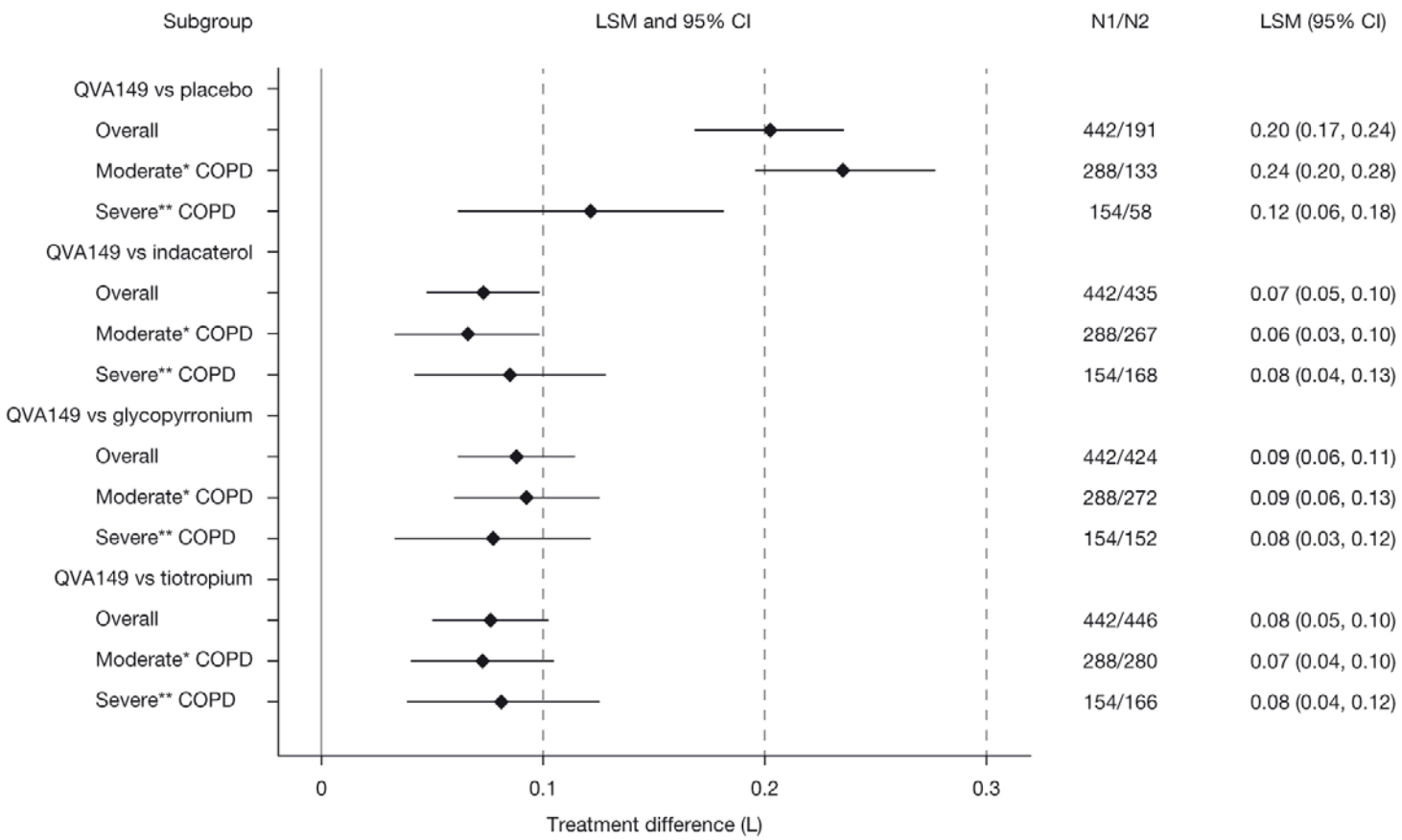

Placebo n=232
QVA149 n=474
Indacaterol n=476
Glycopyrronium n=473
Tiotropium n=480
Trough FVC (L)
3.2
3.1
3.0
2.9
2.8
2.7
2.6
2.5
2.4
0
Day 1
Week 12
Week 26

Figure S3

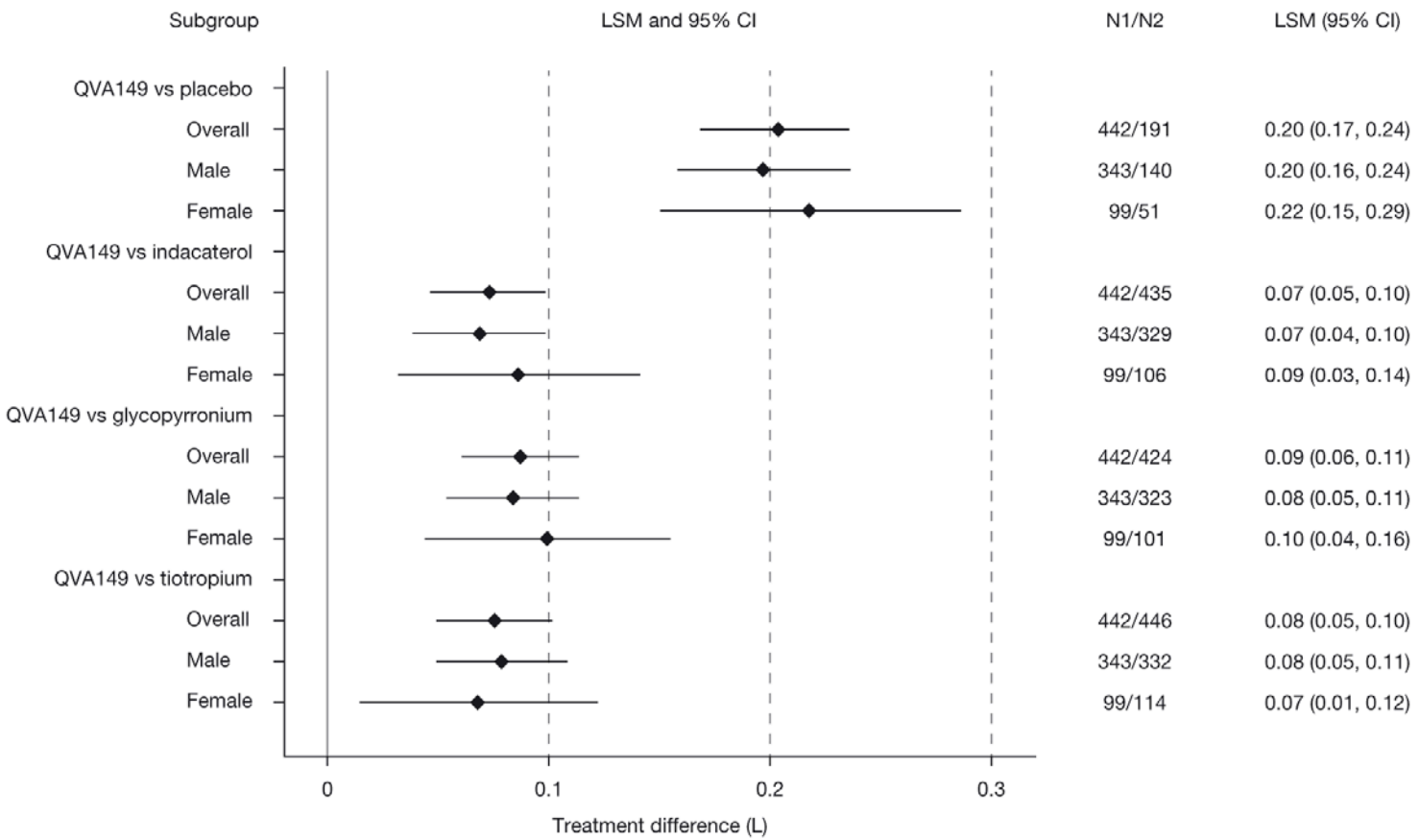
a)


Subgroup
LSM and 95% CI
N1/N2
LSM (95% CI)
QVA149 vs placebo
Overall
442/191
0.20 (0.17, 0.24)
ICS nonusers
188/79
0.24 (0.19, 0.29)
ICS users
254/112
0.18 (0.13, 0.22)
QVA149 vs indacaterol
Overall
442/435
0.07 (0.05, 0.10)
ICS nonusers
188/191
0.06 (0.02, 0.10)
ICS users
254/244
0.09 (0.05, 0.12)
QVA149 vs glycopyrronium
Overall
442/424
0.09 (0.06, 0.11)
ICS nonusers
188/178
0.12 (0.08, 0.16)
ICS users
254/246
0.06 (0.03, 0.10)
QVA149 vs tiotropium
Overall
442/446
0.08 (0.05, 0.10)
ICS nonusers
188/180
0.08 (0.04, 0.12)
ICS users
254/266
0.07 (0.04, 0.11)
0
0.1
0.2
0.3
Treatment difference (L)

b)


Subgroup
LSM and 95% CI
N1/N2
LSM (95% CI)
QVA149 vs placebo
Overall
442/191
0.20 (0.17, 0.24)
Moderate* COPD
288/133
0.24 (0.20, 0.28)
Severe** COPD
154/58
0.12 (0.06, 0.18)
QVA149 vs indacaterol
Overall
442/435
0.07 (0.05, 0.10)
Moderate* COPD
288/267
0.06 (0.03, 0.10)
Severe** COPD
154/168
0.08 (0.04, 0.13)
QVA149 vs glycopyrronium
Overall
442/424
0.09 (0.06, 0.11)
Moderate* COPD
288/272
0.09 (0.06, 0.13)
Severe** COPD
154/152
0.08 (0.03, 0.12)
QVA149 vs tiotropium
Overall
442/446
0.08 (0.05, 0.10)
Moderate* COPD
288/280
0.07 (0.04, 0.10)
Severe** COPD
154/166
0.08 (0.04, 0.12)
0
0.1
0.2
0.3
Treatment difference (L)

c)


Subgroup
LSM and 95% CI
N1/N2
LSM (95% CI)
QVA149 vs placebo
Overall
442/191
0.20 (0.17, 0.24)
Male
343/140
0.20 (0.16, 0.24)
Female
99/51
0.22 (0.15, 0.29)
QVA149 vs indacaterol
Overall
442/435
0.07 (0.05, 0.10)
Male
343/329
0.07 (0.04, 0.10)
Female
99/106
0.09 (0.03, 0.14)
QVA149 vs glycopyrronium
Overall
442/424
0.09 (0.06, 0.11)
Male
343/323
0.08 (0.05, 0.11)
Female
99/101
0.10 (0.04, 0.16)
QVA149 vs tiotropium
Overall
442/446
0.08 (0.05, 0.10)
Male
343/332
0.08 (0.05, 0.11)
Female
99/114
0.07 (0.01, 0.12)
0
0.1
0.2
0.3
Treatment difference (L)

d)

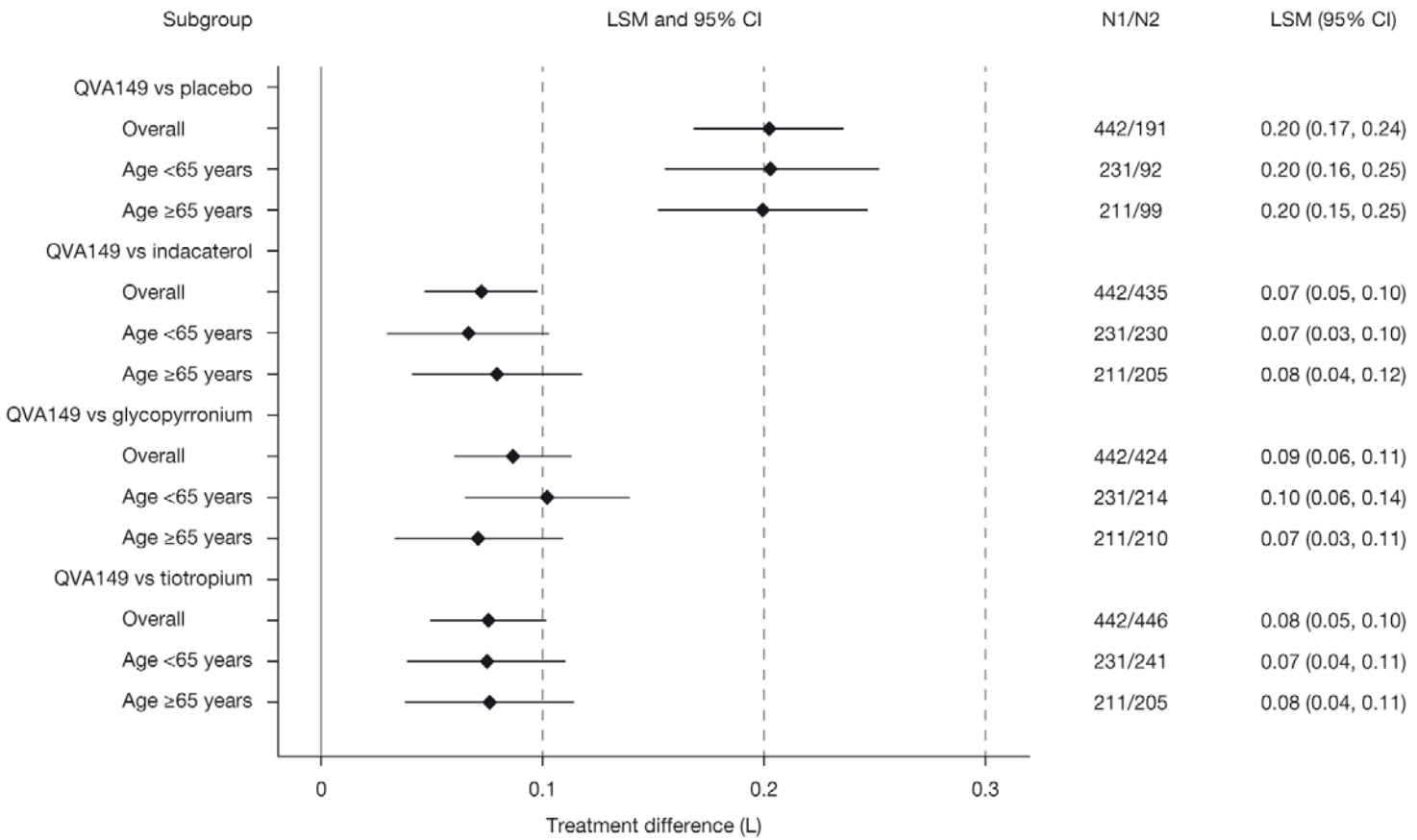
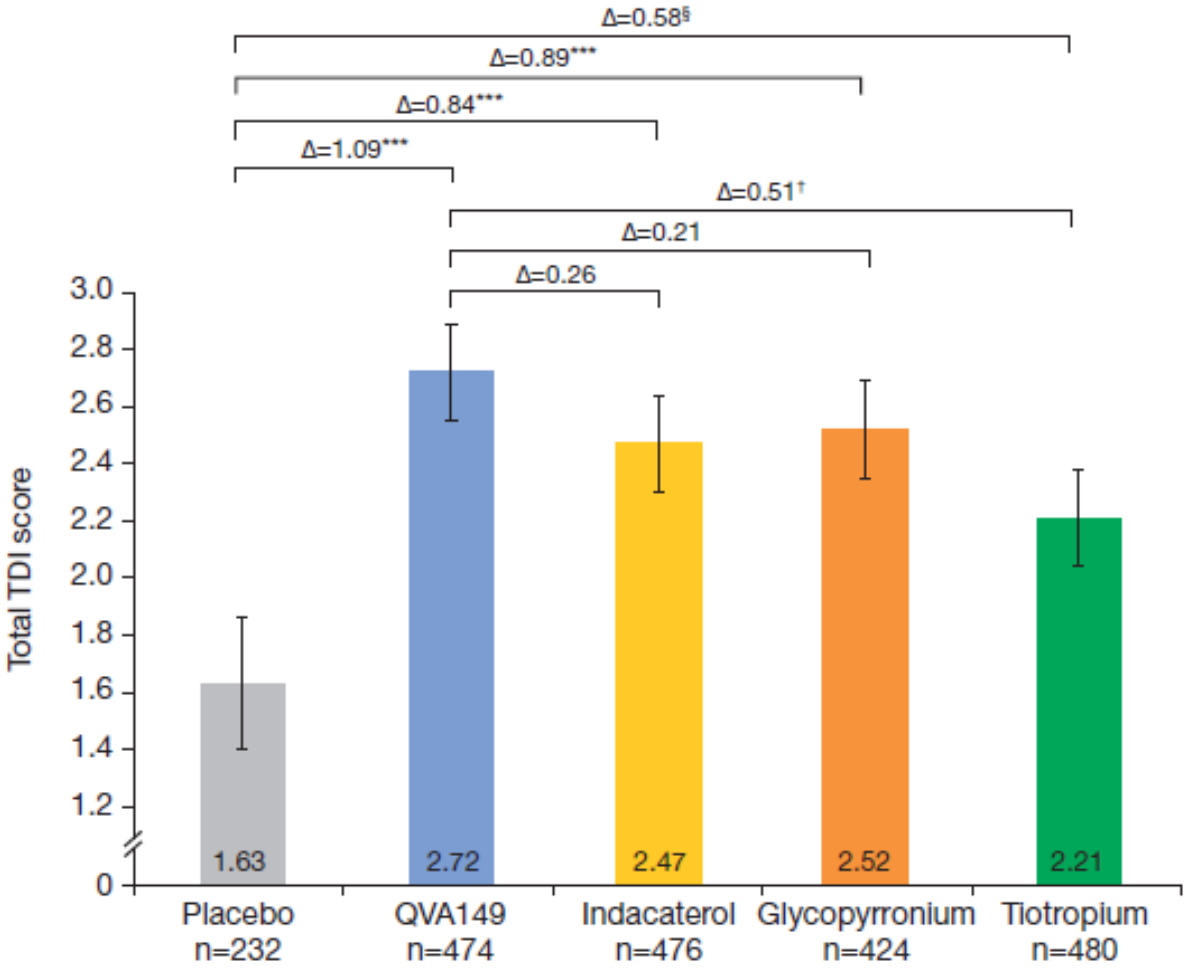

Subgroup
LSM and 95% CI
N1/N2
LSM (95% CI)
QVA149 vs placebo
Overall
442/191
0.20 (0.17, 0.24)
Age <65 years
231/92
0.20 (0.16, 0.25)
Age ≥65 years
211/99
0.20 (0.15, 0.25)
QVA149 vs indacaterol
Overall
442/435
0.07 (0.05, 0.10)
Age <65 years
231/230
0.07 (0.03, 0.10)
Age ≥65 years
211/205
0.08 (0.04, 0.12)
QVA149 vs glycopyrronium
Overall
442/424
0.09 (0.06, 0.11)
Age <65 years
231/214
0.10 (0.06, 0.14)
Age ≥65 years
211/210
0.07 (0.03, 0.11)
QVA149 vs tiotropium
Overall
442/446
0.08 (0.05, 0.10)
Age <65 years
231/241
0.07 (0.04, 0.11)
Age ≥65 years
211/205
0.08 (0.04, 0.11)
0
0.1
0.2
0.3
Treatment difference (L)

Figure S4

a)


Δ=0.58§
Δ=0.89***
Δ=0.84***
Δ=1.09***
Δ=0.51†
Δ=0.21
Δ=0.26
Total TDI score
3.0
2.8
2.6
2.4
2.2
2.0
1.8
1.6
1.4
1.2
0
1.63
2.72
2.47
2.52
2.21
Placebo n=232
QVA149 n=474
Indacaterol n=476
Glycopyrronium n=424
Tiotropium n=480

b)

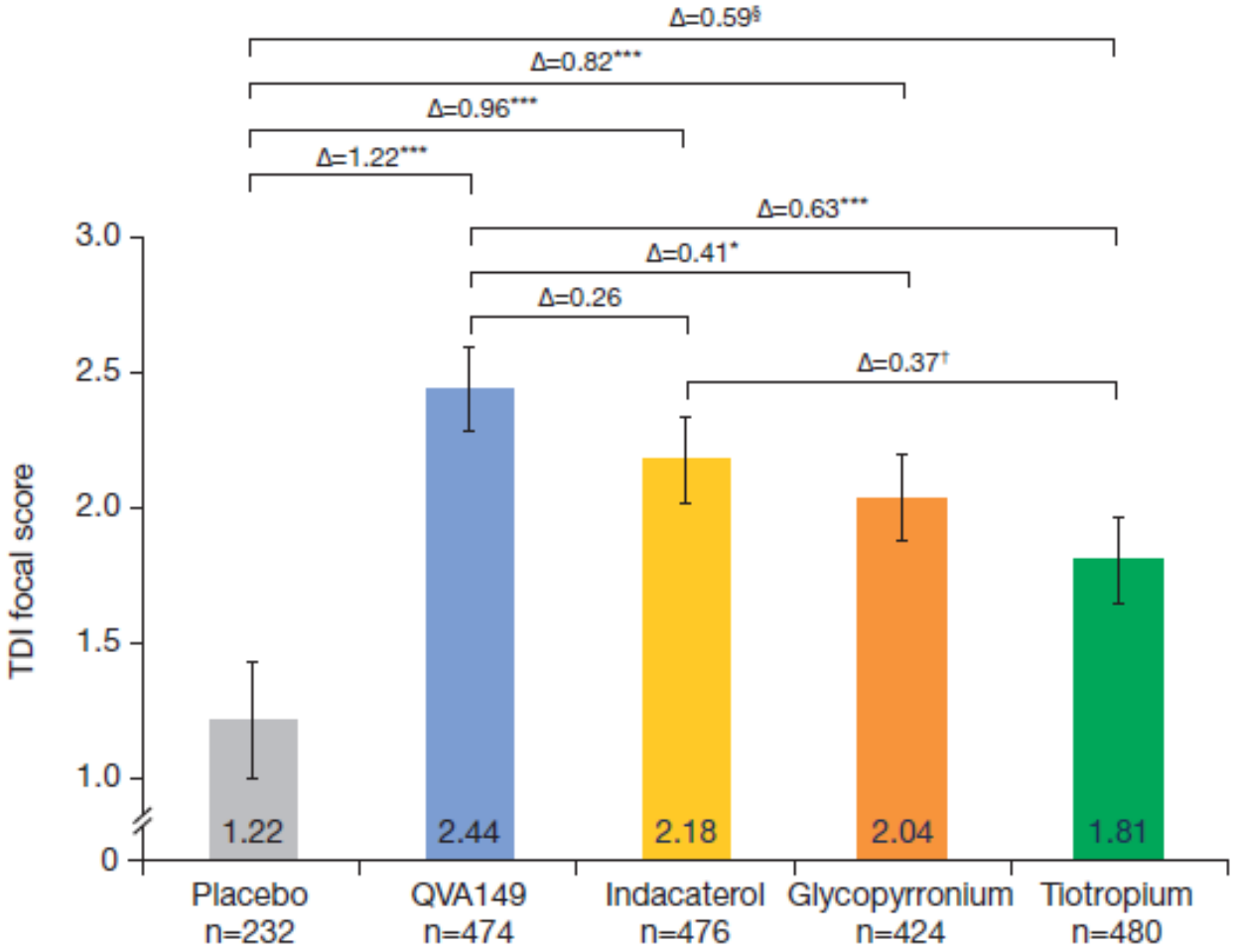

Δ=0.59§
Δ=0.82***
Δ=0.96***
Δ=1.22***
Δ=0.63***
Δ=0.41*
Δ=0.26
Δ=0.37†
TDI focal score
3.0
2.5
2.0
1.5
1.0
0
1.22
2.44
2.18
2.04
1.81
Placebo n=232
QVA149 n=474
Indacaterol n=476
Glycopyrronium n=424
Tiotropium n=480

Figure S5

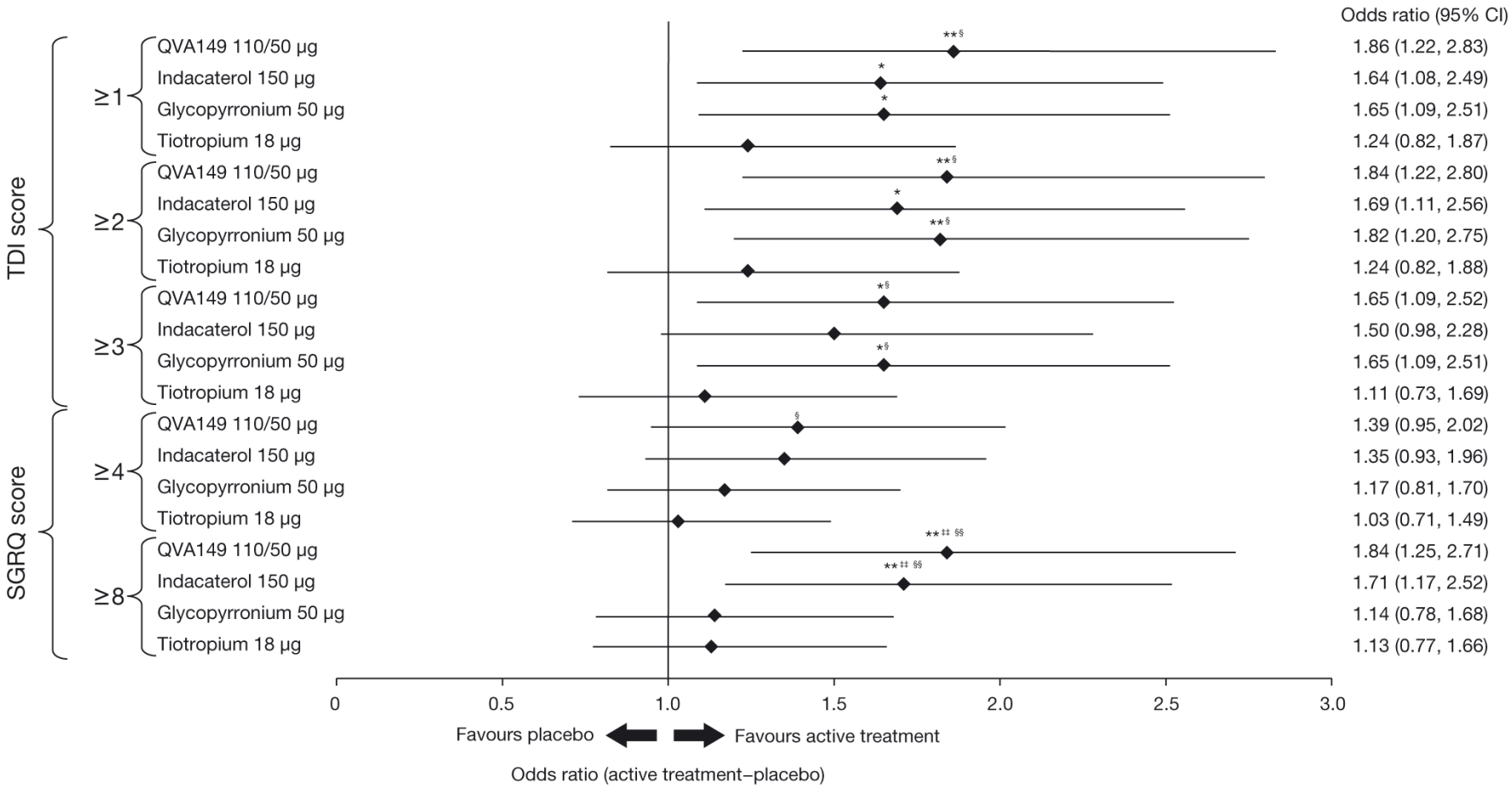
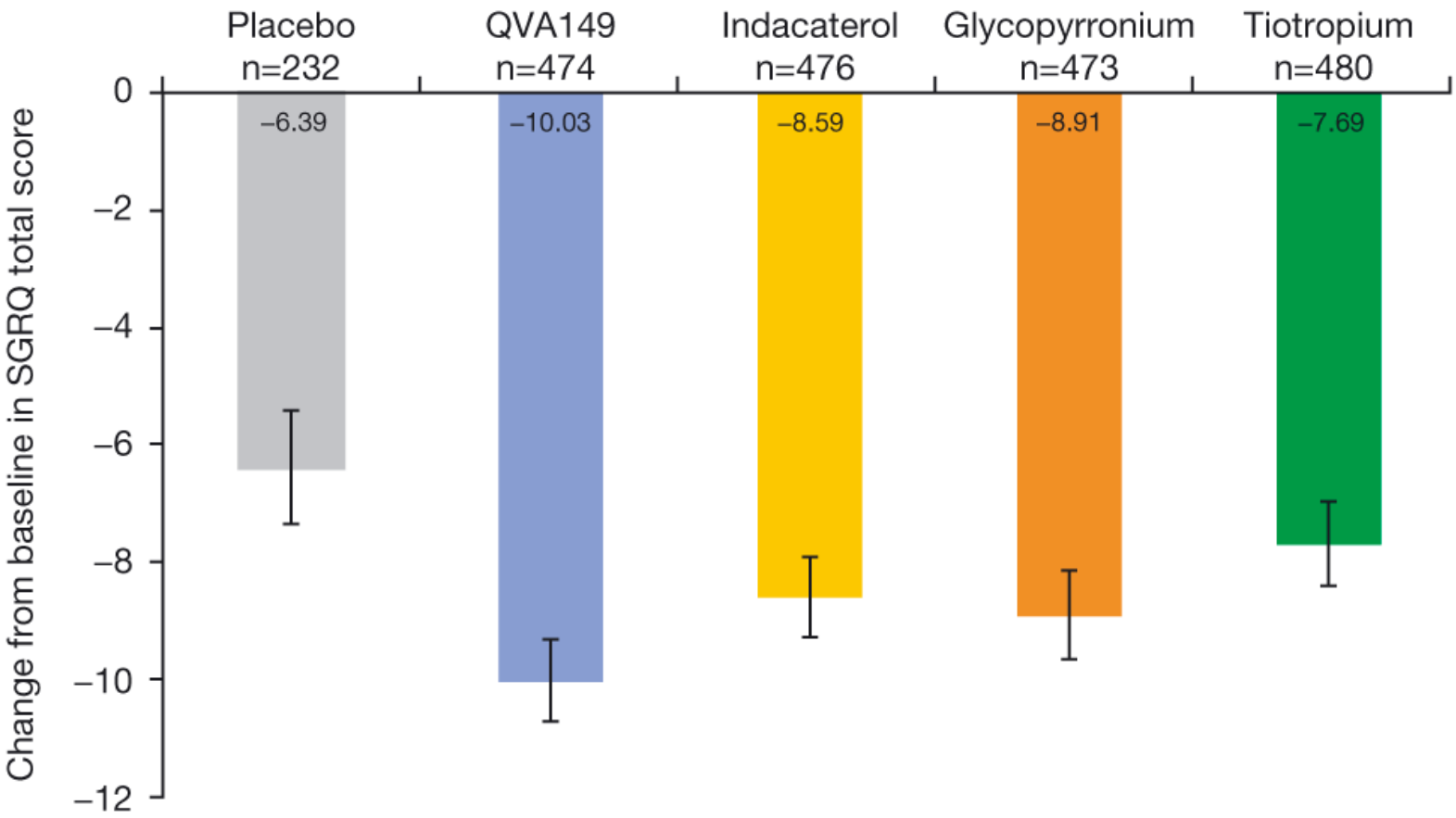


Figure S6


Placebo
n=232
QVA149
n=474
Indacaterol
n=476
Glycopyrronium
n=473
Tiotropium
n=480
0
−2
−4
−6
−8
−10
−12
−6.39
−10.03
−8.59
−8.91
−7.69
Change from baseline in SGRQ total score