

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

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ABSTRACT

We investigated the efficacy and safety of dual bronchodilation with QVA149 versus its mono-components indacaterol and glycopyrronium, and tiotropium and placebo in patients with moderate-to-severe COPD.

This was a multicentre, randomised, double-blind, placebo- and active-controlled, 26-week trial. Patients (n=2144) were randomised (2:2:2:2:1) to once-daily QVA149 110/50 µg, indacaterol 150 µg, glycopyrronium 50 µg, open-label tiotropium 18 µg or placebo. The primary endpoint was trough FEV₁ at Week 26 for QVA149 versus its mono-components. Secondary endpoints included dyspnoea, health status, rescue medication use and safety.

Trough FEV₁ at Week 26 was significantly improved (p<0.001) with QVA149 compared with indacaterol and glycopyrronium (least squares mean [LSM] differences: 0.07 L and 0.09 L, respectively), tiotropium and placebo (LSM differences: 0.08 L and 0.20 L, respectively); these beneficial effects were sustained throughout the 26-week study. QVA149 significantly improved dyspnoea and health status versus placebo (p<0.001 and p=0.002, respectively) and tiotropium (p=0.007 and p=0.009, respectively) at Week 26. All treatments were well tolerated.

Dual bronchodilation with once-daily QVA149 demonstrated superior and clinically meaningful outcomes versus placebo and superiority versus treatment with a single bronchodilator, with a safety and tolerability profile similar to placebo, supporting the concept of fixed-dose LAMA/LABA combinations for the treatment of COPD.

Trial registration NCT01202188.

Keywords: Chronic obstructive pulmonary disease, clinical outcomes, glycopyrronium, indacaterol, lung function, tiotropium

INTRODUCTION

Bronchodilators are the cornerstone of symptomatic management of chronic obstructive pulmonary disease (COPD) [1]. Current guidelines recommend treatment with one or more long-acting bronchodilators for patients with moderate-to-very severe COPD [1]. The use of two bronchodilators with different mechanisms of action has been shown to provide additional benefits compared with either given alone, without significantly increasing side effects [2, 3]. Both indacaterol, a long-acting β_2 -agonist (LABA), and tiotropium, a long-acting muscarinic antagonist (LAMA), are effective as monotherapies and have acceptable safety profiles [4, 5]. In addition, their concurrent use has been shown to provide superior bronchodilation and improvement in air trapping compared with tiotropium alone [6].

Glycopyrronium (NVA237) is a recently approved once-daily LAMA for the treatment of moderate-to-severe COPD, which has been shown to provide rapid and sustained improvements in lung function, dyspnoea, health status, exercise endurance and exacerbation risk, with improvements similar to tiotropium, and a safety profile similar to placebo [7–9]. QVA149 is a novel, once-daily, dual bronchodilator containing a fixed dose of the LABA indacaterol with the LAMA glycopyrronium. In patients with COPD, QVA149 has demonstrated rapid and sustained bronchodilation, which is significantly superior to that observed with indacaterol alone or placebo, and it is well tolerated with an adverse event (AE) profile similar to placebo [10, 11]. In the current SHINE study, we sought to confirm the ‘rule of combination’ [12] that dual bronchodilation with QVA149 will provide additional therapeutic benefits compared to the mono-components, indacaterol and glycopyrronium, as well as compared to tiotropium, the current gold-standard of care, and placebo in patients with moderate-to-severe COPD.

METHODS

Study design

The study was a multicentre, randomised, double-blind, parallel-group, placebo- and active-controlled 26-week trial, and comprised a washout, run-in and the 26-week treatment period, with 30 days of follow-up after the last visit (figure 1). First patient first visit: 21 September 2010; last patient last visit: 10 February 2012. Patients receiving fixed-dose combinations of LABA/inhaled corticosteroid (ICS) were switched to an equivalent dose of ICS monotherapy. After screening, eligible patients were randomised in a 2:2:2:2:1 ratio (via interactive response technology) to treatment with double-blind QVA149 110/50 µg, indacaterol 150 µg, glycopyrronium 50 µg, open-label tiotropium 18 µg or placebo. All medications were administered once daily in the morning via the Breezhaler[®] device except for tiotropium, which was administered via the Handihaler[®] device. Salbutamol/albuterol pressurised metered-dose inhaler (pMDI) was provided as rescue medication. Additional details of the study design and randomisation/blinding procedures are included in the online Appendix.

Patients

Participants were aged ≥ 40 years, had moderate-to-severe stable COPD (Stage II or III according to GOLD 2008 criteria) [13], and a smoking history of ≥ 10 pack-years. At screening, they were required to have a post-bronchodilator forced expiratory volume in 1 second (FEV_1) $\geq 30\%$ and $< 80\%$ of predicted normal and post-bronchodilator FEV_1 /forced vital capacity (FVC) < 0.70 . Further details of inclusion and exclusion criteria are provided in the online Appendix (appendix table 1). All participants provided written informed consent, and the study was approved by relevant national and local ethics review boards and was conducted in accordance with the Declaration of Helsinki, Good Clinical Practice guidelines and all applicable regulatory requirements.

Analysis

Assessments and outcome measures

Spirometry outcomes (FEV₁ and FVC) were assessed at baseline and at Days 1 and 2, and Weeks 2, 4, 8, 12, 16, 20, and 26 during the treatment period. A subset of patients performed 12-hour serial spirometry at Day 1, and 24-hour serial spirometry at Week 26. Inspiratory capacity was measured at baseline and at Days 1 and 2, and Weeks 12 and 26, in a subset of patients. Patients used an electronic diary to record data on symptoms and rescue medication use. Dyspnoea was assessed using the Baseline Dyspnoea Index at baseline and the Transition Dyspnoea Index (TDI) at Weeks 12 and 26. Patients completed the St George's Respiratory Questionnaire (SGRQ) at baseline and Weeks 12 and 26 to evaluate changes in health status. Safety was assessed by recording AEs and serious AEs (SAEs) throughout the study, as well as assessment of electrocardiograms (ECGs), haematology, clinical chemistry, urinalysis, physical condition, and vital signs (pulse, blood pressure). An independent adjudication committee assessed all deaths, serious cardio- and cerebro-vascular (CCV) events, and atrial fibrillation/flutter events that occurred during the study. In a subset of patients, 24-hour Holter monitoring was used as an additional measure of cardiovascular safety.

The primary objective was superiority in trough FEV₁ (defined as the mean of FEV₁ values at 23 hours 15 minutes (min) and 23 hours 45 min post-dose) at Week 26 for QVA149 versus its mono-components indacaterol and glycopyrronium. Key secondary objectives were TDI focal score and SGRQ total score at Week 26, and daily rescue medication use over 26 weeks, for QVA149 versus placebo. Important secondary objectives were to determine the effects of QVA149, indacaterol and glycopyrronium compared with placebo, and to determine whether QVA149 was at least as effective as open-label tiotropium in terms of trough FEV₁ at Week 26. Other secondary objectives included effects of the treatments on dyspnoea, health status, patient symptoms, use of rescue medication, safety and tolerability, and cardiovascular safety, as well as other lung function endpoints (area under the curve [AUC] from 0–4 hours [AUC_{0–4 h}] for FEV₁, peak FEV₁, 12/24 hour serial spirometry in a subset of patients) at different timepoints during the 26-week treatment period. Inspiratory capacity (IC) was investigated as an exploratory objective. Some pre-

planned subgroup analyses were trough FEV₁ at Week 26 according to age, sex, severity of COPD and baseline ICS use.

Statistical methods

The sample size of 380 evaluable patients in each active group and 180 patients in the placebo group was based on reaching acceptable levels of power for the key-endpoints. Assuming a 20% dropout rate at Week 26, a proposed sample size of 2138 randomised patients (475 in each of the QVA149, indacaterol, glycopyrronium and tiotropium groups, 238 in the placebo group) was determined. Additional details on statistical power are included in the Appendix.

To control for multiplicity, a statistical gatekeeping procedure was used to control the family-wise error rate at 5% for the primary, key and important secondary comparisons. A mixed model was used to analyse the primary, key and important secondary endpoints/objectives. Other secondary objectives were analysed using similar methods, without adjustment for multiplicity. Additional details of the statistical analyses are provided in the Appendix.

RESULTS

Of 3625 patients screened, 2144 patients were randomised to receive QVA149 (n=475), indacaterol (n=477), glycopyrronium (n=475), tiotropium (n=483), and placebo (n=234). Almost all patients (99.6%) were included in the full analysis and safety sets; 89.1% of randomised patients completed the study (figure 2).

Patient demographics and baseline characteristics

Patient demographics and other baseline characteristics were similar across the five treatment groups (table 1). The majority of the patients were male (75.4%), had moderate COPD (63.6%), and had no report of exacerbations in the previous year (74.6%). There were no meaningful differences between treatment groups for spirometry measurements at screening. Overall, the mean FEV₁ post-bronchodilator was 55.2% of predicted normal and mean FEV₁ reversibility was 20.3%.

Spirometry

Trough FEV₁ at Week 26 (the primary efficacy endpoint) was significantly improved with QVA149 compared with both indacaterol and glycopyrronium, with treatment differences of 0.07 L and 0.09 L, respectively (both $p < 0.001$; figure 3a). QVA149 also provided significantly higher improvement in trough FEV₁ compared with tiotropium and placebo at Week 26, with treatment differences of 0.08 L and 0.2 L, respectively ($p < 0.001$; figure 3a). QVA149 was non-inferior to tiotropium by the pre-specified margin ($p < 0.001$). These statistically significant differences in trough FEV₁ were maintained throughout the study versus all active treatments and placebo ($p < 0.001$; figure 3b, table 2). All active treatments at Week 26 (last observation carried forward; LOCF) had an increase from baseline in trough FEV₁, the mean increase being highest for the QVA149 group – see appendix for details, along with post-hoc analyses of the proportion of patients with an increase of >100 mL or >200 mL in trough FEV₁ at Week 26.

QVA149 provided rapid bronchodilation following the first dose on Day 1, with significantly higher FEV₁, FEV₁ AUC_{0-4h} and peak FEV₁ compared with placebo, glycopyrronium and tiotropium (all $p < 0.01$; table 2). FEV₁ treatment differences for QVA149 versus placebo at 5 min and 30 min post dose on Day 1, Weeks 12 and 26 were significant (all $p < 0.001$; appendix figure 1). At 5 min post-dose, LSM FEV₁ was 1.40 L on Day 1 and 1.49 L at Week 26 for QVA149; this was significantly higher at both time points, respectively, versus glycopyrronium (LSM FEV₁ 1.36 L and 1.36 L; treatment difference +0.04 L and +0.13 L, respectively; $p < 0.001$) and tiotropium (LSM FEV₁ 1.33 L and 1.38 L; treatment difference +0.07 L and +0.12 L; $p < 0.001$). In addition, QVA149 provided marked statistically significant improvements versus placebo and the active comparators in peak FEV₁ and FEV₁ AUC_{0-4h} at Week 26 (all $p < 0.001$; table 2).

Serial spirometry (conducted in a subset of 294 patients) showed that QVA149 provided rapid and sustained bronchodilation throughout the assessment periods on Day 1 and Week 26, with statistically significant improvements in FEV₁ compared with placebo at all assessed timepoints ($p < 0.001$), and compared with indacaterol, glycopyrronium and tiotropium at almost all of the assessed timepoints on Day 1 and

at Week 26 ($p < 0.05$; figure 4). At Week 26 peak FEV₁ values were seen for QVA149 and tiotropium at 2 hours post-dose, with treatment differences of 0.4 L with QVA149 versus placebo; 0.17 L versus indacaterol; 0.15 L versus glycopyrronium; 0.16 L versus tiotropium (all treatment comparisons $p < 0.001$). Subgroup analysis of improvement in trough FEV₁ at Week 26 by COPD severity (GOLD FEV₁ categories) confirmed a significantly greater improvement with QVA149 versus placebo and mono-bronchodilators in patients with both moderate (LSM treatment differences [all $p < 0.001$]: versus placebo, 0.24 L; indacaterol, 0.06 L; glycopyrronium, 0.09; tiotropium 0.07) and severe (LSM treatment differences [all $p < 0.001$]: versus placebo, 0.12 L; indacaterol, 0.08 L; glycopyrronium, 0.08; tiotropium 0.08) COPD (appendix figure 3). Other subgroup comparisons demonstrated a similar improvement with QVA149, which was consistent with the overall patient population (appendix figure 3). The results of other spirometric analyses are provided in table 2 and are outlined in the appendix.

Dyspnoea

TDI focal score was statistically significantly improved with QVA149 compared with placebo and tiotropium at Week 26, and compared with placebo, glycopyrronium and tiotropium at Week 12 (appendix table 3, appendix figure 4). Statistically significant improvements in TDI focal score versus placebo were observed with indacaterol, glycopyrronium and tiotropium at Weeks 12 and 26. Details on the proportion of patients achieving a minimal clinically important difference (MCID) for TDI score are included in the Appendix.

Health status

At Week 26, SGRQ total score was significantly improved with QVA149 (−10.03 versus baseline) compared with placebo (−6.39 versus baseline; QVA149–placebo LSM treatment difference −3.01, $p = 0.002$) and tiotropium (−7.69 versus baseline; QVA149–tiotropium LSM treatment difference −2.13, $p = 0.009$; appendix table 3, appendix figure 6). There were no significant improvements with any of the other active treatments compared with placebo. A similar improvement was seen at Week

12 – details are provided in the Appendix, along with an analysis of patients achieving the MCID for SGRQ total score.

Rescue medication use

Patients in the QVA149 group used statistically significantly less rescue medication over 26 weeks and had a significantly higher percentage of days with no rescue medication use compared with other treatment groups (appendix table 3).

Patient symptoms

The percentage of nights with no awakenings over the 26-week treatment period was statistically significantly higher for QVA149 compared with placebo and glycopyrronium, and approached statistical significance compared with tiotropium (appendix table 3). The percentage of days with no daytime symptoms was also statistically significantly higher for QVA149 compared with placebo. The percentage of days patients were able to perform their usual daily activities was statistically significantly higher in the QVA149 group compared with placebo and all active comparators over the 26-week treatment period (appendix table 3).

Safety

The overall incidence of AEs was similar across the five treatment groups (table 3). The most frequently reported AE was a COPD exacerbation; 39.2% in the placebo group and 28.9%, 32.1%, 31.7% and 28.8% in the QVA149, indacaterol, glycopyrronium and tiotropium groups, respectively. Fewer patients in the QVA149 group had AEs leading to discontinuation of study drug compared with placebo, indacaterol, glycopyrronium and tiotropium groups (table 3). SAEs occurred with a lower frequency in the QVA149 group compared with placebo (table 3).

There were no reports of serious CCV events in the QVA149 group and few reported and adjudicated in the other treatment groups (table 3). Atrial fibrillation/flutter events (i.e. reported as AEs, SAEs or ECG findings) were uncommon in all groups

(table 3). There were no clinically relevant differences in QTc interval (Fridericia's formula) between treatment groups.

Seven patients died during the study between the first treatment and within 30 days of last study drug administration. There was one death in the QVA149 (colon cancer), two in the indacaterol (lung cancer and sudden death), one in the glycopyrronium (sudden death), and three in the tiotropium group (COPD exacerbation, COPD exacerbation with pneumonia, and rectal cancer). An additional two patients died more than 30 days after the last dose of study drug but before the end of the follow-up visit (indacaterol [n=1]: pneumonia; glycopyrronium [n=1]: colon cancer). None of the deaths were considered by the investigator to be related to the study drug.

DISCUSSION

Combining two bronchodilators with different mechanisms of action has the potential to enhance efficacy compared with single agents without increasing adverse effects [2, 3]. In the SHINE study, dual bronchodilation with QVA149, administered once-daily, provided superior improvements in lung function compared with its mono-components indacaterol and glycopyrronium given alone, as well as tiotropium and placebo. Improvement in the primary endpoint, trough FEV₁ over placebo, was both statistically and clinically significant (considered to be ≥ 100 mL in COPD) and versus active comparators it approached clinical significance. Furthermore, lung function improvements with QVA149 were superior at their peak and, in a subset of patients monitored over 24 hours, throughout the day. Similar trends to the overall population were observed in subgroup analyses. Improvements in lung function versus placebo were greater in patients with moderate versus severe COPD, however, statistically and clinically significant improvements in trough FEV₁ were seen for both moderate and severe patient subgroups. Improvements in lung function were not influenced by patient age, gender or concurrent use of ICS. Further, they were maintained throughout the 26-week treatment period, and the onset of action of QVA149 was confirmed to be rapid, similar to that of a short-acting β_2 -agonist.

These beneficial effects of QVA149 on lung function were paralleled by statistically significant improvements in other clinically important endpoints: dyspnoea, health status and patient symptoms and reduced rescue medication use. QVA149 was

significantly superior to placebo and tiotropium for both the TDI and SGRQ total score at Week 26; no other active treatment achieved a significant improvement in SGRQ versus placebo. Furthermore, a significantly higher proportion of patients on QVA149 achieved a clinically meaningful improvement in TDI (≥ 1 unit) and SGRQ (≥ 4 units) versus placebo and tiotropium.

QVA149 was well tolerated over the 26-week study with an AE profile similar to that of placebo. In addition, no actual or potential safety signals were observed with the combination compared with the single bronchodilators. Despite previous concerns that LABAs and LAMAs may present a risk of cardiovascular events [14–17], the CCV safety profile of this LABA/LAMA combination was similar to that of placebo. The results of this study are consistent with those of several published studies that have investigated the efficacy and safety of free combinations of LABAs and LAMAs in patients with COPD [6, 18–20], but this is the first to demonstrate the additive benefit of the two classes of long-acting bronchodilator in a combination device. Previous studies have been limited by different durations of actions of the LAMA and LABA components (i.e. formoterol or salmeterol having to be administered twice daily). Our study confirms that the additive benefit of indacaterol and glycopyrronium persists over 24 hours, without tachyphylaxis, providing further support for the use of dual bronchodilators.

The present study supports the GOLD 2013 strategy alternate choice recommendation that the addition of a second bronchodilator in patients with moderate-to-severe COPD (groups B–D) may optimise symptom benefit [1]. In ‘low risk’ patients who remain symptomatic on a single bronchodilator (group B), the combination of indacaterol plus glycopyrronium in a single inhaler may lead to significantly improved outcomes compared with LABA or LAMA monotherapy. In ‘high risk’ patients with severe or very severe COPD (high symptom level and historical exacerbation frequency; groups C and D in the GOLD management strategy [1]) a LABA plus a LAMA is recommended as an alternative to a LABA/ICS (group C) or ICS plus LABA and/or LAMA (group D). In comparing LABA plus LAMA and LABA/ICS, improvements in lung function achieved with two bronchodilators are expected to be numerically superior to the single bronchodilator in LABA/ICS combinations. In the TORCH study, combination therapy achieved 50 mL and 44 mL improvement in FEV₁ versus salmeterol and fluticasone propionate alone,

respectively; however, the LABA/ICS is selected for its demonstrated effect on COPD exacerbations [21]. A real-world analysis has indicated that a high proportion of patients at low risk for exacerbations (groups A or B) may be receiving ICS inappropriately [22]. Some patients currently receiving combined LABA/ICS may do better on a LABA/LAMA combination [23]. This would provide dual bronchodilation without the need for ICS treatment, and therefore without the inherent risks of ICS [24], as recommended by the GOLD 2013 strategy [1]. The 26-week ILLUMINATE study supports the use of QVA149 versus LABA/ICS in this population [25]. QVA149 once daily was associated with significant improvements in lung function and dyspnoea versus twice-daily salmeterol/fluticasone. Furthermore, the current SHINE study provides evidence for the additive benefit and safety of a LABA/LAMA combination, demonstrating that QVA149 is superior for most endpoints over tiotropium, which is currently recommended as an alternative to LABA/ICS, alone or in combination with a LABA.

Features of QVA149 that may help to reduce non-adherence to treatment, which remains high in COPD [26] are the convenience of once-daily dosing [27] which is generally preferred by patients [26, 28, 29] and the need for only one single inhaler. Furthermore, the rapid onset of action may be evident to patients as they wake at the nadir of their daily lung function cycle when symptoms are most prominent [30]. However, these advantages of a LABA/LAMA combination and QVA149 are speculative and need to be tested in further prospective studies.

We acknowledge several limitations in our study. Firstly, with regards to the study population, we did not intend to include the full range of COPD severities that might benefit from dual long-acting bronchodilators. Since our main objective was to assess the incremental benefit of two bronchodilators in combination (versus one), we elected to only recruit patients with moderate-to-severe COPD. As in our study, results of studies involving LABA/ICS combinations (e.g. the TORCH study [21]) and tiotropium (e.g. the UPLIFT study [31]), have confirmed that patients with moderate disease showed the greatest improvements in lung function. The apparent high reversibility of FEV₁ (20%) is attributable to the fact that both salbutamol and ipratropium were administered during this test, and reversibility of this magnitude is not unusual in moderate COPD. The inclusion criteria went to lengths to exclude patients with asthma (age of onset of symptoms after 40 years, absence of rhinitis and blood eosinophil count of <600/mm³ [see Appendix]). Finally, unlike most COPD

studies, which enrich for patients with exacerbations, in our study we excluded patients with a recent COPD exacerbation (in the previous 6 weeks) to reduce the impact of withdrawals due to exacerbations on the primary spirometric endpoint. For this reason, along with the fact that patients had milder disease and the study was relatively short (6 months), the present study does not provide useful information on the effect of QVA149 on COPD exacerbations, which has been examined in studies of appropriate design (SPARK study [32]). A further limitation of our study is the difficulty in evaluating the clinical significance of spirometric and other clinical endpoints (TDI and SGRQ) versus active (mono-component) treatments. Although statistically superior to all mono-components, QVA149 attained the MCID for only some comparisons (see figure 3 and appendix table 3). However, it should be noted that the MCID for trough FEV₁ of 100 mL is generally used for comparisons versus placebo, and that the mean improvements of 70, 80 and 90 mL versus indacaterol, glycopyrronium and tiotropium, respectively, approach this threshold value; comparative data for TDI and SGRQ also support this trend.

In conclusion, once-daily QVA149 demonstrated superior efficacy compared with placebo, its mono-components indacaterol and glycopyrronium, and the current standard of care tiotropium in patients with moderate-to-severe COPD. QVA149 was also associated with an AE profile that was similar to placebo with no additional safety signal compared with monotherapies. This is the first study to demonstrate the advantage of dual bronchodilation with a fixed-dose LABA/LAMA combination, compared with a single bronchodilator in patients with moderate-to-severe COPD.

Authors' contributions

Eric Bateman, Nicola Gallagher, Yulia Green, Michelle Henley, and Donald Banerji participated in design and conduct of the study. Eric Bateman was principal study investigator and drafted the manuscript. Neil Barnes was an investigator on the study. All authors participated in analysis and interpretation of results, critical revision of the article for intellectual content, and approved the final version of the manuscript for publication. Eric Bateman and Donald Banerji are the guarantors of the paper.

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Conflicts of interest

All authors have completed the ERJ statement of interest form.

Ethical approval

The study was approved by the Independent Ethics Committee or Institutional Review Board for each centre, and was conducted according to Good Clinical Practice and the ethical principles of the Declaration of Helsinki.

Patient consent

All participants provided informed written consent.

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TABLES

TABLE 1. Demographics and baseline characteristics

	Placebo	QVA149 110/50 µg	Indacaterol 150 µg	Glycopyrronium 50 µg	Tiotropium 18 µg
Subjects, n	232	474	476	473	480
Age (years), mean (SD)	64.4 (8.6)	64.0 (8.9)	63.6 (8.8)	64.3 (9.0)	63.5 (8.7)
Sex, male, n (%)	169 (72.8)	362 (76.4)	354 (74.4)	365 (77.2)	360 (75.0)
Race, n (%)					
Caucasian	155 (66.8)	321 (67.7)	332 (69.7)	315 (66.6)	322 (67.1)
Asian	71 (30.6)	140 (29.5)	131 (27.5)	137 (29.0)	135 (28.1)
Other	6 (2.6)	13 (2.7)	13 (2.7)	21 (4.4)	23 (4.8)
Duration of COPD, years, mean (SD)	6.4 (5.7)	6.0 (5.5)	6.3 (5.6)	6.5 (5.8)	6.1 (5.5)
COPD severity, n (%)					
Moderate	157 (67.7)	313 (66.0)	294 (61.8)	298 (63.0)	296 (61.7)
Severe	75 (32.3)	161 (34.0)	182 (38.2)	173 (36.6)	184 (38.3)
ICS use, %	134 (57.8)	268 (56.5)	269 (56.5)	274 (57.9)	282 (58.8)
Smoking status, n (%)					
Ex-smoker	139 (59.9)	282 (59.5)	292 (61.3)	284 (60.0)	291 (60.6)

	Placebo	QVA149 110/50 µg	Indacaterol 150 µg	Glycopyrronium 50 µg	Tiotropium 18 µg
Current smoker	93 (40.1)	192 (40.5)	184 (38.7)	189 (40.0)	189 (39.4)
COPD exacerbation history, n (%) ^a					
0	184 (79.3)	352 (74.3)	348 (73.1)	346 (73.2)	363 (75.6)
1	37 (15.9)	94 (19.8)	106 (22.3)	91 (19.2)	93 (19.4)
≥2	11 (4.7)	28 (5.9)	22 (4.6)	36 (7.6)	24 (5.0)
Mean (SD) pre-bronchodilator FEV ₁ (L)	1.3 (0.5)	1.3 (0.5)	1.3 (0.5)	1.3 (0.5)	1.3 (0.5)
Mean (SD) FEV ₁ (L) post- bronchodilator	1.5 (0.5)	1.5 (0.5)	1.5 (0.5)	1.5 (0.5)	1.5 (0.5)
Mean (SD) post-bronchodilator FEV ₁ percentage predicted	55.2 (12.7)	55.7 (13.2)	54.9 (12.9)	55.1 (13.4)	55.1 (13.5)
Mean (SD) post-bronchodilator FEV ₁ reversibility, %	19.3 (15.9)	20.4 (16.8)	20.5 (16.8)	20.0 (17.6)	20.6 (17.5)
Mean (SD) post-bronchodilator FEV ₁ /FVC, %	48.6 (10.4)	49.1 (10.1)	48.4 (10.6)	48.2 (10.9)	49.2 (10.8)

^aIn the previous year. COPD: chronic obstructive pulmonary disease; FEV₁: forced expiratory volume in 1 sec; FVC: forced vital capacity; ICS: inhaled corticosteroids; SD: standard deviation.

TABLE 2. Lung function over the 26-week study

	Placebo		Difference versus placebo, LSM (\pm 95% CI)		
	LSM (SE)	QVA149 110/50 μ g	Indacaterol 150 μ g	Glycopyrronium 50 μ g	Tiotropium 18 μ g
Trough FEV ₁ , L					
End of Day 1	1.27 (0.010)	0.19 (0.17, 0.21)***†††‡‡‡§§§	0.11 (0.09, 0.14)***	0.11 (0.09, 0.13)***	0.12 (0.09, 0.14)***
Week 12 ^a	1.24 (0.014)	0.23 (0.19, 0.26)***†††‡‡‡§§§	0.15 (0.12, 0.18)*** [‡]	0.12 (0.09, 0.15)***	0.13 (0.10, 0.17)***
Week 26 ^a	1.25 (0.015)	0.20 (0.17, 0.24)***†††‡‡‡§§§	0.13 (0.10, 0.16)***	0.12 (0.08, 0.15)***	0.13 (0.09, 0.16)***
AUC _{0-4 h} for FEV ₁					
Day 1	1.30 (0.008)	0.22 (0.20, 0.24)***†††‡‡‡§§§	0.16 (0.14, 0.18)***†††§	0.19 (0.17, 0.20)***†††§§§	0.14 (0.12, 0.16)***
Week 26	1.23 (0.015)	0.34 (0.30, 0.37)***†††‡‡‡§§§	0.23 (0.19, 0.26)*** [‡]	0.20 (0.16, 0.23)***	0.20 (0.17, 0.24)***
Peak FEV ₁					
Day 1	1.38 (0.009)	0.21 (0.19, 0.23)***†††‡‡‡§§§	0.15 (0.13, 0.17)***	0.18 (0.16, 0.20)***†††§§§	0.13 (0.11, 0.15)***

	Placebo		Difference versus placebo, LSM (\pm 95% CI)		
	LSM (SE)	QVA149 110/50 μ g	Indacaterol 150 μ g	Glycopyrronium 50 μ g	Tiotropium 18 μ g
Week 26		0.33 (0.29,			0.20 (0.16,
	1.31 (0.016)	0.36)***†††‡‡‡§§§	0.21 (0.18, 0.25)***	0.20 (0.16, 0.23)***	0.23)***
FEV ₁ AUC _{0-12 h}					
Day 1	1.24 (0.023)	0.26 (0.21,	0.16 (0.11, 0.21)***	0.18 (0.13, 0.23)*** ^γ	0.13 (0.08,
		0.31)***†††‡‡‡§§§			0.18)***
Week 26	1.18 (0.036)	0.33 (0.25,	0.20 (0.12, 0.29)***	0.21 (0.12, 0.29)***	0.21 (0.13,
		0.42)***†††‡‡‡§§§			0.29)***
FEV ₁ AUC _{12-24 h} at Week 26	1.11 (0.038)	0.30 (0.21,	0.20 (0.11, 0.28)***	0.20 (0.12, 0.28)***	0.21 (0.13,
		0.38)***†††‡‡‡§§§			0.29)***
FEV ₁ AUC _{0-24 h} at Week 26	1.15 (0.036)	0.32 (0.24,	0.20 (0.12, 0.28)***	0.20 (0.12, 0.28)***	0.21 (0.13,
		0.40)***†††‡‡‡§§§			0.29)***
FEV ₁ 2 h post-dose Week 26	1.19 (0.039)	0.40 (0.31,	0.23 (0.14, 0.32)***	0.25 (0.16, 0.34)***	0.24 (0.15,
		0.49)***†††‡‡‡§§§			0.33)***

***p<0.001 versus placebo; Other symbols denote where significant treatment differences (not shown) occur: †††p<0.001 versus indacaterol; ‡‡‡p<0.001, versus glycopyrronium; §§§p<0.001 versus tiotropium; ††p=0.004 versus indacaterol; ‡p=0.043 versus glycopyrronium; ††p=0.004 versus glycopyrronium; †p=0.013 versus glycopyrronium and tiotropium; §p=0.010 versus tiotropium; ^γp=0.026 versus tiotropium; §§p=0.009 versus tiotropium.

Placebo	Difference versus placebo, LSM (\pm 95% CI)			
LSM (SE)	QVA149 110/50 μ g	Indacaterol 150 μ g	Glycopyrronium 50 μ g	Tiotropium 18 μ g

^aImputed with last observation carried forward. One-sided adjusted p-values are presented for comparisons in the statistical gate keeping procedure and two-sided p-values are presented for all other comparisons. CI: confidence interval; LSM: least squares mean; FEV₁: forced expiratory volume in 1 sec; AUC: area under the curve; SE: standard error.

TABLE 3. Adverse events, serious adverse events, deaths and discontinuations over the 26-week treatment period

	Placebo	QVA149 110/50 µg	Indacaterol 150 µg	Glycopyrronium 50 µg	Tiotropium 18 µg
Subjects, n	232	474	476	473	480
Patients with any adverse event	134 (57.8)	261 (55.1)	291 (61.1)	290 (61.3)	275 (57.3)
COPD	91 (39.2)	137 (28.9)	153 (32.1)	150 (31.7)	138 (28.8)
Nasopharyngitis	23 (9.9)	31 (6.5)	35 (7.4)	46 (9.7)	40 (8.3)
Cough	8 (3.4)	26 (5.5)	38 (8.0)	18 (3.8)	21 (4.4)
Upper respiratory tract infection	13 (5.6)	20 (4.2)	32 (6.7)	20 (4.2)	24 (5.0)
Oropharyngeal pain	7 (3.0)	17 (3.6)	7 (1.5)	10 (2.1)	10 (2.1)
Viral upper respiratory tract infection	7 (3.0)	15 (3.2)	11 (2.3)	13 (2.7)	12 (2.5)
Upper respiratory tract infection bacterial	13 (5.6)	10 (2.1)	13 (2.7)	15 (3.2)	22 (4.6)
Lower respiratory tract infection	5 (2.2)	9 (1.9)	15 (3.2)	7 (1.5)	12 (2.5)
Back pain	5 (2.2)	8 (1.7)	11 (2.3)	17 (3.6)	8 (1.7)
Serious adverse events	13 (5.6)	22 (4.6)	26 (5.5)	29 (6.1)	19 (4.0)
Adjudicated CCV events					
Atrial fibrillation/flutter (new onset)	0	2 (0.4)	3 (0.6)	2 (0.4)	1 (0.2)
Serious CCV events	1 (0.4)	0	6 (1.3)	7 (1.5)	4 (0.8)
MACE	0	0	2 (0.4)	3 (0.6)	3 (0.6)

	Placebo	QVA149 110/50 µg	Indacaterol 150 µg	Glycopyrronium 50 µg	Tiotropium 18 µg
Non-fatal myocardial infarction	0	0	0	1 (0.2)	0
Non-fatal stroke	0	0	1 (0.2)	0	2 (0.4)
Heart failure requiring hospitalisation	0	0	1 (0.2)	1 (0.2)	0
Coronary revascularisation (CABG or PCI)	0	0	0	1 (0.2)	2 (0.4)
non-MACE	1 (0.4)	0	4 (0.8)	6 (1.3)	3 (0.6)
Deaths*	0	1 (0.2)	2 (0.4)	1 (0.2)	3 (0.6)
Discontinuations					
Due to an adverse event	10 (4.3)	6 (1.3)	24 (5.0)	14 (3.0)	10 (2.1)
Due to a serious adverse event	3 (1.3)	3 (0.6)	11 (2.3)	6 (1.3)	5 (1.0)

Data are presented as n (%) unless otherwise stated. Most common events listed for $\geq 3\%$ of patients in any of the active treatment groups.

*Adjudicated events. COPD: chronic obstructive pulmonary disease; CCV: cardio- and cerebrovascular; CABG: coronary artery bypass graft;

MACE: major adverse cardiac event; PCI: percutaneous coronary intervention.

FIGURE LEGENDS

FIGURE 1. SHINE study design

qd: once-daily.

FIGURE 2. Flow diagram for disposition of patients

^aPatients that were randomised but did not receive study drug: n=9 (n=5, major protocol deviation for an inclusion/exclusion criteria [did not meet electronic diary inclusion criteria]; n=1, patient did not meet spirometry criteria; n=1, patient withdrew consent; n=1, patient took tiotropium during Visit 3; n=1, site had issues with the MasterScope and could not continue); ^bFor each treatment group, the full analysis and safety sets comprised the same patients. AE: adverse event.

FIGURE 3. Trough FEV₁ a) at Week 26, and b) over the entire 26-week treatment period

- a) Values are LSM \pm SE. One-sided adjusted p-values are presented for comparisons in the statistical gate keeping procedure and two-sided p-values are presented for all other comparisons. n = number per treatment group in the full analysis set.
- b) QVA149 was superior to all active treatments and placebo at all timepoints (all p<0.001). n = the number per treatment group in the full analysis set.

FEV₁: forced expiratory volume in 1 second; LSM: least squares mean; SE: standard error.

FIGURE 4. Serial spirometry on a) Day 1 and b) Week 26

- a) QVA149 superior to placebo and tiotropium at all assessed timepoints (p<0.001); superior to indacaterol at all assessed timepoints (p<0.01), except at 5 min post-dose; superior to glycopyrronium at all assessed timepoints (p<0.05), except 1

hour post-dose. n = number per treatment group in the serial spirometry subset of the full analysis set.

- b) QVA149 superior to placebo ($p < 0.001$) and indacaterol ($p < 0.05$) at all assessed timepoints; superior to glycopyrronium at all assessed timepoints ($p < 0.05$), except 23 hours 45 min; superior to tiotropium at all assessed timepoints ($p < 0.05$), except 22 hours and 23 hours 45 min. n = number per treatment group in the serial spirometry subset of the full analysis set.

FEV₁: forced expiratory volume in 1 second; LS: least squares.

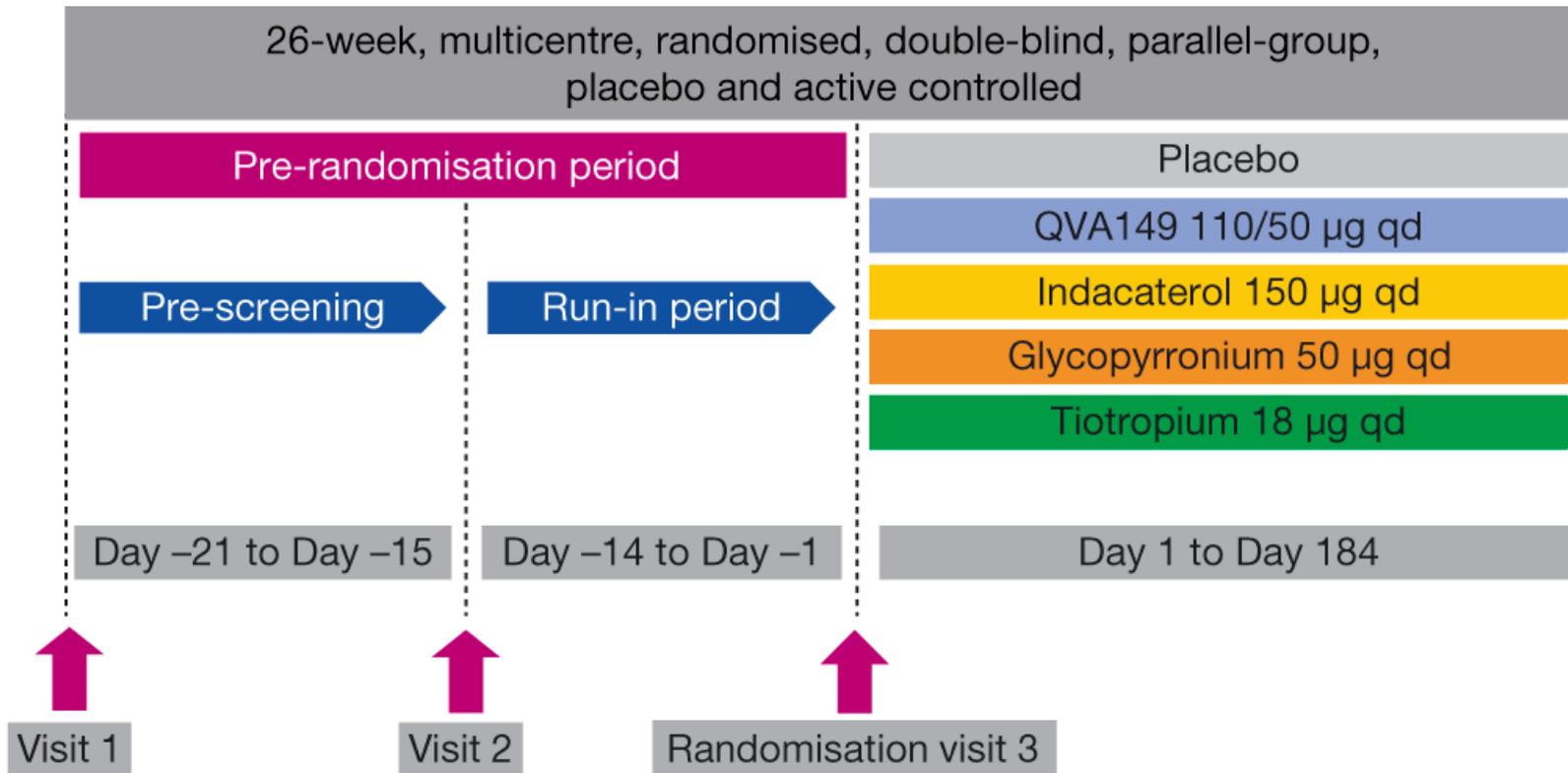
FIGURES**Figure 1**

Figure 2

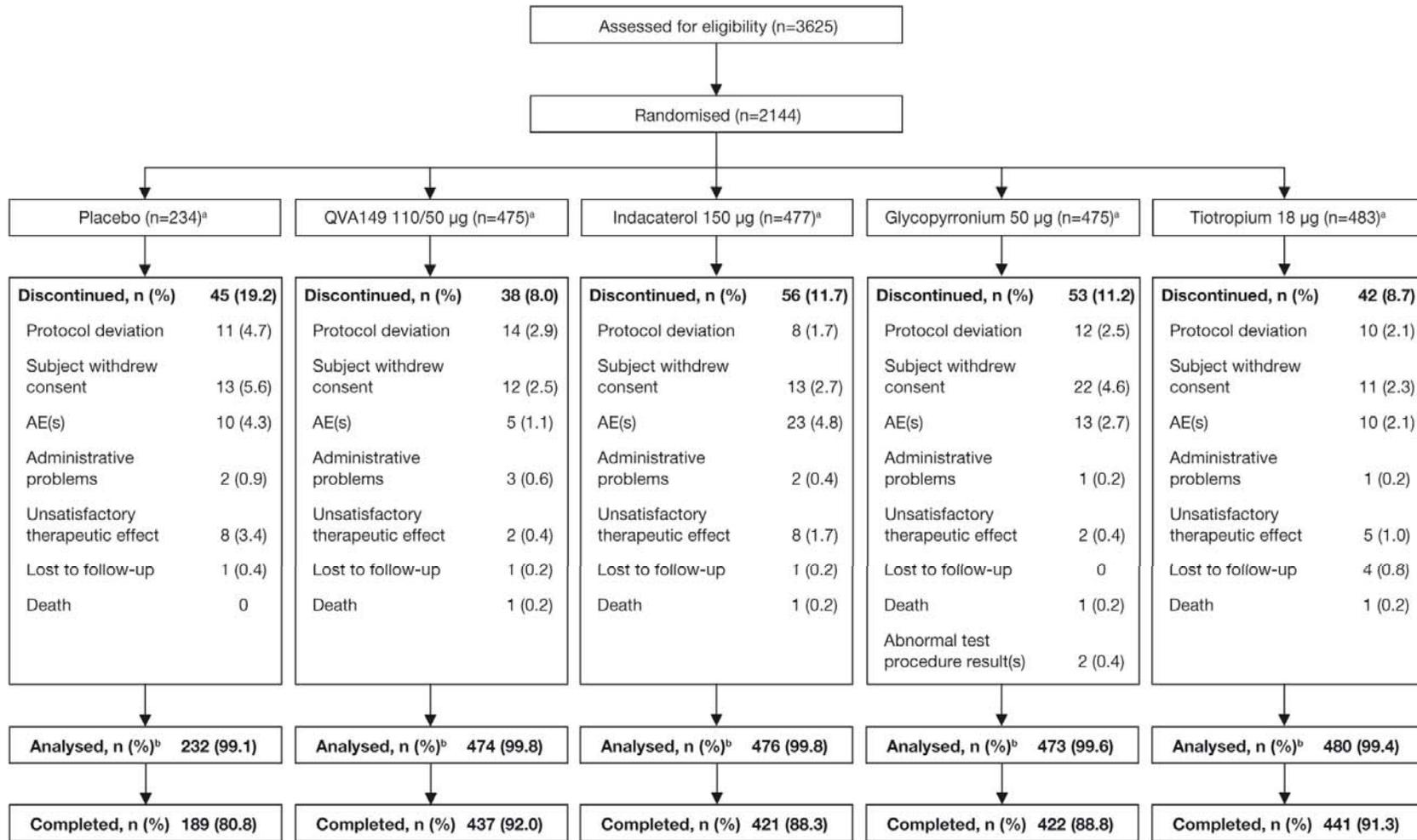
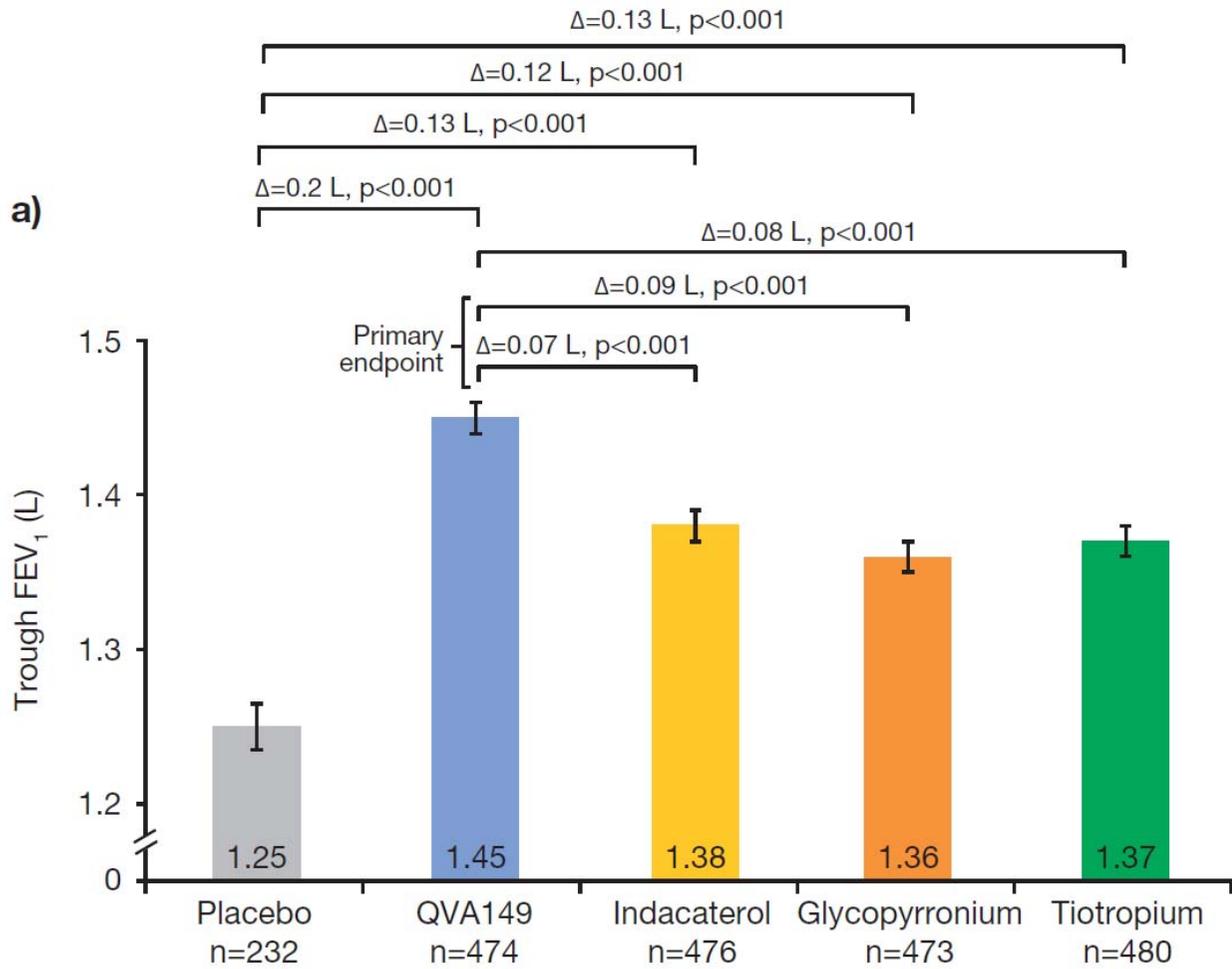


Figure 3



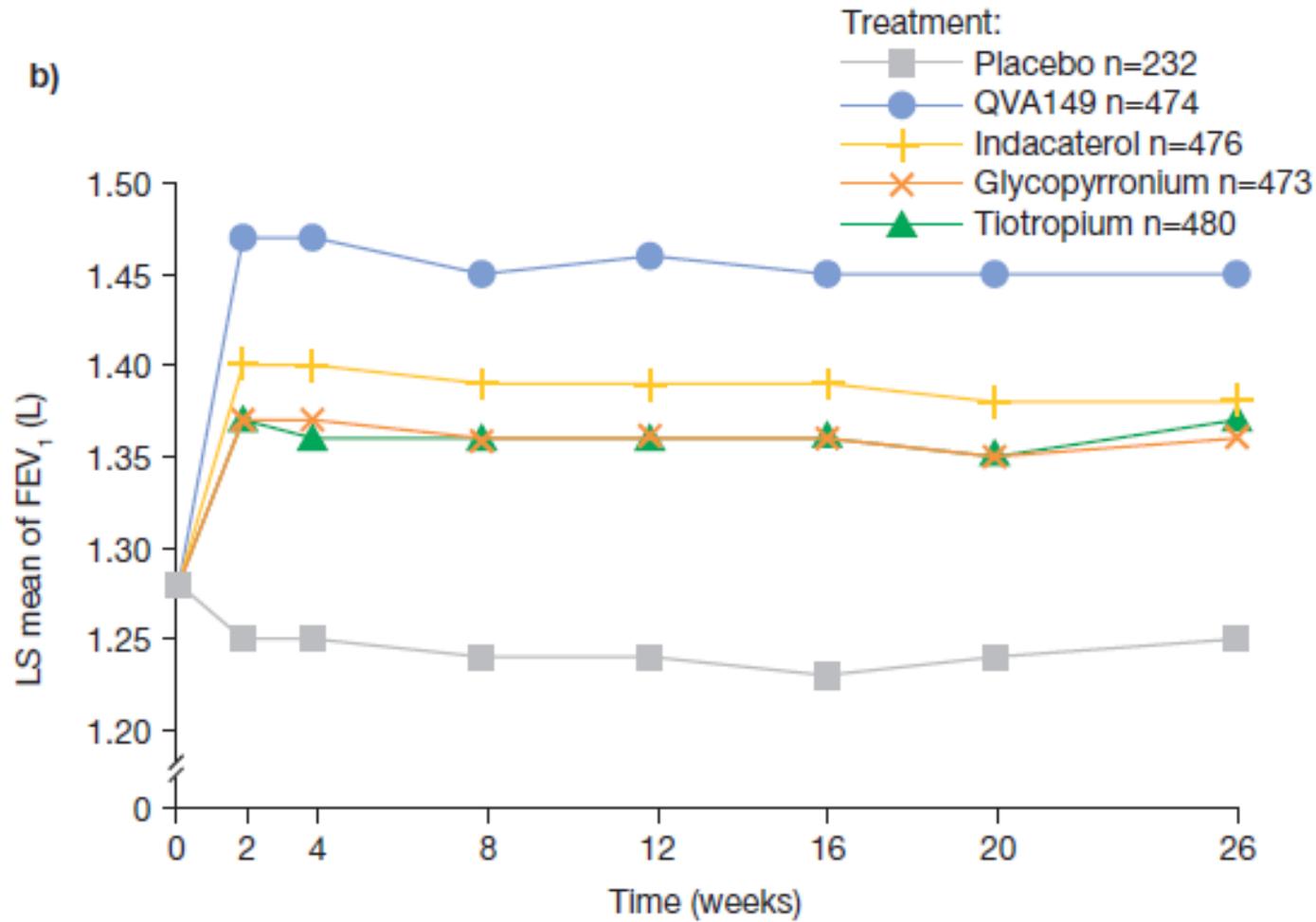


Figure 4

