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COPD

# 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 monocomponents indacaterol and glycopyrronium, tiotropium and placebo in patients with moderate-to-severe chronic obstructive pulmonary disease (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 receive once-daily QVA149 (indacaterol 110 μg/glycopyrronium 50 μg), indacaterol 150 μg, glycopyrronium 50 μg, open-label tiotropium 18 μg or placebo. The primary end-point was trough forced expiratory volume in 1 s ($FEV_1$) at week 26 for QVA149 *versus* its monocomponents. Secondary end-points included dyspnoea, health status, rescue medication use and safety.

Trough $FEV_1$ 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 long-acting muscarinic antagonist/long-acting $\beta_2$-agonist combinations for the treatment of COPD.

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## 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 $\beta_2$-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, and 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 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 (fig. 1). The first patient's first visit was September 21, 2010, and the last patient's last visit was February 10, 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 (indacaterol 110 µg/glycopyrronium 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® (Novartis Pharma AG, Stein, Switzerland) device except for tiotropium, which was administered *via* the HandiHaler® (Boehringer Ingelheim, Ingelheim, Germany) device. A salbutamol/albuterol pressurised metered-dose inhaler was provided as rescue medication. Additional details of the study design and randomisation/blinding procedures are included in the online supplementary material.

### *Patients*

Participants were aged ⩾40 years, had moderate-to-severe stable COPD (stage II or III according to Global Initiative for Chronic Obstructive Lung Disease (GOLD) 2008 criteria [13]) and a smoking history of

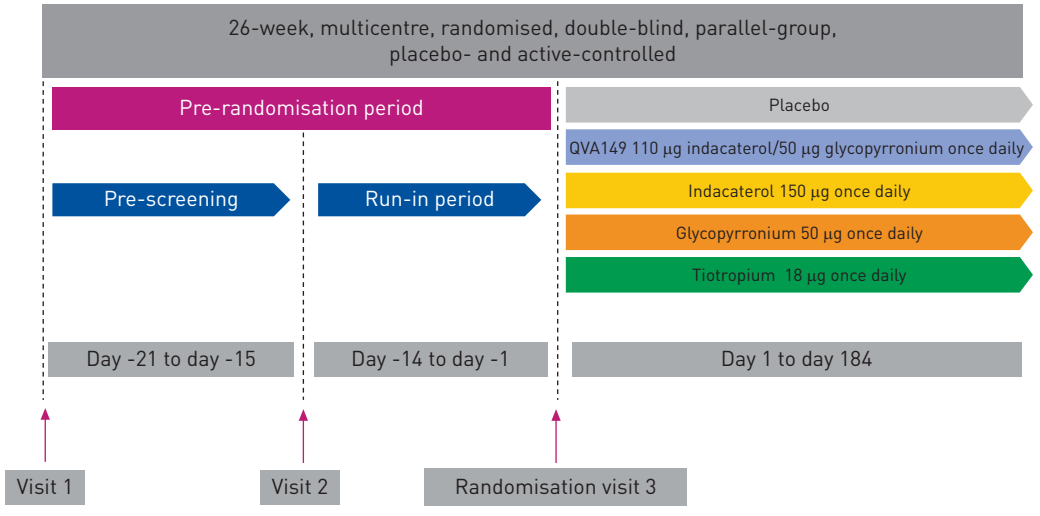


FIGURE 1 The SHINE study design.

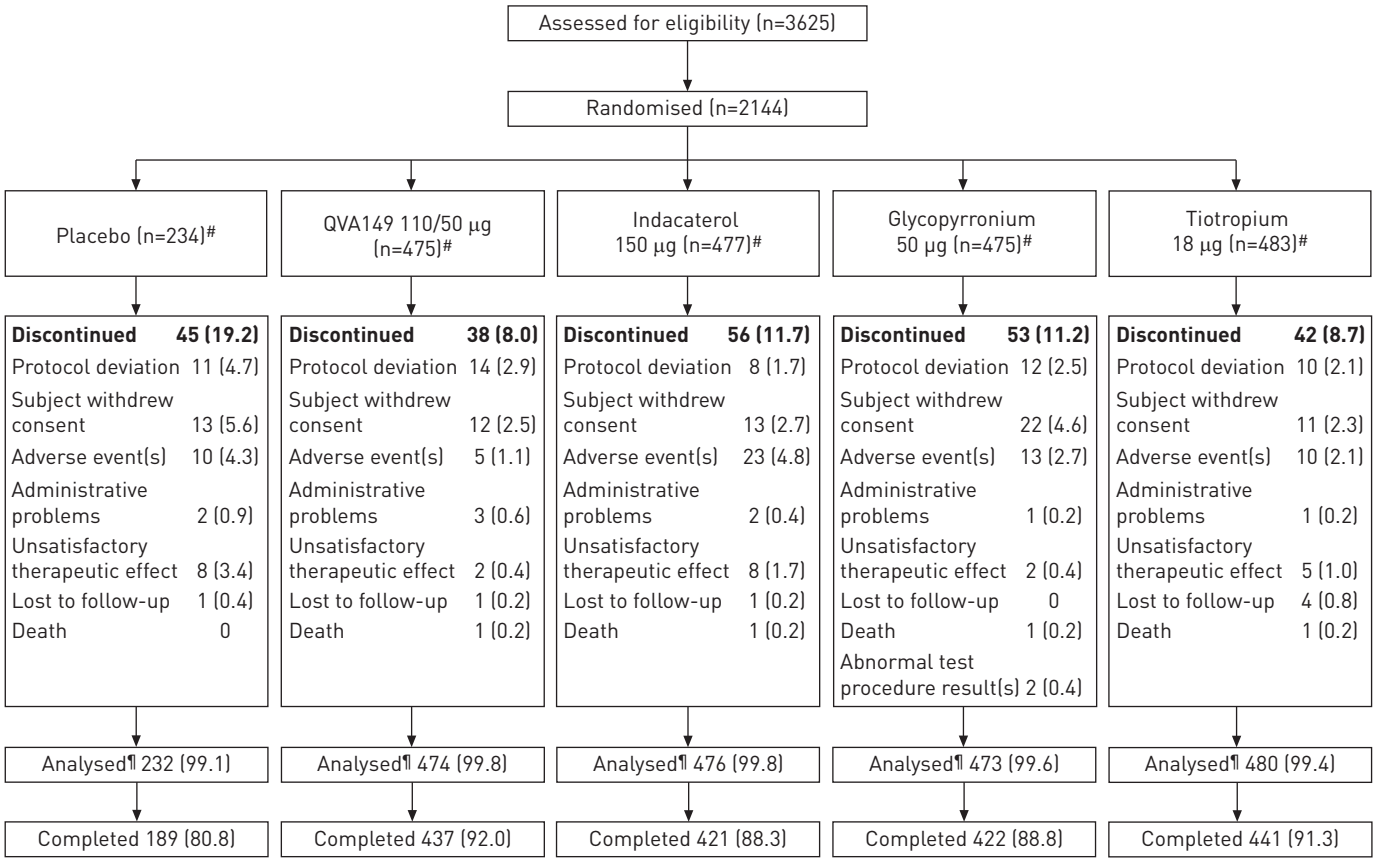


FIGURE 2 Flow diagram for disposition of patients. Data are presented as n (%), unless otherwise stated. #: nine patients were randomised but did not receive the study drug (n=5: major protocol deviation for an inclusion/exclusion criteria (did not meet electronic diary inclusion criteria); n=1: patient 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® (eResearch Technology, Inc, Philadelphia, PA, USA) and could not continue); ¶: for each treatment group, the full analysis and safety sets comprised the same patients.

⩾10 pack-years. At screening, they were required to have a post-bronchodilator forced expiratory volume in 1 s ($FEV_1$) ⩾30% and <80% predicted normal and post-bronchodilator $FEV_1$/forced vital capacity (FVC) ratio <0.70. Further details of inclusion and exclusion criteria are provided in online supplementary table S1. 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 ($FEV_1$ 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-h serial spirometry at day 1 and 24-h 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 adverse events and serious adverse events (SAEs) throughout the study, as well as assessment of ECGs, haematology, clinical chemistry, urinalysis, physical condition and vital signs (pulse and blood pressure). An independent adjudication committee assessed all deaths, serious cardio- and cerebrovascular (CCV) events, and atrial fibrillation/flutter events that occurred during the study. In a subset of patients, 24-h Holter monitoring was used as an additional measure of cardiovascular safety.

The primary objective was superiority in trough $FEV_1$ (defined as the mean of $FEV_1$ values at 23 h 15 min and 23 h 45 min post-dose) at week 26 for QVA149 *versus* its monocomponents 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


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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** | 64.4±8.6 | 64.0±8.9 | 63.6±8.8 | 64.3±9.0 | 63.5±8.7 |
| **Male** | 169 (72.8) | 362 (76.4) | 354 (74.4) | 365 (77.2) | 360 (75.0) |
| **Race** | | | | | |
| 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** | 6.4±5.7 | 6.0±5.5 | 6.3±5.6 | 6.5±5.8 | 6.1±5.5 |
| **COPD severity** | | | | | |
| 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** | | | | | |
| Ex-smoker | 139 (59.9) | 282 (59.5) | 292 (61.3) | 284 (60.0) | 291 (60.6) |
| Current smoker | 93 (40.1) | 192 (40.5) | 184 (38.7) | 189 (40.0) | 189 (39.4) |
| **COPD exacerbation history#** | | | | | |
| 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) |
| **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 |
| **Post-bronchodilator $FEV_1$ L** | 1.5±0.5 | 1.5±0.5 | 1.5±0.5 | 1.5±0.5 | 1.5±0.5 |
| **Post-bronchodilator $FEV_1$ % pred** | 55.2±12.7 | 55.7±13.2 | 54.9±12.9 | 55.1±13.4 | 55.1±13.5 |
| **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 |
| **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 |

Data are presented as mean±SD or n (%), unless otherwise stated. COPD: chronic obstructive pulmonary disease; ICS: inhaled corticosteroids; $FEV_1$: forced expiratory volume in 1 s; % pred: % predicted; FVC: forced vital capacity. #: events in the previous year.

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 $FEV_1$ 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 end-points (area under the curve from 0 to 4 h ($AUC_{0–4}$) for $FEV_1$, peak $FEV_1$ and 12/24-h serial spirometry in a subset of patients) at different timepoints during the 26-week treatment period. Inspiratory capacity was investigated as an exploratory objective. Some pre-planned subgroup analyses were trough $FEV_1$ 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 end-points. 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 and 238 in the placebo group) was determined. Additional details on statistical power are included in the online supplementary material.

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 end-points/objectives. Other secondary objectives were analysed using similar methods, without adjustment for multiplicity. Additional details of the statistical analyses are provided in the online supplementary material.

## 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 (fig. 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 $FEV_1$ post-bronchodilator was 55.2% pred and mean $FEV_1$ reversibility was 20.3%.

### *Spirometry*

Trough $FEV_1$ at week 26 (the primary efficacy end-point) was significantly improved with QVA149 compared with both indacaterol and glycopyrronium, with treatment differences of 0.07 L and 0.09 L, respectively (both $p<0.001$) (fig 3a). QVA149 also provided significantly higher improvement in trough $FEV_1$ compared with tiotropium and placebo at week 26, with treatment differences of 0.08 L and 0.2 L, respectively ($p<0.001$) (fig. 3a). QVA149 was noninferior to tiotropium by the pre-specified margin ($p<0.001$). These statistically significant differences in trough $FEV_1$ were maintained throughout the study *versus* all active treatments and placebo ($p<0.001$) (fig 3b and table 2). All active treatments at week 26 (last observation carried forward) had an increase from baseline in trough $FEV_1$, the mean increase being highest for the QVA149 group (see the online supplementary material for details, along with *post hoc* analyses of the proportion of patients with an increase of >100 mL or >200 mL in trough $FEV_1$ at week 26).

QVA149 provided rapid bronchodilation following the first dose on day 1, with significantly higher $FEV_1$, $FEV_1$ $AUC_{0–4}$ and peak $FEV_1$ compared with placebo, glycopyrronium and tiotropium (all $p<0.01$) (table 2). $FEV_1$ treatment differences for QVA149 *versus* placebo at 5 min and 30 min post-dose on day 1 and weeks 12 and 26 were significant (all $p<0.001$) (online supplementary fig. S1). At 5 min post-dose, least squares mean (LSM) $FEV_1$ was 1.40 L on day 1 and 1.49 L at week 26 for QVA149; this was significantly higher at both timepoints *versus* glycopyrronium (LSM $FEV_1$ 1.36 L and 1.36 L; treatment difference +0.04 L and +0.13 L, respectively; $p<0.001$) and tiotropium (LSM $FEV_1$ 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 $FEV_1$ and $FEV_1$ $AUC_{0–4}$ 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

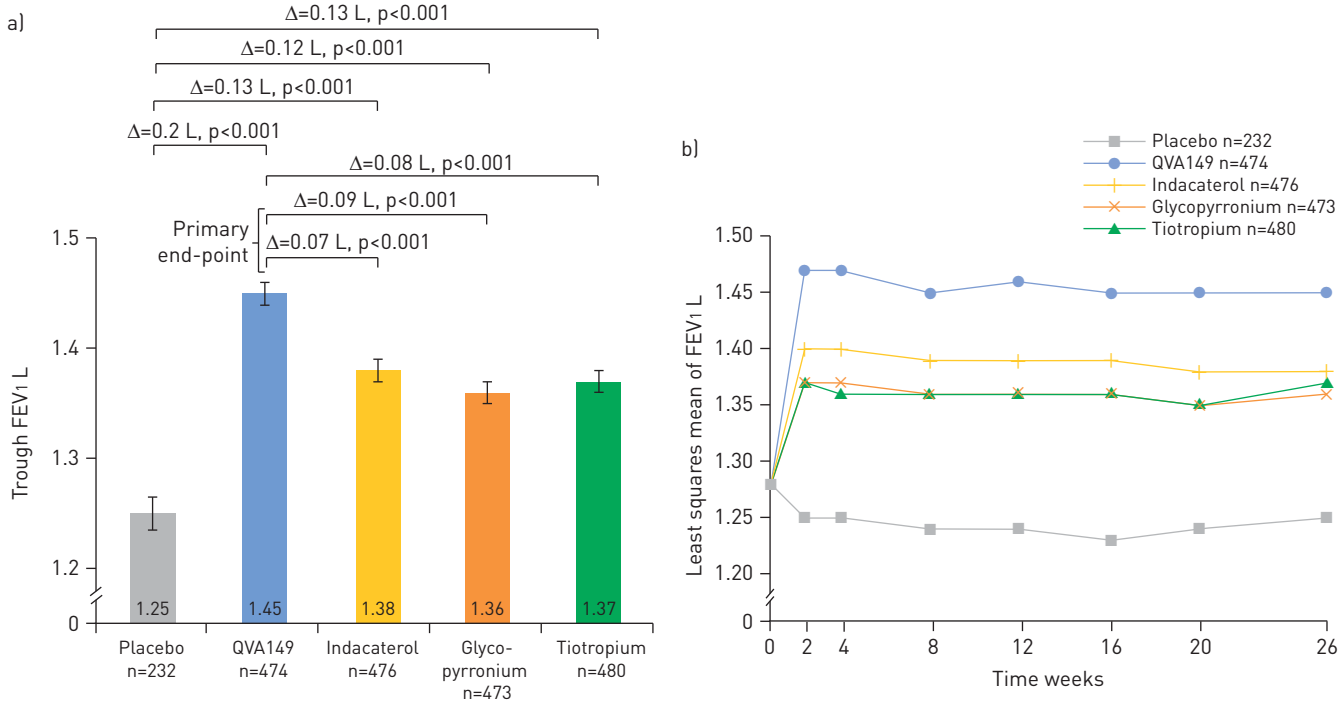


FIGURE 3 Trough forced expiratory volume in 1 s ($FEV_1$) a) at week 26 and b) over the entire 26-week treatment period. a) Data are presented as least squares mean ± SE. One-sided adjusted p-values are presented for comparisons in the statistical gatekeeping procedure and two-sided p-values are presented for all other comparisons. b) QVA149 was superior to all active treatments and placebo at all timepoints (all $p<0.001$). n: number per treatment group in the full analysis set.


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TABLE 2 Lung function over the 26-week study

| | Placebo | Difference *versus* placebo | | | |
|---|---|---|---|---|---|
| | | QVA149 110/50 μg | Indacaterol 150 μg | Glycopyrronium 50 μg | Tiotropium 18 μg |
| **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# | 1.24±0.014 | 0.23 (0.19–0.26)***,¶,+,§ | 0.15 (0.12–0.18)***,ƒ | 0.12 (0.09–0.15)*** | 0.13 (0.10–0.17)*** |
| Week 26# | 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)*** |
| **$FEV_1$ $AUC_{0-4}$** | | | | | |
| 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)*** |
| Week 26 | 1.31±0.016 | 0.33 (0.29–0.36)***,¶,+,§ | 0.21 (0.18–0.25)*** | 0.20 (0.16–0.23)*** | 0.20 (0.16–0.23)*** |
| **$FEV_1$ $AUC_{0-12}$** | | | | | |
| Day 1 | 1.24±0.023 | 0.26 (0.21–0.31)***,¶,+,§ | 0.16 (0.11–0.21)*** | 0.18 (0.13–0.23)***,++ | 0.13 (0.08–0.18)*** |
| Week 26 | 1.18±0.036 | 0.33 (0.25–0.42)***,¶,+,§ | 0.20 (0.12–0.29)*** | 0.21 (0.12–0.29)*** | 0.21 (0.13–0.29)*** |
| **$FEV_1$ $AUC_{12-24}$ at week 26** | 1.11±0.038 | 0.30 (0.21–0.38)***,§§,ƒƒ,### | 0.20 (0.11–0.28)*** | 0.20 (0.12–0.28)*** | 0.21 (0.13–0.29)*** |
| **$FEV_1$ $AUC_{0-24}$ at week 26** | 1.15±0.036 | 0.32 (0.24–0.40)***,¶,+,§ | 0.20 (0.12–0.28)*** | 0.20 (0.12–0.28)*** | 0.21 (0.13–0.29)*** |
| **$FEV_1$ 2 h post-dose week 26** | 1.19±0.039 | 0.40 (0.31–0.49)***,¶,+,§ | 0.23 (0.14–0.32)*** | 0.25 (0.16–0.34)*** | 0.24 (0.15–0.33)*** |

Data are presented as least squares mean±SE or least squares mean (95% CI). One-sided adjusted p-values are presented for comparisons in the statistical gatekeeping procedure and two-sided p-values are presented for all other comparisons. $FEV_1$: forced expiratory volume in 1 s; $AUC_{0-4}$, $_{0-12}$, $_{12-24}$, $_{0-24}$: area under the curve from 0 to 4 h, 0 to 12 h, 12–24 h and 0–24 h, respectively. #: imputed with last observation carried forward. ***: $p<0.001$ *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; ƒ: $p=0.013$ *versus* glycopyrronium and tiotropium; ##: $p=0.010$ *versus* tiotropium; ¶¶: $p=0.043$ *versus* glycopyrronium; ++: $p=0.026$ *versus* tiotropium; §§: $p=0.004$ *versus* indacaterol; ƒƒ: $p=0.004$ *versus* glycopyrronium; ###: $p=0.009$ *versus* tiotropium.

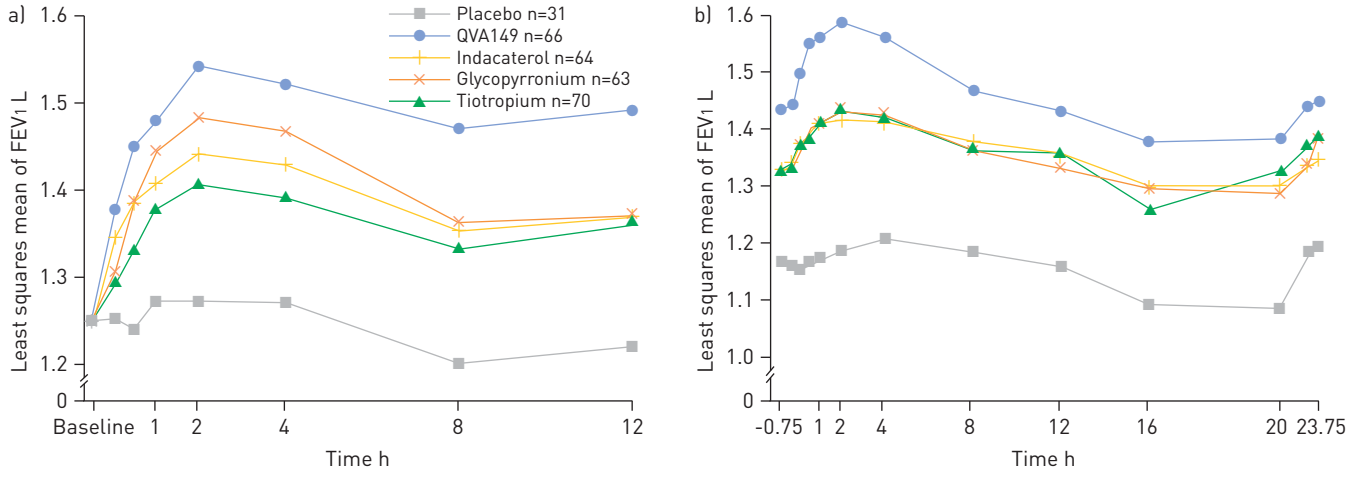


FIGURE 4 Serial spirometry on a) day 1 and b) week 26. a) QVA149 was superior to placebo and tiotropium at all assessed timepoints ($p<0.001$); superior to indacaterol at all assessed timepoints ($p<0.01$), except at 5 min post-dose; superior to glycopyrronium at all assessed timepoints ($p<0.05$), except 1 h post-dose. 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 h 45 min post-dose; superior to tiotropium at all assessed timepoints ($p<0.05$), except 22 h and 23 h 45 min post-dose. n: number per treatment group in the serial spirometry subset of the full analysis set. $FEV_1$: forced expiratory volume in 1 s.

significant improvements in $FEV_1$ 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 ($p<0.05$) (fig. 4). At week 26 peak $FEV_1$ values were seen for QVA149 and tiotropium at 2 h post-dose, with treatment differences of 0.4 L with QVA149 *versus* placebo, 0.17 L *versus* indacaterol, 0.15 L *versus* glycopyrronium and 0.16 L *versus* tiotropium (all treatment comparisons $p<0.001$). Subgroup analysis of improvement in trough $FEV_1$ at week 26 by COPD severity (GOLD $FEV_1$ categories) confirmed a significantly greater improvement with QVA149 *versus* placebo and monobronchodilators in patients with both moderate (LSM treatment differences *versus* placebo 0.24 L; indacaterol 0.06 L; glycopyrronium 0.09 L; and tiotropium 0.07 L; all $p<0.001$) and severe (LSM treatment differences *versus* placebo 0.12 L; indacaterol 0.08 L; glycopyrronium 0.08 L; and tiotropium 0.08 L; all $p<0.001$) COPD (online supplementary fig. 3). Other subgroup comparisons demonstrated a similar improvement with QVA149, which was consistent with the overall patient population (online supplementary fig. 3). The results of other spirometric analyses are provided in table 2 and are outlined in the online supplementary material.

### *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 (online supplementary table S3 and fig. S4). Statistically significant improvements in TDI focal score *versus* placebo were observed with indacaterol, glycopyrronium and tiotropium at weeks 12 and 26. Details of the proportion of patients achieving a minimal clinically important difference (MCID) for TDI score are included in the online supplementary material.

### *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, $p=0.009$) (online supplementary table S3 and fig. S6). 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 online supplementary material, 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 (online supplementary table S3).

### *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


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significance compared with tiotropium (online supplementary table S3). 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 (online supplementary table S3).

### *Safety*

The overall incidence of adverse events was similar across the five treatment groups (table 3). The most frequently reported adverse event 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 adverse events leading to discontinuation of the 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 adverse events, 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 group (colon cancer), two in the indacaterol group (lung cancer and sudden death), one in the glycopyrronium group (sudden death) and three in the tiotropium group (COPD exacerbation, COPD exacerbation with pneumonia and rectal cancer). An additional two patients died >30 days after the last dose of study drug but before the end of the follow-up visit (indacaterol (n=1): pneumonia and glycopyrronium (n=1): colon cancer). None of the deaths were considered by the investigator to be related to the study drug.

TABLE 3 Adverse events, serious adverse events (SAEs), 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) |
| Bacterial upper respiratory tract infection | 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) |
| Nonfatal myocardial infarction | 0 | 0 | 0 | 1 (0.2) | 0 |
| Nonfatal 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[#] | 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 SAE | 3 (1.3) | 3 (0.6) | 11 (2.3) | 6 (1.3) | 5 (1.0) |

Data are presented as n (%), unless otherwise stated. The most common events are listed, affecting ⩾3% of patients in any of the active treatment groups. COPD: chronic obstructive pulmonary disease; CCV: cardio- and cerebrovascular; MACE: major adverse cardiac event. [#]: coronary artery bypass graft or percutaneous coronary intervention; [¶]: adjudicated events.

## 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 monocomponents indacaterol and glycopyrronium given alone, as well as tiotropium and placebo. Improvement in the primary end-point, trough $FEV_1$ was both statistically and clinically significant (considered to be $\geqslant$100 mL in COPD) over placebo, 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 h, 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 $FEV_1$ were seen for both moderate and severe patient subgroups. Improvements in lung function were not influenced by patient age, sex or concurrent use of ICS. Furthermore, 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 $\beta_2$-agonist.

These beneficial effects of QVA149 on lung function were paralleled by statistically significant improvements in other clinically important end-points: 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 ($\geqslant$1 unit) and SGRQ ($\geqslant$4 units) *versus* placebo and tiotropium.

QVA149 was well tolerated over the 26-week study with an adverse event 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 h, without tachyphylaxis, providing further support for the use of dual bronchodilators.

The present study supports the GOLD 2013 strategy alternative 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 combination (group C) or ICS plus LABA and/or LAMA (group D). In comparing LABA plus LAMA and LABA/ICS combination, 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 (Towards a Revolution in COPD Health) study, combination therapy achieved 50 mL and 44 mL improvement in $FEV_1$ *versus* salmeterol and fluticasone propionate alone, respectively; however, the LABA/ICS combination 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 end-points over tiotropium, which is currently recommended as an alternative to LABA/ICS combination, alone or in combination with a LABA.

Features of QVA149 that may help to reduce nonadherence 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


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the need for only a 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 recruit only 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 $FEV_1$ (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. We went to lengths to exclude patients with asthma (inclusion criteria: age of onset of symptoms >40 years, absence of rhinitis and blood eosinophil count of $<600$ cells·mm$^{-3}$ (see the online supplementary material)). 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 withdrawal due to exacerbations on the primary spirometric end-point. 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 end-points (TDI and SGRQ) *versus* active (monocomponent) treatments. Although statistically superior to all monocomponents, QVA149 attained the MCID for only some comparisons (fig. 3 and online supplementary table S3). However, it should be noted that the MCID for a trough $FEV_1$ 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 monocomponents indacaterol and glycopyrronium, and the current standard of care (tiotropium) in patients with moderate-to-severe COPD. QVA149 was also associated with an adverse event 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.

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