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Effect of QVA149 on lung volumes and exercise tolerance in COPD patients: The BRIGHT study

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Summary
Introduction: QVA149 is a novel, inhaled, once-daily dual bronchodilator containing a fixed-dose combination of the long-acting β_2-agonist indacaterol and the long-acting muscarinic antagonist glycopyrronium (NVA237), for the treatment of chronic obstructive pulmonary disease (COPD). This study evaluated the effects of QVA149 on exercise tolerance, hyperinflation, lung function and lung volumes versus placebo and tiotropium.
Methods: Patients with moderate-to-severe COPD were randomized to QVA149 110/50 μg, placebo or tiotropium 18 μg once daily in a blinded, 3-period crossover study for 3 weeks. The primary endpoint was exercise endurance time at Day 21 for QVA149 versus placebo.
Results: Eighty-five patients were randomized; 86% completed the study. QVA149 significantly improved exercise endurance time at Day 21 compared with placebo (least squares mean treatment difference 60 s [$p = 0.006$]). No significant improvements in exercise endurance time at Day 21 between QVA149 and tiotropium were found. Dynamic inspiratory capacity (IC) at exercise isotime, trough forced expiratory volume in 1 s, residual volume and functional residual capacity showed significant improvements with QVA149 from Day 1 of treatment that were maintained throughout the study. The safety profiles were similar across groups.

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Conclusions: In patients with moderate-to-severe COPD, once-daily QVA149 significantly improved exercise endurance time compared with placebo which was associated with sustained reductions of lung hyperinflation as indicated by significant improvement in IC at rest and during exercise.

Trial registration: ClinicalTrials.gov NCT01294787.

Take home message: Dual bronchodilation with QVA149 decreases lung hyperinflation and improves exercise tolerance and lung function in patients with moderate-to-severe COPD.

Introduction

Bronchodilators enhance lung emptying by reducing airway resistance, so patients with COPD are able to achieve alveolar ventilation at lower operating lung volumes, both at rest and during exercise [1]. As a result, patients on bronchodilators can exercise longer before reaching the critical limit of their inspiratory reserve [1]. For symptomatic patients with moderate-to-very severe COPD, current guidelines recommend treatment with an inhaled long-acting bronchodilator β_2-agonist and/or muscarinic antagonist or a fixed combination of inhaled corticosteroid and long-acting bronchodilator in more severe cases [2].

QVA149 is a dual bronchodilator containing a fixed-dose combination of the long-acting β_2-agonist (LABA) indacaterol (110 μg) and the long-acting muscarinic antagonist (LAMA) glycopyrronium (50 μg). In patients with COPD, QVA149 has demonstrated rapid and sustained bronchodilation, which is statistically significant to that observed with its monocomponents (indacaterol and glycopyrronium), open-label tiotropium or placebo [3,4], and it is well tolerated with an adverse event (AE) profile similar to placebo [5]. Both monocomponents are approved for the treatment of moderate-to-severe COPD and were found safe and effective [6—13].

While it is becoming more apparent that dual bronchodilation is superior to monotherapy with regards to classical markers of airflow limitation, the effect of dual bronchodilation on lung volumes, static and dynamic hyperinflation and related outcomes is yet to be established. The BRIGHT study assessed the impact of QVA149 on exercise endurance and lung function (including dynamic hyperinflation) in patients with moderate-to-severe COPD. The study was designed to compare the effect of QVA149 versus placebo; secondary analyses used tiotropium as an active treatment comparator as it is a well characterized standard of care [14,15].

Methods

Study design and treatment

This was a multicenter, randomized, double-blind (investigator-blinded only for tiotropium), double-dummy, placebo-controlled, three-period, cross-over study (Fig. 1; Appendix 1).

QVA149 and its placebo were delivered via the Breezhaler® device; tiotropium and its placebo were delivered via the HandiHaler® device. Tiotropium was used as positive control to assess the assay sensitivity and to compare the results against a well-known comparator. The study was powered for comparison of QVA149 and placebo only. All treatments were given in the morning between 08:00 and 11:00. Short-acting bronchodilators salbutamol or albuterol were provided for rescue use throughout the study, however were not permitted within 6 h of each visit (more details are provided in the online supplement).

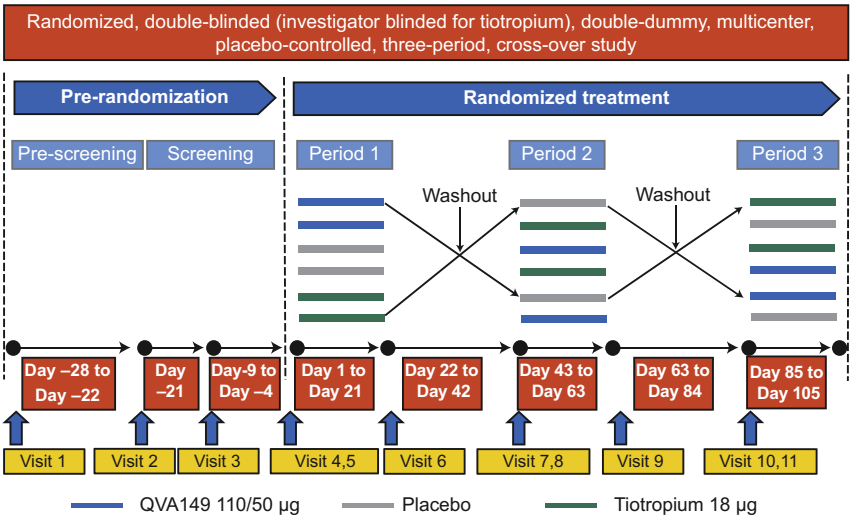

Figure 1 BRIGHT study design.

Patients

The study population comprised patients ≥40 years of age with moderate-to-severe COPD (Stage II or III according to GOLD 2008 criteria [16]), a smoking history of ≥10 pack-years (current or ex-smokers), and a post-bronchodilator forced expiratory volume in 1 s (FEV_1) of ≥40% and <70% of the predicted normal, and post-bronchodilator FEV_1 to forced vital capacity (FVC) ratio of <0.70 at screening. Further details of randomization, and inclusion and exclusion criteria are provided in the online Appendix 1 and 2. All participants provided written informed consent, and the study was approved by relevant national and local ethics review boards.

Endpoints and outcome measures

The primary objective of this study was to compare the effect of QVA149 with that of placebo on the physiological responses to exercise during a sub-maximal constant-load cycle ergometry exercise tolerance test (SMETT) after 3 weeks of treatment. Secondary objectives analyzing QVA149−placebo treatment differences included: isotime inspiratory capacity (IC) during SMETT, trough IC and trough FEV_1 after 3 weeks of treatment; spirometry measurements at rest and during SMETT; pulmonary function (via body plethysmography) after the first dose and after 3 weeks of treatment (at 5 and 15 min post-dose) and comparison of the effect of QVA149 and tiotropium on exercise endurance time. As an important exploratory objective, improvement in exercise endurance time with tiotropium versus placebo during SMETT after 3 weeks of treatment was evaluated. Reduction in rescue medication use and symptoms were also assessed in patients on QVA149 compared with placebo via patient diary data.

Assessments

Exercise endurance time

Baseline durations of exercise endurance were collected during wash-out periods (Visits 3, 6 and 9). Patients commenced load-less pedalling for 3 min at a pedalling frequency of 60 ± 5 revolutions per minute, followed by immediate loaded pedalling at 75% of the maximal workload (W_{max}) that was achieved during a symptom-limited incremental exercise test performed during screening [Visit 2]. Time (in seconds) from the start of loaded pedalling until the point where symptom limitation caused the patient to stop exercising was recorded (exercise endurance time), along with the patient's primary reason for stopping. This was repeated on Days 1 and 21 of each treatment period (visits 4, 5, 7, 8, 10 and 11; commencing 75 ± 15 min post-dose).

Spirometry

On Days 1 and 21 of each treatment period (60 ± 15 min pre-dose) the resting IC, FEV_1 and FVC were recorded via centralized spirometry. Dynamic IC (during patient pedalling) values in duplicate efforts per time-point were recorded and analyzed pre-exercise (75 ± 15 min post-dose) at isotime (the latest matching time-point in the exercise test across all periods at which patients had a valid test result on Day 1 and Day 21), at peak exercise (immediately prior to patient stopping exercise) and post-exercise (at 5 min after completion of exercise) and at trough (60 min pre-dose) on Days 1 and 21 of each treatment period.

Body plethysmography

Constant-volume body plethysmography was performed 60 ± 15 min pre-dose and at 5, 15 and 60 ± 15 min post-dose on Days 1 and 21 of each treatment period. This assessed total lung capacity (TLC), expiratory slow vital capacity (SVC), expiratory reserve volume (ERV), residual volume (RV), specific airway conductance (SGaw) and functional residual capacity (FRC).

Patient symptoms and rescue medication use

Patients completed an electronic patient diary twice daily over the 3-week study period (at the same time each morning and evening) which recorded morning and evening daily symptoms (i.e., coughing, wheezing, chest tightness, ability to clear phlegm/mucus, shortness of breath, fever, cold, sore throat, and sleep habits) and use of rescue medication.

Safety

Safety was assessed by physical examination, vital signs, hematology, clinical chemistry, urinalysis and ECG, as well as by monitoring all adverse events (AEs).

Measures installed for quality assurance (Appendix-3)

Statistical methods and populations for analysis

The study was formally powered to detect a QVA149-placebo treatment difference of 105 s in exercise endurance time after 3 weeks of treatment with 90% power. The primary endpoint was analyzed using a mixed model for the full analysis set (randomized patients who received at least one dose of study drug). Further details on the sample size calculation and statistical methods are given in the online Appendix 4. The model contained patient (sequence) as a random effect, and treatment, pre-treatment exercise period baseline, sequence and period as fixed effects. The estimated treatment difference (QVA149−placebo) was shown as least squares means (LS mean), with the associated 95% confidence interval (CI) and two-sided p-value (significance demonstrated if $p < 0.05$ and when 95% CI lay entirely to the right of 0 s). Similar statistical methods were used to analyze the secondary efficacy endpoints (Appendix 4).

Results

Patients

Of the 126 patients screened, 85 patients were randomized and 73 (85.9%) completed the study (Fig. 2). Patient demographics and other baseline characteristics are shown in Table 1. Mean age was 62.1 years and the majority of patients had moderate COPD (72.6%).

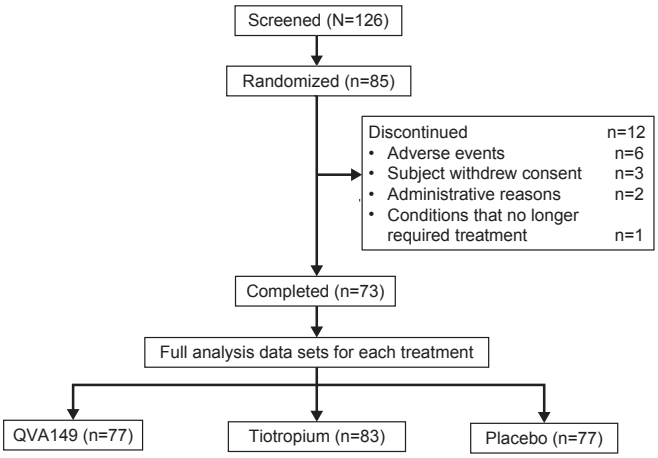

Figure 2 Patient disposition.
Of the 12 patients that discontinued, 1 was not exposed to any study medication, 9 received tiotropium, 2 received placebo and none received QVA149 as the last treatment before discontinuation.

Efficacy

Exercise endurance time

QVA149 significantly improved exercise endurance time at Day 21 compared with placebo (primary endpoint; LS mean treatment difference 60 s (Fig. 3). Although it was an exploratory objective, a similar magnitude of improvement was seen for tiotropium compared with placebo (LS mean treatment difference 66 s (Fig. 3).

At Day 21, in a subgroup of patients with hyperinflation (FRC >120% predicted), the mean change in exercise endurance time from baseline for QVA149 (85 s) and tiotropium (88 s) was greater compared with placebo (−1 s). These results are similar to those seen in the full analysis set.

Table 1 Patient demographics and baseline clinical characteristics (Safety set).

	Total (N = 84)
Mean (SD) age, years	62.1 (8.11)
Gender, male, *n* (%)	53 (63.1)
Race, *n* (%)	
Caucasian	81 (96.4)
Other	3 (3.6)
Mean (SD) duration of COPD, years	8.9 (6.81)
COPD severity, *n* (%)	
Moderate	61 (72.6)
Severe	23 (27.4)
ICS use at baseline, *n* (%)	26 (31.0)
Smoking status, *n* (%)	
Ex-smoker	39 (46.4)
Current smoker	45 (53.6)
COPD exacerbation history[a], *n* (%)	
0	70 (83.3)
1	12 (14.3)
≥2	2 (2.4)
Mean (SD) pre-bronchodilator, % predicted FEV_1	46.5 (10.30)
Mean (SD) post-bronchodilator FEV_1, L	1.6 (0.42)
Mean (SD) post-bronchodilator, % predicted FEV_1	55.9 (8.87)
Mean (SD) post-bronchodilator FEV_1 reversibility, %	22.6 (15.57)
Mean (SD) post-bronchodilator FEV_1/FVC, %	48.5 (9.44)

FEV_1 = forced expiratory volume in 1 s; FVC = forced vital capacity; ICS = inhaled corticosteroid; SD = standard deviation.
[a] In the previous year.

Spirometry

QVA149 treatment significantly improved IC pre-exercise, at isotime, post-exercise and at trough, compared with both placebo and tiotropium on Day 21 (Table 2). The difference between tiotropium and placebo was also significant for these measurements, with the exception of IC at trough (Table 2). A significant improvement was seen in IC at peak exercise when comparing QVA149 with placebo and with tiotropium (Table 2).

At Day 21, mean treatment differences in trough IC, FEV_1, and FVC were significantly higher for QVA149 versus

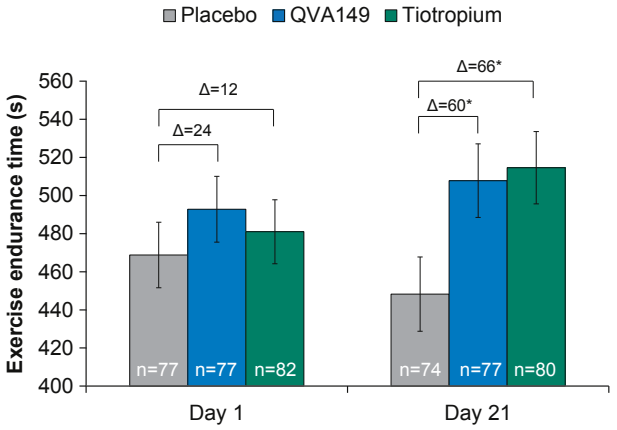

Figure 3 Exercise endurance time (seconds) at Day 1 and Day 21 (Full analysis set).
Data are least squares mean ± standard error; *$p < 0.01$.

Table 2 Treatment differences in lung function on Day 21 (Full analysis set).

	LS means (95% CI) treatment differences on Day 21		
	QVA149—placebo	QVA149—tiotropium	Tiotropium—placebo
IC pre-exercise, L	0.34 (0.25, 0.42)***	0.15 (0.07, 0.23)***	0.18 (0.10, 0.27)***
IC at isotime, L	0.32 (0.23, 0.40)***	0.14 (0.05, 0.22)**	0.18 (0.10, 0.27)***
IC at peak exercise, L	0.21 (0.13, 0.30)***	0.09 (0.00, 0.17)*	0.13 (0.04, 0.21)**
IC post-exercise, L	0.31 (0.20, 0.41)***	0.18 (0.08, 0.29)***	0.12 (0.01, 0.23)*
Trough IC, L	0.19 (0.09, 0.29)***	0.15 (0.06, 0.25)**	0.04 (−0.06, 0.13)
Trough FEV_1, L	0.20 (0.15, 0.26)***	0.10 (0.05, 0.15)***	0.10 (0.05, 0.15)***
Trough FVC, L	0.28 (0.19, 0.37)***	0.11 (0.02, 0.20)*	0.17 (0.08, 0.27)***

CI = confidence interval; IC = inspiratory capacity; FEV_1 = forced expiratory volume in 1 s; FVC = forced vital capacity.
*$p < 0.05$; **$p < 0.01$; ***$p < 0.001$.

placebo (0.19, 0.20 and 0.28 L, respectively) and versus tiotropium (0.15, 0.10 and 0.11 L, respectively; Table 2).

Body plethysmography

On Days 1 and 21, QVA149 significantly improved FRC, RV, SVC and SGaw compared with placebo at 5, 15 and 60 min post-dose (Table 3). Tiotropium also produced superior results to placebo, with the exception of RV at 5 min post-dose on Day 1, while QVA149 was superior to tiotropium for some measurements (in particular SGaw) but was similar for others (Table 3).

Rescue medication use and patient symptoms

Over the 3-week treatment period, QVA149 resulted in less rescue mediation use compared to placebo or tiotropium (mean daily change from baseline: −1.64, −0.42 and −0.42 puffs/day, respectively). QVA149—placebo adjusted treatment difference was statistically significant (mean difference in daily use: −1.23; $p < 0.001$). QVA149—tiotropium adjusted treatment difference was statistically significant (mean difference in daily use: −1.08; $p < 0.001$). QVA149 was also superior to placebo for change from baseline in separate daytime (mean difference −0.81 puffs/day) and night-time (mean difference −0.44 puffs/day) use of rescue medication. A greater reduction in mean daily symptom scores compared to baseline was seen over the 3-week treatment period for QVA149 (−0.64) versus tiotropium (−0.43) or placebo (−0.19).

Exertional dyspnea and leg discomfort in the Borg CR10 scale is given in Table 4. Improvements in exertional dyspnea and leg discomfort were not significant with both QVA149 and tiotropium compared with placebo after 3 weeks treatment.

Safety

The overall incidence of AEs was similar during QVA149 and placebo treatment (37.7% and 36.4%, respectively; Table 5), and slightly lower during the tiotropium treatment period (27.7%). No patient discontinued from study drug due to an adverse event whilst receiving QVA149. Five (6%) and one (1.3%) patients stopped treatment because of an AE in the tiotropium and placebo groups, respectively. AEs reported by at least two patients in any treatment group are shown in Table 5.

The majority of AEs were mild in severity. Serious adverse events (SAEs) were reported by one patient for each treatment, these included colitis (QVA149), acute myocardial infarction (tiotropium), and pneumonia (placebo); none were considered to be related to study medication. There were no deaths reported during the study.

Discussion

The BRIGHT study investigated the effect of 3 weeks treatment with the once-daily dual bronchodilator QVA149 on exercise endurance time and lung function in patients with moderate-to-severe COPD. The primary objective was met as QVA149 significantly improved exercise endurance time versus placebo after 21 days of treatment. The treatment difference of 60 s for QVA149 is within the clinically meaningful difference proposed by the European Respiratory Society (ERS) task force on outcomes in COPD for constant-load endurance tests (46—105 s versus placebo [17]).

In studies evaluating the effects of bronchodilators on cycling endurance time in COPD patients, observed results may vary, with numerically smaller [18,19] or greater [20,21] effects. Differences in patient populations and phenotypes, exercise protocols, methodology used for capturing dynamic IC, and/or study duration make direct comparisons of treatment effect difficult and complicate the issue of defining an accepted minimally clinically important difference for endurance time [22]. Nevertheless, the treatment difference seen for tiotropium versus placebo at Week 3 in this study is comparable to previously published data [23,18] and a subgroup analysis of patients in the present study with baseline hyperinflation of FRC >120% predicted revealed that QVA149 enhanced endurance time after 21 days (+85 s). Previous studies with its monocomponents, indacaterol and glycopyrronium showed a treatment difference of +87.5 s [24] and +88.9 s [11], respectively versus placebo after 3 weeks treatment. In a recent US Food and Drug Administration (FDA) Pulmonary-Allergy Drugs Advisory Committee (PADAC) meeting, the results of two exercise trials also showed that once-daily LABA olodaterol 5 μg increased cycle ergometry endurance time after 6 weeks by 42—52 s versus placebo [25].

The beneficial effects of QVA149 on endurance time versus placebo were associated with statistically significant and clinically important differences in numerous lung function parameters, including traditional markers of

Table 3 Body plethysmography endpoints (Full analysis set).

	LS mean treatment difference (95% CI)					
	QVA149−placebo		QVA149−tiotropium		Tiotropium−placebo	
	Day 1	Day 21	Day 1	Day 21	Day 1	Day 21
FRC, L						
60 min pre-dose		−0.36*** (−0.51, −0.21)		−0.11 (−0.25, 0.04)		−0.26** (−0.40, −0.11)
5 min post-dose	−0.30*** (−0.44, −0.16)	−0.42*** (−0.56, −0.28)	−0.10 (−0.24, 0.04)	−0.08 (−0.22, 0.05)	−0.20** (−0.34, −0.06)	−0.34*** (−0.48, −0.20)
15 min post-dose	−0.30*** (−0.45, −0.16)	−0.41*** (−0.56, −0.26)	−0.01 (−0.15, 0.13)	−0.02 (−0.17, 0.13)	−0.30*** (−0.44, −0.15)	−0.39*** (−0.53, −0.24)
60 min post-dose	−0.35*** (−0.50, −0.21)	−0.52*** (−0.70, −0.35)	−0.05 (−0.19, 0.10)	−0.12 (−0.29, 0.06)	−0.31*** (−0.45, −0.16)	−0.40*** (−0.58, −0.23)
RV, L						
60 min pre-dose		−0.31*** (−0.46, −0.16)		−0.06 (−0.21, 0.08)		−0.24** (−0.39, −0.09)
5 min post-dose	−0.28*** (−0.41, −0.15)	−0.45*** (−0.60, −0.30)	−0.23*** (−0.36, −0.10)	−0.11 (−0.26, 0.03)	−0.05 (−0.18, 0.08)	−0.34*** (−0.48, −0.19)
15 min post-dose	−0.26*** (−0.38, −0.14)	−0.42*** (−0.58, −0.26)	−0.03 (−0.14, 0.09)	−0.05 (−0.21, 0.11)	−0.23*** (−0.35, −0.12)	−0.37*** (−0.53, −0.21)
60 min post-dose	−0.38*** (−0.51, −0.25)	−0.52*** (−0.70, −0.34)	−0.12 (−0.25, 0.01)	−0.11 (−0.28, 0.07)	−0.26*** (−0.38, −0.13)	−0.41*** (−0.59, −0.24)
SVC, L						
60 min pre-dose		0.22*** (0.11, 0.32)		0.12* (0.02, 0.23)		0.09 (−0.01, 0.20)
5 min post-dose	0.23*** (0.16, 0.30)	0.29*** (0.19, 0.40)	0.16*** (0.09, 0.23)	0.10* (0, 0.20)	0.08* (0.01, 0.14)	0.19*** (0.09, 0.29)
15 min post-dose	0.27*** (0.20, 0.33)	0.29*** (0.19, 0.40)	0.11** (0.05, 0.18)	0.09 (−0.01, 0.19)	0.15*** (0.09, 0.22)	0.21*** (0.11, 0.31)
60 min p ost-dose	0.29*** (0.22, 0.36)	0.35*** (0.25, 0.45)	0.10** (0.03, 0.17)	0.10 (0, 0.20)	0.18*** (0.11, 0.26)	0.25*** (0.15, 0.35)
SGaw, 1/kP*s						
60 min pre-dose		0.24*** (0.16. 0.31)		0.14*** (0.06, 0.21)		0.10** (0.03, 0.18)
5 min post-dose	0.21*** (0.14, 0.29)	0.26*** (0.17, 0.35)	0.13*** (0.06, 0.21)	0.12** (0.03, 0.21)	0.08* (0, 0.15)	0.14** (0.04, 0.23)
15 min post-dose	0.22* (0.04, 0.39)	0.32*** (0.26, 0.38)	−0.07 (−0.25, 0.10)	0.12*** (0.06, 0.18)	0.29*** (0.12, 0.46)	0.20*** (0.14, 0.26)
60 min post-dose	0.24*** (0.16, 0.33)	0.37*** (0.30, 0.43)	0.01 (−0.07, 0.10)	0.13*** (0.06, 0.19)	0.23*** (0.15, 0.31)	0.24*** (0.18, 0.31)

CI = confidence interval; FRC = functional residual capacity; RV = residual volume; SGaw = specific airway conductance; SVC = slow vital capacity.
*$p < 0.05$; **$p < 0.01$; ***$p < 0.001$.

airflow (FEV_1 and FVC), static and dynamic lung volumes and airway resistance, as captured by IC and whole-body plethysmography serial measurements. QVA149 provided rapid (at 5 and 15 min post-dosing on Day 1) and sustained (up to Day 21) improvements in lung function, with statistical significance versus placebo and tiotropium. While the fast onset of action for the single components of QVA149, indacaterol and glycopyrronium, has been well documented by standard measures of airflow (FEV_1) against both placebo and active comparators (tiotropium, salmeterol/fluticasone) [6,10,13], our study extends these findings to a full onset of action profile of QVA149 versus placebo on lung volumes and resistance. While this study was not specifically powered to quantify differences in onset of action between QVA149 and tiotropium under steady state conditions, the observed changes in airway conductance (SGaw) post-dose on Day 21 favoring QVA149 over tiotropium indicate that plethysmographic measurement of airway resistance under non-forced conditions may be a promising tool to detect pharmacological differences between bronchodilators' in COPD. However, whether these differences are associated with relevant patient-centered outcomes, e.g. perception of dyspnea, needs to be evaluated in further studies.

Although, the study was powered to compare the differences between QVA149 and placebo only, exploratory analyses of QVA149 versus tiotropium were also performed. Statistically significant treatment differences were seen for QVA149 versus tiotropium for several trough lung function parameters, suggesting superiority of dual

Table 4 Exertional dyspnea and leg discomfort Borg score at pre-exercise and at isotime after 3 weeks treatment.

	LS mean treatment difference (95% CI)		
	QVA149–placebo	QVA149–tiotropium	Tiotropium–placebo
Exertional dyspnea			
Pre-exercise	−0.07 (−0.20, 0.06)	0.03 (−0.09, 0.16)	−0.10 (−0.23, 0.03)
Isotime	−0.10 (−0.64, 0.44)	0.19 (−0.33, 0.70)	−0.29 (−0.82, 0.24)
Leg discomfort			
Pre-exercise	−0.10 (−0.25, 0.05)	−0.03 (−0.18, 0.11)	−0.07 (−0.21, 0.08)
Isotime	0.10 (−0.44, 0.65)	−0.04 (−0.56, 0.48)	0.14 (−0.39, 0.68)

versus single bronchodilation as shown elsewhere [3,4], but these findings were extended by evidence of superior effects on lung volumes that directly or indirectly affected lung hyperinflation. Further, the statistical superiority of QVA149 versus tiotropium on dynamic IC at isotime suggests that the documented effects on static volumes also persisted under exercising conditions. However, although it has been shown that increases in dynamic IC contribute to improvements in endurance time [26], but no difference in this outcome was seen between QVA149 and tiotropium. Thus, the superior bronchodilation with QVA149 over 21 days on trough lung function and dynamic IC at isotime did not translate into superior exercise performance with dual versus single component bronchodilation. As recent exercise studies with free or a novel investigational fixed LABA/LAMA combination also failed to demonstrate superiority of dual versus single bronchodilation with regard to endurance time [27], it is worthwhile to discuss possible explanations for these findings. Firstly, patients in this study (as in many others) performed their exercise tests at post-dose and not under trough conditions, so that differences in bronchodilator effects between the two active regimens may have been diluted by this approach. However, differences in lung volumes favoring QVA149 over tiotropium were still present post-dose in a magnitude comparable to trough values, hence it is unlikely that these small numerical changes explain the lacking difference in endurance time.

Secondly, patients in this study represented a population not specifically selected for exercise limitation, for the sake of harmonizing patient populations enrolled in the QVA149 IGNITE phase III development program [3,28]; therefore, on average, patients had airflow obstruction of moderate severity (GOLD Stage II). Patients were not selected on the basis of presence of resting hyperinflation or respiratory discomfort as their main reason for exercise limitation. In other studies, the presence of resting hyperinflation (FRC>120% predicted) is characteristic of a patient phenotype with a higher likelihood of dynamic hyperinflation during activity and exercise limitation due to respiratory complaints [11,23]. Thus the presence of other, non-pulmonary factors may have contributed to exercise limitation in our study. In fact, leg fatigue was the primary reason for symptom-limited exercise discontinuation with QVA149 (45.5%) and tiotropium (43.8%), but occurred less frequently with placebo (37.8%), and neither QVA149 nor tiotropium provided a treatment effect on Borg dyspnea score during exercise. This may indicate, that the patient population itself may have reached 'ceiling effect' for endurance time achievable by bronchodilation, and leads us to believe that extra-pulmonary limitations such as leg fatigue [29,30] prevented a distinction of the active treatments based on endurance time, despite improved bronchodilation with dual versus single therapy. This is further supported by the fact that even in those subjects with baseline hyperinflation of FRC >120% predicted, despite larger overall improvements versus placebo, a difference between QVA149 and tiotropium was not evident. Of interest, in a study comparing dual (tiotropium plus formoterol) versus single (formoterol) bronchodilation, it was shown that patients with relevant increases in cycling endurance time with dual over single bronchodilator therapy had more severe airways obstruction and lower exercise capacity at baseline [30].

It should be noted that the comparison of endurance time with QVA149 versus tiotropium was exploratory, and tiotropium was administered in a single-blinded fashion. Thus, the lack of an observed difference in our study between QVA149 and tiotropium does not preclude the possibility that a difference actually exists, and this could be explored by studies with extended study duration and/or patient phenotype with more severe COPD, evidence of resting (and dynamic) hyperinflation at screening, plus respiratory symptoms as their primary cause for exercise limitation. As with other outcomes (exacerbation [4,31,32]), treatment effects may be better to distinguish in 'enriched' populations, although, it should be noted that

Table 5 AEs (by preferred term) reported in ≥2 patients with any one treatment.

AE, *n* (%)	QVA149 (*N* = 77)	Tiotropium (*N* = 83)	Placebo (*N* = 77)
Any AE	29 (37.7)	23 (27.7)	28 (36.4)
Mild AE	18 (23.4)	12 (14.5)	14 (18.2)
Moderate AE	10 (13.0)	10 (12.0)	11 (14.3)
Severe	1 (1.3)	1 (1.2)	3 (3.9)
COPD worsening[a]	7 (9.1)	5 (6.0)	3 (3.9)
Cough	5 (6.5)	0	1 (1.3)
Nasopharyngitis	3 (3.9)	1 (1.2)	3 (3.9)
Sputum increased	2 (2.6)	0	0
Back pain	1 (1.3)	1 (1.2)	2 (2.6)
Dyspnea	1 (1.3)	2 (2.4)	2 (2.6)
Headache	1 (1.3)	1 (1.2)	2 (2.6)
Contusion	0	2 (2.4)	0

[a] Data on incidence of COPD exacerbations were combined with AE data and reported under the preferred term of "COPD worsening" together with all other events with the same preferred term.

this approach limits the generalizability of any observed findings.

A major strength of the present study is its uniqueness in terms of the measures implemented for coordinated quality assurance in the methodology used, including, for the first time, fully centralized capturing and evaluation of serial dynamic IC manoeuvers, with duplicate measurements for most time-points. Furthermore, we implemented a thorough quality check for all plethysmographic measurements with central overread following published recommendations for determination of lung volumes and resistance, thus adding external validity to our data. On the other hand, limitations were present due to patient population as discussed and study design. The crossover approach, while permitting recruitment of smaller patients numbers, thereby minimizing the amount of patients exposed to an investigational drug, resulted in a large number of exercise tests (11 per individual); this may have led to a bias in the results due to a 'training effect', although on average, the comparable endurance times collected at baseline prior to each 3-week treatment period clearly counter such an argument.

Conclusions

After 3 weeks of treatment, the once-daily dual bronchodilator QVA149 provided a statistically significant and clinically meaningful improvement in markers of hyperinflation, associated with improved exercise endurance time versus placebo in patients with moderate-to-severe COPD. Overall, there were no clinically relevant differences between QVA149 and placebo (or tiotropium) with respect to safety and tolerability.

Clinical trial

This study is registered at ClinicalTrials.gov with clinical trial identifier number NCT01294787.

Conflict of interests

This study was sponsored by Novartis Pharma AG. K-MB and JB have received compensation for organizing or participating in advisory boards for Cytos, Boehringer Ingelheim, AstraZeneca, Novartis and Revotar Biopharmaceuticals. K-MB has participated as a speaker in scientific meetings or courses organized and financed by various pharmaceutical companies (AstraZeneca, Boehringer, Novartis, Pfizer and Takeda) in the past 5 years. The institution where K-MB and JB are currently employed has received compensations for the design, performance or participation in single or multicenter clinical trials in the past 5 years from several companies including Almirall Prodesfarma, Altana, AstraZeneca, Boehringer Ingelheim, Cytos, GSK, Medapharma, Merck Sharp & Dohme, Mundipharma, Novartis, Pfizer and Revotar Biopharmaceuticals. SK has received reimbursement for attending scientific conferences, and/or fees for speaking and/or consulting from Novartis. SK was an investigator in several QVA149 trials.

DJ, MH, PD'A and DB are employees of Novartis.

Authors' contributions

All authors read and approved the final draft.

K-MB, JB and SK assisted in acquisition of data, analysis and interpretation of data, and was involved in drafting the manuscript.

DJ was the clinical trial head, and developed the design and concept of the study and participated in the interpretation of the results and drafting the manuscript.

MH was the trial statistician and was involved in developing the study design, interpretation of the data and provided critical inputs to the manuscript.

PD'A and DB participated in the development of the design and concept of the study and the interpretation of the data, and was involved in drafting the manuscript.

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Appendix A. Supplementary data

Supplementary data related to this article can be found at http://dx.doi.org/10.1016/j.rmed.2014.01.006.

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