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Dual bronchodilation with QVA149 reduces patient-reported dyspnoea in COPD: BLAZE study

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ABSTRACT

We evaluated the effect of QVA149, a dual bronchodilator combining indacaterol and glycopyrronium, on direct patient-reported dyspnoea in patients with moderate-to-severe COPD.

In this multicentre, blinded, double-dummy, three-period crossover study, 247 patients were randomised to once-daily QVA149 110/50 µg, placebo or tiotropium 18 µg. Superiority of QVA149 versus placebo (primary objective) and tiotropium (secondary objective) was assessed for improvement in dyspnoea via the Self-Administered Computerised (SAC) version of the Baseline and Transition Dyspnoea Index (BDI/TDI) after 6 weeks. Secondary endpoints included lung function, rescue medication use and safety.

After 6 weeks, the SAC TDI total score was significantly higher with QVA149 versus placebo (least squares mean [LSM] treatment difference: 1.37, $p<0.001$) and tiotropium (LSM treatment difference: 0.49, $p=0.021$). QVA149 provided significant improvements in lung function, with higher FEV_1 area under the curve from 0 to 4 hours post-dose versus placebo and tiotropium at Day 1 and Week 6 (all $p<0.001$).Rescue medication use was significantly lower with QVA149 versus placebo ($p<0.001$) and tiotropium ($p=0.002$). All treatments were well tolerated,

Once-daily QVA149 provided superior improvements in patient-reported dyspnoea and lung function versus placebo and tiotropium. These benefits were associated with improvements in other symptoms and reduced use of rescue medication.

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INTRODUCTION

Dyspnoea (breathlessness) is a cardinal symptom of chronic obstructive pulmonary disease (COPD) and a major cause of disability associated with this disease [1]. Patients report dyspnoea as the most bothersome COPD symptom and the primary reason to seek medical attention[1]. As reducing symptoms is one the main goals of pharmacological therapy of COPD [2], evaluation of dyspnoea is critical to establish appropriate management strategies .

In clinical trials, dyspnoea is considered to be one of the most important and robust clinical outcome, along with mortality and health-related quality of life [3]. The severity of dyspnoea is commonly measured using the interviewer-administered Baseline Dyspnoea Index (BDI) and the Transition Dyspnoea Index (TDI) questionnaires [3]. These instruments reflect interviewer-based assessments of breathing difficulty related to activities of daily living as reported by patients. A self-administered computerised (SAC) version of the BDI/TDI has been developed to remove any interviewer bias and to provide direct, patient-reported ratings of dyspnoea [4]. These innovative instruments, which ha**v**e been validated versus the standard interviewer-administered method BDI/TDI, have been shown to be reliable during re-testing [5] and responsive to bronchodilator therapy in COPD [6, 7]. However, to our knowledge, these instruments have never been used as primary endpoints in a randomized clinical trial.

Bronchodilators play a central role in the management of COPD, with long-acting muscarinic antagonists (LAMAs) and long-acting β_2 agonists (LABAs) recommended for maintenance therapy [2]. As dyspnoea is not always adequately controlled by bronchodilator monotherapy, the addition of a second bronchodilator is recommended in patients with moderate-to-severe COPD to achieve better symptom control [2]. Studies have shown that combining two bronchodilators with different mechanisms of action can provide greater improvement in lung function and better symptom management than monotherapy [7-11]. QVA149 is a novel, inhaled, once-daily dual bronchodilator combining a fixed-dose of the LABA indacaterol and LAMA glycopyrronium (NVA237), in development as a maintenance treatment for COPD. Both components of QVA149 are approved as single agents for the treatment of moderate-to-severe COPD, and their efficacy and safety have been demonstrated in large, randomised, Phase III studies [12-19]. Pivotal Phase III studies have recently

demonstrated the efficacy and safety profiles of once-daily QVA149 in patients with moderate to very severe COPD [20-22].

The BLAZE study was designed to evaluate the effect of QVA149 versus placebo and tiotropium on patient-reported dyspnoea, using the SAC BDI/TDI instruments in patients with moderate-to-severe COPD. The hypothesis of the present study was that the potent bronchodilator effect of QVA149 would translate into improved patient-reported dyspnoea.

METHODS

Patients

Participants were aged ≥40 years with moderate-to-severe stable COPD (Stage II or III according to GOLD 2009 criteria) [23], and were either current smokers or ex-smokers with a smoking history of ≥10 pack-years, had a post-bronchodilator FEV_1 of ≥30% and <80% of the predicted normal, had a post-bronchodilator forced expiratory volume in 1 second (FEV_1) to forced vital capacity (FVC) ratio of <0.70 at screening (Visit 2, Day −14) and a modified Medical Research Council (mMRC) dyspnoea scale grade of at least 2 at Visit 2. Inclusion and exclusion criteria are described in the Appendix. First patient was enrolled on 26 October 2011; last patient completed on 29 August 2012. The study was approved by institutional review boards and ethics committees at participating centres, and was conducted in accordance with Declaration of Helsinki and Good Clinical Practice. All patients provided written informed consent.

Study Design and Treatment

This was a multicentre, randomised, blinded, double-dummy, placebo-controlled, three-period crossover study (Figure 1). Blinded tiotropium was included as an active comparator. The study included a pre-screening wash-out period (up to 7 days, depending upon medication) and a 14-day screening period. After the screening period and before receiving any study treatments (i.e. at Visit 3), baseline SAC BDI data were collected for eligible patients. Patients were then randomised to receive QVA149 110/50 µg, tiotropium and placebo in six treatment sequences (Figure 1). All

medications were administered once daily in the morning (between 08:00 and 11:00): QVA149 and placebo to QVA149 via the Breezhaler® device, and tiotropium and placebo to tiotropium via the HandiHaler® device. The first medication was continued through Visits 3, 4, and 5 (Period 1), the second medication through Visits 6, 7, and 8 (Period 2), and the third medication through Visits 9, 10, and 11 (Period 3). Each treatment period lasted 6 weeks, with a 14-day washout period between treatments.

Use of long-acting bronchodilators or short-acting muscarinic antagonists was not permitted during the study, but treatment with ICS was maintained. Patients taking combined LABA/ICS therapy were transitioned to the equivalent ICS monotherapy. Salbutamol/albuterol was provided as rescue medication. Additional details of the study design, randomisation and blinding procedures are included in the Appendix.

Objectives and assessments

The primary objective was to demonstrate superiority of QVA149 versus placebo in improvement of patient-reported dyspnoea, as assessed by SAC BDI/TDI, after 6 weeks. Superiority of QVA149 versus tiotropium was a key secondary objective. The translation and validation of the SAC BDI/TDI instrument was performed by the MAPI Institute (Lyon, France) [24]. Patients completed the SAC BDI/TDI on a desktop computer, by following instructions provided on the screen. SAC BDI was completed at the beginning of each treatment period (Visits 3, 6 and 9) and SAC TDI at the end of each treatment period (Visits 5, 8 and 11). In all cases, the questionnaires were completed prior to any study assessment or administration of study medication. To gain familiarity with the computer, patients completed a practice session at each visit by rating their tiredness on a typical day. For the BDI questionnaire, patients were then asked to select one of five sentences that best described each of the three components of the BDI. For the TDI, patients were reminded of their responses on the computer screen during their previous BDI and were asked to indicate the magnitude of improvement or deterioration along a bidirectional visual analogue scale [4]. In a study assessing comprehension and acceptability of the SAC BDI/TDI in five COPD patients in seven different countries (n=35), this instrument was very well accepted [24]. Any difficulties with the patients' ability to select answers on the TDI were resolved after the practice question about tiredness. This was designed to help the patients become familiar with using the up-and-down arrows to select the appropriate TDI score [24].

The study sponsor utilised eResearchTechnology GmbH (Estenfeld, Germany) to implement the SAC BDI/TDI on the MasterScope platform (VIAConnect PC) as an independent application. To start the assessment, the site staff used the workflow tasks on the MasterScope to dispense the BDI or TDI assessment to the patient using a secure memory stick which contains an encrypted, unique patient and visit identifier. The memory stick was then inserted into the VIAConnect PC, which activates the dispensed assessment, at the end of which it was inserted back into the MasterScope allowing assessment data to be downloaded to the centralised database of the study sponsor.

Secondary endpoints also included evaluation of lung function (post-dose FEV_1, standardised area under the curve [AUC] from 0 to 4 hours [$AUC_{0–4hours}$] for FEV_1 and FVC) use of rescue medication for QVA149 versus placebo and tiotropium. Spirometry outcomes were assessed at baseline, and at the beginning and end of each treatment period (Visits 3, 5, 6, 8, 9, and 11). Measurements were taken 45 and 15 minutes pre-dose, with 4-hour serial spirometry conducted post-dose. Patients used an electronic diary, three times daily, to record their morning and evening symptoms, and rescue-medication use. A post-hoc analysis was conducted by COPD severity.

Safety and tolerability were assessed at the scheduled visits by monitoring adverse events (AEs) and serious AEs (SAEs), conducting physical examinations, laboratory assessments and ECGs, and measuring vital signs. Safety follow-ups were conducted for 30 days after the patient completed the study. An independent adjudication committee reviewed all data relating to deaths, cardio- and cerebrovascular (CCV) AEs, and atrial fibrillation and flutter events.

Statistical Analysis

Detailed statistical methods are provided in the appendix. Efficacy was assessed in the full analysis set (FAS), which comprised all randomised patients who received at least one dose of study drug. A mixed model was used to analyse the primary and key secondary objectives/endpoints. Other secondary endpoints were analysed using similar methods, without adjustment for multiplicity.

Safety was assessed in the safety population, which included all patients who received at least one dose of study drug, whether or not they were randomised.

Additional post-hoc analyses were conducted by COPD severity for the primary and secondary objectives.

RESULTS

Patients

Of the 411 patients screened, 247 were randomised to 1 of the 6 crossover treatment sequences, with overall total exposure to treatment being: QVA149, n=223; tiotropium, n=220; and placebo, n=218. Overall, 77.3% patients (n=191) completed the study (Figure 2). The most common reason for discontinuation was AEs. One randomised patient was excluded before receiving any treatment because of an error in randomisation; this patient was not included in either the efficacy or safety analysis.

The majority of patients included in the analyses had moderate COPD (68.3%) (Table 1) and approximately 82% had an mMRC dyspnoea scale Grade 2 [25].

Table 1 Patient demographics and baseline clinical characteristics

	Total (N=246)
Mean (SD) age, years	62.8 (8.2)
<65 years old, n (%)	142 (57.7)
≥65 years old, n (%)	104 (42.2)
Gender, male, n (%)	173 (70.3)
Race, Caucasian, n (%)	246 (100)
Mean (SD) BMI, kg/m^2	27.2 (5.1)
Mean (SD) duration of COPD, years	7.6 (5.9)
Severity of COPD (GOLD 2009), n (%)	
Moderate	168 (68.3)
Severe	78 (31.7)
Very severe	0 (0.0)
Number of COPD exacerbations in the previous year, n (%)	
0	172 (69.9)
1	57 (23.2)
≥2	17 (6.9)
Smoking history, n (%)	
Ex-smoker	134 (54.5)
Current smoker	112 (45.5)
Mean (SD) number of pack-years	46.0 (21.7)
Patients on ICS at baseline, n (%)	135 (54.9)
Patients on LAMA at baseline, n (%)	87 (35.4)
Patients on LABA at baseline, n (%)	136 (55.3)
mMRC Dyspnoea Scale, n (%)	
Grade 2	203 (82.5)
Grade 3	42 (17.1)
Grade 4	1 (0.4)
Mean (SD) pre-bronchodilator FEV_1 (L)	1.35 (0.44)
Mean (SD) pre-bronchodilator FEV_1 (% predicted FEV_1)	47 (12.14)
Mean (SD) post-bronchodilator FEV_1 (L)	1.6 (0.47)
Mean (SD) post-bronchodilator FEV_1 (% predicted FEV_1)	56 (12.3)
Mean (SD) FEV_1 reversibility (% increase)	21 (15.0)
Mean (SD) post-bronchodilator FEV_1/FVC (%)	48 (10.4)

BMI = body mass index; COPD, chronic obstructive pulmonary disease; FEV_1 = forced expiratory volume in 1 second; FVC = forced vital capacity; GOLD, Global Initiative for Chronic Obstructive Lung Disease; ICS = inhaled corticosteroid; LABA = long-acting β_2 agonists; LAMA = long-acting muscarinic antagonists; mMRC = modified Medical Research Council; SD = standard deviation.

Efficacy

Dyspnoea

Previous treatments did not influence BDI at the start of a new treatment period as there were no significant differences for the interaction of treatments (QVA149, tiotropium, and placebo) versus periods (1–3) at baseline (Appendix Table 1). The SAC TDI total score was significantly improved with QVA149 versus placebo and tiotropium after 6 weeks (Figure 3). The improvement with QVA149 versus placebo was also clinically meaningful as defined by the minimal clinically important difference (MCID) of ≥1 point improvement for comparisons between active treatments and placebo [26].

Although a statistically significant improvement in SAC TDI total score was observed with tiotropium versus placebo, this did not achieve the MCID of 1 unit change (Figure 3). Analyses by COPD severity confirmed that, after 6 weeks, QVA149 provided a statistically significant and clinically meaningful improvement in SAC TDI total score in patients with both moderate (least squares mean [LSM] treatment difference: 1.11; 95% CI 0.60, 1.61; p<0.001) and severe (LSM treatment difference: 1.92; 95% CI 1.19, 2.65; p<0.001) COPD compared with placebo. QVA149 also provided a statistically significant improvement in SAC TDI total score versus tiotropium in patients with severe COPD (LSM treatment difference: 0.76; 95% CI 0.03, 1.49; p=0.042); however, the difference between treatments was not significant in patients with moderate COPD (LSM treatment difference: 0.36; 95% CI –0.15, 0.87; p=0.167).

Although the MCID for comparisons between active treatments has yet to be established, a TDI responder analysis was performed to directly compare QVA149 with tiotropium. The proportion of patients who achieved the MCID of at least one unit in the SAC TDI total score was higher with QVA149 than with either placebo (35.9% vs. 18.1%, odds ratio [OR] 2.78; p<0.001) or tiotropium (24.4%, OR 1.78; p=0.012). Details of the proportion of patients with moderate and severe COPD achieving the MCID for TDI are given in the Appendix.

Spirometry

Previous treatments did not influence FEV_1 at the beginning of a new treatment period as there were no significant differences for the interaction of treatments (QVA149, tiotropium, and placebo) versus periods (1–3) at baseline (Appendix Table 1). After 6 weeks, QVA149 significantly improved mean FEV1 at all time points from 45 minutes pre-dose to 4 hours post-dose versus placebo and tiotropium ($p<0.001$; Figure 4a); these improvements were also clinically meaningful [27].

QVA149 provided rapid bronchodilation following the first dose on Day 1, with statistically significant and clinically meaningful improvements in FEV_1 versus placebo and tiotropium at all timepoints from 0 to 4 hours post-dose (Figure 4b; all $p<0.001$). On Day 1, the FEV_1 LSM treatment difference for QVA-placebo and QVA-tiotropium was 126 ml and 70 ml at 5 minutes, respectively, and 182 ml and 62 ml at 30 minutes, respectively (all $p<0.001$). FEV_1 $AUC_{0–4\ hours}$ post-dose was significantly higher for QVA149 versus tiotropium and placebo at Day 1 and Week 6 (all $p<0.001$; Table 2). Analyses by disease severity also confirmed these data, with FEV_1 $AUC_{0–4hours}$ LSM treatment difference for QVA149−placebo of 370 mL in moderate patients and 254 mL in severe patients after 6 weeks (all $p<0.001$;Table2). At Day 1 and Week 6, QVA149 provided significantly superior improvements in FVC $AUC_{0–4hours}$ versus tiotropium and placebo (all $p<0.001$; Appendix Table -2).

Table 2 Standardised FEV_1 (L) $AUC_{0\text{-}4hours}$ on Day 1 and Week 6

Treatment	n	Baseline Mean (SE)	Treatment LSM (SE)	Comparison	-------- Treatment difference -------- LSM (SE)	95% CI	p-value
Day 1							
All patients							
QVA149 (N=223)	220	1.32 (0.03)	1.56 (0.01)	QVA149 vs. Placebo	0.21 (0.01)	(0.19, 0.23)	<0.001
				QVA149 vs. Tiotropium	0.07 (0.01)	(0.05, 0.09)	<0.001
Tiotropium (N=220)	219	1.33 (0.03)	1.50 (0.01)	Tiotropium vs. Placebo	0.14 (0.01)	(0.13, 0.16)	<0.001
Placebo (N=218)	217	1.33 (0.03)	1.35 (0.01)				
Moderate COPD							
QVA149 (N=151)	148	-	-	QVA149 vs. Placebo	0.23 (0.01)	(0.21, 0.26)	<0.001
				QVA149 vs. Tiotropium	0.07 (0.12)	(0.05, 0.10)	<0.001
Tiotropium (N=149)	148	-	-	Tiotropium vs. Placebo	0.16 (0.01)	(0.14, 0.19)	<0.001
Placebo (N=149)	148	-	-				
Severe COPD							
QVA149 (N=72)	72	-	-	QVA149 vs. Placebo	0.17 (0.02)	(0.13, 0.20)	<0.001
				QVA149 vs. Tiotropium	0.06 (0.02)	(0.03, 0.10)	<0.001

Tiotropium (N=71)	71	-	-	Tiotropium vs. Placebo	0.10 (0.02)	(0.07, 0.14)	<0.001
Placebo (N=69)	69	-	-				
Week 6							
All patients							
QVA149 (N=223)	205	1.33 (0.03)	1.64 (0.01)	QVA149 vs. Placebo	0.33 (0.01)	(0.31, 0.36)	<0.001
				QVA149 vs. Tiotropium	0.11 (0.01)	(0.08, 0.13)	<0.001
Tiotropium (N=220)	209	1.34 (0.03)	1.53 (0.01)	Tiotropium vs. Placebo	0.23 (0.01)	(0.20, 0.25)	<0.001
Placebo (N=218)	206	1.35 (0.03)	1.30 (0.01)				
Moderate COPD							
QVA149 (N=151)	136	-	-	QVA149 vs. Placebo	0.37 (0.02)	(0.34, 0.40)	<0.001
				QVA149 vs. Tiotropium	0.11 (0.02)	(0.08, 0.15)	<0.001
Tiotropium (N=149)	142	-	-	Tiotropium vs. Placebo	0.26 (0.02)	(0.23, 0.29)	<0.001
Placebo (N=149)	142	-	-				
Severe COPD							
QVA149 (N=72)	69	-	-	QVA149 vs. Placebo	0.25 (0.02)	(0.21, 0.30)	<0.001

				QVA149 vs. Tiotropium	0.09 (0.02)	(0.05, 0.14)	<0.001
Tiotropium (N=71)	67	-	-	Tiotropium vs. Placebo	0.16 (0.02)	(0.12, 0.21)	<0.001
Placebo (N=69)	64	-	-				

CI = confidence interval; COPD = chronic obstructive pulmonary disease; LSM = least squares mean; SE = standard error.

Other patient symptoms

The percentage of nights with no awakenings over 6-weeks was significantly higher for QVA149 versus placebo ($p<0.001$; Appendix Table3). The percentage of days with no daytime symptoms was also significantly higher for QVA149 compared with placebo ($p=0.001$; Appendix Table3). For both assessments, QVA149 was numerically but not statistically superior to tiotropium. The percentage of days patients were able to perform their usual daily activities was significantly higher in the QVA149 group versus placebo ($p<0.001$) but not versus tiotropium (Appendix Table3). Mean daily total and individual symptom scores were significantly reduced (improved) with QVA149 versus placebo ($p<0.001$ for daily total score and $p<0.001$, $p=0.002$, $p<0.001$ and $p=0.007$ for respiratory symptoms, cough, wheeze and amount of sputum scores, respectively) but not versus tiotropium (Appendix Table3).

Rescue medication

Patients in the QVA149 group used significantly less rescue medication and had a significantly higher percentage of days with no rescue medication use compared with those in the placebo $p<0.001$ for both) and tiotropium ($p=0.002$ and $p<0.001$, respectively) groups (Appendix Table3).

Safety

The overall incidence of AEs was similar across QVA149 and tiotropium treatment groups and slightly higher for the placebo group (Table 3). A similar number of patients from each group discontinued the study due to AEs (Table 4).

Table 3 Number (%) of adverse events, serious adverse events and deaths

	QVA149 N=223 n (%)	Tiotropium N=220 n (%)	Placebo N=218 n (%)
Patients with any AE(s)	78 (35.0)	78 (35.5)	86 (39.4)
Adverse events in ≥1·% of any group			
COPD worsening	18 (8.1)	21 (9.5)	20 (9.2)
Nasopharyngitis	14 (6.3)	8 (3.6)	13 (6.0)
Cough	7 (3.1)	8 (3.6)	5 (2.3)
Hypertension	3 (1.3)	3 (1.4)	4 (1.8)
Influenza like illness	3 (1.3)	0 (0)	1 (0.5)
Throat irritation	3 (1.3)	1 (0.5)	2 (0.9)
Headache	2 (0.9)	6 (2.7)	3 (1.4)
Upper respiratory tract infection	1 (0.4)	2 (0.9)	4 (1.8)
Dyspnoea	0 (0)	6 (2.7)	9 (4.1)
Fatigue	0 (0)	4 (1.8)	3 (1.4)
Hypercholesterolaemia	0 (0)	4 (1.8)	0 (0)
Hyperlipidaemia	0 (0)	2 (0.9)	1 (0.5)
Influenza	0 (0)	1 (0.5)	4 (1.8)
Patients with any SAE(s)	6 (2.7)	6 (2.7)	5 (2.3)
Death	1 (0.4)	0 (0)	0 (0)
Discontinuations			
due to AE(s)	11 (4.9)	12 (5.5)	9 (4.1)
due to SAE(s)	3 (1.3)	4 (1.8)	3 (1.4)
due to non-SAE(s)	8 (3.6)	8 (3.6)	6 (2.8)

AE = adverse event; COPD = chronic obstructive pulmonary disease; SAE = serious adverse event;

A similar number of patients experienced SAEs across the three groups (Table 4). Serious CCV events were infrequent in all groups. There was one death in the QVA149 treatment group, which was adjudicated by an independent mortality adjudication committee; the cause of death was determined as cardiovascular sudden death (left ventricular failure leading to cardiac arrest). This patient had active medical conditions of myocardial ischemia, hypertension and leg oedema prior to enrolment in the study.

DISCUSSION

The results of the BLAZE study demonstrated that dual bronchodilation with once-daily QVA149 provides superior and clinically meaningful improvements in patient-reported dyspnoea after 6 weeks versus placebo in patients with moderate-to-severe COPD. The improvement for QVA149 versus tiotropium was also significant; however it is not possible to determine whether it was also clinically meaningful, as the MCID is not established for comparisons between active treatments [26]. Nonetheless, results of the responder analysis suggested that patients are more likely to achieve a clinically meaningful improvement in TDI with QVA149 than with tiotropium. Further, treatment with tiotropium failed to achieve the MCID versus placebo, despite resulting in significant improvements in dyspnoea. The current study further supports the concept that combining two bronchodilators may extend the improvements seen in dyspnoea with single agents.

Improvements in dyspnoea were greater in patients with severe COPD versus both placebo and tiotropium than in those with moderate COPD. This is noteworthy in light of evidence showing that patient-reported rating of dyspnoea are related to the degree of disease severity, with severe patients more heavily affected by breathlessness than moderate patients [5]. Notably, improvements in patient-reported dyspnoea were associated with significant improvements in lung function versus placebo and tiotropium. These improvements were observed in patients with both moderate and severe COPD. Furthermore, these beneficial effects on dyspnoea and lung function were paralleled by significant improvements in additional clinical outcomes, including other symptoms and reduced rescue medication use.

To our knowledge, BLAZE is the first trial to use the SAC BDI/TDI instruments to assess improvements in dyspnoea as the primary endpoint. As these instruments provide a direct measure of patient-reported severity of breathlessness related to activities of daily living, they avoid any interpretation by the interviewer and are therefore expected to reduce measurement errors and variability in assessing dyspnoea, the hallmark symptom of COPD. Furthermore, the cross over design of the present study allowed a more rigorous evaluation of dyspnoea than a parallel group design because within-patient variability for this parameter is expected to be lower than between-patient variability, with patients acting as their own controls. The results of the present study support previous findings from the QVA149 SHINE and ILLUMINATE studies in which superior bronchodilation after 26 weeks of treatment in patients with moderate-to-severe COPD resulted in significant improvements in the interviewer-based TDI total score with QVA149 versus placebo and tiotropium[20] and the LABA/ICS combination salmeterol/fluticasone [21]. In the BLAZE study, improvements in FEV_1 with QVA149 were smaller than those seen in ILLUMINATE and SHINE. A possible explanation could be that patients included in the BLAZE study had more severe airflow limitations that those in ILLUMINATE and SHINE. This is supported by the results of the subgroup analysis performed in the present study, which indicates a greater improvement in lung function in patients with moderate versus severe COPD. Nevertheless, the agreement of our results with those of previous studies with regards to improvements in breathlessness suggests that SAC BDI/TDI instruments are sensitive enough in a head-to-head comparison to show a statistical and clinically meaningful difference in patient-reported outcomes. Data from the present study, combined with data from the other studies in the QVA149 IGNITE clinical programme [20-22] also demonstrate the overall benefits of dual bronchodilation with a fixed-dose LABA/LAMA combination in symptomatic patients with COPD. In this study QVA149 was well tolerated with an AE profile similar to that of tiotropium and placebo over 6 weeks. Taken together, these findings support the GOLD 2013 strategy recommendation that the addition of a second bronchodilator in patients with moderate-to-severe COPD may optimise symptom benefit without increasing side effects [2].

There are a few limitations of this study. Although these results suggest that the SAC BDI/TDI allow an accurate assessment of the severity of breathlessness related to activities of daily living, these instruments have not been extensively evaluated in clinical trials. In addition, the SAC instruments require the patient to have a basic ability to use a computer with mouse to select grades for breathlessness at an initial

visit and to report changes from baseline after treatment. At all visits in which the SAC instruments were used, patients were familiarised with the mouse and computer by answering a question about tiredness. After completing this practice question, study participants were able to directly select grades for breathlessness without assistance. Additional studies of longer duration are needed to fully establish the clinical applicability of the SAC BDI/TDI for evaluating the efficacy of therapies in COPD.

In conclusion, the BLAZE study was novel based on three features: a dual bronchodilator in a single dry powder inhaler was investigated; the SAC versions of the BDI/TDI were used as the primary objective; and the study design incorporated three periods of randomized treatments. The results showed that after 6 weeks, dual bronchodilation with once-daily QVA149 provided superior improvements in both patient-reported dyspnoea, and lung function compared with placebo and tiotropium. The findings of the BLAZE study add to the growing body of evidence that improved lung function with QVA149 translates into greater relief of breathlessness and improved patient-reported outcomes.

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Competing interests

Donald A. Mahler, M.D. serves as a consultant to Boehringer Ingelheim, Forest, GlaxoSmithKline, Novartis, and Sunovion; and serves on advisory boards of Forest, GlaxoSmithKline, Merck, Novartis, Pearl, and Sunovion. The Clinical Trials Office at Dartmouth-Hitchcock Medical Center has received grant support from Boehringer Ingelheim, GlaxoSmithKline, Novartis, and Sunovion for which Dr. Mahler was the principal investigator. Marc Decramer has received speaker fees from AstraZeneca, GlaxoSmithKline, Boehringer-Pfizer, and Novartis, consulting fees from AstraZeneca, Boehringer-Pfizer, Dompé, GlaxoSmithKline, Novartis, Takeda/Nycomed and Vectura, and grant support from AstraZeneca, Boehringer-Pfizer, GlaxoSmithKline and Chiesi. He has no stock holdings in pharmaceutical companies and never received grant support from the Tobacco Industry. Dr D'Urzo has received research, consulting and lecturing fees from GlaxoSmithkline, Sepracor, Schering Plough, Altana, Methapharma, AstraZeneca, ONO pharma, Merck Canada, Forest Laboratories, Novartis Canada/USA, Boehringer Ingelheim (Canada) Ltd, Pfizer Canada, SkyePharma, and KOS Pharmaceuticals. Prof. Heinrich Worth received speaker fees from Almirall, Berlin Chemie, Boehringer-Pfizer, Chiesi, Glaxo Smith Kline, Klosterfrau, Mundipharma, Takeda and Novartis and consulting fees from Almirall, Berlin Chemie, Bionorica, Novartis and Takeda/Nycomed. Prof. Heinrich Worth received grant support from Boehringer-Pfizer, Astra Zeneca, Klosterfrau and Takeda/Nycomed and has never received grant support from the Tobacco industry. Prof. Heinrich Worth has no stock holdings in any of these companies. Tracy White, Vijay K. T. Alagappan, Hungta Chen, Nicola Gallagher, Károly Kulich and Donald Banerji are employee of Novartis Pharma AG.

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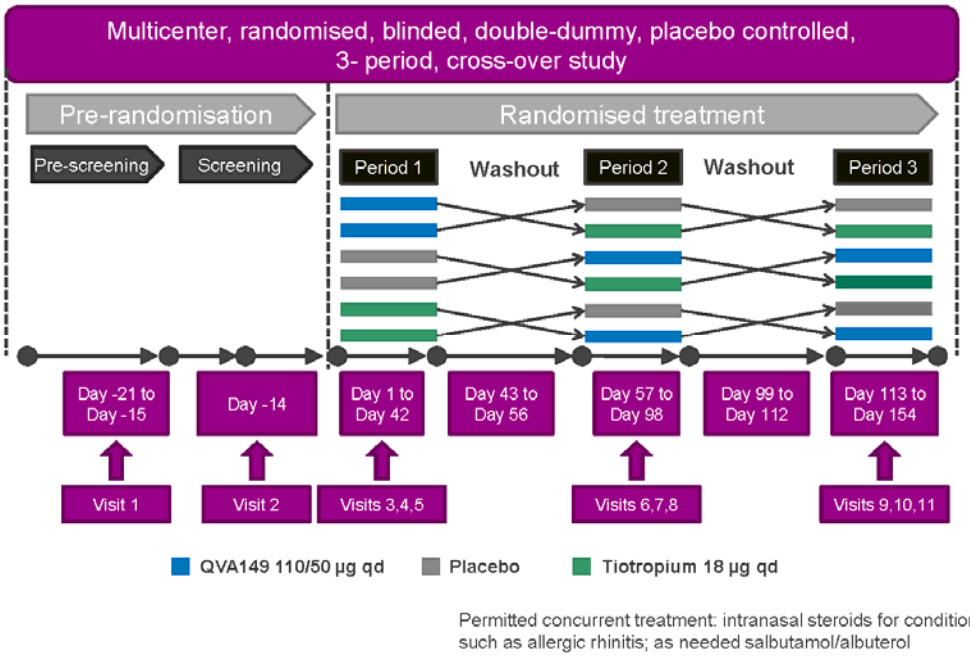
FIGURE LEGENDS

Figure 1. BLAZE study design. After the screening period, patients were randomised to receive QVA149 110/50 µg, placebo or tiotropium. To minimise the order effect, in periods 2 and 3 patients received treatments in two different orders, which resulted in six treatment sequences.

Figure 1



Permitted concurrent treatment: intranasal steroids for conditions such as allergic rhinitis; as needed salbutamol/albuterol

Figure 2. Patient disposition

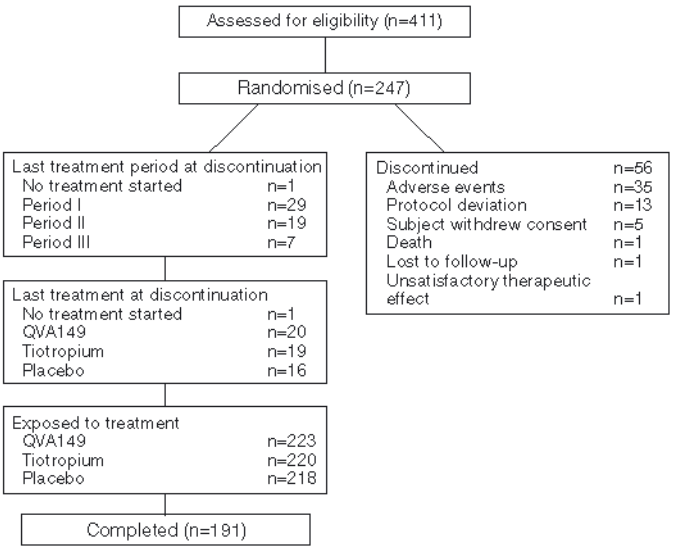
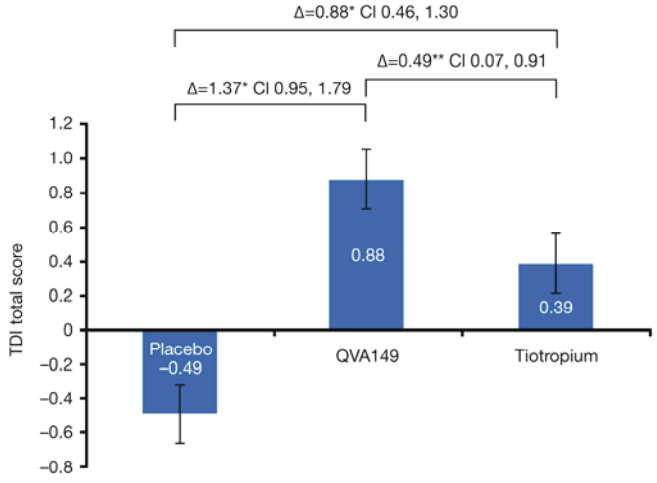


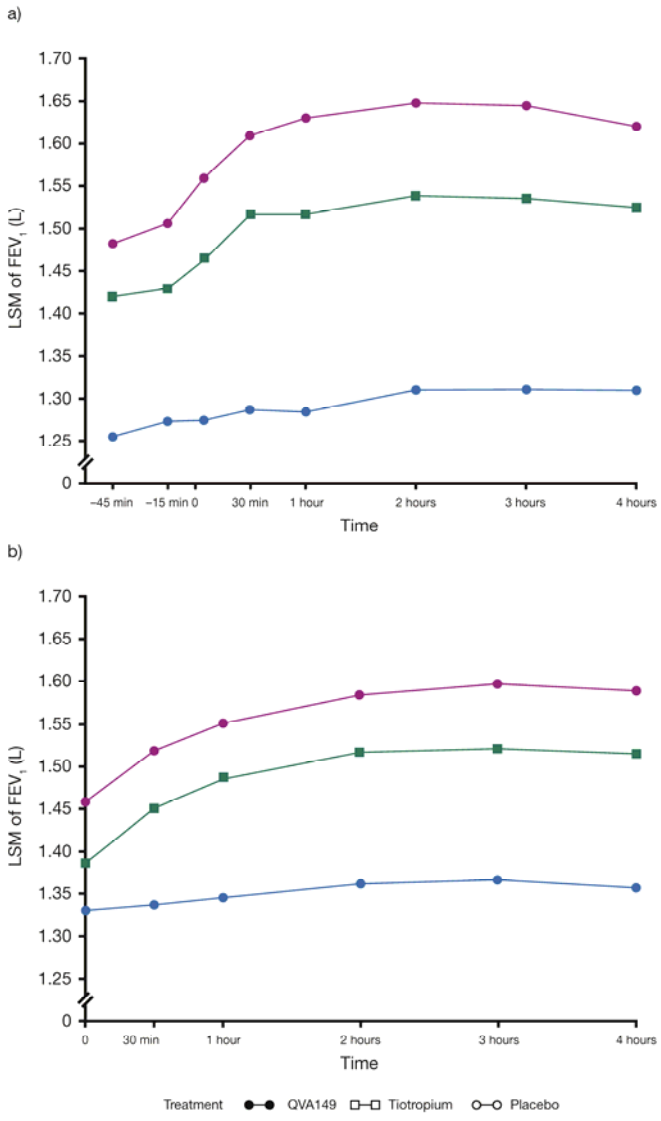
Figure 3. Patient-reported dyspnoea scores after 6 weeks treatment



Data are LSM ± SE. *p<0.001; **p=0.021; CI, confidence interval; LSM, least squares mean; SE, standard error; TDI, Transition Dyspnoea Index

Data are LSM ± SE. *p<0.001; **p=0.021; CI, confidence interval; LSM, least squares mean; SE, standard error; TDI, Transition Dyspnoea Index.

Figure 4. Profile of least squares means of FEV_1 (L) for: a) 45 minutes pre-dose to 4 hours post-dose after 6 weeks of treatment; b) 0 to 4 hours post-dose after first dose on Day 1



Clinically meaningful and statistically significant improvements ($p<0.001$) in FEV_1 were observed with QVA149 versus placebo and tiotropium across all time points. LS, least squares; FEV_1, forced expiratory volume in 1 second