Dual bronchodilation with QVA149 reduces patient-reported dyspnoea in COPD: the 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 chronic obstructive pulmonary disease.

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 after 6 weeks. Secondary end-points included lung function, rescue medication use and safety.

After 6 weeks, the SAC Transition Dyspnoea Index 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 forced expiratory volume in 1 s area under the curve from 0–4 h 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 of 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 outcomes, 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 have been validated *versus* the standard interviewer-administered 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 end-points in a randomised 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 the 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 has 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 $\geqslant$40 years with moderate-to-severe stable COPD (stage II or III according to the 2009 Global Initiative for Chronic Obstructive Lung Disease (GOLD) criteria) [23], were either current smokers or ex-smokers with a smoking history of $\geqslant$10 pack-years, had a post-bronchodilator forced expiratory volume in 1 s (FEV_1) of $\geqslant$30% and $<$80% of predicted normal, had a post-bronchodilator FEV_1/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 online supplementary data. The first patient was enrolled on October 26, 2011 and the last patient completed the study on August 29, 2012. The study was approved by institutional review boards and ethics committees at participating centres, and was conducted in accordance with the Declaration of Helsinki and Good Clinical Practice guidelines. All patients provided written informed consent.

Study design and treatment

This was a multicentre, randomised, blinded, double-dummy, placebo-controlled, three-period crossover study (fig. 1). Blinded tiotropium was included as an active comparator. The study included a pre-screening wash-out period (up to 7 days, depending on 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 (fig. 1). All medications were administered once daily in the morning (between 08:00 h and 11:00 h): QVA149 and placebo to QVA149 *via* the Breezhaler® device (Novartis Pharma AG, Stein, Switzerland), and tiotropium and placebo to tiotropium *via* the HandiHaler® device (Boehringer Ingelheim, Ingelheim, Germany). 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

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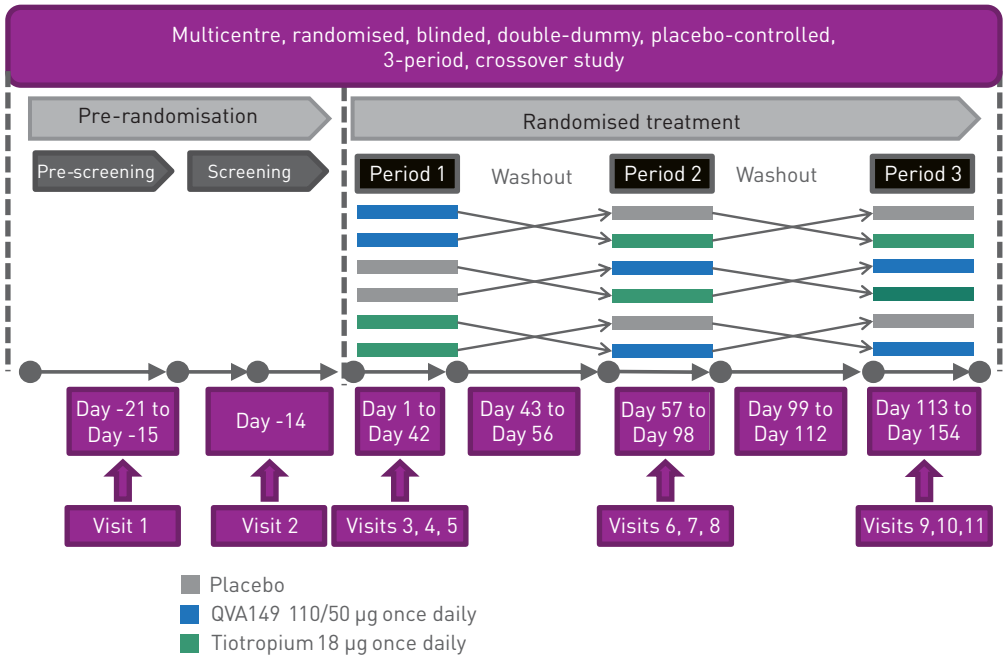

FIGURE 1 The BLAZE study design. After the screening period, patients were randomised to receive placebo, QVA149 110/50 µg or tiotropium 18 µg. To minimise the order effect, in periods 2 and 3 patients received treatments in two different orders, which resulted in six treatment sequences. Permitted concurrent treatment included intranasal steroids for conditions such as allergic rhinitis, and as needed salbutamol/albuterol.

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 inhaled corticosteroids (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 online supplementary data.

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; eResearchTechnology GmbH, Estenfeld, Germany) 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

contained an encrypted, unique patient and visit identifier. The memory stick was then inserted into the VIAConnect PC, which activated 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 end-points also included evaluation of lung function (post-dose FEV_1, and standardised area under the curve from 0 to 4 h ($AUC_{0–4\ h}$) for FEV_1 and FVC) and 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 min and 15 min pre-dose, with 4-h 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 and serious adverse events, 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 adverse events, and atrial fibrillation and flutter events.

Statistical analysis

Detailed statistical methods are provided in the online supplementary data. Efficacy was assessed in the full analysis set, 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 end-points. Other secondary end-points 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 one of the six crossover treatment sequences, with overall total exposure to treatment being: QVA149, n=223; tiotropium, n=220; and placebo, n=218. Overall, 191 (77.3%) patients completed the study (fig. 2). The most common reason for discontinuation was adverse events. 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 ~ 82% had an mMRC dyspnoea scale grade 2 [25].

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

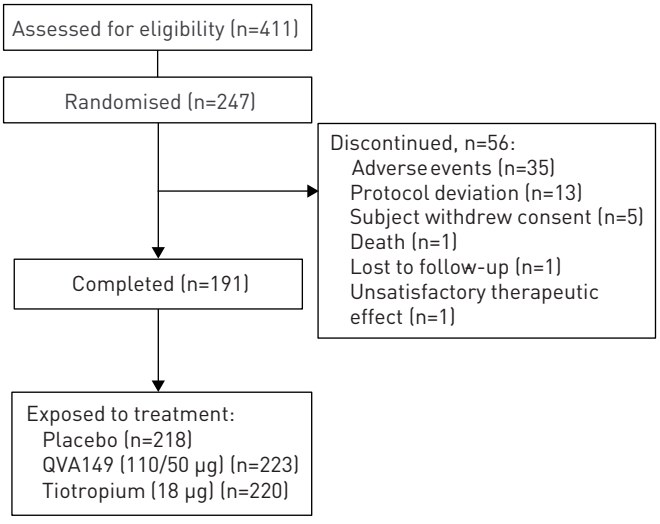

FIGURE 2 Patient disposition.

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TABLE 1 Patient demographics and baseline clinical characteristics

Total subjects	246
Age years	62.8±8.2
<65 years	142 (57.7)
⩾65 years	104 (42.3)
Male	173 (70.3)
Caucasian	246 (100)
BMI kg·m^{-2}	27.2±5.1
Duration of COPD years	7.6±5.9
Severity of COPD#	
Moderate	168 (68.3)
Severe	78 (31.7)
Very severe	0
COPD exacerbations in the previous year	
0	172 (69.9)
1	57 (23.2)
⩾2	17 (6.9)
Smoking history	
Ex-smoker	134 (54.5)
Current smoker	112 (45.5)
Pack-years	46.0±21.7
Patients on ICS at baseline	135 (54.9)
Patients on LAMA at baseline	87 (35.4)
Patients on LABA at baseline	136 (55.3)
mMRC dyspnoea scale	
Grade 2	203 (82.5)
Grade 3	42 (17.1)
Grade 4	1 (0.4)
Pre-bronchodilator FEV$_1$ L	1.35±0.44
Pre-bronchodilator FEV$_1$ % pred	47.3±12.1
Post-bronchodilator FEV$_1$ L	1.60±0.47
Post-bronchodilator FEV$_1$ % pred	56.1±12.3
FEV$_1$ reversibility % increase	20.6±15.0
Post-bronchodilator FEV$_1$/FVC %	48.0±10.4

Data are presented as n, mean±SD or n (%). BMI: body mass index; COPD: chronic obstructive pulmonary disease; ICS: inhaled corticosteroid; LAMA: long-acting muscarinic antagonists; LABA: long-acting β_2-agonists; mMRC: modified Medical Research Council; FEV$_1$: forced expiratory volume in 1 s; FVC: forced vital capacity. #: Global Initiative for Chronic Obstructive Lung Disease 2009 classification [23].

baseline (table S1). The SAC TDI total score was significantly improved with QVA149 *versus* placebo and tiotropium after 6 weeks (fig. 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 (fig. 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% *versus* 18.1%, 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 online supplementary data.

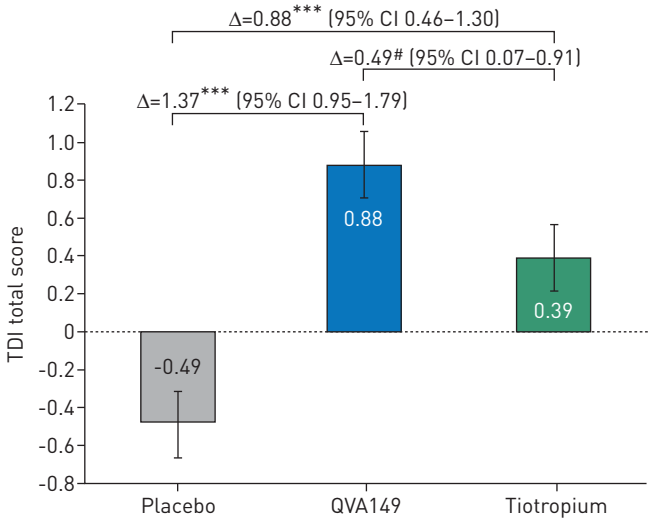

FIGURE 3 Patient-reported dyspnoea scores after 6 weeks of treatment. Data are presented as least squares mean±SE. TDI: Transition Dyspnoea Index. ***: $p<0.001$; #: $p=0.021$.

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 (table S1). After 6 weeks, QVA149 significantly improved mean FEV_1 at all time-points from 45 min pre-dose to 4 h post-dose *versus* placebo and tiotropium ($p<0.001$) (fig. 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 time-points from 0 to 4 h post-dose (all $p<0.001$) (fig. 4b). On day 1, the FEV_1 LSM treatment difference for QVA149–placebo and QVA149–tiotropium was 126 mL and 70 mL at 5 min, respectively, and 182 mL and 68 mL at 30 min, respectively (all $p<0.001$). FEV_1 $AUC_{0–4\ h}$ 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 $AUC_{0–4\ h}$ LSM treatment difference for QVA149–placebo of 370 mL in moderate patients and 254 mL in severe patients after 6 weeks (all $p<0.001$) (table 2). At day 1 and week 6, QVA149 provided significantly superior improvements in FVC $AUC_{0–4\ h}$ *versus* tiotropium and placebo (all $p<0.001$) (table S2).

Other patient symptoms

The percentage of nights with no awakenings over 6 weeks was significantly higher for QVA149 *versus* placebo ($p<0.001$) (table S3). The percentage of days with no daytime symptoms was also significantly higher for QVA149 compared with placebo ($p=0.001$) (table S3). 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 (table S3). 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 (table S3).

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 (table S3).

Safety

The overall incidence of adverse events was similar across the QVA149 and tiotropium treatment groups, and was slightly higher for the placebo group (tables 3 and S4). A similar number of patients from each group discontinued the study due to adverse events (tables 3 and S5).

A similar number of patients experienced serious adverse events across the three groups (tables 3 and S5). Serious cardio- and cerebrovascular adverse events were infrequent in all groups. There was one death in the

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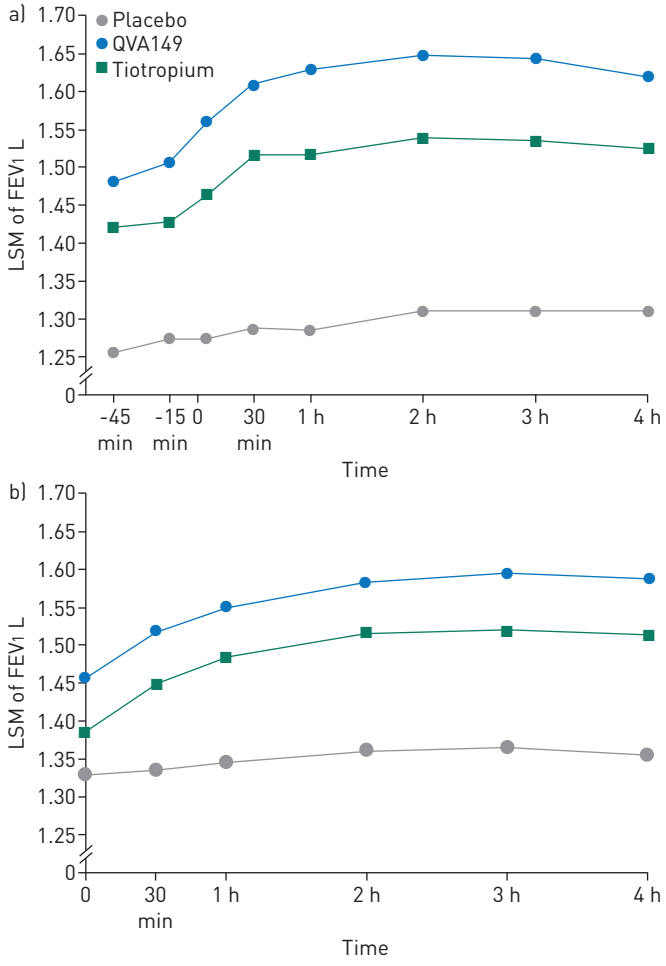

FIGURE 4 Profile of least squares means (LSM) of forced expiratory volume in 1 s (FEV_1) for a) 45 min pre-dose to 4 h post-dose after 6 weeks of treatment, and b) 0–4 h post-dose after the first dose on day 1. Clinically meaningful and statistically significant improvements ($p<0.001$) in FEV_1 were observed with QVA149 *versus* placebo and tiotropium across all time-points.

QVA149 treatment group, which was adjudicated by an independent mortality adjudication committee; the cause of death was determined as sudden cardiovascular death (left ventricular failure leading to cardiac arrest). This patient had active medical conditions of myocardial ischaemia, 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. Furthermore, 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 in dyspnoea seen 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 ratings 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.

TABLE 2 Forced expiratory volume in 1 s standardised area under the curve from 0–4 h on day 1 and week 6

Treatment (randomised patients n)	Patients in the analysis model n	Baseline	Treatment	Comparison	Treatment difference		
		Mean±SE	LSM±SE		LSM±SE	95% CI	p-value
Day 1							
All patients							
QVA149 (n=223)	220	1.32±0.03	1.56±0.01	QVA149 *versus* placebo	0.21±0.01	0.19–0.23	<0.001
				QVA149 *versus* tiotropium	0.07±0.01	0.05–0.09	<0.001
Tiotropium (n=220)	219	1.33±0.03	1.50±0.01	Tiotropium *versus* 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 *versus* placebo	0.23±0.01	0.21–0.26	<0.001
				QVA149 *versus* tiotropium	0.07±0.01	0.05–0.10	<0.001
Tiotropium (n=149)	148			Tiotropium *versus* placebo	0.16±0.01	0.14–0.19	<0.001
Placebo (n=149)	148						
Severe COPD							
QVA149 (n=72)	72			QVA149 *versus* placebo	0.17±0.02	0.13–0.20	<0.001
				QVA149 *versus* tiotropium	0.06±0.02	0.03–0.10	<0.001
Tiotropium (n=71)	71			Tiotropium *versus* 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 *versus* placebo	0.33±0.01	0.31–0.36	<0.001
				QVA149 *versus* tiotropium	0.11±0.01	0.08–0.13	<0.001
Tiotropium (n=220)	209	1.34±0.03	1.53±0.01	Tiotropium *versus* 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 *versus* placebo	0.37±0.02	0.34–0.40	<0.001
				QVA149 *versus* tiotropium	0.11±0.02	0.08–0.15	<0.001
Tiotropium (n=149)	142			Tiotropium *versus* placebo	0.26±0.02	0.23–0.29	<0.001
Placebo (n=149)	142						
Severe COPD							
QVA149 (n=72)	69			QVA149 *versus* placebo	0.25±0.02	0.21–0.30	<0.001
				QVA149 *versus* tiotropium	0.09±0.02	0.05–0.14	<0.001
Tiotropium (n=71)	67			Tiotropium *versus* placebo	0.16±0.02	0.12–0.21	<0.001
Placebo (n=69)	64						

LSM: least squares mean; COPD: chronic obstructive pulmonary disease.

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TABLE 3 Number of adverse events, serious adverse events and deaths

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

Data are presented as n or n (%). COPD: chronic obstructive pulmonary disease.

To our knowledge, BLAZE is the first trial to use the SAC BDI/TDI instruments to assess improvements in dyspnoea as the primary end-point. 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 crossover 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 than 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 adverse event 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 allows 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 a 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: 1) a dual bronchodilator in a single dry powder inhaler was investigated, 2) the SAC versions of the BDI/TDI were used as the primary objective, and 3) the study design incorporated three periods of randomised 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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