Revised version

Online Appendix for:

Dual bronchodilation with indacaterol/glycopyrronium (QVA149) reduces patient-reported dyspnoea and improves lung function in COPD patients (BLAZE): a randomised, blinded study

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METHODS

Patients (additional details)

Patients were required to have Grade ≥2 on the modified Medical Research Council Dyspnoea Scale, and be able to demonstrate that they could use a computer mouse to navigate a computer display. Patients were excluded if they: required long-term oxygen therapy; had a COPD exacerbation (requiring antibiotics, systemic steroids or hospitalisation) in the 6 weeks before screening, or between screening and randomisation; had a respiratory tract infection in the weeks before or during screening; had concomitant pulmonary disease or had undergone a lung lobectomy, volume reduction or transplantation; had asthma, eczema, known high IgE levels, blood eosinophil count >600/mm^3 at screening, or a known positive skin prick test in the previous 5 years; had allergic rhinitis and used an H_1 antagonist or intra-nasal corticosteroids; or if they had α-1 antitrypsin deficiency. Patients were also excluded if they had long QT syndrome or QTc >450 ms at screening; a clinically significant electrocardiogram abnormality; a body mass index >40 kg/m^2; or were contraindicated or had had adverse reactions to inhaled anticholinergics, long and short-acting β_2-agonists.

Study design and treatments (additional details)

The study involved 42 centres in 5 countries: Belgium, Canada, Germany, Spain and the United Kingdom. Data were collected in a clinical setting.

Patients were requested not to take short-acting bronchodilators in the 6 hours prior to the start of each visit.

Blinding of patients, investigator staff, personnel performing assessments and data analysts was maintained by ensuring randomisation data remained strictly confidential and inaccessible to anyone involved in the study until the time of unblinding. In addition, the identity of the treatments was concealed by the use of study drugs that were all identical in packaging, labelling, schedule of administration, appearance, taste and odour. Investigators and study personnel performing study assessments remained blinded to study drug. They did not observe patient loading capsule or inhaling drug. Instead study drug was dispensed, administered and collected from patients by a third party study personnel not involved in the study. A

double-dummy design was used because the identity of the study drugs could not be disguised, nor could their need for administration by different inhaler devices.

Investigators used an automated, interactive response technology to assign randomisation numbers to patients who met the criteria for the study. Randomisation numbers were used to link patients to treatment arms, and were not communicated to the caller. The randomisation numbers generated using this procedure ensured that treatment assignment was unbiased and concealed from patients and investigators. Randomisation data were kept strictly confidential until the time of unblinding, and were not accessible by anyone else involved in the study.

Statistics (additional details)

Sample size was based on a within-patient standard deviation (SD) of 3 total score units for the Self-Administered Computerised Transition Dyspnea Index (SAC TDI),[1] and a treatment difference of ≥1 total score unit as the minimal clinically important difference for the TDI.[2] Adjusting for 15% discontinuation rate, it was calculated that 234 patients needed to be randomised to treatment sequences at a 5% two-sided significance level with 90% power. This would detect a 60 mL difference (and a within-patient SD of 200 mL) in pre-dose mean FEV_1 $AUC_{0\text{-}4hours}$ (QVA149 versus tiotropium), at 84% power.

The primary efficacy variable (SAC Baseline Dyspnea Index [BDI]/TDI versus placebo) and the key secondary efficacy variable (SAC BDI/TDI versus tiotropium) were analysed using a mixed model with treatment, BDI assessment at baseline, reversibility components at screening (FEV_1 before and after bronchodilator inhalation), country, sequence and period as fixed effects, and patient (sequence) as a random effect. QVA149 was superior to placebo if the difference in the TDI total score was statistically significant at the 5% level and when 95% confidence intervals (CIs) were higher than 0 units.

RESULTS (additional results)

After 6 weeks of treatment, the proportion of patients with an MCID of ≥1 in the SAC TDI total score was significantly greater for QVA149 than for placebo in patients with both moderate (33.1% vs. 16.3%; p=0.001) and severe (41.7% vs. 21.7%; p=0.007)

COPD. A statistically greater proportion of patients with moderate COPD also had an SAC TDI improvement of ≥1 with QVA149 than with tiotropium (33.1% vs. 21.8%; p=0.031).

Table S1. Baseline BDI and FEV_1 by treatment period

	Mean BDI total score (SD)			Mean FEV_1, L (SD)		
Treatment	**Period 1**	**Period 2**	**Period 3**	**Period 1**	**Period 2**	**Period 3**
QVA149	7.41 (2.06)	7.49 (1.89)	6.94 (2.29)	1.38 (0.44)	1.28 (0.47)	1.28 (0.45)
Tiotropium	7.15 (2.21)	7.17 (2.30)	7.64 (2.04)	1.29 (0.44)	1.33 (0.44)	1.40 (0.52)
Placebo	7.58 (1.96)	7.49 (2.01)	6.85 (2.59)	1.33 (0.45)	1.35 (0.49)	1.33 (0.46)

An interaction test for treatment by baseline period (F-test) was conducted for BDI and FEV_1 separately to address any potential carry-over effect. There were no significant differences for the interaction of treatments (QVA149, tiotropium and placebo) vs periods (1–3) at baseline for BDI or FEV_1. BDI, baseline dyspnoea index; FEV_1, forced expiratory volume in 1 second; SD, standard deviation.

Table S2. Standardised FVC (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							
QVA149 (N=223)	220	2.98 (0.06)	3.34 (0.02)	QVA149 vs. Placebo	0.32 (0.02)	(0.28, 0.36)	<0.001
				QVA149 vs. Tiotropium	0.09 (0.02)	(0.05, 0.13)	<0.001
Tiotropium (N=220)	219	2.98 (0.06)	3.25 (0.02)	Tiotropium vs. Placebo	0.23 (0.02)	(0.19, 0.27)	<0.001
Placebo (N=218)	217	2.98 (0.06)	3.0 (0.02)				
Week 6							
QVA149 (N=223)	205	3.0 (0.06)	3.39 (0.03)	QVA149 vs. Placebo	0.44 (0.03)	(0.38, 0.50)	<0.001
				QVA149 vs. Tiotropium	0.12 (0.03)	(0.07, 0.18)	<0.001
Tiotropium (N=220)	209	3.0 (0.06)	3.27 (0.03)	Tiotropium vs. Placebo	0.31 (0.03)	(0.25, 0.37)	<0.001
Placebo (N=218)	206	3.0 (0.06)	2.95 (0.03)				

CI, confidence interval; LSM, least squares mean; SE, standard error.

Table S3 Patient symptoms and rescue medication use over 6 weeks.

	QVA149 110/50 µg			
	Difference vs placebo (LSM ± 95% CI)	p values	Difference vs tiotropium (LSM ± 95% CI)	p values
Change from baseline in rescue medication use, puffs/day	−1.43 (−1.72, −1.13)	<0.001	−0.45 (−0.74, −0.16)	0.002
Days with no rescue medication use, %	19.9 (15.7, 24.0)	<0.001	9.1 (5.0, 13.2)	<0.001
Nights with 'no nighttime awakenings', %	5.6 (2.6, 8.6)	<0.001	2.6 (−0.4, 5.5)	0.090
Days with 'no daytime symptoms', %	3.5 (1.4, 5.6)	0.001	1.5 (−0.6, 3.5)	0.165
Days 'able to perform usual daily activities', %	8.8 (5.1, 12.4)	<0.001	−0.4 (−4.1, 3.2)	0.812
Total symptom score	−0.72 (−0.94, −0.49)	<0.001	−0.03 (−0.26, 0.19)	0.759
Respiratory symptoms	−0.16 (−0.21, −0.11)	<0.001	−0.01 (−0.06, 0.04)	0.627
Cough	−0.09 (−0.14, −0.03)	0.002	−0.01 (−0.06, 0.05)	0.769
Wheeze	−0.19 (−0.24, −0.13)	<0.001	−0.03 (−0.08, 0.03)	0.353
Amount of sputum	−0.07 (−0.12, −0.02)	0.007	0.01 (−0.04, 0.06)	0.733

CI, confidence interval; LSM, least squares mean; SE, standard error.

Table S4. Most frequent AEs (at least two patients on any treatment)

	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)
AEs (preferred term)			
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)
Arthralgia	2 (0.9)	0 (0)	1 (0.5)
Constipation	2 (0.9)	0 (0)	0 (0)
Diarrhoea	2 (0.9)	1 (0.5)	1 (0.5)
Headache	2 (0.9)	6 (2.7)	3 (1.4)
Lower respiratory tract infection	2 (0.9)	2 (0.9)	1 (0.5)
Oropharyngeal pain	2 (0.9)	1 (0.5)	2 (0.9)
Upper respiratory tract infection bacterial	2 (0.9)	0 (0)	1 (0.5)
Urinary tract infection	2 (0.9)	2 (0.9)	2 (0.9)
Vomiting	2 (0.9)	1 (0.5)	0 (0)
Back pain	1 (0.4)	2 (0.9)	1 (0.5)
Dry mouth	1 (0.4)	2 (0.9)	0 (0)
Sinusitis	1 (0.4)	0 (0)	2 (0.9)
Upper respiratory tract infection	1 (0.4)	2 (0.9)	4 (1.8)
Anaemia	0 (0)	2 (0.9)	0 (0)
Bronchitis	0 (0)	0 (0)	2 (0.9)
Dyspnoea	0 (0)	6 (2.7)	9 (4.1)
Fatigue	0 (0)	4 (1.8)	3 (1.4)
Gastroenteritis	0 (0)	0 (0)	2 (0.9)
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)
Insomnia	0 (0)	1 (0.5)	2 (0.9)
Respiratory tract infection	0 (0)	0 (0)	2 (0.9)
Rhinorrhoea	0 (0)	0 (0)	2 (0.9)
Sciatica	0 (0)	0 (0)	2 (0.9)
Somnolence	0 (0)	0 (0)	2 (0.9)
Sputum increased	0 (0)	2 (0.9)	0 (0)

AE, adverse event; COPD, chronic obstructive pulmonary disease.

Table S5. Deaths, other SAEs and discontinuations reported during the study

	QVA149 N=223 n (%)	Tiotropium N=220 n (%)	Placebo N=218 n (%)

Death	1 (0.4)	0 (0)	0 (0)
Patients with SAE(s)	6 (2.7)	6 (2.7)	5 (2.3)
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)
SAEs (preferred term)			
Cardiac arrest	1 (0.4)	0 (0)	0 (0)
Left ventricular failure	1 (0.4)	0 (0)	0 (0)
Atrial fibrillation	0 (0)	1 (0.5)	0 (0)
Abdominal pain upper	0 (0)	0 (0)	1 (0.5)
Influenza like illness	1 (0.4)	0 (0)	0 (0)
Pleural infection bacterial	1 (0.4)	0 (0)	0 (0)
Bronchopneumonia	0 (0)	0 (0)	1 (0.5)
Lower respiratory tract infection	0 (0)	1 (0.5)	0 (0)
Pneumonia	0 (0)	1 (0.5)	1 (0.5)
Synovial cyst	1 (0.4)	0 (0)	0 (0)
Salivary gland neoplasm	1 (0.4)	0 (0)	0 (0)
Gastric cancer	0 (0)	1 (0.5)	0 (0)
Metastases to bone	0 (0)	1 (0.5)	0 (0)
Cerebral artery occlusion	0 (0)	0 (0)	1 (0.5)
Ischaemic stroke	0 (0)	0 (0)	1 (0.5)
Alcohol abuse	0 (0)	0 (0)	1 (0.5)
Depression	0 (0)	1 (0.5)	0 (0)
COPD	3 (1.3)	2 (0.9)	1 (0.5)

SAE, serious adverse event; COPD, chronic obstructive pulmonary disease.

REFERENCES

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2. Mahler DA, Witek TJ, Jr. The MCID of the transition dyspnea index is a total score of one unit. *COPD* 2005;2:99-103.