Introduction To benefit symptomatic patients with moderate-to-severe COPD not managed by single bronchodilator, COPD management strategies recommend combining bronchodilators with different mechanisms. We compared, once-daily dual bronchodilation by co-administration of the long-acting muscarinic antagonist (LAMA) glycopyrronium 50 g (GLY) and the long-acting $_2$-agonist (LABA) indacaterol 150 g (IND), with IND 150 g monotherapy.

Methods In this randomised, multicentre, placebo-controlled, double-blind, parallel-group study, patients with moderate-to-severe COPD were administered with GLY + IND or IND + placebo (1:1; all delivered via Breezhaler® device) for 12 weeks. We assessed lung function, dyspnoea (via the transition dyspnoea index [TDI]), patient-reported symptoms, and safety and tolerability over 12 weeks.

Results Of the 449 patients randomised (GLY + IND [n = 226]; IND [n = 223]), 94.0% completed the study. At Week12, GLY + IND demonstrated a statistically significant improvement in mean trough forced expiratory volume in one second (FEV_1)over IND (least squares mean treatment difference [Td]: 64 mL; $p < 0.001$). Significantly greater improvements in FEV_1 area under curve from 30 min to 4h ($FEV_1AUC_{30min-4h}$) and trough forced vital capacity were observed with GLY + IND vs IND on Day1 (Td: 105 mL, 112 mL, respectively) and at Week12 (Td: 111 mL, 93 mL, respectively), all $p < 0.01$. GLY + IND demonstrated significant improvements in inspiratory capacity versus IND at most timepoints on Day1 and Week12 (Td: 59 to 159 mL). GLY + IND significantly improved TDI total score versus IND (Td: 0.49, $p = 0.037$) and a higher proportion of patients on GLY + IND achieved a clinically meaningful improvement (≥1 point) versus IND at Week12 (odds ratio 1.97 favouring GLY + IND; $p = 0.004$). GLY + IND was also associated with significantly greater improvements in mean daytime respiratory symptom score and the percentage of days being able to perform usual daily activities vs IND over 12 weeks of treatment (Td: -0.1 and 6.2, respectively; both $p < 0.05$). The overall incidence of adverse events (AEs) and serious AEs (SAEs) was comparable for the GLY + IND and IND groups (AEs: 37.6% vs 34.1%; SAEs: 2.2% vs 2.3%, respectively).

Conclusion In patients with moderate-to-severe COPD, compared with indacaterol monotherapy, once-daily co-administration of glycopyrronium and indacaterol delivered via Breezhaler® device provided superior improvements lung function and early post-dose bronchodilation (from Day1), dyspnoea, symptoms and activities, without adversely affecting safety and tolerability.

P233 EFFICACY AND SAFETY OF ONCE-DAILY GLYCOPYRRONIUM COMPARED WITH BLINDED TIOTROPIUM IN PATIENTS WITH COPD: THE GLOW5 STUDY

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10.1136/thoraxjnl-2013-204457.385

Background Glycopyrronium, a once-daily long-acting muscarinic antagonist (LAMA), has demonstrated a similar efficacy and safety profile to open-label tiotropium in patients with moderate-to-severe chronic obstructive pulmonary disease (COPD).[1] The GLOW5 study compared the efficacy and safety of glycopyrronium with blinded tiotropium.

Methods In this multicentre, 12-week, blinded study, patients ≥ 40 years with moderate-to-severe COPD (post-bronchodilator FEV_1 ≥ 30% and < 80% of the predicted normal, post-bronchodilator $FEV_1/FVC < 0.70$) and a smoking history of ≥10 pack-years were randomised to glycopyrronium 50μg (via Breezhaler® device) or tiotropium 18μg (via HandiHaler® device). The primary objective was to demonstrate non-inferiority of glycopyrronium versus tiotropium for trough FEV_1 at Week 12 (non-inferiority margin: –50 mL). Other endpoints included FEV_1 area under the curve from 0 to 4 hours (AUC_{0-4hr}) on Day 1, Transition Dyspnoea Index (TDI), St George's Respiratory Questionnaire (SGRQ), rescue medication use, exacerbation rate, safety and tolerability.

Results Of the 657 patients randomised, (glycopyrronium [n = 327]; tiotropium [n = 330]; mean age: 63.5 years, mean post-bronchodilator FEV_1: 53.5% predicted), 95.9% completed the study. Glycopyrronium demonstrated non-inferiority to tiotropium for trough FEV_1 at Week 12 (Least Squares Mean [LSM] = 1.41L for both the groups; 95% confidence interval [CI]: –0.032, 0.031L). Glycopyrronium had a rapid onset of bronchodilation in the morning as demonstrated by a higher FEV_1 AUC_{0-4hr} on Day 1 compared to tiotropium (LSM treatment difference [Td] = 58mL; $p < 0.001$). At Week 12, TDI total score (Td = –0.188; $p = 0.385$), SGRQ total score (Td = 0.65; $p = 0.488$) and percentage of days with no rescue medication use (Td = –1.5; $p = 0.528$) were comparable between the groups. No significant treatment difference was observed with respect to rate of moderate/severe COPD exacerbations per year (glycopyrronium 0.38 versus tiotropium 0.35 [rate ratio = 1.10, 95% CI: 0.62, 1.93]; $p = 0.754$). Overall, the incidence of adverse events was similar in the glycopyrronium (40.4%) and tiotropium (40.6%) groups.

Conclusion Glycopyrronium and blinded tiotropium showed similar improvements in lung function, dyspnoea, health status, exacerbation rate and rescue medication use, with a similar safety and tolerability profile. Onset of bronchodilation with glycopyrronium was significantly more rapid following the first dose.

REFERENCE

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P234 QVA149 ONCE DAILY IMPROVES LUNG FUNCTION, DYSPNOEA AND HEALTH STATUS INDEPENDENT OF PRIOR MEDICATIONS AND DISEASE SEVERITY: THE SHINE STUDY

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10.1136/thoraxjnl-2013-204457.386

Introduction QVA149 is a novel, inhaled, once-daily, fixed-dose combination of the long-acting $_2$-agonist (LABA) indacaterol and the long-acting muscarinic antagonist (LAMA) glycopyrronium (NVA237) in development for the maintenance treatment of chronic obstructive pulmonary disease (COPD). The SHINE study compared the effects of QVA149 110/50 g, indacaterol 150 g, glycopyrronium 50 g, tiotropium 18 g and placebo in

Abstract P234 Table 1. Lung function, dyspnoea and health status improvements in QVA149 vs placebo subgroup analyses based on prior medicationuse and disease severity.

	LSM (SE) treatment difference of QVA149 vs placebo			
1	FEV_1 $AUC_{5min-4h}$(L)	Trough FEV_1(L)	TDI total score	SGRQ total score
Prior medication use				
-agonist plus steroid	0.34 (0.030)***	0.19 (0.030)***	1.21 (0.406)**	–4.09 (1.705)*
LABA	0.36 (0.059)***	0.25 (0.058)***	0.71 (0.798)^{ns}	–0.34 (3.103)^{ns}
LAMA	0.33 (0.028)***	0.22 (0.029)***	1.48 (0.443)***	–5.94 (1.770)***
SABA	0.37 (0.032)***	0.22 (0.031)***	1.29 (0.430)**	–3.10 (1.780)^{ns}
SAMA	0.30 (0.074)***	0.18 (0.073)*	2.27 (1.135)*	–3.24 (4.495)^{ns}
-agonist plus anticholinergic	0.31 (0.075)***	0.08 (0.079)^{ns}	1.13 (1.222)^{ns}	–4.66 (4.935)^{ns}
None	0.30 (0.033)***	0.17 (0.034)***	0.97 (0.500)^{ns}	–2.30 (2.198)^{ns}
COPD severity				
Moderate	0.37 (0.021)***	0.24 (0.021)***	1.17 (0.294)***	–2.74 (1.257)*
Severe	0.26 (0.031)***	0.12 (0.031)***	1.00 (0.433)*	–3.77 (1.840)*

***P<0.001; **P<0.01; *P<0.05; ns, non-significant
LSM, least squares mean; SABA,short-acting $_2$-agonist; SAMA, short-acting muscarinic antagonist; SE, standard error

patients with COPD.[1] Here, we present the data on improvements in lung function (forced expiratory volume in 1 second area under the curve [FEV_1 $AUC_{5\ min\text{-}4\ h}$] and trough FEV_1), transition dyspnoea index (TDI) and St George's Respiratory Questionnaire (SGRQ - total score) by prior medication use and COPD disease severity subgroups.

Methods In this 26-week, multicentre, double-blind, parallel-group, placebo- and active-controlled (open-label tiotropium) study, patients aged ≥40 years with moderate-to-severe COPD (post-bronchodilator FEV_1/forced vital capacity (FVC) <0.7 and FEV_1 ≥30% to <80% predicted) and a smoking history of ≥10 pack-years were randomised to receive once-daily QVA149, indacaterol, glycopyrronium, tiotropium or placebo (2:2:2:2:1).

Results Of the 2144 patients (mean age 63.9 years; mean FEV_1 post-bronchodilator 55.2% predicted) who were randomised (QVA149 [n = 475], indacaterol [n = 477], glycopyrronium [n = 475], tiotropium [n = 483] and placebo [n = 234]), 89.1% completed the study. QVA149 showed significant improvements in lung function, dyspnoea and health status compared with placebo in patient subgroups based on prior medication use and COPD disease severity (Table 1). Additionally, FEV_1 $AUC_{5\ min\text{-}4\ h}$was significantly improved for QVA149 versus placebo (p < 0.001) regardless of the prior medication use and disease severity.

Conclusion With once-daily QVA149, significant improvements were seen in both moderate and severe COPD patients and independent of medications used before recruitment and randomisation into the SHINE study.

REFERENCE

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P235 DUAL-BRONCHODILATION WITH ONCE-DAILY QVA149 IN PATIENTS WITH MODERATE-TO-SEVERE COPD: OVERVIEW OF THE IGNITE PROGRAM

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10.1136/thoraxjnl-2013-204457.387

Introduction In patients with moderate-to-severe chronic obstructive pulmonary disease (COPD) whose symptoms are insufficiently controlled by monotherapy, current treatment strategies recommend the addition of a second bronchodilator with a different mechanism of action. Once-daily QVA149 is a dual bronchodilator combining the long-acting $_2$-agonist indacaterol (IND) and long-acting muscarinic antagonist glycopyrronium (GLY). The IGNITE program comprises a series of randomised

Abstract P235 Table 1. IGNITE data overview

			Treatment differences (QVA149 vs comparator)				
Parameters	**Study (N)**		**PBO**	**IND**	**GLY**	**TIO**	**SFC**
Lung function	SPARK	Trough FEV_1, mL	-	-	70***	60***	-
	(2224)						
	SHINE		200***	70***	90***	80***	-
	(2144)	FEV_1 $AUC_{0–12h}$, mL	330***	130***	130***	120***	-
	ILLUMINATE		-	-	-	-	140***
	(523)						
	BLAZE	FEV_1 $AUC_{0–4h}$, mL	250***	-	-	90***	-
Dyspnoea	(247)	TDI score	1.37***	-	-	0.49*	-
	ILLUMINATE		-	-	-	-	0.76**
Health status	SPARK	SGRQ score	-	-	–2.07***	–2.69***	-
Rate reduction of exacerbations, %		Moderate-to-severe	-	-	12	10	-
					RR 0.88*	RR 0.90	
		All	-	-	15	14	-
					RR 0.85***	RR 0.86**	
	ILLUMINATE	Moderate-to-severe	-	-	-	-	20
							RR 0.80
		All	-	-	-	-	31
							RR 0.69

*p<0.05; **p<0.01; ***p≤0.001; †free combination; GLY=glycopyrronium; IND=indacaterol; PBO=placebo; SFC=salmeterol/fluticasone; RR=rate ratio;TIO=tiotropium