Abstract P190 Table 1 QVA149 versus placebo least squares mean (LSM) differences in FEV₁ and FVC

Visit	QVA149-placebo LSM treatment difference (SE) in mL			
	FEV ₁		FVC	
	30 min post-dose	60 min post-dose	30 min post-dose	60 min post-dose
Day 1	156 (14.2)	200 (16.9)	221 (29.7)	255 (35.8)
Week 3	255 (24.8)	275 (25.1)	342 (43.3)	335 (44.7)
Week 6	266 (26.2)	275 (27.2)	341 (47.3)	342 (46.5)
Week 12	236 (25.4)	260 (26.7)	277 (43.2)	294 (44.1)
Week 26	265 (31.5)	270 (29.6)	345 (49.7)	331 (48.1)
Week 39	240 (32.4)	286 (32.7)	296 (51.0)	340 (51.7)
Week 52	247 (33.3)	255 (33.6)	289 (52.9)	317 (56.9)

all p<0.001

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P191 QVA149 ONCE DAILY IMPROVES EXERCISE TOLERANCE AND LUNG FUNCTION IN PATIENTS WITH MODERATE TO SEVERE COPD: THE BRIGHT STUDY

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¹KM Beeh, ²S Korn, ¹J Beier, ³D Jadayel, ³M Henley, ⁴J Tylek, ⁴I Berhane, ⁴P D'Andrea, ⁴D Donald Banerji. ¹Insaf Respiratory Research Institute, Wiesbaden, Germany; ²Pulmonary, Department, Mainz University Hospital, Mainz, Germany; ³Novartis Horsham Research Centre, Horsham, UK; ⁴Novartis Pharmaceuticals Corporation, East Hanover, New Jersey, USA

Introduction QVA149 is a novel once-daily fixed-dose combination of the long-acting β_2 -agonist indacaterol and the long-acting muscarinic antagonist glycopyrronium (NVA237) in development for the treatment of chronic obstructive pulmonary disease (COPD). The BRIGHT study evaluated the effects of QVA149 versus placebo and tiotropium on exercise tolerance and lung function in patients with moderate-to-severe COPD.

Methods In a double-blind, double-dummy, 3-period crossover study, patients with moderate-to-severe COPD were randomised to QVA149 110/50 μ g, placebo or tiotropium 18 μ g once daily for 3 weeks. The primary endpoint was exercise endurance time for QVA149 versus placebo during a submaximal exercise tolerance test (SMETT) via cycle ergometry at Day 21. Dynamic inspiratory capacity (IC) at isotime during exercise, trough IC, trough FEV₁ and trough forced vital capacity (FVC) were also measured.

Results Eighty five patients were randomised; mean age was 62 years, mean post-bronchodilator FEV₁ 56% predicted. 86% patients

completed the study. At Day 21, QVA149 significantly improved exercise endurance time by 59.5 seconds versus placebo (p=0.006), which was of a similar magnitude to the improvement seen with tiotropium versus placebo (66.3 seconds; p=0.002). More patients stopped exercise due to dyspnoea with placebo (43% versus 36% with both QVA149 and tiotropium) and due to muscle fatigue with QVA149 and tiotropium (44–46% versus 38% with placebo). QVA149 also produced significant and clinically meaningful improvements in trough FEV₁, dynamic IC at exercise isotime, trough IC and trough FVC versus placebo and tiotropium (table).

Conclusion QVA149 once daily provided significant and clinically meaningful improvements in exercise tolerance and lung function in patients with moderate-to-severe COPD. Despite superior bronchodilation demonstrated by QVA149 versus tiotropium, improvements seen in exercise endurance were similar, perhaps due to extra-pulmonary factors (muscle fatigue, ceiling effect). There were no safety concerns.

P192 QVA149 ONCE DAILY PROVIDES SUPERIOR BRONCHODILATION VERSUS INDACATEROL, GLYCOPYRRONIUM, TIOTROPIUM AND PLACEBO: THE SHINE STUDY

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¹N Barnes, ²E Bateman, ³N Gallagher, ³Y Green, ³R Horton, ³M Henley, ⁴D Banerji. ¹London Chest Hospital, Barts Health NHS Trust, London, UK; ²Department of Medicine, University of Cape Town, Cape Town, South Africa; ³Novartis Horsham Research Centre, Horsham, West Sussex, UK; ⁴Novartis Pharmaceuticals Corporation, East Hanover, NJ, USA

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 NVA237 (glycopyrronium) in development for the maintenance treatment of COPD. This study evaluated the effect of QVA149 on

Abstract P191 Table 1

	Treatment differences on Day 21		
	Least squares means (95% Confidence interval)		
	QVA149–Placebo	QVA149–Tiotropium	Tiotropium–Placebo
Exercise endurance time (seconds)	59.5 (17.7, 101.3)**	–6.7 (–47.5, 34.0)	66.3 (24.8, 107.7)**
IC at isotime (L) [†]	0.32 (0.23, 0.40)***	0.14(0.05, 0.22)**	0.18(0.10,0.27)***
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)***

***p<0.001; **p<0.01; *p<0.05; [†]Isotime is the latest matching point during exercise at which for all periods for a patient there is an IC assessment; IC: inspiratory capacity; FEV₁: forced expiratory volume in 1 sec; FVC: forced vital capacity.

lung function compared with indacaterol, glycopyrronium, open-label tiotropium and placebo in patients with moderate-to-severe COPD.

Methods This 26 week, multicentre, double-blind, parallel-group, placebo and active controlled (open-label tiotropium) study randomised male or female patients ≥ 40 years of age with moderate-to-severe COPD (post-bronchodilator $FEV_1/FVC < 0.7$ and $FEV_1 \geq 30\%$ to $< 80\%$ predicted) and smoking history ≥ 10 pack-years to receive once-daily QVA149 (110/50 μ g), indacaterol (150 μ g), glycopyrronium (50 μ g), placebo (all delivered via the Breezhaler[®] device) and tiotropium (18 μ g; delivered via the Handihaler[®] device) (2:2:2:1:2). The primary objective was to demonstrate superiority in trough FEV_1 (mean of 23h 15min and 23h 45min post-dose) of QVA149 versus indacaterol and glycopyrronium at Week 26. We also present results of trough FEV_1 at Day 1 and Week 12, serial spirometry for FEV_1 and forced vital capacity (FVC) at Day 1, Weeks 12 and 26.

Results Of the 2144 patients randomised, (QVA149 [n=475]; indacaterol [n=477]; glycopyrronium [n=475]; tiotropium [n=483]; placebo [n=234]), 89.1% completed the study. 75.4% were male; mean age: 63.9 years; mean post-bronchodilator FEV_1 : 55.2% predicted. At Day 1, Weeks 12 and 26, QVA149 was statistically superior to indacaterol, glycopyrronium, tiotropium and placebo for mean trough FEV_1 and trough FVC (all $p < 0.001$, table).

Serial spirometry in a subset of patients (QVA149 [n=66]; indacaterol [n=64]; glycopyrronium [n=63]; tiotropium [n=70]; placebo [n=31]) showed statistically significant improvements in FEV_1 with QVA149 versus placebo at all time-points ($p < 0.001$) and versus indacaterol, glycopyrronium and tiotropium at almost all assessed time-points on Day 1, and Weeks 12 and 26.

Conclusion QVA149 once daily provided significant and clinically meaningful improvements in lung function versus the component monotherapies indacaterol and glycopyrronium, as well as significant improvements versus tiotropium and placebo over 26 weeks in patients with COPD.

Abstract P192 Table 1 Trough FEV_1 and FVC at Day 1, Weeks 12 and 26

	Least squares mean treatment (SE) difference in mL			
	QVA149– placebo	QVA149– indacaterol	QVA149– glycopyrronium	QVA149– tiotropium
Trough FEV_1				
Day 1	190 (11)	80 (9)	80 (9)	80 (9)
Week 12 (LOCF)	230 (16)	80 (13)	100 (13)	90 (13)
Week 26 (LOCF)	200 (17)	70 (14)	90 (14)	80 (13)
Trough FVC				
Day 1	300 (23)	130(18)	100 (18)	110 (18)
Week 12	320 (29)	110 (23)	120 (23)	110 (23)
Week 26	280 (31)	100 (24)	80 (24)	90 (24)

all $p < 0.001$

P193

GLYCOPYRRONIUM ONCE DAILY PROVIDES RAPID AND SUSTAINED BRONCHODILATION AND IS WELL TOLERATED IN PATIENTS WITH COPD: THE SHINE STUDY

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¹E Bateman, ²S Hashimoto, ³N Gallagher, ³Y Green, ³R Horton, ³M Henley, ⁴D Banerji. ¹Department of Medicine, University of Cape Town, Cape Town, South Africa; ²Nihon University School of Medicine, Itabashi Hospital, Tokyo, Japan; ³Novartis Horsham Research Centre, Horsham, West Sussex, UK; ⁴Novartis Pharmaceuticals Corporation, East Hanover, NJ, USA

Introduction NVA237 (glycopyrronium bromide) is a once-daily inhaled long-acting muscarinic antagonist for the treatment of COPD. The SHINE study evaluated the efficacy and safety of QVA149, a fixed-dose combination of indacaterol and glycopyrronium, compared with indacaterol, glycopyrronium, open-label tiotropium and placebo in patients with COPD.

Methods This 26 week, multicentre, double-blind, parallel-group, placebo and active controlled (open-label tiotropium) study randomised male or female patients ≥ 40 years of age with moderate-to-severe COPD (post-bronchodilator $FEV_1/FVC < 0.7$ and $FEV_1 \geq 30\%$ to $< 80\%$ predicted) and smoking history ≥ 10 pack-years to receive once-daily QVA149 (110/50 μ g), indacaterol (150 μ g), glycopyrronium (50 μ g refers to the quantity of the glycopyrronium moiety present in the capsule, which corresponds to a delivered dose of 44 μ g), placebo (all delivered via the Breezhaler[®] device) and tiotropium (18 μ g; delivered via the Handihaler[®] device) (2:2:2:1:2). The primary efficacy endpoint was trough FEV_1 (mean of 23h 15min and 23h 45min post-dose) at Week 26. Here we report the results of the efficacy and safety of glycopyrronium versus tiotropium and placebo.

Results Of the 1192 patients randomised (glycopyrronium [n=475]; tiotropium [n=483]; placebo [n=234]); 88.3% completed the study with the mean age in glycopyrronium, tiotropium and placebo groups being 64.3, 63.5 and 64.4 years, respectively. At Week 26, glycopyrronium was superior to placebo for mean trough FEV_1 (treatment difference: 120mL; $p < 0.001$). A similar significant improvement was observed with tiotropium versus placebo (treatment difference: 130mL; $p < 0.001$). Significant improvement was also seen with glycopyrronium compared with placebo in other outcome measures evaluating lung function (table).

Serial spirometry in a subset of patients (glycopyrronium [n=63]; tiotropium [n=70] and placebo [n=31]) showed statistically significant improvements in FEV_1 with glycopyrronium and tiotropium versus placebo at all assessed time-points on Week 26. The incidence of adverse events was similar between groups (61.3% glycopyrronium; 57.3% tiotropium and 57.8% placebo).

Conclusion Glycopyrronium 50 μ g once daily provided rapid and sustained bronchodilation over 26 weeks and was well tolerated. The onset of action of glycopyrronium was faster than tiotropium on Day 1 and the FEV_1 AUC 0–12h, 12–24h and 0–24h profiles at Week 26 were similar, thereby showing good 24-hour efficacy.

Abstract P193 Table 1 Least squares mean (LSM) treatment difference on Day 1 and Week 26

	Total number of patients (n)	LSM treatment difference (SE) in mL		
		Glycopyrronium–placebo	Tiotropium–placebo	Glycopyrronium–tiotropium
Day 1				
FEV_1 AUC _{0–4h}	1165	190 (9)*	140 (9)*	50 (8)*
FEV_1 AUC _{0–12h}	164	180 (25)*	130 (25)*	50 (20) [†]
Week 26				
FEV_1 AUC _{0–12h}	152	210 (41)*	210 (41)*	–10 (33) ^{NS}
FEV_1 AUC _{12–24h}	152	200 (43)*	210 (42)*	–10 (33) ^{NS}
FEV_1 AUC _{0–24h}	152	200 (41)*	210 (40)*	–10 (32) ^{NS}

* $p < 0.001$; [†] $p < 0.05$; NS = not significant.