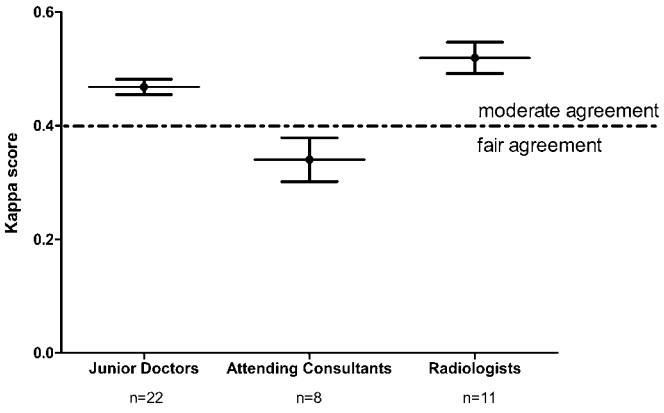

Abstract P251 Figure 1 Consistency between doctors when reporting CXRs in the context of possible CAP (κ with 95% CI).

Conclusions In the context of possible pneumonia, the CXR was not consistently reported by any group. Junior doctors were more consistent than attending consultants and radiologists were most consistent. A possible explanation for these differences is that junior doctors, by necessity, have developed similar ideas of what they will consider pneumonic where as consultants who less frequently make the initial diagnostic decision vary in their criteria for diagnosing pneumonia. This study does not present a "gold standard" interpretation and therefore does not address the issue of accuracy but it does raise questions about to what extent the CXR ever be regarded as a "reliable" diagnostic test.

COPD and drugs: new and old concepts

P252 ONCE-DAILY NVA237 IMPROVES SYMPTOMS, AND REDUCES COPD EXACERBATIONS AND ASSOCIATED HOSPITALISATIONS: THE GLOW1 TRIAL

doi:10.1136/thoraxjnl-2011-201054c.252

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Introduction Symptoms profoundly impact daily life of COPD patients. We assessed the influence of the once-daily (qd) long-acting muscarinic antagonist (LAMA) NVA237 (glycopyrronium bromide) on symptoms and exacerbations in patients with moderate-to-severe COPD.

Methods Patients were randomised (2:1) to 26 weeks double-blind treatment with NVA237 50 μg qd or placebo (PBO) via a single-dose dry powder inhaler (Breezhaler® device). Efficacy was assessed by bronchodilation (trough FEV_1 at Week 12), breathlessness on the transition dyspnoea index (TDI), HRQoL via the St. George's Respiratory Questionnaire (SGRQ), and rescue medication use. The effect on COPD exacerbations and related hospitalisations was also assessed.

Results 822 patients were randomised; 80.5% completed. NVA237 significantly increased total TDI focal score vs PBO at Week 26 (difference 1.04, 95% CI 0.583 to 1.504; p<0.0001); exceeding the minimum clinically important difference ([MCID] =1 point). Significantly more patients achieved MCID in TDI score with NVA237 (61.3% vs 48.3%; OR 1.74, 95% CI 1.249 to 2.415; p=0.001). SGRQ total score was significantly reduced with NVA237 (−2.81; p=0.004); % of patients achieving a clinically meaningful improvement in SGRQ (=4 point reduction) was significantly higher with NVA237 (56.8% vs 46.3%; OR 1.58, 95% CI 1.138 to 2.196; p=0.006). NVA237 significantly reduced rescue medication use at Week 26 (−0.46 puffs/day, p=0.005). NVA237 significantly prolonged time to first moderate/severe COPD exacerbation by 31% (HR 0.69, 95% CI 0.50 to 0.949; p=0.023) and time to first severe COPD exacerbation necessitating hospitalisation (HR 0.35, 95% CI 0.141 to 0.857; p=0.022). NVA237 significantly reduced hospitalisations due to COPD exacerbation (OR 0.34; p=0.024).

Conclusion Once-daily NVA237 provided significant improvements in dyspnoea and SGRQ total score, with lower rescue medication use, and reduced risk of exacerbation and associated hospitalisations vs PBO.

P253 NVA237 ONCE DAILY OFFERS RAPID AND CLINICALLY MEANINGFUL BRONCHODILATION IN COPD PATIENTS THAT IS MAINTAINED FOR 24 H: THE GLOW1 TRIAL

doi:10.1136/thoraxjnl-2011-201054c.253

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Introduction NVA237 (glycopyrronium bromide) is an inhaled long-acting muscarinic antagonist (LAMA) in development for the once-daily (qd) treatment of COPD. The GLOW1 study evaluated the efficacy and safety of NVA237 in patients with moderate-to-severe COPD.

Methods Patients were randomised (2:1) to 26 weeks double-blind treatment with NVA237 50 μg qd or placebo (PBO). Study drugs were administered via a single-dose dry powder inhaler (Breezhaler® device). Primary efficacy endpoint: trough FEV_1 (mean of 23 h 15 min and 23 h 45 min post-dose values) vs PBO after 12 weeks.

Results 822 patients were randomised; mean age was 63.9 years, mean post-bronchodilator FEV_1 was 55% predicted. 80.5% completed the study. At Week 12 there was a statistically significant and clinically relevant difference between NVA237 vs PBO in mean trough FEV_1 (108 ml; p<0.001). Trough FEV_1 was also significantly higher at Day 1 and Week 26 (treatment difference: 105 ml and 113 ml, respectively; p<0.001). Serial spirometry in a subpopulation of patients showed statistically superior (p<0.001) and clinically meaningful improvements in FEV_1 with NVA237 vs PBO at all timepoints on Day 1, Week 12 and Week 26. NVA237 had a rapid onset of action with an increased FEV_1 of 93 ml at 5 min and 144 ml at 15 min vs PBO after the first dose on Day 1 (p<0.001). Overall, the incidence of adverse events (AEs) was similar between treatment groups (NVA237: 57.5%; PBO: 65.2%). Serious AEs were reported by 7.5% of NVA237- vs 9.0% of PBO-treated patients.

Conclusion NVA237 50 μg once daily was generally safe and well tolerated. Improvements in bronchodilation were rapid, clinically meaningful and maintained for 24 h throughout the study.

P254 NVA237 ONCE DAILY IMPROVES EXERCISE ENDURANCE IN PATIENTS WITH COPD FROM THE FIRST DOSE: THE GLOW3 TRIAL

doi:10.1136/thoraxjnl-2011-201054c.254

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Introduction The fundamental characteristics of COPD are exertional dyspnoea and exercise limitation, which are associated with

dynamic hyperinflation. We assessed the effects of NVA237 (glycopyrronium bromide), a once-daily long-acting muscarinic antagonist (LAMA), on exercise endurance in patients with moderate-to-severe COPD.

Methods Patients with COPD were randomised to a cross-over design of NVA237 50 μg or placebo once daily for 3 weeks, with a 14-day washout. The primary endpoint was endurance time during a submaximal constant-load cycle ergometry test (SMETT) on Day 21 of treatment. Endurance time after first dose, dynamic hyperinflation (inspiratory capacity [IC] at isotime during exercise), and morning trough FEV_1 and plethysmographic lung volumes were also measured.

Results 108 patients were randomised; mean age was 60.5 years, mean post-bronchodilator FEV_1 was 57.1% predicted. 88.0% completed the study. Endurance time on Day 21 significantly increased by 21% with NVA237 vs placebo; the effect was significant from Day 1, with an increase of 10%. Both dynamic IC at exercise isotime and trough FEV_1 showed significant and clinically relevant improvements from Day 1 that were maintained for the study duration (Abstract P254 table 1). This was accompanied by inverse decreases in residual volume and functional residual capacity (Abstract P254 table 1). Overall, the safety profile of NVA237 was similar to that of placebo.

Abstract P254 Table 1 NVA237 treatment effects vs placebo

	NVA237 (LS means, 95% CI)	PBO (LS means, 95% CI)	NVA237−placebo (LS means diff, 95% CI)	p Value
Endurance time (s)				
Day 1	490.9 (458.5 to 523.4)	447.78 (415.1 to 480.5)	43.1 (10.9 to 75.4)	<0.001
Day 21	505.6 (466.6 to 544.7)	416.70 (377.8 to 455.6)	88.9 (44.7 to 133.2)	<0.001
IC at isotime (l)				
Day 1	2.25 (2.18 to 2.31)	2.02 (1.96 to 2.08)	0.23 (0.17 to 0.28)	<0.001
Day 21	2.22 (2.15 to 2.29)	2.02 (1.95 to 2.09)	0.20 (0.13 to 0.28)	<0.001
Functional residual capacity (l) % predicted				
Day 1	4.41 (4.32 to 4.51)	4.77 (4.67 to 4.86)	−0.36 (−0.49 to −0.22)	–
Day 21	4.32 (4.22 to 4.42)	4.78 (4.68 to 4.87)	−0.46 (−0.58 to −0.33)	
Residual volume (l)				
Day 1	3.49 (3.38 to 3.59)	3.92 (3.82 to 4.02)	−0.44 (−0.58 to −0.29)	–
Day 21	3.46 (3.36 to 3.55)	3.95 (3.86 to 4.05)	−0.50 (−0.63 to −0.36)	
Total lung capacity (l)				
Day 1	7.01 (6.90 to 7.12)	7.08 (6.97 to 7.19)	−0.07 (−0.22 to −0.08)	–
Day 21	6.86 (6.75 to 6.97)	7.10 (6.99 to 7.21)	−0.25 (−0.39 to −0.10)	
Specific airway conductance (Sec (−1)*kP)				
Day 1	0.68 (0.65 to 0.71)	0.41 (0.38 to 0.45)	0.26 (0.22 to 0.30)	–
Day 21	0.66 (0.63 to 0.70)	0.42 (0.39 to 0.46)	0.24 (0.19 to 0.29)	
Trough FEV_1 (l)				
Day 1	1.46 (1.43 to 1.49)	1.35 (1.31 to 1.38)	0.11 (0.06 to 0.16)	<0.001
Day 21	1.44 (1.40 to 1.48)	1.33 (1.29 to 1.37)	0.11 (0.06 to 0.16)	<0.001

Conclusion Once-daily NVA237 provided immediate and significant improvement in exercise endurance from Day 1. This was accompanied by sustained and significant improvements in IC at isotime, meaningful improvements in trough FEV_1, and sustained reductions of lung hyperinflation. There was an improvement in endurance time during the study period, suggesting that mechanisms beyond improved lung function play a part in superior exercise tolerance.

P255 ATTAIN: TWICE-DAILY ACLIDINIUM BROMIDE IN PATIENTS WITH MODERATE TO SEVERE CHRONIC OBSTRUCTIVE PULMONARY DISEASE

doi:10.1136/thoraxjnl-2011-201054c.255

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Introduction and Objectives The Phase III ATTAIN study investigated the effect of two twice daily doses of aclidinium bromide, a second-generation, long-acting muscarinic antagonist with low systemic activity, in patients with moderate to severe chronic obstructive pulmonary disease (COPD).

Methods In this 24-week, double-blind study, patients were randomised (1:1:1) to receive aclidinium (200 μg, 400 μg) or placebo, twice daily. The primary endpoint was change from baseline in trough forced expiratory volume in 1 second (FEV_1) at Week 24. Other study assessments at 24 weeks included: change from baseline in peak FEV_1; percentage of patients achieving a clinically meaningful improvement in St George's Respiratory Questionnaire total score and Transition Dyspnoea Index; COPD symptoms as assessed by the EXACT Respiratory Symptoms score; exacerbation rate based on two definitions (healthcare resource utilisation and EXAcerbations of Chronic pulmonary disease Tool). Adverse events (AEs), clinical laboratory measures, vital signs and ECGs were also assessed.

Results A total of 819 patients were included in intention-to-treat (ITT) and safety populations. At Week 24, aclidinium 200 μg and 400 μg significantly improved trough FEV_1 from baseline compared with placebo (by 99 ml and 128 ml, respectively; both $p<0.0001$). Aclidinium was significantly superior to placebo at Week 24 for all other study assessments (Abstract P255 table 1). Aclidinium was well tolerated and the incidence of anticholinergic AEs was low and similar to placebo. Changes in laboratory tests, vital signs and ECGs were similar between all groups.

Abstract P255 Table 1 Study assessments at Week 24 (ITT population)

	Placebo twice daily n=273	Aclidinium 200 μg twice daily n=277	Aclidinium 400 μg twice daily n=269
Change from baseline in trough FEV_1 vs placebo (ml) (±SE)	–	99*** (0.02)	128*** (0.02)
Change from baseline in peak FEV_1 vs placebo (ml) (±SE)	–	185*** (0.02)	209*** (0.02)
Clinically meaningful improvement (≥1 unit) in TDI focal score (% patients)	45.5	53.3*	56.9**
Clinically meaningful improvement (≥4 units) in SGRQ total score (% patients)	39.5	54.9***	54.3***
E-RS total score (±SE)	−0.43 (0.53)	−3.59*** (0.52)	−4.08*** (0.53)
Exacerbation frequency, HCRU (rate ratio vs placebo) (95% CI)	–	0.72* (0.52 to 0.99)	0.67* (0.48 to 0.94)
Exacerbation frequency, EXACT (rate ratio vs placebo) (95% CI)	–	0.72* (0.55 to 0.94)	0.71* (0.54 to 0.93)

*p<0.05, **p<0.01, ***p<0.001 vs placebo.
ER-S, EXACT Respiratory Symptoms; EXACT, EXAcerbations of Chronic pulmonary disease Tool; FEV_1, forced expiratory volume in 1 second; HCRU, healthcare resource utilisation; SGRQ, St George's Respiratory Questionnaire; TDI, Transition Dyspnoea Index.