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

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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.

Conclusion Aclidinium 200 μg and 400 μg twice daily provided clinically meaningful improvements in bronchodilation, health status, symptoms, breathlessness and exacerbation rate. Aclidinium was well tolerated with a similar safety profile for both doses; the incidence of AEs was similar to placebo.

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P256 ACLIDINIUM BROMIDE: A PHASE IIB, DOSE-FINDING STUDY

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Introduction and Objectives Aclidinium bromide, a second-generation, long-acting muscarinic antagonist with low systemic activity, is in clinical development for the twice daily maintenance treatment of chronic obstructive pulmonary disease (COPD). This Phase IIb study investigated the dose-response bronchodilation of aclidinium twice daily vs placebo and an active control (formoterol 12 μg twice daily) in patients with moderate to severe COPD.

Methods In this double-blind, double-dummy, cross-over study, 79 patients received 7-day treatments of aclidinium 100 μg, 200 μg and 400 μg, formoterol 12 μg and placebo twice daily over five treatment periods separated by a 7-day washout. The primary endpoint was change from baseline in normalised forced expiratory volume in 1 second (FEV_1) area under the curve $(AUC)_{0-12}$ at Day 7. Other efficacy assessments included change from baseline at Day 7 in normalised FEV_1 AUC_{0-24} and morning pre-dose (trough) and peak FEV_1. Adverse events (AEs) were reported throughout the study.

Results Aclidinium provided dose-dependent bronchodilation compared with placebo as assessed by change from baseline in normalised FEV_1 AUC_{0-12} and FEV_1 AUC_{0-24} at Day 7 (Abstract P256 table 1). The bronchodilation provided by aclidinium 400 μg during the first 12 h was comparable to the active control, formoterol 12 μg. Aclidinium improved morning pre-dose trough FEV_1 and peak FEV_1 after 7 days compared with placebo; the 400 μg dose was most comparable to formoterol 12 μg. Aclidinium was well tolerated; the safety profile of all doses was comparable to that of placebo.

Abstract P256 Table 1 Adjusted mean (SE) change from baseline (L) on Day 7

	Aclidinium 100 μg	Aclidinium 200 μg	Aclidinium 400 μg	Formoterol 12 μg	Placebo
Normalised FEV_1 AUC_{0-12h}	0.128* (0.022)	0.151* (0.022)	0.183* (0.022)	0.185* (0.022)	−0.026 (0.022)
Normalised FEV_1 AUC_{0-24h}	0.089* (0.021)	0.100* (0.021)	0.133* (0.021)	0.163* (0.020)	−0.062 (0.021)
Morning pre-dose FEV_1	0.081* (0.023)	0.089* (0.023)	0.130* (0.023)	0.123* (0.023)	−0.025 (0.023)
Morning peak FEV_1	0.287* (0.023)	0.299* (0.023)	0.340* (0.023)	0.344* (0.023)	0.098 (0.023)

*p<0.0001 vs placebo.

Conclusion A dose-dependent bronchodilation was observed with aclidinium twice daily. The bronchodilation provided by the highest dose of aclidinium (400 μg) twice daily was comparable to formoterol 12 μg twice daily. The safety profile of aclidinium was similar to placebo, with no dose-dependent AEs observed.

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P257 EFFECTS OF EXTRA-FINE INHALED AND ORAL CORTICOSTEROIDS ON ALVEOLAR NITRIC OXIDE IN COPD

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Introduction and Objectives Alveolar nitric oxide or (CA_{NO}), has been used as a surrogate marker of distal airway inflammation, which isimportant in COPD. Coarse particle inhaled corticosteroids (ICS) have been shown not to suppress CA_{NO}. We evaluated whether extra-fine particlesize inhaled corticosteroids (HFA-BDP) or systemic oral corticosteroids could suppress CA_{NO} in COPD.

Methods COPD patients with a smoking pack history >15 years, FEV_1/FVC ratio <0.7, FEV_1<80% predicted with small airways inflammation characterised by CANO >2 ppb underwent a double-blind randomised controlled crossover trial with an open label systemic steroid comparator. Following a 2 wk steroid washout period, patients were randomised to 3 weeks, 100 mcg HFA-BDP twice daily and then 3 weeks 400 mcg HFA-BDP twice daily or matched placebos with subsequent crossover. All patients then received 1 week open-label, 25 mg/day prednisolone. Spirometry, bodyplethysmography, impulse oscillometry, plasma cortisol and exhaled nitric oxide were recorded. CA_{NO} was corrected for axial diffusion.

Results 16 patients completed per protocol. Compared to respective placebo there were no significant differences seen with either dose of HFA-BDP. Oral prednisolone caused a significant reduction in FE_{NO} and $J'aw_{NO}$ but not CA_{NO}. Plasma cortisol was significantly suppressed by oral prednisolone compared to all other treatments. There was no suppression seen with HFA-BDP at either dose verses placebo.

Conclusions While CA_{NO} remains a biomarker of interest in COPD, it is not suppressed by systemic or extra-fine particle ICS. Hence CA_{NO} is unlikely to be a useful marker for monitoring response of small airway disease to therapies in COPD.

P258 ROLE OF 7-DAY AND 14-DAY COURSES OF ORAL PREDNISOLONE TREATMENT IN ACUTE EXACERBATION OF COPD

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Purpose The purpose of this study was to compare the efficacy of 7-day and 14-day courses of oral prednisolone treatment in patients with acute exacerbation of COPD with FEV_1<50% predicted.

Methods It was a prospective randomised, single blind study in a tertiary care centre, the study patients were included and randomised into two groups: 7-day group received oral prednisolone 30 mg/day for 7 days, and 14-day group was administered the same dosage of oral prednisolone for 14 days. There was no significant difference between the groups for age, smoking pack years, symptoms of COPD in years, no. of previous exacerbations, blood eosinophilia, baseline FEV_1, and FVC levels. One patient from 7-day group developed pneumothorax and one from 14-day group died of acute Myocardial Infarction.

Results Both groups showed significant improvements of FEV_1 and FVC on D-1, D-3, D-5, D-7, D-10 and Day-14 from the baseline (7-day group, p=0.0001, 0.0001, 0.008, 0.009, 0.008, 0.011and 14-day group, p=0.000, 0.000, 0.000, 0.000, 0.000, 0.000) and the improvement of FVC is also significant in both the groups, but there was no significant difference of improvement between the two groups on day-7 and day-14 (p=0.100, 0.079). There was also significant improvement of symptom score from baseline on day-7 and day-14, but no significant difference of improvement between two groups.