96. Bronchodilators in asthma and COPD

P860

Efficacy of indacaterol is maintained in patients with moderate or less and severe or worse COPD

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Introduction: Indacaterol is a once-daily inhaled β_2-agonist bronchodilator for COPD.
Aim: Pooled analysis to determine if efficacy of indacaterol was maintained in subgroups of patients (pts) with moderate or less ("mod") and severe or worse ("sev") COPD.
Methods: Data from 4082 pts in 3 randomized, double-blind, placebo-controlled studies of indacaterol 150 & 300µg od, tiotropium (TIO) 18µg od (open-label), formoterol (FOR) 12µg bid & salmeterol (SALM) 50µg bid were pooled; 58% pts had "mod" (GOLD stages II or less), 42% "sev" COPD (GOLD III+). Endpoints at 6 mo: trough FEV_1, transition dyspnoea index (TDI) & St George's Resp Questionnaire (SGRQ) total scores. The% of pts with clinically important difference in TDI & SGRQ were analysed as odds ratios (OR).
Results: Differences vs placebo (n=675 "mod", n=509 "sev") (*p<0.05, **p<0.01, ***p≤0.001) in subgroups with "mod" and "sev" COPD severity (†p<0.05 vs TIO, ‡p<0.05 vs formoterol, §p<0.05 vs SALM, ¶p<0.05 vs indacaterol 150µg).

		Indacaterol 150µg	Indacaterol 300µg	TIO	FOR	SALM
n	Mod	448	496	236	309	189
	Sev	298	356	179	244	143
Trough FEV1 (mL)	Mod	180***‡	200***†‡§	140***	110***	130***
	Sev	130***‡§	120***‡§	130***‡§	80***	60*
TDI score	Mod	1.1***	1.2***‡	1.0***	0.7*	0.8**
	Sev	0.8***	1.4***†¶	0.8*	0.8*	1.2***
TDI OR	Mod	1.99***	2.44***†	1.59*	1.91***	1.72*
	Sev	1.79**	3.11***†¶	1.40	2.18***	1.95**
SGRQ score	Mod	–4.5***†	–3.9***	–1.8	–3.0**	–4.2***
	Sev	–4.1***	–2.6*	–1.6	–2.6*	–4.1**
SGRQ OR	Mod	2.14***	1.78***	1.46*	1.63**	1.98***
	Sev	1.69**	1.42*	1.08	1.42	1.66*

Conclusions: Indacaterol improved FEV_1 & clinical outcomes after 6 mo irrespective of COPD severity. Indacaterol 300µg was notably effective for breathlessness in the more severe subgroup.

P861

Efficacy of indacaterol in COPD is maintained irrespective of inhaled corticosteroid (ICS) use

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Introduction: Indacaterol is a once-daily inhaled β_2-agonist bronchodilator for COPD.
Aim: Pooled analysis to determine indacaterol efficacy in subgroups of COPD patients (pts) receiving ICS or not.
Methods: Data from 4088 pts with moderate-to-severe COPD in 3 randomized, double-blind, placebo-controlled studies of indacaterol 150 and 300µg od, tiotropium 18µg od (open-label), formoterol 12µg bid & salmeterol 50µg bid were pooled: 44% of pts had baseline ICS use, 56% no ICS use. Endpoints at 6 months: trough FEV_1, transition dyspnoea index (TDI) and St George's Respiratory Questionnaire (SGRQ) total scores. The% of pts with clinically important difference in TDI and SGRQ were analysed as odds ratios (OR).
Results: Differences vs placebo (n=661 not on ICS, 524 on ICS) (*p<0.05, **p<0.01, ***p≤0.001) in pts not on ICS ("no") or on ICS ("ICS") (†p<0.05 vs tiotropium, ‡p<0.05 vs formoterol, §p<0.05 vs salmeterol, ¶p<0.05 vs indacaterol 150µg).

		Indacaterol 150µg	Indacaterol 300µg	Tiotropium	Formoterol	Salmeterol
n	No	438	455	270	276	181
	ICS	308	398	145	280	152
Trough FEV1 (mL)	No	180***‡§	170***‡§	140***	120***	120***
	ICS	130***‡§	170***†‡§¶	120***	80***	80***
TDI score	No	1.2***	1.2***	0.8**	0.9**	0.6*
	ICS	0.8***	1.4***‡¶	1.0***	0.6*	1.2***
TDI OR	No	2.17***†	2.59***†§	1.41	2.25***	1.47
	ICS	1.64**	2.84***†¶	1.64*	1.88**	2.19***
SGRQ score	No	–5.4***†‡	–3.3***¶	–1.7	–2.6*	–3.9***
	ICS	–3.0**	–3.6***	–1.7	–3.2**	–4.1**
SGRQ OR	No	2.56***†‡	1.85***	1.33	1.51*	2.10***
	ICS	1.37	1.43*	1.28	1.55*	1.50

Conclusions: Indacaterol improved FEV_1 and clinical outcomes after 6 months in patients not receiving ICS and those on ICS.

P862

The efficacy of the assistant use of short-acting β_2 stimulant procaterol on the daily activity in COPD patients. Niigata multicenter study

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Background and purpose: COPD patients have some dyspnoea on exertion in spite of medication. Guidelines suggest the use of short-acting β_2 antagonist (SABA) as necesarry. There are few reports to see whether the supplementary use of SABA inhalation imporves their physical activity, ADL and QoL in the daily life. We evaluated the efficacy and safety of assistant use of procaterol inhalation.
Methods: COPD patients were enrolled and asked to keep as active as possible. Physical activities were measured by the uni-axial accelerometer. COPD patients were divided into two groups. One was the group as controls (Group C) and the

other was those who used procaterol before or after the exertion when they felt dyspnoea (Group P). Physical activities, ADL and QoL in the daily life were compared during the observational and the experimental periods for each one month. Statistical analyses were done by two-way ANOVA. A $p < 0.05$ was considered significant.
Results: Forty four patients were enrolled and 37 completed the study.

Table 1

	Group C		Group P		
M/F	19/0		16/2		n.s.
Age (years)	73.5±5.7		69.0±8.7		n.s.
%FEV_1 (%)	57.4±15.1		51.0±17.1		n.s.
	OB	EX	OB	EX	
Average steps per day	5659±3267	5314±3436	5230±3130	5453±3013	n.s.
Mild level of physical activity (%)	24.6±8.4	22.6±7.6	27.4±11.1	28.1±11.3	p <0.05

OB, observational period; EX, experimental period.

And vitality domain of the SF-36 improved in Group P during the experimental period.
Conclusion: The assistant use of SABA inhalation may maintain the mild level of physical activity and increase vitality in the daily life in COPD patients.

P863
Onset of action and effect of withdrawal of roflumilast in COPD
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Background/Rationale: Roflumilast (ROF) is an oral, selective phosphodiesterase 4 inhibitor licensed for the maintenance treatment of severe COPD associated with chronic bronchitis and a history of frequent exacerbations. It improves lung function and reduces the rate of exacerbations in these patients. Limited data are available on the onset of action of ROF and the effects of treatment withdrawal.
Methods: Patients aged 40–75 years with stable COPD, fixed airways obstruction, post-bronchodilator FEV_1 35–75% predicted and ≥10 pack years smoking history were randomised to 1 of 3 groups: once-daily ROF 500μg for 24 weeks, once-daily placebo (PBO) for 24 weeks, and ROF 500μg for 12 weeks then PBO for 12 weeks (ROF/PBO).
Results: A total of 581 patients were randomised (ROF, n=200; PBO, n=186; ROF/PBO, n=195). Demographic and baseline characteristics were similar in all groups. FEV_1 increased with ROF: at weeks 1, 4, 8 and 12 least squares mean (SEM) differences between ROF and PBO were 35 (30) mL (p=0.2437), 60 (22) mL (p=0.0061), 67 (23) mL (p=0.0033) and 77 (24) mL (p=0.0013). Following ROF withdrawal at 12 weeks, FEV_1 decreased but remained higher than in the PBO group, with no significant differences between treatments. The most common AEs in the pooled ROF group were bronchitis (13.7%), diarrhoea (2.8%), nausea (2.5%), headache (1.8%) and back pain (1.8%), compared with 16.1%, 0%, 1.1%, 1.6% and 0.5%, respectively with PBO.
Conclusions: ROF was associated with an increase in FEV_1 that was evident at week 1 and plateaued at about 8 weeks of therapy. Following ROF withdrawal at 12 weeks, lung function remained above the level reported in the PBO group in the following 12 weeks, with no evidence of a rebound effect.

P864
Doxofylline: Efficacy and safety in complex treatment of COPD
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Aim of study: To evaluate efficacy and safety of Aerofylline, ABC Farmaceutici (doxofylline) in patients with stable COPD.
Study population and methods: 30 out-patients (pts) with stable COPD, stage II were divided on two groups: 15 pts (11 men, mean age 47.5±8.6 yrs) treated with inhaled bronchodilators and doxofylline 400 mg bid (Group 1) and 15 pts (12 men, mean age 50.3±9.0 yrs), treated with inhaled bronchodilators only (Group 2). Pulmonary function tests, respiratory muscles fatigue (by MasterLab, Jager), Holter ECG and dyspnoea (by MRC score) were evaluated in all pts before and 30 days after start of treatment.
Results: Both groups were similar regarding to age, sex, duration of disease, FEV1, PImax, and dyspnoea level at the beginning of treatment. 30 days after start of treatment the results were following: FEV1 did not change statistically significant in both groups. At the same time, dyspnoea score decrease significantly in Groupe 1 but not in Group II (down to 0.7±0.4 scores and 1.9±0.5 scores respectively). PImax in Groupe 1 increase on 21.3%, in Group 2 – on 11.9% only. We did not find any difference in tachycardia and premature beat rate between the groups.
Conclusions: Doxofilline did not improve pulmonary function, but significantly decrease respiratory muscles fatigue and dyspnoea in patients with COPD, stage II. Doxifilline did not influence significantly on a heart rhythm.

P865
Efficacy and safety of nebulized glycopyrrolate (EP-101) for administration using high efficiency nebulizer in patients with COPD
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Introduction: EP-101 is a long-acting muscarinic antagonist formulation of glycopyrrolate optimized for nebulization in development for the treatment of COPD. This dose-ranging study assessed the efficacy and safety of single doses of nebulized EP-101 in patients with COPD.
Methods: This was a randomized, double-blind, placebo-controlled, 6-period cross-over study in 42 patients with moderate-to-severe COPD. Patients were randomized to receive single doses of EP-101 (12.5, 50, 100, 200 and 400 μg) and placebo via a high efficiency nebulizer, with a 5-12 days of washout between treatments. Plasma PK was assessed in a subset of patients.
Results: The study patients had a mean age of 62 years, COPD duration of 7.5 years, post-bronchodilator FEV_1 of 54% predicted normal, FEV_1/FVC of 44.9%, FEV_1 reversibility of 27.3%. All treatments were well tolerated with similar AE rates between all treatments and no clinically relevant changes in vital signs (heart rate, systolic and diastolic blood pressure) and ECG parameters including QTc interval. Following treatment with EP-101 at all doses there was a rapid bronchodilatory response at 5 minutes. Statistically significant improvements in mean change in trough FEV_1 at 24 hours were reported at doses ≥50 μg compared with placebo (37mL, 72mL, 104mL, 118mL and 95mL at doses 12.5, 50, 100, 200 and 400 μg, respectively).
Conclusion: Single doses of EP-101 ranging from 12.5 μg to 400 μg were well tolerated. EP-101 demonstrated rapid onset of bronchodilation with clinically meaningful improvements in lung function over 24 hours following nebulization in patients with COPD.
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P866
NVA237 once daily provides rapid, clinically meaningful and sustained 24-h bronchodilation in patients with COPD: The GLOW1 trial
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Introduction: NVA237 (glycopyrronium bromide) is a once-daily (QD) inhaled long-acting muscarinic antagonist in development for the treatment of COPD.
Methods: Patients with moderate-to-severe COPD were randomized (2:1) to double-blind NVA237 50 μg QD or placebo (PBO) for 26 wks. Study medication was administered via a low-resistance single-dose dry powder inhaler (Concept1 device). The primary efficacy endpoint was trough FEV_1 (mean of 23 h 15 min and 23 h 45 min post-dose values) vs PBO after 12 wks.
Results: A total of 822 patients were randomized; 80.5% completed the study. Mean age was 63.9 yrs, mean post-bronchodilator FEV_1 was 55% predicted. At Wk 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 Wk 26 (treatment difference: 105 mL and 113 mL, respectively; $p<0.001$). At all time points on Day 1, Wk 12 and Wk 26, NVA237 demonstrated statistically superior ($p<0.001$) and clinically meaningful improvement in FEV_1 compared with PBO. 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 ($p<0.001$). The incidence of adverse events (AEs) was similar between NVA237 and PBO (57.5% vs 65.2%, respectively). Serious AEs were reported by 7.5% of NVA237- vs 9.0% of PBO-treated patients.
Conclusion: NVA237 50 μg once daily was safe and well tolerated, and produced clinically meaningful bronchodilation that was rapid in onset and maintained for 24 hrs throughout the study.

P867
NVA237 once daily improves dyspnea and health-related quality of life (HRQoL) in patients with COPD: The GLOW1 trial
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Introduction: A high level of unmet need exists in the treatment of COPD patients. NVA237 (glycopyrronium bromide) is a once-daily (QD) long-acting muscarinic antagonist in development for the treatment of COPD.
Methods: Patients with moderate-to-severe COPD were randomized (2:1) to 26

wks' double-blind treatment with NVA237 50 μg QD or placebo (PBO) administered via a low-resistance single-dose dry powder inhaler (Concept1 device). In addition to FEV_1 (primary endpoint: trough FEV_1 after 12 wks) efficacy was assessed by symptoms (via the transition dyspnea index [TDI]), HRQoL (via the St George's Respiratory Questionnaire [SGRQ]), and rescue medication use.
Results: A total of 822 patients (mean age 63.9 yrs; post-bronchodilator FEV_1 54.6% predicted) were randomized; 80.5% completed. At Wk 26, NVA237 significantly increased total TDI focal score vs PBO (difference: 1.04, $p<0.0001$) exceeding the minimum clinically important difference ([MCID] ≥1 point). The% of patients achieving a MCID in TDI score was significantly higher with NVA237 vs PBO (62.5% vs 50.8%; odds ratio [OR] 1.74; p=0.001). NVA237 significantly reduced rescue medication use vs PBO after 26 wks of treatment (–0.46 puffs/day, p=0.005). SGRQ total score was significantly reduced with NVA237 vs PBO (–2.81; OR 1.58; p=0.004). The% of patients achieving a clinically meaningful improvement in SGRQ (≥4 point reduction) was significantly higher with NVA237 vs PBO (56.3% vs 46.0%; p=0.006).
Conclusion: NVA237 50 μg once daily provided a significant and clinically relevant improvement in dyspnea at 26 wks vs PBO, which was accompanied by a significant improvement in HRQoL and reduced rescue medication use.

P868
Efficacy and safety of AZD3199, an inhaled ultra long-acting β_2-agonist, in patients with COPD
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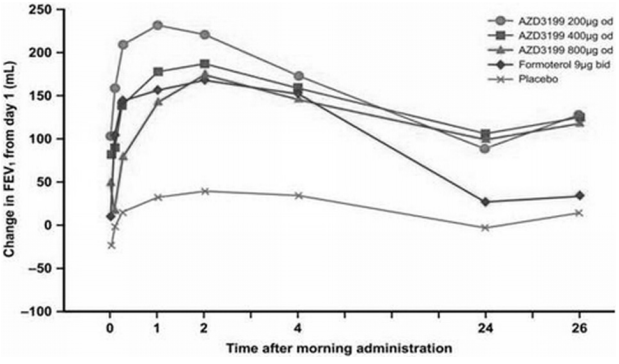
Objective: To study the efficacy and safety of three once-daily doses of AZD3199 inhaled via Turbuhaler compared with twice-daily formoterol and placebo over 4 weeks in COPD patients.
Methods: This was a 4-week randomised, double-blind, parallel-group multicentre Phase II study to compare once-daily inhaled doses of AZD3199 (200, 400 and 800 μg delivered) with formoterol (9 μg *bid*) and placebo in 329 adults with moderate/severe COPD (NCT00929708). Bronchodilation was assessed by average post-dose FEV_1 values from 0–4 hrs ($E_{0\text{-}4}$, peak) and FEV_1 values from 24–26 hrs ($E_{24\text{-}26}$, trough). Use of β_2-agonist reliever medication, salbutamol reversibility, symptom scores (CCQ) and safety were also assessed.
Results: For all 3 doses of AZD3199, FEV_1 $E_{0\text{-}4}$ and $E_{24\text{-}26}$ were statistically significantly greater vs. placebo after 4 weeks' treatment ($E_{0\text{-}4}$ 106–171 mL, $E_{24\text{-}26}$ 96.5–110 mL) but no dose response was seen (Figure). Formoterol *bid* was superior to placebo for FEV_1 $E_{0\text{-}4}$ but not $E_{24\text{-}26}$. All 3 AZD3199 groups used less reliever medication than the placebo group. AZD3199 did not impact on the acute bronchodilating effect of salbutamol. All AZD3199 groups showed a reduction in symptom scores with the 800 μg dose reaching significance vs. formoterol and placebo. AZD3199 was well tolerated with no safety concerns.



Conclusions: AZD3199 is a safe and effective uLABA with a 24-hour duration of action.

P869
Clinical efficacy and patients' satisfaction for 100 consequent COPD patients using tiotropium respimat
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Tiotropium Respimat® is a newly developed device which delivered the drug with ease. In this paper we've described the efficacy and patients' satisfaction for two groups of patients, 1; the first users of anti-muscarinic inhelor (33 patients) 2; changed users from Tiotropium Handyhelor® to Respimat® (67 patiens).
Methods: One hundred consequent COPD patients administered Tiotropium Respimat® were enrolled. Eight weeks later, impressions about the devices and pulmonary function tests were recorded. Patients satisfaction was measured by the following, 1) Easily understand how to use the device, 2) time consumption to inhale, 3) irritability of the inhaled drug, 4) easy to mobile the device, 5) adherence. Visual analogue scale from 1 (most negative) to 5 (most positive) were used.
Results: 1) - 1 Patients mean impression score of first users showed rather positive impression, Q1: 3.78, Q2: 3.89, Q3: 4.27, Q4: 4.03, Q5: 3.55. 1) - 2 Patients impression score of the changed users (from Handyhelor® to Respimat®) were significantly improved. Q1: 2.75±0.09 to 3.80±0.08. Q2: 1.32±0.07 to 3.40±0.07, Q3: 2.54±0.07 to 3.68±0.07, Q4: 1.91±0.08 to 3.80±0.08, and Q5: 1.55±0.09 to 3.77±0.08 (p=0.001∼0.0001). 2) Pulmonary function tests of the changed users showed no significant improvement about VC and IC and showed not significant but a little improvement of FEV1 and FEV1% (G) (FEV1; 1.65±0.09 to 1.69±0.09, FEV1% (G); 59.04±2.21 to 60.99±2.40 (%), (p=0.08). Peak expiratory flow was significantly improved after changed the device (4.53±0.35 to 4.77±0.28,p=0.004).
Conclusion: Tiotropium Respimat® was a simple and comfortable device and it may improve the pulmonary function for the patients with COPD.

P870
Influence of tiotropium bromid on airway inflammation and symptom in COPD patients
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Aim: Chronic obstructive pulmonary disease (COPD) is characterized by abnormal inflammatory response of lungs to noxious particles or gases. The aim of this study is to search the influence of tiatropim bromur treatment on airway inflammation and symptom score in stable COPD patients.
Methods: Tiatropium bromide treatment with 18 mcg daily dose, was started in newly diagnosed, consecutive mild –moderate stable COPD patients. Peroxynitrite, interleukin-6 (IL-6), 8- isoprostan and tumour necrosis factor- alpha (TNF-α) were measured in the expired breath condensate fluid before the treatment and at the end of first month. Each symptom (cough, sputum production and dyspnea) was evaluated on a 4-point scale by the patients.
Results: Twenty-two patients (81% men), with a mean age 65.4±10.1 years were included in the study. The mean nitrotirozine and 8-isoprostan levels for oxidative stress marker in EBC before and after treatment were 4.5±2.3, 3.5±1.9 pg/ml (p:0.06) and 7.3±10.8, 8.1±11.7 pg/ml (p: 0.28) respectively. The mean IL-6 and TNF-alpha levels for inflammation marker in EBC before and after treatment were 1.03±1.1, 0.77±0.8 (p: 0.41) and 27.8±2.6, 29.2±5.7 pg/ml (p: 0.36) respectively. The mean symptom scores decreased significantly with tiatropium and also a mean 124.6±0.86 ml increase was observed in Forced expiratory volume in first second (FEV_1).
Conclusion: There were no significant changes for inflammatory and oxidative stress markers in expired breath condensate fluid after a tiataropium treatment of one month, but tiatropium treatment helps to control symptoms in COPD with an increase in FEV_1.

P871
The impact of tiotropium on mortality when added to inhaled corticosteroids and long-acting beta agonist therapy in COPD
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Background and objectives: Tiotropium (TIO) has been shown to improve lung function, quality of life and reduce mortality and exacerbations in COPD.However it remains unclear whether such benefits are seen when TIO is used in conjunction with inhaled corticosteroid (ICS) plus long acting beta-2 agonists (LABA).
Methods: Retrospective Cohort study using linked NHS databases on hospital admissions, COPD outcomes, prescribing and mortality. Cox proportional hazard regression analysis was used to assess the addition of TIO to ICS+LABA on mortality and exacerbations. History of respiratory and cardiovascular disease, Sex, Age and smoking history were used as covariates. We observed lung function in each group over the study period.
Results: 3004 COPD patients were included in the study. 2082 patients were prescribed ICS+LABA+Tio and 922 were prescribed ICS+LABA. Mean follow-up 4.65 years. Mean age 68.5 years. 1035 patients died during the study. The adjusted hazard ratio for all-cause mortality for ICS+LABA+TIO vs ICS+LABA was 0.67 (95% CI, 0.58-0.76) $p<0.001$. Adjusted hazard ratios for respiratory hospital admissions and oral corticosteroid use were 0.86 (95% CI 0.74-0.99) p=0.043 and 0.72 (95% CI 0.65-0.81) $p<0.001$. In the ICS+LABA group (mean FEV1% pred 66.8%), mean first and last FEV1 and FVC (L) were 1.56 vs 1.57 and 2.64 vs 2.72. In the ICS+LABA+Tio group, (mean FEV1% pred 51.6%), mean first and last FEV1 and FVC (L) were 1.24 vs 1.20 and 2.47 vs 2.50.

Conclusions: We have shown that the addition of TIO to ICS+LABA reduces all-cause mortality in our COPD population. Reductions in COPD exacerbations and oral steroid use reaffirm findings of previous studies.

P872

Assessments of protective effects of tiotropium bromide against methacholine- and neurokinin A-induced bronchoconstriction in patients with asthma

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Rationale: Previous studies using short-acting anticholinergics have suggested a possible protective effect on bronchoconstriction induced by the sensory neuropeptide neurokinin A (NKA).
Aim: To assess the effect of tiotropium bromide, a longacting anticholinergic agent, on NKA-induced bronchoconstriction.
Methods: PC_{20} NKA and PC_{20} methacholine were investigated in asthmatic patients after 20 days of treatment with tiotropium bromide (18 μg/od) or placebo. PC_{20} was expressed in log_2 doubling concentrations (DC). Values were reported as median with 25th-75th percentiles. Pairwise comparisons of the log_2 PC_{20} values at screening and at the end of active and placebo treatments were performed.
Results: 16 patients with asthma (9 male; age: 24 (18-63) years) were included. PC_{20} NKA was 0.18 (0.06 - 0.29) μmol/ml at screening, 0.34 (0.09 - 3.34) μmol/ml after placebo, and 0.77 (0.08 - 3.34) μmol/ml after tiotropium bromide. PC_{20} methacholine was 0.5 (0.3 - 0.7) mg/ml at screening, 0.3 (0.2- 1.5) mg/ml after placebo, and 256.0 (11.7 – 256.0) mg/ml after tiotropium bromide. Differences between active treatment and screening log_2PC_{20} were 2.4 (0.4 – 3.2) DC for NKA ($p = 0.06$) and 7.6 (4.8 – 9.0) DC for methacholine ($p < 0.0001$). Differences between placebo treatment and screening for log_2PC_{20} NKA and log_2PC_{20} methacholine were not observed.
Conclusions: Inhaled tiotropium bromide protects against methacholine-induced bronchoconstriction, but not against bronchoconstriction induced by NKA, suggesting that cholinergic mechanisms are not involved in the contractile effects of NKA in patients with asthma.

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ACCORD COPD I: Improvements in nighttime symptoms and rescue medication use in COPD with twice-daily aclidinium bromide

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Introduction: Nighttime symptoms in COPD patients can reduce quality of life. In this Phase III study, nighttime symptoms and rescue medication use were assessed during twice-daily (BID) treatment with aclidinium bromide, a long-acting muscarinic antagonist in development for COPD.
Methods: In this 12-week, double-blind study, COPD patients (FEV_1/FVC <70%) were randomised (1:1:1) to aclidinium 200 μg, 400 μg, or placebo. Nighttime symptoms were recorded daily using electronic diaries via a COPD Nighttime Symptoms Questionnaire, which assessed frequency and severity of symptoms and their impact on activity and sleep. Rescue medication use was also assessed.
Results: Of 561 randomised patients, 467 completed the study. At Week 12, aclidinium 200 μg and 400 μg reduced nighttime COPD symptom frequency vs placebo ($p<0.05$ and $p<0.005$, respectively). Both aclidinium doses reduced severity and impact of nighttime breathlessness and cough on morning activities vs placebo ($p<0.01$ and $p<0.05$, respectively). Severity of early morning breathlessness and activity restriction due to breathlessness were reduced with aclidinium 200 μg ($p<0.01$) and 400 μg ($p<0.001$) vs placebo. Compared to placebo, 24-h sputum production was significantly reduced with the 200 μg ($p<0.05$) and 400 μg ($p<0.01$) doses at Week 12 but not sputum production during sleep. Aclidinium 400 μg improved the severity and impact of breathing symptoms on sleep vs placebo at 12 weeks ($p<0.01$). Both aclidinium doses reduced total daily rescue medication use vs placebo ($p\leq0.001$ for both).
Conclusions: Aclidinium 200 μg and 400 μg BID significantly reduced nighttime/early morning symptoms and daily rescue medication use.

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Improvement in symptoms and rescue medication use with aclidinium bromide in patients with chronic obstructive pulmonary disease: Results from ATTAIN

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Introduction: The ATTAIN study investigated the efficacy and safety of two twice-daily doses of aclidinium bromide, a long-acting muscarinic antagonist, in patients with moderate to severe chronic obstructive pulmonary disease (COPD).
Methods: In this 24-week, double-blind trial, 828 patients were randomised (1:1:1) to twice-daily aclidinium (200 μg or 400 μg) or placebo. COPD symptoms were assessed using the Transitional Dyspnoea Index (TDI), patient-reported daily electronic diaries and Total Exact score. Reliever medication use was also assessed.
Results: Baseline characteristics were similar between the groups; FEV_1% predicted 56.8±12.8%, focal BDI 6.8±2.1. More patients treated with aclidinium 200 μg or 400 μg had a clinically meaningful improvement in TDI focal score (≥1 unit) vs placebo at Week 24 (53.3% and 56.9% vs 45.5%; p=0.032 and 0.004, respectively). Aclidinium dose-dependently improved TDI focal score at Week 24, which was clinically meaningful for aclidinium 400 μg (1.0 unit) and statistically significant for both doses vs placebo (200 μg, $p<0.05$; 400 μg, $p<0.001$). Over the study period, aclidinium (both doses) was associated with a lower incidence of night-time ($p<0.0001$) and early-morning ($p<0.01$) COPD symptoms, a greater reduction in Total Exact score ($p\leq0.0001$) and more days without reliever medication (p=0.0003) vs placebo.
Conclusions: Aclidinium 200 μg and 400 μg twice-daily provided statistically significant and clinically meaningful improvements in COPD symptoms in patients with moderate to severe COPD.
This study was supported by Almirall S.A., Barcelona, Spain, and Forest Laboratories, Inc, New York, USA.

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The ATTAIN study: Bronchodilatory effect of aclidinium bromide in chronic obstructive pulmonary disease (COPD)

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Introduction: Aclidinium bromide is a long-acting muscarinic antagonist in clinical development for the treatment of COPD.
Aims: To assess the bronchodilatory effect of aclidinium 200 μg and 400 μg in patients with COPD.
Methods: In this 24-week, double-blind, Phase III study (NCT01001494), patients were randomised to aclidinium 200 μg, 400 μg or placebo BID. The primary endpoint was change from baseline in trough FEV_1 at Week 24. Other endpoints included: trough response over time; change from baseline in peak FEV_1; time to peak FEV_1 and normalised $AUC_{0\text{-}3h}$ FEV_1.
Results: A total of 828 patients were randomised and 737 (89.0%) patients completed the study. Aclidinium 200 μg and 400 μg significantly improved trough FEV_1 vs placebo; these improvements were maintained throughout the 6-month treatment period. At Week 24, increases in trough FEV_1 from baseline vs placebo for aclidinium 200 μg and 400 μg were 99 mL and 128 mL, respectively (both $p<0.0001$). Aclidinium 200 μg and 400 μg increased peak FEV_1 vs placebo (185 mL and 209 mL, respectively; both $p<0.0001$). Time to peak FEV_1 was ≤2 h post-dose (aclidinium 200 μg, 108 min; aclidinium 400 μg, 100 min). Aclidinium 200 μg and 400 μg significantly improved normalised $AUC_{0\text{-}3h}$ FEV_1 vs placebo at Week 24 (183 mL and 210 mL, respectively; both $p<0.0001$).
Conclusions: Aclidinium 200 μg and 400 μg twice-daily significantly improved bronchodilation in patients with moderate to severe COPD.
This study was supported by Almirall S.A., Barcelona, Spain, and Forest Laboratories, Inc, New York, USA.

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ACCORD COPD I: Twice-daily aclidinium bromide improves quality of life and dyspnea in COPD patients

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Introduction: Aclidinium bromide is a long-acting muscarinic antagonist in development for treatment of COPD. In this Phase III study, the effects of twice-daily aclidinium on health outcomes were assessed.
Methods: In this 12-week, double-blind study, moderate to severe COPD patients were randomised to receive aclidinium 200 μg, 400 μg, or placebo BID. Health outcomes were assessed monthly via SGRQ and TDI.
Results: Of the 561 patients randomised, 467 (83%) completed the study. At

baseline, the mean (SD) pre-bronchodilator FEV_1 and percent predicted were 1.36 (0.54) L and 47.2 (14.1)%, respectively. Baseline mean (SD) SGRQ total score and BDI focal score were 46.5 (17.1) and 6.4 (2.1), respectively. Adjusted mean differences vs placebo in change from baseline in SGRQ total score at Week 12 were -2.7 (p=0.01) and -2.5 (p=0.02) for aclidinium 200 μg and 400 μg, respectively. At all time points, statistically greater percentages of aclidinium patients achieved clinically significant improvements in SGRQ vs placebo (≥4 points; p<0.05 for all except Week 12, 400 μg group). Both aclidinium doses provided significant improvements vs placebo in TDI focal score (p<0.05, range 0.6 to 1.4) throughout the study; with the exception of aclidinium 200 μg at Week 8 (p=0.06). Significantly greater percentages of patients achieved clinically meaningful improvements in TDI (≥1 unit) with both aclidinium doses at all time points vs placebo (p<0.05).
Conclusions: In this 12-week study, aclidinium 200 μg and 400 μg BID significantly improved quality of life and reduced dyspnea for patients with moderate to severe COPD.

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Aclidinium bromide in patients with chronic obstructive pulmonary disease: Improvement in health status in ATTAIN
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Introduction: The ATTAIN study investigated the efficacy and safety of two twice-daily doses of aclidinium bromide, a long-acting muscarinic antagonist, in patients with moderate to severe chronic obstructive pulmonary disease (COPD).
Methods: In this 24-week, double-blind trial, patients were randomised (1:1:1) to receive aclidinium (200 μg or 400 μg) or placebo, twice-daily. Health status was assessed using the St George's Respiratory Questionnaire (SGRQ) and the EuroQol Questionnaire (EQ-5D; both the weighted health status index and the visual analogue scale [VAS]).
Results: There were 819 patients in the intent-to-treat population; forced expiratory volume in 1 second [FEV_1%] predicted 56.8±12.8%, baseline SGRQ total score 46.3±16.8 units. At Week 24, more patients had a clinically significant improvement in SGRQ total score (decrease of ≥4 units) with aclidinium 200 μg and 400 μg than placebo (54.9% and 54.3% vs 39.5%; p=0.0004 and 0.0014, respectively). At Week 24, the improvement with aclidinium 400 μg was 4.3 units, p<0.0001. SGRQ domain scores (Symptoms, Activity, Impacts) were also significantly improved with both doses vs placebo at Week 24 (p<0.05 all domains). Aclidinium 200 μg and 400 μg also improved the EQ-5D weighted index and VAS compared with placebo at Week 24; the 400 μg dose reached statistical significance for the weighted index (p=0.041) and VAS (p=0.005) vs placebo.
Conclusions: Aclidinium 200 μg and 400 μg twice-daily provided statistically and clinically significant improvements in health status.
This study was supported by Almirall S.A., Barcelona, Spain, and Forest Laboratories, Inc, New York, USA.

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Dose-related efficacy of GSK573719, a new long-acting muscarinic receptor antagonist (LAMA) offering sustained 24-hour bronchodilation, in COPD
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Introduction: GSK573719 is an inhaled LAMA with sustained 24-hour activity under development as a once-daily therapy for COPD.
Objective: To evaluate the dose response of GSK573719 in patients with COPD.
Methods: This was a multicentre, randomised, double-blind, placebo-controlled, parallel-group study evaluating GSK573719 administered once daily via a novel single-step activation dry powder inhaler in patients with COPD (FEV_1 of ≥35 and ≤70% predicted). The primary endpoint was morning pre-dose (trough) FEV_1 after 28 days of treatment.
Results: All doses of GSK573719 significantly increased trough FEV_1 compared with placebo, with improvement ranging from 150 to 168mL (p<0.001). All doses significantly increased 0–6 hour weighted mean FEV_1 compared with placebo with differences ranging from 113 to 211mL (p<0.001). Additionally, all doses demonstrated significant improvements over placebo in serial FEV_1 at each measured time point over 24 hours (p≤0.038). Reductions in albuterol use and improvements in FVC were also noted for all doses. All doses were well tolerated.
Conclusion: Once-daily dosing with GSK573719 provides clinically significant and sustained improvement in lung function and is well tolerated over 24 hours in patients with COPD.
Funded by GSK (AC4113589; NCT01030965)

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Fixed combination of glycopyrrolate and formoterol MDI (GFF-MDI) demonstrates superior inspiratory capacity (IC) compared to tiotropium DPI (Tio) following 7 days dosing, in a randomized, double-blind, placebo-controlled phase 2b study in patients with COPD
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Rationale: In COPD, IC is inversely correlated to dyspnea with exercise. Tio is an inhaled anticholinergic that improves IC. GFF-MDI is an inhaled bronchodilator comprised of glycopyrrolate and formoterol fumarate. Pearl evaluated improvements in IC of GFF-MDI compared to Tio and placebo (PL) following chronic dosing in a large Phase IIb study.
Methods: Randomized, double-blind, customized, unbalanced, incomplete block, crossover study was conducted in patients with moderate to very severe COPD. One objective was to assess changes in IC on Day7 between 2 doses of GFF-MDI, Tio and PL. MDIs were administered BID for 1 week; Tio was administered QD for 1 week.
Results: 118 patients randomized. GFF-MDI (72/9.6 and 36/9.6 μg) and Tio were superior to Pl on morning pre-dose trough assessments (255mL, 271mL and 166mL, respectively; P≤0.0004 all comparisons) and for Peak IC assessments (265mL, 293mL and 170 mL, respectively; P≤ 0.0016 all comparisons). Both GFF-MDI 72/9.6 μg and GFF-MDI 36/9.6 μg were superior to Tio for pre-dose trough IC (90mL and 105mL, respectively; P<0.05 both doses) and Peak IC on Day 7 (95mL and 124mL, respectively; P<0.05 both doses).
Conclusion: Both doses of GFF-MDI were superior to PL and Tio for morning pre-dose and Peak IC assessments. These findings support the further development of GFF-MDI in patients with COPD.

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