245. COPD treatments: efficacy and safety

P2101

Effectiveness of indacaterol and tiotropium in patients with severe dyspnoea

Donald Mahler[1], Roland Buhl[2], David Lawrence[3], Danny McBryan[4]. *[1]Section of Pulmonary & Critical Care Medicine, Dartmouth Medical School, Lebanon, NH, United States; [2]Pulmonary Department, Mainz University Hospital, Mainz, Germany; [3]Respiratory Department, Novartis Horsham Research Centre, Horsham, United Kingdom; [4]Respiratory Department, Novartis Pharma AG, Basel, Switzerland*

Introduction: Dyspnoea is a common, troublesome symptom of COPD. It is useful to know how patients (pts) with varying degrees of breathlessness respond to treatment.

Aim: We explored the effectiveness of the once-daily(od) long-acting inhaled bronchodilators indacaterol(IND) and tiotropium(TIO) in COPD pts according to baseline dyspnoea severity(median modified Medical Research Council [mMRC] score <2.0 or ≥ 2.0[ie less or more dyspnoea]).

Methods: Data were pooled from three randomized studies of double-blind IND 150μg od(n=745), IND 300μg od(n=849) and placebo(PBO; n=1171) and open-label(o/l) TIO 18μg od(n=411) in pts with moderate-to-severe COPD. Trough FEV_1, transition dyspnoea index(TDI), St George's Respiratory Ques-

tionnaire(SGRQ) and odds ratios(OR) for clinically relevant response in TDI(≥1 point) and SGRQ(≥ −4 units) were evaluated at 6 months.
Results: In pts with mMRC <2/≥2 respectively(n=1425/1752), mean age was 63.1/63.9 years, FEV_1 57.6/51.8% predicted, FEV_1/FVC 53.9/51.6%. Differences vs PBO for outcomes in each subgroup are shown in table($p<0.05$ vs *PBO, † TIO or ‡ IND 150).

	mMRC <2			mMRC ≥2		
	IND150	IND300	TIO	IND150	IND300	TIO
n	341	373	173	404	476	238
Trough FEV_1, mL	180*	180*	150*	140*	170*†	130*
TDI total score	1.21*	1.33*	1.26*	0.83*	1.24*†	0.63*
TDI responder OR	2.09*	2.44*	1.79*	1.77*	2.91*†‡	1.34
SGRQ total score	−4.7*	−3.9*	−2.3	−4.0*†	−3.0*	−1.6
SGRQ responder OR	2.03*	1.56*	1.40	1.90*†	1.74*	1.29

Conclusions: In pts with less severe dyspnoea(mMRC <2), IND 150, IND 300 and o/l TIO were similarly effective. In pts with more severe dyspnoea(mMRC ≥2), IND 300 was more effective than IND 150 and o/l TIO in improving dyspnoea. Increasing the IND dose to 300μg may be useful for pts with more severe dyspnoea.

P2102
Once-daily NVA237 improves lung function in COPD patients: Pooled results of the GLOW1 and GLOW2 studies
Donald Banerji[1], Vijay Alagappan[2], Carmen Martin[2], Ellie He[3], Hungta Chen[3], Tim Overend[2]. *[1]Primary Care, Novartis Pharmaceuticals Corporation, East Hanover, NJ, United States; [2]Primary Care, Novartis Horsham Research Centre, Horsham, West Sussex, United Kingdom; [3]Integrated Information Sciences (Respiratory), Novartis Pharmaceuticals Corporation, East Hanover, NJ, United States*

Introduction: NVA237 (glycopyrronium bromide) is safe and effective once-daily (QD) inhaled long-acting muscarinic antagonist for maintenance treatment of COPD.
Methods: This pooled analysis of the GLOW1 and 2 studies assessed the efficacy of NVA237 50μg QD vs placebo (PBO) and open-label tiotropium (TIO) 18μg QD over 26 to 52 wks in patients with moderate-to-severe COPD. Results include trough forced expiratory volume in 1 second (FEV_1) and forced vital capacity (FVC) at Day 1 and Wks 12, 26 and 52, 24-hr serial spirometry in a subset of patients, and FEV_1 AUC.
Results: 1888 subjects were randomized, 98.2% analyzed (NVA237=1059, TIO=267, PBO=528); male: 71.5%, mean age: 63.9yr, mean post-bronchodilator FEV_1: 55.5% predicted. All trough FEV_1 and FVC values for NVA237 and TIO were significantly greater than PBO ($p<0.001$) and NVA237 was numerically higher than TIO at all-time points (Table).

Table: Trough FEV_1 and FVC least square mean treatment difference (SE) from PBO (mL)

	FEV_1		FVC	
	NVA237	TIO	NVA237	TIO
Day 1	98 (7.7)	88 (11.5)	187 (15.1)	178 (22.7)
Wk 12	103 (11.2)	88 (16.7)	190 (21.5)	172 (32.0)
Wk 26	125 (12.6)	78 (18.6)	205 (22.7)	133 (33.9)
Wk 52	108 (19.5)	89 (22.3)	179 (34.4)	180 (39.4)

The improvement in FEV_1 with NVA237 was seen immediately after the first dose on Day 1 (90mL at 5min and 144mL at 15min versus PBO, $p<0.001$) and sustained throughout the 52 Wk period. FEV_1 AUC for 0-4h, 0-12h, 0-24h and 12-24h for NVA237 was significantly greater than PBO ($p<0.05$) and numerically greater than TIO on Day 1, Wk 12, 26 and 52.
Conclusion: NVA237 50μg QD provided rapid, sustained and clinically meaningful bronchodilation over 52 wks with efficacy similar to tiotropium.

P2103
Safety and efficacy of NVA237 once daily in Japanese patients: The GLOW4 trial
Mitsuaki Sekiya[1], Tomotaka Kawayama[2], Yoshinosuke Fukuchi[1], Yota Takahashi[3], Tetsuya Kaiso[3], Kimitoshi Ikeda[3], Tim Overend[4], Donald Banerji[5]. *[1]Juntendo University, Bunkyo-ku, Tokyo, Japan; [2]Kurume University, Kurume-city, Fukuoka, Japan; [3]Primary Care, Novartis Pharma K.K., Tokyo, Japan; [4]Primary Care, Novartis Horsham Research Centre, Horsham, United Kingdom; [5]Primary Care, Novartis Pharmaceuticals Corporation, East Hanover, NJ, United States*

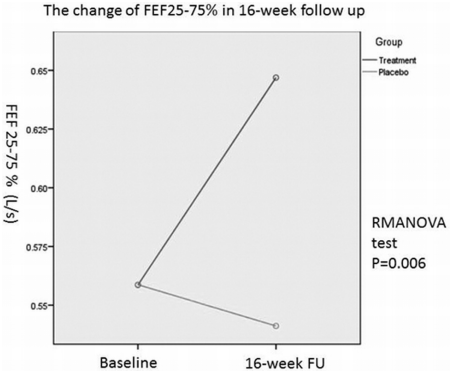
Introduction: NVA237 (glycopyrronium bromide) is a once-daily (QD) inhaled long-acting muscarinic antagonist for the maintenance treatment of COPD.
Methods: The primary objective of the 52-week, multi-center, randomized, open label, parallel group GLycopyrronium bromide in COPD airWays clinical study 4 (GLOW4) was to assess the safety and tolerability of NVA237 50μg QD for 52 wks in Japanese patients with moderate-to-severe COPD. A secondary objective was to compare the safety and efficacy of NVA237 to open-label tiotropium 18 μg QD (TIO).
Results: 163 patients were randomized (NVA237=123, TIO=40); 84% completed. Mean age was 68.7 yrs, 97.5% male. Overall adverse events (AE) incidence was similar between NVA237 and TIO. The only AEs with >10% incidence in any group were COPD worsening (24.4 and 32.5%) and nasopharyngitis (30.9 and 32.5%) for NVA237 and TIO, respectively. Serious AEs occurred in 13 and 15% patients for NVA237 and TIO, respectively, with no deaths. There were no reports of notable pulse rate (>130 bpm, or ≥120 and +15 bpm from baseline) and QTc interval (Fridericia) >500ms over 52 wks. Dry mouth incidence was less frequent with NVA237 (1.6%) vs TIO (5%). A clinically significant increase from baseline in pre-dose FEV_1 was observed for NVA (101 mL) and TIO (173 mL) at Wk 12. The event-free rate for moderate or severe COPD exacerbation was 78.9% for NVA237 and 76.6% for TIO at Wk 52.
Conclusion: NVA237 once daily had a safety and tolerability and efficacy profile similar to tiotropium in Japanese patients with moderate-to-severe COPD over 52 weeks.

P2104
Sputum neutrophil monitoring is useful for long-term oxygen therapy in patients with COPD
Masahide Miyamoto[1,2], Ken Takao[1], Yohko Okada[1], Minako Maruyama[1], Eri Tsurugai[1], Yohko Nakazato[1], Mitsuru Adachi[1,2]. *[1]Respiratory Medicine, IMS Group, Ohta Fukushima General Hospital, Ohta City, Japan; [2]Respiratory Medicine and Allergology, Showa University Hospital, Japan*

Long-term oxygen therapy (LTOT) is the treatment proven to improve survival in chronic respiratory failure patients, especially chronic obstructive pulmonary disease (COPD). Participation of airway neutrophil inflammation is suggested to be a part of illness, such as COPD.
The aim of this study is to evaluate whether sputum neutrophil monitoring is useful for LTOT in patients with COPD exacerbations.
Twenty two patients, mean age were 72 years, were participated in this study. Twenty patients survived to the follow-up after 14 months of this study. Before recieving LTOT, mean sputum neutrophil was 8%. However, after LTOT administrations, sputum neutrophil was decreased to approximately 3% and reduced the number of hospitalizations including outpatient service. Also St.George's Respiratory Questionnarie score (SGRQ) was significantly improved. In peripheral blood, downward tendency was seen, but not so significant. Before outpatient service in COPD patients, average neutrophil percentage in the sputum was gradually raised up to 18%(±6). So we could respond for COPD exacerbations at an early stage,using corticosteroid and antibiotic drugs.While this neutrophil participate mechanism is still unknown, further study should be needed including cytokine evaluation. However, this study indicates that in patients with COPD, long-term oxygen therapy is associated with airway sputum neutrophil reduction.

P2105
The effect of high dose N-acetylcysteine (1200mg daily) on airway function and airway trapping in COPD patients – A double blinded randomized placebo controlled trial
Hoi Nam Tse[1], King ying Wong[2], Kwok Sang Yee[2], Lai yun Ng[1]. *[1]Medical Department, Kwong Wah Hospital, Hong Kong, Hong Kong; [2]Department of TB and Chest Unit, Wong Tai Sin Hospital, Hong Kong, Hong Kong*

Introduction: High dose N-acetylcysteine (NAC) has both antioxidant and mucolytic effect. However, there was a lack of study to demonstrate its beneficial use in COPD patients.
Aims: To investigate the effect of high dose NAC (1200mg daily) on airway function in stable COPD patients
Methods: This is a 16-week double-blinded randomized placebo-controlled trial conducted in a government hospital in Hong Kong. Spirometry confirmed COPD patients (FEV1/FVC <70%) were recruited and randomized into treatment (NAC 1200mg daily) and placebo groups. Both patients and doctors were blinded for



the group allocation. Lung function tests were measured at the beginning and 16-week-follow up.
Results: 107 eligible COPD subjects (93.5% male) with mean age of 70.8±8.0 and %FEV1 54.3±21.5% were recruited. Baseline characteristics were comparable between the 2 groups. At 16-week, there was significant improvement in small airway function in treatment group (FEF25-75% from 0.53 to 0.65L/s) compared with placebo (0.55 to 0.54L/s) (p=0.006). Airtrapping was also improved in treatment group (RV/TLC ratio from 0.71 to 0.6) compared with placebo (ratio from 0.67 to0.64) in the emphysematous subtype of COPD patients (p=0.03).
Conclusions: High dose N-acetylcysteine improves small airway function in COPD patients. It reduces airtrapping in the emphysematous subgroup of COPD patients.

P2106
Cost-effectiveness of adding budesonide/formoterol to tiotropium in severe COPD patients in four Nordic countries
Rune Nielsen[1,2], Hannu Kankaanranta[3], Leif Bjermer[4], Peter Lange[5,6], Sofie Arnetorp[7], Morten Hedegaard[8], Anna Stenling[8], Nicole Mittmann[9]. *[1]Department of Thoracic Medicine, Haukeland University Hospital, Bergen, Norway; [2]Institute of Medicine, University of Bergen, Norway; [3]Department of Respiratory Medicine, Seinäjoki Central Hospital, Seinäjoki, Finland; [4]Department of Respiratory Medicine & Allergology, Skane University Hospital, Lund, Sweden; [5]Department of Public Health, Copenhagen University, Copenhagen, Denmark; [6]Pulmonary Section, Hvidovre Hospital, Hvidovre, Denmark; [7]Health Economics & Outcomes Research, AstraZeneca R&D, Mölndal, Sweden; [8]Health Economics, AstraZeneca Nordic, Södertälje, Sweden; [9]Health Outcomes and PharmacoEconomics (HOPE) Research Centre, Sunnybrook Health Sciences Centre, University of Toronto, Toronto, Canada*

Objective: To assess the cost-effectiveness of budesonide/formoterol (B/F)+tiotropium (TIO) versus placebo (PBO)+TIO for the treatment of chronic obstructive pulmonary disease (COPD) patients eligible for inhaled corticosteroid/long-acting β2-agonist from societal and healthcare perspectives in Denmark, Finland, Norway and Sweden.
Method: The cost-effectiveness analysis was based on the 12-week, randomised, double-blind CLIMB trial (NCT00496470) of 659 COPD patients with pre-bronchodilator FEV1 ≤50%, and at least one severe exacerbation (hospitalisation, emergency room visit or systemic glucocorticosteroids) the preceding year. Subjects were treated with B/F 320/9μg bid+TIO 18μg qd or PBO bid+TIO 18μg qd. Effectiveness was defined as the number of exacerbations avoided. A sub-analysis included antibiotics in the definition of an exacerbation. Resource use from the trial was combined with 2010 Danish (DKK), Finnish (€), Norwegian (NOK) and Swedish (SEK) unit costs. The incremental cost-effectiveness ratios (ICERs) were estimated by bootstrapping.
Results: From a societal perspective, the ICER was estimated at €174 per exacerbation avoided (pEA) in Finland while B/F+TIO was dominant in the other countries. From a healthcare perspective, B/F+TIO was dominant in Norway and the ICERs were estimated at DKK 1,580 (€212), €307, SEK 1,573 (€165) pEA for Denmark, Finland and Sweden, respectively. Including antibiotics decreased ICERs by 8-15%. Sensitivity analyses showed that results were overall robust.
Conclusion: The results indicate that B/F+TIO represents a clinical and economic benefit to health systems and society for the treatment of COPD in the Nordic countries.

P2107
Effect of once-daily indacaterol in a predominantly Chinese COPD population: A 26-week Asia-Pacific study
Wanzhen Yao[1], Changzheng Wang[2], Nanshan Zhong[3], Wei Yang[4], Michelle Henley[5], Benjamin Kramer[4]. *[1]Department of Respiratory Medicine, Peking University Third Hospital, Beijing, China; [2]Institute of Respiratory Diseases, Xinqiao Hospital, Third Military Medical University, Chongqing, China; [3]State Key Lab of Respiratory Disease, 1st Affiliated Hospital,Guangzhou Medical College, Guangzhou, China; [4]Primary Clinical Science Unit, Novartis Pharmaceuticals Corporation, East Hanover, United States; [5]Integrated Information Sciences, Novartis Pharmaceuticals UK Ltd, Horsham, United Kingdom*

Rationale: The efficacy and safety of indacaterol (IND), a once-daily (qd) inhaled LABA for the treatment of COPD, was investigated in a predominantly Chinese COPD popn.
Methods: This double-blind placebo (PBO)-controlled 26-week study, randomized pts with moderate-to-severe COPD (≥40 yrs, post-bd $FEV_1/FVC<70\%$, $FEV_1 \geq 30$ to <80% pred, smoking history ≥10 pack-years) to IND 150 or 300 μg or PBO qd. Variables included trough FEV_1 (mean of 23h 10min and 23h 45min post-dose) at Wk12 (primary) and 26; and health status (St George's Respiratory Questionnaire; SGRQ) and transition dyspnea index (TDI) at Week 26.
Results: Of 563 pts randomized (89.8% Chinese, 94.3% male, mean age 65.4 yrs, post-bd FEV_1 49.9% pred), 85.6% completed. Both IND doses significantly improved trough FEV_1 vs PBO ($p<0.001$), with IND-PBO diffs exceeding the prespecified MCID (0.12L) at Wk12 (0.15 & 0.13L for 150 & 300 μg) and Wk26 (both 0.13L). TDI total score at Wk26 was superior to PBO for both IND doses (0.82 & 1.15, $p<0.01$), as was % pts with a clinically relevant (≥1 point) TDI score (74.1 & 78.6% vs 55.5%, $p<0.05$ for IND 150 & 300μg vs PBO). Both doses provided improvements (i.e., decreases) from baseline in SGRQ total score of ≥4 units at Wk26 that were numerically greater than with PBO (raw mean changes: –9.6 & –8.8 vs –7.0 units), with a similar pattern in the % of pts with a clinically relevant SGRQ score (≤–4 units; 65.0 & 61.5% vs 60.6%). The incidence of AEs was 49.2%, 54.3% & 45.2% for IND 150, 300μg & PBO.
Conclusion: Indacaterol provided effective bronchodilation in this predominantly Chinese population, with significant improvements in breathlessness and a trend towards improved health status.

P2108
Budesonide/formoterol vs formoterol, both via Turbuhaler®, in patients with moderate to severe COPD: Phase III study results
Masakazu Ichinose[1], Ronnie Samoro[2], Rustem Fassakhov[3], Mitsuru Oguri[4], Jan Ekelund[5], Lars-Goran Carlsson[5], Yoshinosuke Fukuchi[6]. *[1]Third Department of Internal Medicine, Wakayama Medical University, Wakayama, Japan; [2]Department of Medicine, Healthlink Medical-Surgical-Dental Clinics and Diagnostic Center, Iloilo City, Philippines; [3]Department of Medicine, Institute of Epidemiology and Microbiology, Kazan, Russian Federation; [4]Department of Medicine, Oji General Hospital, Hokkaido, Japan; [5]Clinical Sciences, AstraZeneca R&D, Molndal, Sweden; [6]Department of Respiratory Medicine, Juntendo University, Tokyo, Japan*

Background: This study evaluated the efficacy and tolerability of budesonide/formoterol (BUD/FORM) vs formoterol (FORM) in patients with moderate to severe COPD.
Methods: In this randomised, double-blind, parallel-group, phase III study (NCT01069289) patients with moderate to severe COPD for ≥2 years received either BUD/FORM 160/4.5 μg 2 inhalations twice daily via Turbuhaler® or FORM 4.5 μg 2 inhalations twice daily via Turbuhaler® for 12 weeks. Reliever medication: salbutamol 100 μg/actuation via pMDI. Primary outcome variable: change from baseline over the treatment period in predose FEV_1; secondary outcome variables included: lung function, time to first exacerbation, tolerability.
Results: 1293 patients were randomised. Both BUD/FORM and FORM improved predose FEV_1 (improvements of 4.6% and 1.5%, respectively); the change from baseline was significantly greater with BUD/FORM vs FORM (BUD/FORM:FORM ratio: 1.032; 95% CI: 1.013–1.052; p=0.0011). Significantly greater improvements in other lung function measures were also observed. BUD/FORM patients had a statistically significantly prolonged time to first exacerbation vs FORM patients (hazard ratio: 0.679; 95% CI: 0.507–0.909; p=0.0094). Both treatments were well tolerated. The incidence and type of adverse events were similar in both groups; most commonly reported adverse events (BUD/FORM vs FORM): COPD (8.0% vs 9.4%), nasopharyngitis (5.5% vs 4.9%) and bronchitis (2.0% vs 2.3%).
Conclusions: BUD/FORM 160/4.5 μg two inhalations twice daily was more effective than FORM 4.5 μg two inhalations twice daily in patients with moderate to severe COPD. Both treatments were well tolerated.
Funding: AstraZeneca.

P2109
Effect of roflumilast on hospitalizations in COPD patients
Eric Bateman, José Jardim, Udo-Michael Goehring, Manja Brose, Peter Calverley. *Division of Pulmonology, Department of Medicine, University of Cape Town, Cape Town, South Africa Respiratory Division at Federal University of São Paulo, Rua Botucatu, São Paulo, SP, Brazil Department of Respiratory Medicines, Nycomed: a Takeda Company, Konstanz, Germany Department of Data Science, Nycomed: a Takeda Company, Konstanz, Germany School of Clinical Sciences (Aintree Campus), University Hospital Aintree, Liverpool, United Kingdom*

Background: Severe exacerbations of COPD require hospitalization and have serious long-term consequences for patients. Roflumilast (ROF) is a PDE4 inhibitor that significantly reduced moderate-to-severe exacerbations in clinical studies. Its effects on severe exacerbations and any adverse events leading to hospitalization have not been described previously.
Aim: To investigate the effects of ROF on the rate of hospitalizations resulting from severe exacerbations or any other adverse events in two 1-year studies (M2-124 and M2 125).
Methods: In a post-hoc pooled analysis of the pivotal studies of ROF 500μg (n=1537) vs placebo (n=1554), statistical analyses were performed on the overall population and in patient subgroups with: A) severe/very severe COPD; B) frequent COPD exacerbations; and C) severe/very severe COPD and frequent COPD exacerbations. Negative binomial regression analyses were used to investigate the rate reduction for hospitalizations.
Results: In the overall population, ROF decreased the rate of hospitalizations resulting from severe exacerbations vs placebo by 21.6% (rate ratio 0.784, [95% CI 0.619, 0.993, p=0.0439), and overall there were trends towards extended times-to-onset of severe exacerbations leading to hospitalization. Although not statistically significant, ROF reduced hospitalizations resulting from any adverse event compared with placebo. In all subgroups analyzed, ROF had a positive numerical but not statistically significant effect on rate reduction of all-cause hospitalizations, time to hospitalization and risk of hospitalizations.
Conclusions: Roflumilast significantly reduces the rate of severe exacerbations leading to hospitalization vs placebo.

P2110

The effect of tiotropium on lung dynamic hyperinflation and treadmill exercise capacity in mild to moderate COPD

Richard Casaburi[1], Francois Maltais[2], Janos Porszasz[1], Frank Albers[3], Qiqi Deng[3], Ahmar Iqbal[4], Heather Paden[3], Denis O'Donnell[5]. *[1]Division of Respiratory and Critical Care Physiology and Medicine, Rehabilitation Clinical Trials Center, Los Angeles Biomedical Research Institute at Harbor-UCLA Medical Center, Torrance, CA, United States; [2]Centre de Recherche, Institut Universitaire de Cardiologie et de Pneumologie de Québec, Université Laval, Quebec, Canada; [3]Medical Affairs Respiratory, Boehringer Ingelheim Pharmaceuticals Inc, Ridgefield, CT, United States; [4]Respiratory Medical Affairs, Pfizer Inc, New York, NY, United States; [5]Department of Medicine, Queen's University & Kingston General Hospital, Kingston, ON, Canada*

Rationale: In previous studies tiotropium improved cycle exercise duration in GOLD II-IV COPD patients. This double-blind crossover study (NCT01072396) compared tiotropium with placebo in GOLD I and II COPD using treadmill exercise testing.
Methods: Patients were current or ex-smokers aged ≥40 y with post-bronchodilator FEV_1/FVC <70%, FEV_1 ≥50% predicted, and dynamic hyperinflation (≥100 mL inspiratory capacity [IC] decrease during incremental treadmill exercise). Patients received tiotropium 18 μg qd and placebo for 6 weeks each (random order, 4-week washout). Patients performed constant work rate treadmill exercise at 80% of peak incremental test work rate before and after each treatment period. The primary endpoint was the difference in exercise isotime IC change from baseline to Week 6 between tiotropium and placebo. Secondary endpoints included change in exercise duration.
Results: Patients (n=126, 52% male) had mean age 61 y, post-bronchodilator FEV_1/FVC 59% and FEV_1 77% predicted. Baseline IC was 2.27 L and exercise duration 447 s. The difference in change in isotime IC from baseline to Week 6 between tiotropium and placebo was statistically significant (65 mL, *P*=0.009). The difference in change from baseline in exercise duration between tiotropium and placebo was not significant in the combined GOLD I+II (29.3 s, *P*=0.109) and GOLD I (-23.5 s, *P*=0.415) groups, but was statistically significant for GOLD II (63.0 s, *P*=0.007).
Conclusions: Tiotropium was associated with reduced lung hyperinflation at rest and during exercise in GOLD I and II COPD patients. Significantly improved exercise duration was observed in GOLD II patients but not the combined or GOLD I groups.

P2111

Pretreatment with inhaled procaterol improves symptoms of dyspnea and quality of life in patients with severe COPD

Hiroyuki Ohbayashi[1,2], Mitsuru Adachi[2]. *[1]Department of Allergy and Respiratory Medicine, Tohno-Chuo Clinic, Mizunami, Gifu, Japan; [2]Department of Respiratory and Allergy Medicine, Showa University, Tokyo, Japan*

Objectives: To investigate the efficacy of the inhaled supplementary short-acting beta2-agonists (SABA) administered before the performance of daily activity (the SABA Assust Use) in patients with COPD.
Methods: Thirty outpatients with moderate to severe COPD (Stage II - IV), regular use of tiotropium bromide alone, and dyspnea during daily activities, were enrolled. Subjects self-administered 20μg of inhaled procaterol hydrochloride before daily activities no more than four times daily. Dyspnea symptom scores, St George's Respiratory Questionnaire (SGRQ) activity domains, impulse oscillometry system parameters, and pulmonary function tests were recorded at the beginning and end of the 2-week study.
Results: More than 80% of subjects reported dyspnea when performing the following activities: walking up a slope (100.0%), climbing stairs (100.0%), gardening (93.3%), walking on flat ground (90.0%), bathing (86.7%), getting on a bus or train (83.3%), and changing clothes (80.0%). After 2 weeks, subjects with Stage III significantly improved dyspnea scores (walking up a slope (p=0.047), climbing stairs (p=0.014), gardening (p=0.034), walking on flat ground (p=0.006), getting on a bus or train (p=0.039), and changing clothes (p=0.045)). Both symptoms and activity SGRQ domains significantly improved in subjects with Stage III (p=0.036 and p=0.028, respectively). Resistance of small airways (R5-R20) and low-frequency reactance area (AX) significantly improved in subjects with Stage III (p=0.003 and p=0.004, respectively). No significant changes were found in pulmonary function tests.
Conclusion: The SABA Assist Use improved dyspnea symptoms in subjects with Stage III COPD.

P2112

The impact of treatment of chronic obstructive pulmonary disease (COPD) on functional status and quality of life of patients

Drosos Tsavlis[1], Mamas Theodorou[2], Anna Tzoumaka[1], Hellie Lithoxopoulou[1], Panagiotis Minogiannis[3], Vassilios Tsaousis[1], Anastasia Tektonidou[4], Daphne Kaitelidou[5]. *[1]Dept.t of Pulmonology, School of Medicine, Aristotle University, Thessaloniki, Makedonia, Greece; [2]Health Care Management Programme, Open University of Cyprus, Nicosia, Cyprus; [3]Dept. of Health Policy and Management, Mailman School of Public Health, Columbia University, New York, United States; [4]Health Care Management Programme, Open University of Cyprus, Nicosia, Cyprus; [5]Nursing Dept., University of Athens, Greece*

Purpose: To determine a possible correlation between objective laboratory data on the health of patients with Chronic Obstructive Pulmonary Disease (COPD) and the subjective perception of disease and quality of life by patients themselves. Also to investigate whether these two factors are consistent and whether there are corresponding changes over time after therapeutic intervention.
Methods: We studied 100 patients with COPD who completed the general health questionnaire SF-36 and the qualified for COPD questionnaire St. George's (SGRQ) and were classified into four groups (four stages of COPD by GOLD) based on their spirometric performance (FEV_1) during the first session of the investigation. After 6 months of specific treatment for each group, the patients returned for a new spirometry and completed the two questionnaires again. The same happened with 20 controls who received absolutely no treatment.
Results: There was a direct correlation between FEV_1 values with the scores of both SGRQ and SF-36 questionnaires in all study groups during both sessions. Following the therapeutic intervention, improvement of FEV_1 values with corresponding changes in the scores of questionnaires were observed in all patient groups. However, statistically significant differences emerged in only two groups of patients raising issues of medication revision taken by the other two groups.
Conclusion: It was confirmed that the subjective perception of COPD patients are consistent with objective findings that characterize its course, and therefore both questionnaires used to measure the quality of life are reliable and record the changes.

P2113

Safety of fluticasone furoate (FF), an inhaled corticosteroid in combination with vilanterol (VI), a long-acting beta agonist in management of COPD exacerbations

Peter M.A. Calverley[1], Mark T. Dransfield[2], Jean Bourbeau[3], Paul Jones[4], Nicola A. Hanania[5], Donald A. Mahler[6], Jørgen Vestbo[7], Andrew Wachtel[8], Fernando Martinez[9], Frank Barnhart[10], Lisa Sanford[11], Sally Lettis[11], Courtney Crim[10]. *[1]Clinical Science Centre, University Hospital Aintree, Liverpool, United Kingdom; [2]Division of Pulmonary, Allergy and Critical Care Medicine, University of Alabama at Birmingham, United States; [3]Medicine, McGill University Health Centre, Montreal, Canada; [4]Division of Clinical Science, St. George's University, London, United Kingdom; [5]Pulmonary and Critical Medicine, Baylor College of Medicine, Houston, United States; [6]Section of Pulmonary & Critical Care Medicine, Darmouth Medical School, Hanover, United States; [7]Respiratory Research Group, Manchester Academic Health Sciences Centre, Manchester, United Kingdom; [8]UCLA School of Medicine, UCLA, Los Angeles, United States; [9]Department of Internal Medicine, University of Michigan, Ann Arbor, United States; [10]Respiratory Medicine Development Center, GlaxoSmithKline, Research Triangle Park, United States; [11]Quantitative Sciences Division, GlaxoSmithKline, Uxbridge, United Kingdom*

Introduction: FF and VI are in development as combined once-daily (OD) therapy for COPD
Objectives: Assess the safety of FF/VI (3 strengths) and VI in COPD
Methods: In two replicate 1 year studies, after a 28 day run-in with ADVAIR DISKUS® 250/50mcg, subjects received FF/VI 50/25, 100/25, 200/25mcg or VI 25mcg OD. Primary endpoint: annual rate of moderate/severe exacerbations (described separately). Safety endpoints included all, serious and fatal Adverse Events (AEs), Local Steroid Effects (LSE, including candidiasis), bone disorders (BD, including fractures) and pneumonia
Results: Pooled safety findings are shown in the table.

	VI	FF/VI		
ITT: n (%)	25 (N=818)	50/25 (N=820)	100/25 (N=806)	200/25 (N=811)
AE*	575 (70)	620 (76)	621 (77)	622 (77)
AE* (drug-related)	113 (14)	169 (21)	134 (17)	140 (17)
Serious AE*	126 (15)	136 (17)	123 (15)	124 (15)
Fatal AE†	13 (2)	16 (2)	10 (1)	14 (2)
LSE*	96 (12)	142 (17)	121 (15)	140 (17)
BD*	9 (1)	24 (3)	27 (3)	21 (3)
Pneumonia*	27 (3)	48 (6)	51 (6)	55 (7)
Pneumonia HR (95%CI) vs VI		1.7 (1.1, 2.8)	1.8 (1.2, 3.0)	2.0 (1.3, 3.2)
		p=0.025	p=0.010	p=0.003

HR, Hazard Ratio. *On-treatment, †On-/Post-treatment. HR for LSE and BD were significantly higher for FF/VI vs VI in all comparisons except LSE at 100/25 (p=0.065).

Conclusions: In COPD patients FF/VI exhibited similar rates of serious and fatal AEs to VI, although rates of AE, BD, LSE and pneumonia were greater with FF/VI than VI alone. The efficacy of the combination is reported separately
Funded by GSK: HZC102871:NCT01009463, HZC102970:NCT01017952.

P2114

Inhaled corticosteroid/long-acting beta-2 agonist (ICS/LABA) combination can decrease mortality of COPD patients, a nationwide population-based cohort study in Taiwan

Ming-Cheng Chan, Gin-Hen Lin. *Section of Chest Medicine, Department of Internal Medicine, Taichung Veterans General Hospital, Taichung, Taiwan Department of Medical Research, Taichung Veterans General Hosptial, Taichung, Taiwan*

Background: Chronic Obstructive Pulmonary Disease (COPD) remains a major public health problem. Current treatments, including pharmacological and non-pharmalogical, can only alleviate symptoms, prevent exacerbation and improve quality of life. Previous large-scale studies failed to demonstrate benefit of mortality reduction which is also important for a chronic illness.
Objective: The aim of this study is to determine whether ICS/LABA combination can reduce mortality of COPD by using Taiwan National Health Insurance Database.
Method: This was a nationwide population-based cohort study. A total of 1989 COPD patients were identified from one million sampling cohort dataset between January to December in 2005. Patients with diagnosed in 2005 as COPD were grouped as non-controller use (n=1638), ICS/LABA (n=265) and LAMA (n=86). Cox regression model was used to evaluate the incidence of mortality and pneumonia in the following 3 years to December 2008.
Result: The incidence of pneumonia was not different among three groups. However, COPD patients with older age (H.R. 1.398 for every increase of 10 years, $p < 0.0001$) and male gender (H.R. 1.414, $p < 0.001$) had higher incidence to have pneumonia. The mortality rate was lower in patients who use ICS/LABA combination as compared with non-controller group (H.R. 0.694, $p = 0.0165$)
Conclusion: In the selected Taiwanese population, COPD mortality was lower among patients who used ICS/LABA. Incidence of pneumonia was not increased with ICS/LABA, but significantly related increased age and male gender.

P2116

Effect of formoterol alone and in combination with aclidinium on electrocardiograms in dogs

Amadeu Gavaldà, Marisa Vinyals, Jordi Aubets, Jordi Gras. *R & D, Almirall, Barcelona, Spain*

Introduction: Co-administration of a long-acting β-agonist with an anticholinergic is common clinical practice for the management of COPD, but there are concerns that systemic exposure to both drugs could cause undesirable pharmacodynamic effects on the heart.
Aims: To evaluate the cardiovascular safety of formoterol alone and in combination with aclidinium in conscious dogs.
Methods: Formoterol (1, 3, 10 μg/kg iv), aclidinium (50, 167 μg/kg iv) and formoterol+aclidinium (1+17, 3+50, 10+167 mg/kg iv) were administered to fasting, male Beagle dogs (n=4; 13–16 kg) in a 3-min perfusion. Each dog received each dose with >6-day washout. Electrocardiograms were recorded at baseline (for 1 h) and 24 h post-administration (for 90 min) and assessed for ventricular tachycardia (VT) and premature ventricular complexes (PVC).
Results: Formoterol alone showed a dose-dependent trend to induce VT. VT was observed in 0, 1 and 4 animals treated with formoterol 1, 3 and 10 μg/kg, respectively. Aclidinium alone (both doses) did not induce VT. The combination of formoterol+aclidinium resulted in VT in a similar number of animals as formoterol alone (2 and 3 animals with 3+50 and 10+167 μg/kg, respectively). Similar results were observed for PVC. At the highest doses of formoterol and aclidinium, the plasma concentrations corresponded to 32 and 4000 times those reported in human plasma after clinically relevant doses.
Conclusions: Addition of aclidinium does not alter the incidence or rate of formoterol-induced VT or PVC in dogs. These results suggest that aclidinium has no synergistic interaction on cardiac function with β-agonists.
This study was supported by Almirall S.A., Barcelona, Spain.

P2117

Risk of pneumonia related to budesonide use in COPD: An updated pooled analysis

Don Sin[1], Donald Tashkin[2], Finn Radner[3], Ulf Sjobring[3], Anders Thoren[3], Peter Calverley[4], Stephen Rennard[5]. *[1]Department of Medicine, University of British Columbia, Vancouver, Canada; [2]Division of Pulmonary and Critical Care Medicine, David Geffen School of Medicine, Los Angeles, United States; [3]Clinical Sciences, AstraZeneca R&D, Molndal, Sweden; [4]School of Clinical Sciences, University of Liverpool, United Kingdom; [5]Internal Medicine Section of Pulmonary and Critical Care, Nebraska Medical Center, Omaha, United States*

Background: A meta-analysis of 7 clinical trials reported no increase in the risk of pneumonia as an adverse event (AE) in COPD patients taking the inhaled corticosteroid (ICS) budesonide; however, others have reported a numerical increase. Recently, an eighth trial (NCT00419744) fulfilling the meta-analysis inclusion criteria has been completed. This updated meta-analysis includes data from all 8 clinical trials of budesonide.
Methods: Patient data were pooled from 8 clinical trials of inhaled budesonide (320–1280 μg/day), with or without formoterol, vs control (placebo or formoterol alone) in patients with stable COPD and ≥6 months of follow-up. The primary analysis compared treatment groups for the risk of pneumonia as an AE or serious AE (SAE) during the trial or within 15 days of the trial end. Cox proportional hazards regression was used to analyse the data on an intention-to-treat basis.
Results: Data from 8260 patients were included; 4616 received budesonide and 3644 received control treatment, with 3395 and 2647 patient-years of exposure to treatment, respectively. No statistically significant difference was found between the budesonide and non-ICS treatment groups for the occurrence of pneumonia as an AE (3.9% [n=179 patients] vs 3.3% [n=120]; HR 1.13, 95% CI: 0.90–1.43) or a SAE (1.8% [n=82] vs 1.6% [n=59]; HR 1.02, 95% CI: 0.72–1.43). Similarly, there was no statistically significant difference between the budesonide and non-ICS treatment groups for time to pneumonia as an AE (log-rank test 0.30) or a SAE (0.926).
Conclusion: The updated pooled analysis shows that budesonide (320–1280 μg/day) does not increase the risk of pneumonia over 12 months in patients with COPD.
Funding: AstraZeneca.

P2118

Long-term safety of twice-daily aclidinium bromide in COPD patients: A one-year, double-blind study

Arthur Gelb[1], Donald Tashkin[2], Barry Make[3], Xiaoyun Zhong[4], Esther Garcia Gil[5], Cynthia Caracta[6]. *[1]Southern California Clinical Trials, Lakewood, United States; [2]Division of Pulmonary & Critical Care Medicine, David Geffen School of Medicine at UCLA, Los Angeles, United States; [3]Department of Medicine, National Jewish Health, Denver, United States; [4]Biostatistics, Forest Research Institute, Jersey City, United States; [5]R&D Centre, Almirall, S.A., Barcelona, United States; [6]Clinical Development, Forest Research Institute, Jersey City, United States*

Introduction: Aclidinium bromide is a novel, long-acting muscarinic antagonist currently under investigation for the maintenance treatment of COPD. Safety data from a long-term efficacy and safety trial of twice-daily (BID) aclidinium are presented here.
Methods: In this 52-week study, moderate-to-severe COPD patients were randomized (1:1) to receive aclidinium 200 μg or 400 μg BID. Safety was assessed via adverse events (AEs), vital signs, and 12-lead ECG.
Results: A total of 605 patients were randomized, and 602 (99.5%) were included in the safety population. Postbronchodilator FEV_1 and percent predicted at screening were (mean ±SD) 1.55±0.54 L and 52.3±13.2 L. The incidence of AEs was similar across the aclidinium 200 μg and 400 μg groups and most were mild or moderate. The most common AE and most frequently reported AE leading to discontinuation was COPD exacerbation, with a similar percentage of patients between groups who discontinued due to exacerbations [200 μg, 9 (2.9%); 400 μg, 8 (2.7%)]. The incidence of typically expected anticholinergic AEs was low and similar between groups (e.g. dry mouth: 200 μg, 1.3%; 400 μg, 2.7%; constipation: 200 μg, 2.9%; 400 μg, 1.7%). Cardiac and cerebrovascular AEs did not occur in a dose-related manner. The 200 μg and 400 μg groups had similar incidences of serious AEs, with values [n (%)] of 29 (9.3) and 29 (10.0), respectively. One patient in each treatment group died during the study (200 μg, biliary sepsis; 400 μg, subarachnoid hemorrhage), but neither death was deemed to be related to treatment.
Conclusions: Twice-daily aclidinium 200 μg and 400 μg were safe and well tolerated over 52 weeks with a similar safety profile for both doses.

P2119

Effect of augmentation therapy on immune function of patients with severe Alpha1-antitrypsin deficiency

Ilaria Ferrarotti[1], Tomàs P. Carroll[2], Simona Inghilleri[1], Stefania Ottaviani[1], Maurizio Luisetti[1], Noel G. McElvaney[2]. *[1]Dept of Molecular Medicine, Pneumology, IRCCS San Matteo Hospital Foundation, University of Pavia, Italy; [2]Dept of Medicine, Respiratory Research Division, Royal College of Surgeon on Ireland, Education and Research Centre, Beaumont Hospital, Dublin, Ireland*

Alpha-1 antitrypsin (AAT) deficiency is a hereditary disorder caused by mutations in the SERPINA1 gene. Individuals homozygous for the most common mutation Z have markedly reduced AAT concentrations and are predisposed to developing early-onset emphysema. Approximately 5% of AATD individuals have other deficiency alleles including Null alleles which do not express AAT. Although AAT production in monocytes is relatively small in comparison with hepatocytes, local regulation of the antiprotease shield represents an important first line of defence in times of infection and inflammation.
Our aim was to investigate the anti-inflammatory properties of AAT by studying individuals homozygous for Null mutations who were receiving augmentation therapy with human plasma derived AAT, and comparing them to ZZ individuals and MM healthy controls.
We isolated peripheral blood monocytes from Null/Null and ZZ patients (with/without therapy), and MM controls. To investigate cytokine production, monocytes were maintained for 24 hours in the presence/absence of LPS. ELISAs and quantitative RT-PCRs were used to evaluate cytokine expression. Superoxide production and chemotactic activity were measured in monocytes.
Augmentation therapy appeared to attenuate IL-6 and IL-8 production from ZZ monocytes at both. Moreover, we noted a reduced chemotactic activity and superox-

ide production in AATD individuals receiving augmentation therapy in comparison to untreated AATD patients.
Augmentation therapy in AATD individuals (ZZ and Null/Null) appears to modulate immune function and may provide a rationale for reduced exacerbations in subjects receiving augmentation therapy.

P2120
NFAT subtypes in regulating Th2 lymphocytes
Xin Yao[1], Yue Teng[1], Hao Huang[1], Ian Adcock[2], Peter Barnes[2]. [1]*Respiratory Medicine, The First Affiliated Hospital of Nanjing Medical University, Nanjing, China;* [2]*Airway Disease, NHLI, Imperial College, London, United Kingdom*

Background: Nuclear factor of activate T cells (NFAT), consists of five members and plays a pivotal role in regulating T lymphocyte activation. Among the five subtypes of NFAT, NFAT1, NFAT2 and NFAT4 were recognized as the key family members associated with allergic diseases. However, evidence regarding the functions of NFAT1 and NFAT2 in Th2 cells are still conflicting.
Aims and objectives: Therefore, we explored the functions of NFAT1 and NFAT2 on Th2 lymphocytes.
Methods: Knockdown of NFAT1 and NFAT2 using small interfering RNA (siRNA) was performed in the murine Th2 lymphocyte cell line (D10.G4.1). Real-time qPCR, Western Blotting and ELISA were performed to test the relatively expression ofTh2 cytokine mRNA and protein in cells and culture supernatant.
Results: D10 cells express IL-4, IL-5, IL13 and GATA3mRNA level. NFAT1 siRNA and NFAT2 siRNA selectively suppressed the expression of NFAT1 and NFAT2 respectively at both the mRNA and protein level. Higher levels of IL-4, IL-5 and IL-13 were seen in NFAT1 siRNA treated Th2 cells. This suggests that NFAT1 may play a negative role in Th2 cytokine expression. Interestingly, the opposite effect was seen with NFAT2 siRNA. NFAT2 siRNA down-regulated the expression of IL-4, IL-5 and IL13 mRNA levels. This was associated with a reduction in the expression of GATA3 mRNA and protein.
Conclusions: NFAT1 may play a negative role in regulating Th2 cytokines whilst NFAT2 may have the opposite effect.