314. Trials in COPD: novel treatments and insights

P2876

Quantification and treatment patterns of real-world patients classified by the GOLD 2011 strategy

Mark Small, Sarah Broomfield, Victoria Higgins. *Respiratory DSP, Adelphi Real World, Macclesfield, Cheshire, United Kingdom*

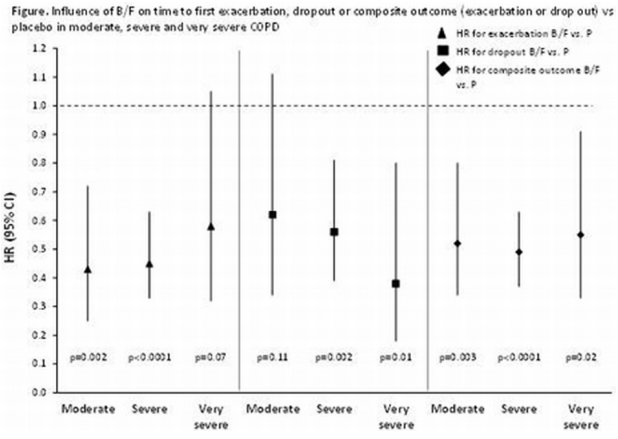
Objectives: The Global Initiative for Chronic Obstructive Lung Disease (GOLD) 2011 Strategy classifies COPD patients into 4 categories (A: low risk, less symptoms; B: low risk, more symptoms; C: high risk, less symptoms; D: high risk, more symptoms) based on risk ($FEV_1 \geq$ or <50% predicted *and/or* exacerbation history < or ≥2 per year) and symptoms (COPD Assessment test [CAT] score < or ≥10 *or* modified Medical Research Council [mMRC] dyspnoea scale < or ≥2). We examined the proportion of patients in each category when evaluated by CAT or mMRC, and corresponding pharmacological treatment (CAT classification).
Methods: GOLD 2011 criteria were applied to a real-world international COPD population sampled from the Adelphi Respiratory Disease Specific Programme undertaken June to September 2011. Physicians and patients completed matched questionnaires.
Results: 2392 patients completed a questionnaire, of which 1508 with all 4 GOLD classification parameters were analyzed. The proportion of patients in categories A, B, C and D, respectively, when evaluated by CAT was 10, 49, 1 and 40%, and when evaluated by mMRC was 39, 20, 13 and 28%. By CAT evaluation in categories A, B, C, and D, patients were using a long-acting β_2-agonist (LABA) alone (8, 6, 0 and 1%), long-acting muscarinic antagonist (LAMA) alone (37, 25, 8 and 5%), inhaled corticosteroid plus LABA (ICS/LABA) alone (22, 18, 8 and 8%), and ICS/LABA plus LAMA only (11, 20, 46, 43%).
Conclusion: CAT assessment increased the number of patients in the more symptomatic categories (B and D), compared with mMRC. Contrary to the GOLD 2011 recommendations, by CAT assessment, a high proportion of low-risk patients (A and B) were using ICS/LABA.

P2877

Differential dropout may affect exacerbation risk estimates differently in moderate-to-very severe COPD

Peter Calverley[1], Göran Eriksson[2,3], Dirkje Postma[4], Christine Jenkins[5], Antonio Anzueto[6], Barry Make[7], Anders Persson[8], Malin Fagerås[2], Thomas Similowski[9]. *[1]Pulmonary and Rehabilitation Research Group, University Hospital Aintree, Liverpool, United Kingdom; [2]Research and Development, AstraZeneca, Lund, Sweden; [3]Department of Respiratory Medicine and Allergology, University Hospital, Lund, Sweden; [4]Department of Pulmonary Medicine and Tuberculosis, University Medical Center Groningen, GRIAC Research Institute, University of Groningen, Netherlands; [5]Woolcock Institute of Medical Research, University of Sydney, Camperdown, Australia; [6]Department of Pulmonology, University of Texas Health Sciences Center, San Antonio, TX, United States; [7]Division of Pulmonary Sciences and Critical Care Medicine, National Jewish Health, University of Colorado, Denver, CO, United States; [8]Research and Development, AstraZeneca, Mölndal, Sweden; [9]Service de Pneumologie et Réanimation, Groupe Hospitalier Pitié-Salpêtrière, Paris, France*

Background: Differential withdrawal of patients from clinical trials (dropout) complicates interpretation of the effect of intervention on the exacerbation frequency in COPD studies. We examined the impact of differential dropout on exacerbations in moderate-to-very severe COPD (GOLD grades 2–4).
Methods: Patients in 3 pooled COPD studies[1,2,3] were randomised to budesonide/formoterol (B/F 320/9μg bid) or placebo (P) via Turbuhaler®. Exacerbations, dropouts and a composite of the two outcomes were examined over the first 3 months of treatment.



Results: 1583 COPD patients were studied (24% moderate; 61% severe, 14% very severe). B/F improved time to first exacerbation in moderate and severe but not very severe COPD ($HR_{B/F/P}$: 0.43 [95% CI 0.25–0.72], 0.45 [0.33–0.63] and 0.58 [0.32–1.05]) vs. P.
Time to dropout was improved by B/F vs. P, the differences being larger with increasing COPD severity ($HR_{B/F/P}$: 0.62 [0.34–1.11], 0.56 [0.39–0.81] and 0.38 [0.18–0.80]). A composite measure of time to first exacerbation or dropout showed a significant effect of B/F in all severities.
Conclusions: Differential study dropout (greater with P than B/F) increased as the severity of COPD worsened. This should be considered when interpreting clinical COPD trial data.
References:
[1] Calverley et al.*ERJ*2003;22:912–9.
[2] Szafranski et al.*ERJ*2003;21:74–81.
[3] Welte et al.*AJRCCM*2009;180:741–50.

P2878

A randomized, crossover study to examine the pharmacodynamics and safety of a new antimuscarinic (TD-4208) in COPD

Peter Potgieter[1], Alan Hopkins[1], Phillip Liu[1], Dean Quinn[2], Craig Amburgey[1], Edmund Moran[1]. *[1]Research and Development, Theravance Inc., South San Francisco, CA, United States; [2]Wellington Research Unit, P3 Research, Wellington, New Zealand*

Background: TD-4208 is a potent and selective inhaled muscarinic antagonist with functional lung selectivity and long duration in preclinical models of bronchoconstriction.
Aims: To investigate the bronchodilatory profile, safety and tolerability of nebulized TD-4208 in patients with COPD.
Methods: Thirty-two patients aged 45-75 years with moderate or severe COPD were randomized in a double blind, complete 4-way crossover study. Single doses of 350 μg or 700 μg TD-4208, ipratropium (500 μg) or placebo were administered using a PARI LC Plus nebulizer in each period. Baseline and serial post-dose spirometry assessments (0-25 hrs) were performed. Safety evaluation included AEs, vital signs, ECGs, and clinical lab results.
Results: A statistically significant improvement in peak FEV1 versus placebo of 174 mL (95% CI: 112, 235), 169 mL (95% CI: 108, 231) and 176 mL (95% CI: 114, 237), for TD-4208 350 μg, 700 μg, and ipratropium, respectively, was observed ($p<0.001$ for each comparison). Similar to ipratropium, onset of action of TD-4208 was rapid and bronchodilation was sustained over the 25-hr monitoring period. FEV1 difference from placebo at 12 hrs was 112.5 mL, 123.4 mL, and 15.3 mL; $p<0.001$; <0.001 and 0.669, and at 24 hrs was 102.8 mL, 136.6 mL, and -24.2 mL; $p<0.001$; <0.001 and 0.327, for TD-4208 350 μg, 700 μg, and ipratropium, respectively. AEs were generally mild and occurred with similar frequencies in all groups, with the most common being headache and dyspnea. No SAEs occurred.
Conclusions: TD-4208 was well tolerated and demonstrated significant peak bronchodilation with rapid onset that was sustained over 24 hrs suggesting a once daily dosing regimen.

P2879

Association of β_2-adrenoreceptor genotypes with prevention of COPD exacerbations by tiotropium or salmeterol in the POET-COPD® trial

Harald Koegler[1], Klaus F. Rabe[2], Kai M. Beeh[3], Thomas Glaab[1], Hendrik Schmidt[4], Leonardo M. Fabbri[5], Claus Vogelmeier[6]. *[1]Medical Affairs Germany, Boehringer Ingelheim, Ingelheim, Germany; [2]Center of Pulmonary Diseases and Thoracic Surgery, Hospital Grosshansdorf, Germany; [3]Insaf, Respiratory Research Institute, Wiesbaden, Germany; [4]Biometrics and Data Management, Boehringer Ingelheim, Ingelheim, Germany; [5]Department of Oncology Haematology and Respiratory Diseases, University of Modena & Reggio Emilia, Modena, Italy; [6]Division for Pulmonary Diseases, Hospital of the Universities of Giessen and Marburg, Marburg, Germany*

Background: β_2-adrenoreceptor (ADRB2) polymorphisms are found at positions B16 (G16R) and B27 (Q27E). The POET-COPD® trial allowed assessing the effects of these polymorphisms on exacerbations in patients treated with tiotropium (Tio) or salmeterol (Sal).
Methods: RCT comparing Tio 18 μg qd vs Sal pMDI 50 μg bid over 1 y. 7376 COPD patients aged ≥40 y, with a smoking history ≥10 pack-y, postBD FEV_1 ≤70% pred., FEV_1/FVC ratio ≤0.7, ≥1 exacerbation in past year.
Results: Genotype distribution and baseline characteristics of 5125 patients (69.5%) (Tio 2564; Sal 2561) who consented to genotyping were balanced between groups. Exacerbations in the Tio group were unaffected by B16 or B27 genotypes. While B27 did not affect Sal outcomes, B16 significantly modified the efficacy of Sal: The fraction of patients with ≥1 exacerbation was 32.3% in R16R, 39.8% in G16R, and 42.1% in G16G carriers (log rank *P*-values vs R16R: 0.0130 and 0.0018, respectively). Among R16R carriers, exacerbation risk was similar between groups, while for G16G and G16R, Tio was more effective than Sal.
Conclusions: In R16R carriers (16.5% of patients), Sal prevented exacerbations as effectively as Tio. In the majority of patients (83.5%), Tio was superior to the

ADRB2	Tio %	Sal %	HR (95% CI) Tio vs Sal	Treatment by genotype interaction
G16G	37	37	0.76 (0.66, 0.88)	
G16R	46	47	0.83 (0.73, 0.95)	P=0.0381
R16R	17	16	1.08 (0.86, 1.37)	
Q27Q	34	32	0.86 (0.73, 1.01)	
Q27E	46	48	0.85 (0.75, 0.97)	P=0.7312
E27E	20	20	0.78 (0.64, 0.95)	

β_2-AR agonist due to the limited benefit from the latter in G16G or G16R patients, while Tio was equally efficacious in all B16 genotypes.
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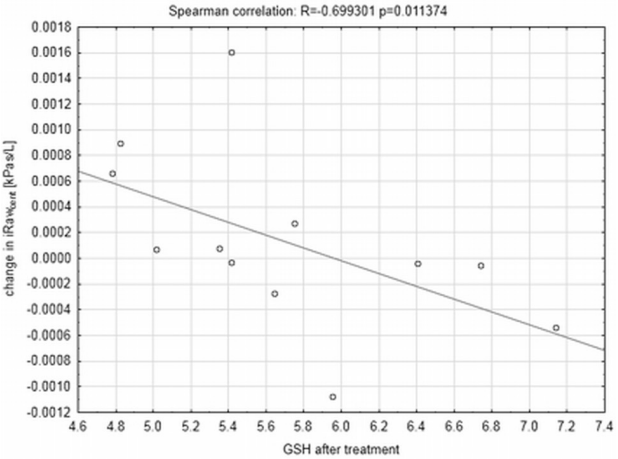
P2880

Effects of high dose N-acetylcysteine in COPD patients

Wilfried De Backer[2], Cedric Van Holsbeke[1], Anna Sadowska[2], Jan De Backer[1], Rita Claes[2], Wim Vos[1]. *[1]Respiratory, FluidDA nv, Kontich, Belgium; [2]Respiratory Medicine, University Hospital Antwerp, Edegem, Belgium*

Aim: Studies suggest that NAC can reduce inflammation and hyperinflation in COPD patients, but little data is published about effects of high dose NAC (3x600mg daily) on airway remodeling. Since hdNAC may induce high levels of GSH, this study focuses on the effect of hdNAC on airway structure/function in relation to GSH.
Method: A double blind randomized placebo-controlled 2way crossover pilot study in 12 GOLDII patients was performed. Patients were treated twice for 3m with either hdNAC or placebo (provided by Zambon S.p.A.) on top of their usual medication according to GOLD guidelines. Respiratory functional imaging (RFI) was used to assess airway volume (iVaw) and resistance (iRaw) (De Backer et al. Radiol. 2010;257(3):854-862). Data was collected at baseline and after both treatment periods.
Result: A clear drop in iRaw is seen in patients with a higher anti-oxidant reserve (i.e. low baseline GPx) despite lack of overall improvement in the entire population. This drop in iRaw is observed in patients that were already treated according to GOLD criteria.



Conclusion: For the first time reduction in iRaw caused by anti-oxidant mucolytic drug is shown using highly sensitive RFI methods. It would be interesting to study in a larger population whether this indicates recovery of the β-receptor sensitivity subject to oxidative impairment. The results demonstrate the potential of using RFI to assess anti-inflammatory characteristics of existing and newly developed compounds.

P2881

Acute effect of erdosteine on preventing recurrence of exacerbation in COPD patients after hospital discharge

Maurizio Moretti[1], Maria Ballabio[2]. *[1]Respiratory Medicine, ASL1 di Massa e Carrara, Carrara, Italy; [2]Medical Department, Edmond Pharma, Paderno Dugnano, Italy*

Introduction: Acute exacerbations of chronic obstructive pulmonary disease (AECOPD) are frequent cause of hospital admission and associated to high risk of recurrence. Preventing exacerbations is a key treatment goal.
Objectives: To evaluate the effect of erdosteine, an anti-oxidant mucolytic agent, given on acute setting during hospitalization for severe AECOPD to prevent subsequent recurrence of exacerbations.
Methods: 15 COPD patients hospitalized for severe AECOPD randomly received erdosteine 900mg daily or placebo for 10 days in combination with standard treatment. Recurrence of exacerbations after hospital discharge was assessed at 30 and 60 days. Data were correlated to pulmonary function indices and serum C-reactive protein (CRP) measured at 10 and 30 days after hospitalization.
Results: Table 1. The mean exacerbation recurrence was significantly higher ($p<0.05$) in the placebo group. The recurrence of exacerbation was inversely correlated to FEF25-75% value at 10d ($p<0.05$), 30d ($p<0.05$) and positively correlated to serum CRP marker of systemic inflammation at 10d ($p<0.05$) and 30d ($p<0.05$).

Table 1

Treatment	CRP, mg/100ml		FEF25–75%, mL/sec		No. exacerbations	
	10 d	30 d	10 d	30 d	30 d	60 d
Erdosteine	0.38	0.29	619	811	0	0.25*
Placebo	1.36	0.67	375	472	0	1.14

Data are mean values. *$p<0.05$ vs. placebo.

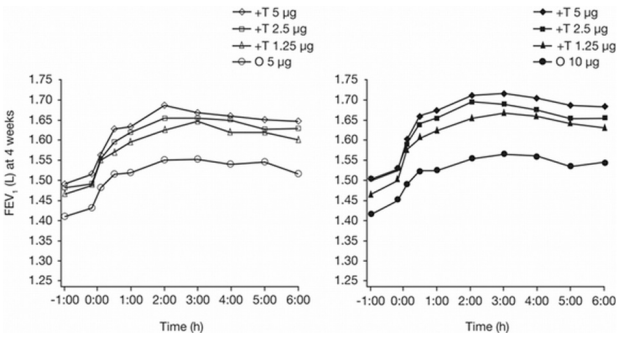
Conclusions: Treatment with erdosteine plus standard therapy in severe AECOPD reduced their early recurrence after hospital discharge. These results were related to improvement in small airway obstruction and decrease of serum CRP at recovery from AECOPD. Mucolytic agents with relevant antioxidant activity may improve clinical outcome after AECOPD by reducing the burst of airway inflammation.

P2882

Dose-finding study for tiotropium and olodaterol when administered in combination via the Respimat® inhaler in patients with COPD

René Aalbers[1], M. Reza Maleki-Yazdi[2], Alan Hamilton[3], Stella Waitere-Wijker[4], Anna Pivovarova[5], Olaf Schmidt[6], Leif Bjermer[7]. *[1]Department of Pulmonary Disease, Martini Hospital, Van Swietenplein 1, Groningen, Netherlands; [2]Division of Respiratory Medicine, Women's College Hospital, University of Toronto, ON, Canada; [3]Boehringer Ingelheim, Burlington, Ontario, Canada; [4]Boehringer Ingelheim bv, Comeniusstraat 6, Alkmaar, Netherlands; [5]Boehringer Ingelheim, Pharma GmbH and Co. KG, Biberach, Germany; [6]Lungen- und Bronchialheilkunde, Emil-Schüller-Straße 29, Koblenz, Germany; [7]Department of Respiratory Medicine and Allergology, Skåne University Hospital, Lund, Sweden*

Background: The novel long-acting β_2-agonist olodaterol (O) and long-acting muscarinic antagonist tiotropium (T) have a duration of action of at least 24 h in clinical studies. Dual administration may provide improved bronchodilation with convenient once-daily dosing.
Objective: To determine the optimum once-daily combination of T+O delivered via the Respimat® inhaler in patients with COPD.
Methods: In a randomised, double-blind, 4-period, incomplete crossover study, patients with post-bronchodilator forced expiratory volume in 1 second (FEV_1) of ≥30% and <80% of predicted normal received combinations of T and O, with both agents delivered via separate Respimat® inhalers, as well as O monotherapy,



once daily for 4 weeks (NCT 01040403). The primary end point was trough FEV_1 response (L) at the end of week 4.
Results: In total, 232 COPD patients (133 male; 99 female) received treatment. FEV_1 responses (trough and up to 6 h post-dose) for O 5 and 10 μg monotherapy were similar. For all doses of T, FEV_1 responses were significantly increased when added to O 5 and 10 μg. Dose ordering for T when added to O was evident. No safety or tolerability concerns were identified.
Conclusions: Addition of T to O resulted in significant improvements in FEV_1 versus O alone. These data support further investigation of T 2.5 and 5 μg combined with O 5 μg in the Phase III T+O clinical trial programme.

P2883
Anti-inflammatory effects of add-on atorvastatin therapy during the treatment of COPD patients
Robert Mroz[1], Agnieszka Tycinska[2], Pawel Lisowski[3], Joanna Bierla[4], Lukasz Minarowski[1], Robert Milewski[5], Anna Lisowska[2], Piotr Boros[6], Elzbieta Chyczewska[1], William MacNee[7]. *[1]Department of Lung Diseases and Tuberculosis, Medical University of Bialystok, Poland; [2]Department of Cardiology, Medical University of Bialystok, Poland; [3]Department of Molecular Biology, Institute of Genetics and Animal Breeding, Jastrzebiec n/Warsaw, Poland; [4]Department of Physiology and Pathophysiology, Medical University of Warsaw, Poland; [5]Department of Statistics and Medical Informatics, Medical University of Bialystok, Poland; [6]Lung Function Laboratory, National Institute of Tuberculosis and Lung Diseases, Warsaw, Poland; [7]ELEGI Colt Research Labs, UoE/MRC Centre for Inflammation Research, The Queen's Medical Research Institute, Edinburgh, United Kingdom*

We have performed a parallel group study to compare the effects of Atorvastatin 40mg once daily for 3 months (n=13) or placebo (n=5) as an add-on treatment to Formoterol therapy in 18 patients with mild to moderate COPD (mean FEV1% predicted 59.58±SD 20.43 and 50.4±SD 11.55 for study group and control respectively). Fiberoptic bronchoscopy and transbronchial lung biopsy (TBB) was carried out at baseline and after 3 months of treatment. Twelve subjects, (11 male, 1 female, mean age 64.58 ± SD 7.03 and Control: 5 males, mean age 68.4± SD 6.5 completed the study. TBB specimens were processed for: microarrays and immunohistochemistry. Patients had spirometry, lung volumes, SGRQ, 6MWD, serum lipids and hs-CRP measured before and after treatment.
Results: After therapy symptoms measured by SGRQ and 6MWD significantly improved within study group. There was no significant change in FEV1 nor lung volumes. In TBB there was a significant decrease in inflammatory cells numbers (CD45+ cells decreased from 62,51 to 27.01% before and after treatment within study group (p=0,008) and in comparison to placebo 27.01 vs 50,05 (p=0,002). Gene expression profiling revealed over 600 genes that met the criteria for differential expression (logFC>0.05, p<0.05). Atorvastatin therapy had a significant impact on gene expression in lung tissue of atorvastatin treated patients, mainly by downregulation of genes involved in inflammatory pathways.
Conclusion: These data indicate that atorvastatin may have potential beneficial effects in COPD patients through an anti-inflammatory mechanism.

P2884
An audit of oxygen prescribing practices in a district general hospital
Anna Szulc[1], Richard Berry[1], S. Fayyaz Hussain[2]. *[1]Medical School, Leicester University, Leicester, United Kingdom; [2]Respiratory Care Consultant, Kettering General Hospital, Kettering, United Kingdom*

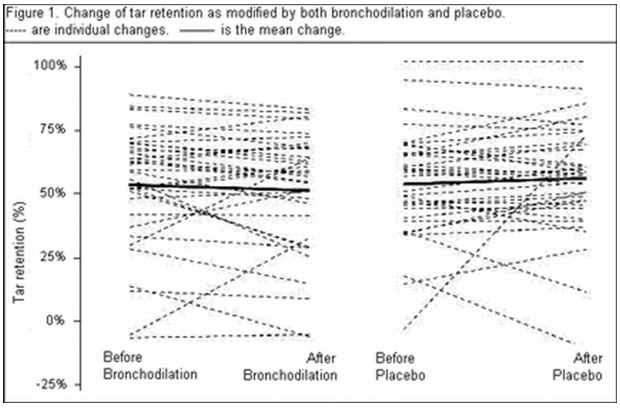
Introduction: Oxygen is a drug and should be prescribed. Yet the attitudes about oxygen prescription are extremely different to that of other prescription only medications. We wished to evaluate that a) correct prescription was filled out for patients receiving oxygen in hospital and b) in patients with COPD oxygen saturation (SpO2) was maintained at 88-92%(1).
Methods: On a single day in January 2012 all patients on 14 wards (medical and surgical) were observed for supplemental oxygen therapy. All patients receiving oxygen therapy had their prescription charts and clinical notes assessed for quality of the oxygen prescription and presence of COPD.
Results: Out of a total of 259 patients seen, 51 (19.6%) were on oxygen. Of these 21 (41%) patients had the oxygen prescribed correctly. Thirteen patients were diagnosed to have COPD; in 6 (46%) the actual bedside oxygen saturations matched the correct safe target set by BTS guideline, but in only 3 (23%) the target oxygen saturations was correctly specified.
Conclusions: This audit highlights significant gaps in oxygen prescribing in secondary care. Almost half of COPD patients receiving supplemental oxygen remain at risk of oxygen toxicity. Education of doctors and nurses on oxygen prescription should be reinforced regularly.
Reference:
[1] BTS guideline for emergency oxygen use in adult patients. B R O'Driscoll et al. British Thoracic Society. Thorax 2008;63(Suppl VI):vi1–vi68.

P2885
Once-daily NVA237 reduces exacerbations and improves symptoms in COPD patients: A pooled analysis 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 a safe and effective once-daily (QD) inhaled long-acting muscarinic antagonist for the maintenance treatment of COPD.
Methods: This is a pooled analysis of the GLycopyrronium bromide in COPD airWays clinical studies (GLOW1 and 2) which assessed the efficacy of NVA237 50μg QD vs placebo (PBO) and open-label tiotropium 18 μg QD (TIO) over 26 to 52 wks in COPD patients. Results include exacerbations, symptoms (transition dyspnea index [TDI]) and Health Status (St George's Respiratory Questionnaire [SGRQ]).
Results: 1854 patients were analyzed (NVA237=1059, TIO=267, PBO=528). NVA237 statistically significantly prolonged the time to first moderate/severe exacerbation vs PBO (Wk 26: hazard ratio [HR] 0.64; Wk 52: HR 0.67, both p<0.001), which was comparable to TIO (Wk 26: HR 0.70, p=0.026; Wk 52: HR 0.61, both p<0.001). NVA237 had a statistically significantly lower rate of moderate/severe exacerbations vs PBO (Wk 26: rate ratio [RR] 0.66; Wk 52: RR 0.66; both p<0.005), while TIO was not significantly different from PBO (Wk 26; RR 0.74, p=0.085 and Wk 52: RR 0.80, p=0.179). Treatment difference in TDI total score was significant for NVA237 (Wk 26: 0.93 and Wk 52: 0.57) and TIO (Wk 26: 1.05 and Wk 52: 0.66) vs PBO, all p<0.05. SGRQ score (LS Mean [SE]) was significant for NVA237 (Wk 26; -3.07 [0.683] and Wk 52; -3.32 [1.004]; p<0.001) and TIO (Wk 26; -2.43 [1.014] and Wk 52; -2.84 [1.155]; p<0.05) vs PBO.
Conclusion: NVA237 once daily significantly reduced COPD exacerbations and improved symptoms vs PBO over 52 wks. Overall, the effects of NVA237 were similar to tiotropium.

P2886
Cigarette smoke retention and bronchodilation in patients with COPD: A controlled randomized trial
Wouter van Dijk[1], Yvonne Heijdra[2], Jacques Lenders[3,4], Walther Klerx[5], Reinier Akkermans[1], Anouschka van der Pouw[7], Chris van Weel[1], Paul Scheepers[6], Tjard Schermer[1]. *[1]Department of Primary and Community Care, Radboud University Nijmegen Medical Centre, Nijmegen, Netherlands; [2]Department of Pulmonary Diseases, Radboud University Nijmegen Medical Centre, Nijmegen, Netherlands; [3]Department of Internal Medicine, Radboud University Nijmegen Medical Centre, Nijmegen, Netherlands; [4]Department of Internal Medicine III, University Hospital Carl Gustav Carus, Dresden, Germany; [5]Chemics, Food and Consumer Product Safety Authority, Eindhoven, Netherlands; [6]Department of Epidemiology, Biostatistics and HTA, Radboud University Nijmegen Medical Centre, Nijmegen, Netherlands; [7]Department of Pulmonary Diseases, Alysis Medical Centre, Arnhem, Netherlands*

Many COPD patients use bronchodilators while continuing cigarette smoking. We hypothesized that these agents interact with cigarette smoking and hence affect the risk to develop smoking-related (cardiovascular) disease. In this study we explored if bronchodilation increases pulmonary retention of cigarette smoke and smoking-related biomarkers in patients with COPD.
Methods: We performed a double-blinded, placebo-controlled, randomized crossover trial. COPD patients smoked cigarettes during undilated conditions at one session and maximal bronchodilated conditions at the other session. Cigarette smoke was measured by pulmonary proportional retention of tar and nicotine. Secondary outcomes included smoke inhalation patterns, and the biomarkers C-reactive protein and fibrinogen. We excluded measurements with possible contamination in a secondary analysis.



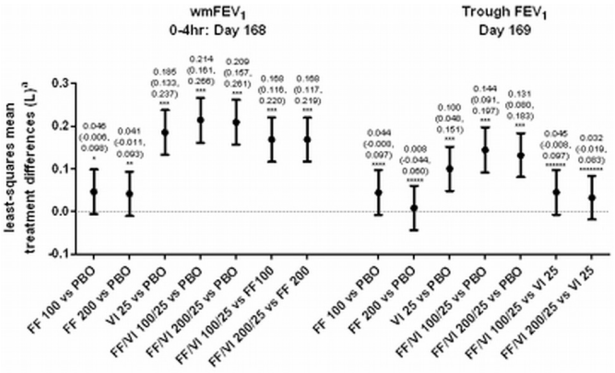
Results: In 35 patients analyzed, bronchodilation did not significantly increase tar retention (-4.5%, p=0.20), or nicotine retention (-2.6%, p=0.11).
Bronchodilation did not significantly affect our secondary outcomes. Secondary analysis revealed potentially less retention due to bronchodilation: tar retention -3.8% (p=0.13), and nicotine retention -3.4% (p=0.01).
Conclusions: Our results do not support the hypothesis that bronchodilation increases cigarette tar and nicotine retention in COPD patients. Instead, we observed a possibility for less retention.

P2887

Lung function effects and safety of fluticasone furoate (FF)/vilanterol (VI) in patients with COPD: Mid-high dose assessment

Fernando Martinez[1], Joseph Boscia[2], Gregory Feldman[3], Catherine Scott-Wilson[4], Sally Kilbride[5], Leonardi Fabbri[6], Peter M.A. Calverley[7], Courtney Crim[4]. *[1]Department of Medicine, University of Michigan, Ann Arbor, United States; [2]Clinical Research, CU Pharmaceutical Research, Union, United States; [3]Clinical Research, S. Carolina Pharmaceutical Research, Spartanburg, United States; [4]Respiratory Medicine Development Center, GlaxoSmithKline, Research Triangle Park, United Kingdom; [5]Department of Oncology Haematology and Respiratory Diseases, University of Modena & Reggio Emilia, Modena, Italy; [6]Clinical Science Centre, University Hospital Aintree, Liverpool, United Kingdom*

Rationale: FF/VI is a novel once-daily (OD) inhaled corticosteroid/long-acting beta$_2$ agonist in development as combination therapy for COPD.
Objective: To evaluate the efficacy and safety of FF/VI (200/25 and 100/25) vs placebo (PBO), FF (200 and 100mcg) and VI (25mcg), given OD via novel dry powder inhaler in moderate-severe COPD patients for 168 days.
Methods: A multicentre, randomised, PBO-controlled, double-blind, parallel-group study (N=1224 (ITT)). Co-primary endpoints: weighted mean (wm) FEV$_1$ 0–4h (Day 168) to assess the contribution of VI, and trough FEV$_1$ (Day 169) to assess the contribution of FF and 24h duration of VI. Additional endpoints included CRQ-SAS dyspnoea, and safety.
Results: Co-primary endpoints, see Figure. Treatment differences from PBO for dyspnoea scores were -0.12, -0.01, 0.07, 0.24 and 0.10 for FF 100, 200, VI 25, FF/VI 100/25, 200/25, respectively. On-treatment AEs were similar between active treatment groups (38–47%) and PBO (47%). No treatment effects on 24h urinary cortisol, laboratory values, or cardiac monitoring parameters were seen.



* p=0.085, ** p=0.123, *** p<0.001, **** p=0.095, ***** p=0.756, ****** p=0.093, ******* p=0.224. a - In order to account for multiplicity across treatment comparisons and key endpoints, a step-down testing procedure was applied , whereby inference for a test in the pre-defined hierarchy is dependent upon statistical significance having been achieved for the previous tests in the hierarchy. Endpoints were assessed in the order VI 25 vs PBO, FF/VI 200/25 vs PBO, FF/VI 200/25 vs FF 200 for wmFEV$_1$ and VI 25 vs PBO, FF/VI 200/25 vs PBO, FF/VI 200/25 vs VI 25 for trough FEV$_1$ then the same comparisons for lower dose. Inference for secondary endpoints required significance at <0.05 for the primary endpoint at that dose.

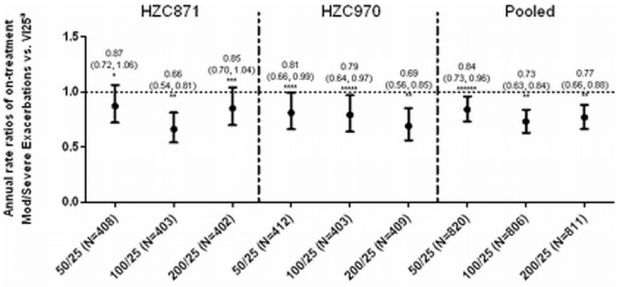
Conclusion: Addition of VI to FF produced a clinically significant improvement in wmFEV$_1$ (0-4h). Addition of FF to VI provided numerical improvements only in trough FEV$_1$. FF/VI at both strengths was superior to PBO for both primary endpoints. All treatments were well tolerated.
Funded by GSK (HZC112207; NCT01054885).

P2888

Efficacy of the novel inhaled corticosteroid, fluticasone furoate (FF)/long-acting beta$_2$-agonist, vilanterol (VI) combination in reducing COPD exacerbations

Mark T. Dransfield[1], Peter M.A.C. Calverley[2], Jean Bourbeau[3], Paul Jones[4], Nick A. Hanania[5], Doug A. Mahler[6], Jørgen Vestbo[7], Andrew Wachtel[8], Fernando Martinez[9], Frank Barnhart[10], Lisa Sanford[11], Sally Lettis[11], Courtney C. Crim[10]. *[1]Division of Pulmonary, Allergy and Critical Care Medicine, University of Alabama at Birmingham, AL, United States; [2]Clinical Science Centre, University of Liverpool, United Kingdom; [3]Medicine, McGill University, 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, Dartmouth Medical School, Hanover, United States; [7]Respiratory Research Group, Manchester Academic Health Sciences Centre, Manchester, United Kingdom; [8]Pulmonary Medicine, Cedars-Sinai Medical Center, Ann Arbor, MI, United Kingdom; [9]Department of Internal Medicine, University of Michigan, Ann Arbor, United Kingdom; [10]Respiratory Medicine Development Center, GlaxoSmithKline, Research Triangle Park, United States; [11]Quantitative Sciences Division, GlaxoSmithKline, Uxbridge, United Kingdom*

Introduction: FF/VI is in development as once-daily (OD) combination therapy for COPD.
Objectives: Assess effect of FF/VI on exacerbation rates in COPD compared to VI. Safety is described separately.
Methods: In two replicate 1 year studies (HZC871;N=1622,HZC970;N=1633), 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 was the annual rate of moderate/severe exacerbations (MSE). Secondary efficacy endpoints included time to first 1st MSE and trough FEV$_1$.
Results: Rate ratios (95%CI) for MSE with FF/VI vs VI (by-study & pooled data) are shown (Figure). There was a reduction in risk in time to 1st MSE vs VI (p≤0.036) for FF/VI 200/25 (HZC970 & pooled) and 100/25mcg (all). Trough FEV$_1$ vs VI at week 52 was greater (p≤0.011) for all FF/VI strengths in HZC871 (50/25=41mL, 100/25=58mL, 200/25=64mL) and pooled data (50/25=38mL, 100/25=42mL, 200/25=46mL) but for 50/25 only (34 mL, p=0.034) in HZC970.



* p=0.181, ** p<0.001, *** p=0.109, **** p=0.040, ***** p=0.024, ****** p=0.014, ratios calculated against moderate/severe exacerbation rates observed with VI in study 871 (N=409), 970 (N=409) and pooled data (N=818) a - In order to account for multiplicity across treatment comparisons and key endpoints, a step-down testing procedure was applied , whereby inference for a test in the pre-defined hierarchy is dependent upon statistical significance having been achieved for the previous tests in the hierarchy. Order of testing: FF/VI 200/25 vs. VI 25, FF/VI 100/25 vs. VI 25, FF/VI 50/25 vs. VI 25. Inference for secondary endpoints required significance at <0.05 for the primary endpoint at that dose

Conclusions: Addition of FF to VI reduced the annual rate of MSE and time to onset of 1st MSE, with evidence of a consistent effect of the 100/25mcg strength in individual studies and the pooled analysis. Lung function improved at all strengths of FF/VI vs VI in pooled analysis. The safety of the combination is reported separately.
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Efficacy of combination fluticasone furoate/vilanterol (FF/VI) and salmeterol/fluticasone propionate (SFC) over 12 weeks in patients with COPD

Alvar Agusti[1], Wilfried De Backer[2], Luis de Teresa[3], Michael Zvarich[4], Nick Locantore[4], Neil Barnes[5], Jean Bourbeau[6], Courtney Crim[4]. *[1]Thorax Institute, Hospital Clinic, University of Barcelona, Spain; [2]Respiratory Medicine, University of Antwerp, Wilrijk, Belgium; [3]Internal Medicine, Clinica Mediterranea de Neurociencias, Alicante, Spain; [4]Respiratory Medicine Development Center, GlaxoSmithKline Inc, Research Triangle Park, NC, United States; [5]Respiratory Medicine, Barts and the London NHS Trust, London, United Kingdom; [6]Medicine, McGill University Health Centre, Montreal, QC, Canada*

Introduction: The novel combination of FF, an inhaled corticosteroid and VI, a long-acting beta$_2$ agonist, is under development as a once-daily (OD) therapy for COPD and asthma.
Objectives: To compare the efficacy of OD FF/VI and twice-daily (BD) SFC in moderate-to-severe COPD.
Methods: In a randomised, double-blind, double-dummy, parallel-group study, COPD patients (mean post-bronchodilator %predicted FEV$_1$ = 48%) received FF/VI 100/25mcg OD AM (N=266) via a novel dry powder inhaler or SFC 50/500mcg BD (N=262) via DISKUS™. Primary efficacy: change from baseline in 0–24h weighted mean (wm) FEV$_1$. Secondary endpoints included time to 100mL FEV$_1$ improvement over baseline on Day 1 (speed of onset), SGRQ-C; safety endpoints included adverse events (AEs).
Results: There were non-significant trends favouring FF/VI (130mL) versus SFC (108mL) for wmFEV$_1$ (22ml [95%CI: –18,63], p=0.282) and speed of onset; FF/VI=16min, SFC=28min (p=0.280). A clinically meaningful improvement (–4.8) in SGRQ-C score was seen with FF/VI, but not SFC (–3.3), though the difference (–1.5 [95%CI: –3.9, 0.9]) was not statistically significant (p=0.215). Both treatments were well tolerated. 3 (1%) and 6 (2%) patients in the FF/VI and SFC arms experienced serious AEs; the same numbers withdrew as a result of on-treatment AEs. Safety profiles, including pulse rate, were similar.
Conclusions: OD FF/VI and BD SFC improved lung function in patients with moderate-to-severe COPD without substantial safety concerns. Primary and sec-

ondary efficacy outcomes were numerically but not statistically superior for FF/VI vs SFC.
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P2890

Effects of twice-daily aclidinium bromide in COPD patients: A long-term extension of ACCORD-COPD I

Anthony D'Urzo[1], Edward Kerwin[2], James Donohue[3], Stephen Rennard[4], Arthur Gelb[5], Hassan Lakkis[6], Esther Garcia Gil[7], Cynthia Caracta[8].
[1]Department of Family & Community Medicine, University of Toronto, Canada; [2]Clinical Research Institute, Medford, United States; [3]Department of Medicine, University of North Carolina, Chapel Hill, United States; [4]Department of Internal Medicine, University of Nebraska Medical Center, Omaha, United States; [5]Southern California Clinical Trials, Lakewood, United States; [6]Biostatistics, Forest Research Institute, Jersey City, United States; [7]R&D Centre, Almirall, S.A., Barcelona, Spain; [8]Clinical Development, Forest Research Institute, Jersey City, United States

Introduction: The long-term effects of twice-daily (BID) aclidinium 200 μg and 400 μg were assessed in patients with moderate-to-severe COPD.
Methods: In this 52-week, double-blind, extension study, COPD patients on aclidinium 200 μg or 400 μg BID during the 12-week lead-in continued the same treatment while patients in the placebo group were re-randomized (1:1) to aclidinium 200 μg or 400 μg BID. Baseline was prespecified as Visit 2 of the lead-in study. Spirometry, SGRQ, and adverse events (AEs) were assessed.
Results: A total of 467 patients completed the lead-in study and 291 patients volunteered for the extension study. At study end, placebo patients re-randomized to aclidinium 400 μg and those on either dose of continuous aclidinium treatment showed improvements from baseline in trough FEV_1. All groups showed improvements from baseline in SGRQ Total score (range, 4.85-7.92 point improvement). The percentages of patients with an AE were similar for both doses. Incidence of anticholinergic AEs was low and similar for both groups; dry mouth occurred in 1 patient (400 μg). The incidence of cardiac AEs was low across treatments (<5%, any event) and did not occur in a dose-related manner. The incidence of serious AEs (SAE) was comparable in the 200 μg (14.6%) and 400 μg (13.2%) groups; the most frequently reported SAE was COPD exacerbation. One patient from each treatment group died during the study and both deaths were deemed unrelated to treatment.
Conclusions: Patients continuing long-term treatment with aclidinium 200 μg or 400 μg BID maintained improvements in lung function and health status compared to baseline. Aclidinium was well tolerated throughout this 1-year extension study.

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Pooled analysis of twice-daily aclidinium bromide in COPD patients: Dyspnea and health status in the ACCORD-COPD I and ATTAIN trials

Paul Jones[1], Edward Kerwin[2], Eric Bateman[3], Rosa Lamarca[4], Cynthia Caracta[5], Esther Garcia Gil[6]. *[1]Division of Clinical Sciences, St. George's University, London, United Kingdom; [2]Clinical Research Institute, Medford, United States; [3]Respiratory Medicine, University of Cape Town Lung Institute, Cape Town, South Africa; [4]Clinical Statistics, Almirall, S.A., Barcelona, Spain; [5]Clinical Development, Forest Research Institute, Jersey City, United States; [6]R&D Centre, Almirall, S.A., Barcelona, Spain*

Introduction: Aclidinium is a novel, long-acting muscarinic antagonist in development for COPD treatment. Pooled analyses of dyspnea and health status data are shown here.
Methods: Patients (N=1389) were randomized (1:1:1) to aclidinium 200 μg, 400 μg or pbo BID for 12- and 24-weeks for the ACCORD and ATTAIN trials, respectively. Endpoints for both studies included TDI focal score, SGRQ total score and rescue medication use.
Results: The 200 μg and 400 μg groups showed statistically significant improvements from baseline to Week 12 in TDI focal score vs pbo (200 μg, 0.58, $p<0.01$; 400 μg, 0.92, $p<0.0001$), with numerically greater improvements seen with the higher dose. Clinically significant improvements (≥1-unit increase) in TDI at Week 12 were seen in a significantly higher proportion of patients in the 200 μg (51.3%, p=0.0001) and 400 μg (54.8%, $p<0.0001$) groups vs pbo (38.8%). Both doses resulted in statistically significant improvements from baseline to Week 12 in SGRQ total score vs pbo (200 μg, -5.10; 400 μg, -5.51, both $p<0.0001$). Clinically significant improvements (≥4-unit decrease) in SGRQ total score were seen in a significantly higher percentage of patients in the 200 μg (51.0%) and 400 μg (51.8%) groups (both $p<0.001$) vs pbo (38.1%) at Week 12. Both doses of aclidinium resulted in a significant reduction over pbo in daily rescue medication use (-0.6 puffs, 200 μg; -0.9 puffs, 400 μg; both $p<0.005$).
Conclusions: Aclidinium 200 μg and 400 μg BID resulted in significantly more COPD patients who experienced clinically meaningful benefits in dyspnea and health status (>12% more in every case) as well as less rescue medication use versus placebo.

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Twice-daily aclidinium bromide in COPD patients: A pooled analysis of lung function in the ACCORD-COPD I and ATTAIN trials

Edward Kerwin[1], Paul Jones[2], Anthony D'Urzo[3], Ludmyla Rekeda[4], Esther Garcia Gil[5], Cynthia Caracta[6]. *[1]Clinical Research Institute, Medford, United States; [2]Division of Clinical Sciences, St. George's University, London, United Kingdom; [3]Family & Community Medicine, University of Toronto, Canada; [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 is a novel, long-acting muscarinic antagonist being investigated for maintenance treatment of COPD. Pooled analyses of lung function data from the ACCORD and ATTAIN trials are presented here.
Methods: Patients (N=1389) were randomized to aclidinium 200 μg, 400 μg, or pbo BID for 12- and 24-weeks for ACCORD and ATTAIN, respectively. Endpoints included change from baseline in FEV_1 over 3h postdose on Day 1 as well as trough and peak FEV_1 at Week 12.
Results: Mean (SD) baseline and % predicted FEV_1 were 1.45 (0.52)L and 50.3 (14.3)L, respectively. Significant improvements in lung function were seen following the first dose, as measured by change from baseline in FEV_1 at 0.5h postdose (first time point assessed) on Day 1 (200 μg, 99 mL; 400 μg, 128 mL; both $p<0.0001$ vs pbo). The lung function improvements seen after the first dose were sustained throughout the study. Both doses resulted in statistically significant improvements from baseline to Week 12 in trough FEV_1; a greater improvement and a clinically significant effect in trough FEV_1 was seen with the higher dose (200 μg, 80 mL; 400 μg, 112 mL; both $p<0.0001$ vs pbo). Mean change from baseline to Week 12 in peak FEV_1 was 167 mL and 191 mL for 200 μg and 400 μg, respectively (both $p<0.0001$ vs pbo), with numerically greater improvements following treatment with the 400 μg vs 200 μg dose at all measured time points from 0.5h to 3h postdose.
Conclusions: Both doses of aclidinium produced significant improvements in lung function in COPD patients, with the 400 μg dose being consistently more effective. Maximal improvements in lung function were seen at Day 1 and were maintained over 12 weeks.

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Long-term efficacy of twice-daily aclidinium bromide in COPD patients: A one-year study

Donald Tashkin[1], Arthur Gelb[2], Barry Make[3], Xiaoyun Zhong[4], Esther Garcia Gil[5], Cynthia Caracta[6]. *[1]Division of Pulmonary & Critical Care Medicine, David Geffen School of Medicine at UCLA, Los Angeles, United States; [2]Southern California Clinical Trials, Lakewood, 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, Spain; [6]Clinical Development, Forest Research Institute, Jersey City, United States*

Introduction: Aclidinium bromide is a long-acting muscarinic antagonist currently under investigation for the long-term maintenance treatment of COPD. In this study, the long-term efficacy and safety of twice-daily (BID) aclidinium 200 μg and 400 μg in moderate-to-severe COPD patients were assessed. The efficacy results are reported here.
Methods: Patients were randomized (1:1) to receive aclidinium 200 μg or 400 μg BID in a double-blind manner. The primary endpoint was change from baseline to Week 52 in trough FEV_1. Other efficacy parameters included change from baseline to Week 52 in peak FEV_1, trough and peak FEV_1 by study visit, normal-

Table

	Aclidinium 200 μg n=310	Aclidinium 400 μg n=290
Baseline values		
FEV_1, L, Mean (SD)	1.44 (0.57)	1.37 (0.61)
FEV_1, % of predicted, Mean (SD)	47.45 (13.93)	45.52 (14.26)
Morning Pre-dose (Trough) FEV_1, change from baseline		
Week 1, L, LSM (SE)	0.064 (0.011)	0.091 (0.012)
Week 24, L, LSM (SE)	0.062 (0.014)	0.101 (0.014)
Week 52, L, LSM (SE)	0.034 (0.015)	0.072 (0.015)
Peak FEV_1 at Week 52, change from baseline, L, LSM (SE)	0.185 (0.015)	0.214 (0.015)
Normalized AUC_{0-3} FEV_1 at Week 52, change from baseline, L, LSM (SE)	0.116 (0.015)	0.144 (0.015)
SGRQ Total Score at Week 52, change from baseline, LSM (95% CI)	-5.3 (-6.8, -3.8)	-5.2 (-6.7, -3.6)
EuroQoL at Week 52, change from baseline, LSM		
Weighted State Health Index	0.01	0.01
VAS	2.6	2.0

L, liters; SD, standard deviation; FEV_1, forced expiratory volume in 1 second; LSM, least squares mean; SE, standard error; AUC_{0-3}, area under the curve from 0-3 hours; SGRQ, St. George's Respiratory Questionnaire; CI, confidence interval; VAS, visual analogue scale

ized FEV_1 AUC_{0-3}, and change from baseline to Week 52 in SGRQ and EuroQol scores.

Results: A total of 605 patients were randomized to this study. Both aclidinium 200 μg and 400 μg BID resulted in improvements from baseline to Week 52 in trough and peak FEV_1 (Table), with numerically larger increases seen with the 400 μg dose. At study end, change from baseline in normalized AUC_{0-3} FEV_1 was also improved for both groups, with greater improvements seen with the higher aclidinium dose (Table). Both treatment groups showed clinically significant improvements in SGRQ Total score and improvements in EuroQoL parameters from baseline to Week 52 (Table).

Conclusions: Treatment with aclidinium 200 μg or 400 μg BID results in benefits in lung function and health status in COPD patients over 1 year.