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Automated ordering of nucleic acid amplification testing leads to significant reduction in airborne infectious isolation for pulmonary tuberculosis

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RATIONALE: Nucleic acid amplification testing (NAAT) has been shown to be an effective alternative to acid fast bacilli (AFB) smear to identify patients with active pulmonary tuberculosis, however its adoption is not widespread. We sought to improve adoption of NAAT testing in by creating an automated order set and evaluated its effect on airborne infectious isolation (AII).

METHODS: We created an order set in our electronic medical record that automatically ordered two sputum collections testing for AFB smear, culture, and NAAT using Xpert MTB/RIF 8 hours apart. We analyzed the results of those tests for the two years before and after implementation. We calculated the earliest possible time to clearance of AII based on two negative NAAT tests or three negative AFB smears. We measured the accuracy of NAAT compared to AFB smear, the time to obtain results for each component of the order set, length of stay, and time on AII. We used parametric and non-parametric independent sample tests to compare the differences between patients who used the order set versus those who did not.

RESULTS: Between May, 2014 and June, 2018, 759 patients were placed on AII and underwent sputum collection to rule out pulmonary tuberculosis. A total of 35 patients (4.6%) tested positive for tuberculosis based on culture, and 129 (17%) tested positive for NTM. There were two patients culture positive for both NTM and TB. The diagnostic performance of NAAT and AFB smear in our sample are detailed in tables 1-4.

Our hospital's microbiology lab processes specimens for multiple facilities, but 630 (83%) of the patients were at the main hospital and included in the analysis of outcomes. An additional 11 patients were excluded due to: being ruled out clinically for tuberculosis, having known pulmonary tuberculosis, or being started empirically on treatment prior to completion of testing.

Of the 619 patients, 321 used the order set and 298 did not. After the introduction of the power plan, it was used 82% of the time.

The mean age was 51.7 years (SD 14), 66% were male, 50% were black, and 38% were Hispanic. The most common diagnoses on admission were: shortness of breath (12.1%), pneumonia (11.6%), cough (10.2%), fever (5.8%), hemoptysis (4.4%), and chest pain (3.7%).

After excluding 23 patients who were diagnosed with tuberculosis based on PCR, there was a significant difference in the earliest possible time to discontinue AII (3.7 SD 2.5 vs 3.1 SD 3.2; Z -3.1, p=0.002), but not in isolation time (4.0 SD 2.7 vs 3.7 SD 2.5), or hospital length of stay (9.3 SD 9.2 vs 9.0 SD 8.3).

CONCLUSIONS: The use of an automated order set for patients undergoing AII has the potential to shorten time to diagnosis and AII. Further analysis of our larger population will clarify the utility of this practice and areas to improve. A single NAAT is a powerful tool to detect contagious, smear positive patients with pulmonary tuberculosis in our population.

Funding: none

SEVEN factors predictive of Severe outcomes in INfluenza (SEVIN) tool

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Introduction: Seasonal influenza continues to be a burden on the healthcare industry with almost 80,000 deaths associated with influenza infection yearly. A validated prognostic tool to predict composite adverse outcomes is not yet available.

Methodology: We conducted a retrospective review of the Hospital Corporation of America (HCA) database from January 2016 to December 2018 selecting for patients in Florida who were admitted for influenza and tested PCR positive. Data analyzed included demographics, comorbidities and routine labs. Adverse outcomes included ICU admission, progression to respiratory failure, septic shock, acute kidney injury, intubation and death. The aim was to identify the seven factors that are most likely associated with adverse outcomes.

Results: A total of 10360 patients were included. The seven most significant factors were age, history of COPD, history of sleep apnea, presence of anemia, acute MI, history of CKD and diagnosis of pneumonia on admission. The strongest correlation was the presence of myocardial infarction on admission. Using logistic regression and likelihood ratios the risk factors were weighted and scored using a point system. The tool was created using 90% of the data and validated with 10% of the data set. The tool validated well with a ROC of .763.

Conclusion: Further analysis is needed to define cut off values for creatine and hemoglobin in anemia and CKD. Individualized analysis of each adverse outcome needs to be carried out and the tool needs to be validated on other populations.

Funding: none

Rising to the challenge: A community hospital experience in creating a dedicated COPD clinic

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Statement of purpose: Acute exacerbations of Chronic Obstructive Pulmonary Disease (AECOPD) have always presented challenges to both pulmonologists and the greater health care system alike^{1,2}. In order to adapt to the harsh realities of thirty day hospital readmissions currently enforced by the Center of Medicare and Medicaid Services (CMS)^{2,3} there has been a recent initiative to establish a more targeted and comprehensive outpatient approach to patients with COPD^{2,4}. The aim of this discussion is to outline our experience in creating a dedicated ambulatory COPD clinic at New York City Hospital.

Statement of methods: Over a 2 year period all patients that were admitted to our hospital were logged into a quality improvement database. Baseline demographics, severity of COPD, compliance with medications, COPD assessment test (CAT) score, and peak inspiratory flows were among the many data points collected. This information was used to identify particular areas of care that would be prioritized in the outpatient setting to help prevent readmissions. A weekly interdisciplinary COPD clinic was established in the fellowship affiliated pulmonary clinic and included palliative care physicians, smoking cessation specialists, physical therapists, respiratory therapists, and pulmonary fellows.

Summary of results: Establishing a new disease specific clinic required first overcoming the hurdles of resource allocation. In our model we were able to work with the faculty of the pulmonary department to make one afternoon clinic session available so that the same resources of our existing clinics could be utilized without incurring an additional cost. Support from the hospital administration was paramount in the acquisition of additional specialty support such as palliative care medicine and tobacco cessation. A clear set of objectives were established which focused on improving quality of life, patient knowledge of their own disease, and decreasing utilization of the Emergency department (ED) and hospital resources. Communication and follow up was enhanced with a specific email for the clinic, a direct phone line connecting the ED, and appointment scheduling privileges were afforded to the ED. Quality measures collected included patient satisfaction, inpatient admission rate, COPD exacerbation rate, and rate of follow up, among others. An additional obstacle encountered during the development of this clinic was establishing relationships and trust with non-faculty pulmonologists whose patients may also benefit from the resources of the clinic, and emphasizing that the COPD clinic is a complementary tool to the services they already provide. Lastly streamlining workflow of the interdisciplinary team involved was also key.

Conclusion: With AECOPD being such a large burden on the health care system, in addition to the penalties enforced by CMS, establishing a targeted and comprehensive approach to reduce readmissions due to this specific disease state is in high demand. In order to meet the needs of our patient population and to help with unburdening our hospital, we have established a dedicated COPD clinic. We hope that in sharing our experience, creating such a clinic may help other centers to achieve the same goal.

Funding: none

Lung cancer risk of patients with asthma-COPD overlap

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Introduction: Chronic obstructive pulmonary disease (COPD) is a well-established independent risk factor for lung cancer. Meta-analyses have shown mixed results about the potential association between asthma and lung cancer. Even less is known about the relationship between Asthma COPD Overlap (ACO) and lung cancer risk. In this study, we used data from the National Lung Cancer Screening Trial (NSLT), a large randomized controlled trial of lung cancer screening, to compare lung cancer risk among patients with ACO vs. COPD and other conditions associated with airway obstruction.

Methods: We studied 13,939 patients, all with at least 30 pack-years of smoking, from the American College of Radiology Imaging Network (ACRIN) subcohort of the NSLT who had baseline pulmonary function testing. Based on spirometry we categorized NLST participants into smokers without airway obstruction, GOLD-Unclassified (GOLD-U, ratio of forced expiratory flow in 1 second over forced vital capacity FEV₁/FVC ≥ 0.7 and FEV₁ <80% predicted), and patients with history of childhood asthma, COPD (FEV₁/FVC <0.7), or ACO (childhood asthma and FEV₁/FVC <0.7). We used Poisson regression to compare adjusted lung cancer risk among these groups.

Results: Unadjusted comparisons showed that patients with ACO (n=208) had an increased risk for lung cancer compared to smokers without airway obstruction (n=6,447), GOLD-U (n=2,547) and asthmatic smokers (n=281; incidence risk ratio [IRR]: 3.23, 95% confidence interval [CI]: 1.93-5.40, 1.73, 95% CI: 1.03-2.92 and 7.58, 95% CI: 2.21-26.0, respectively), and a similar risk for lung cancer compared to COPD (n=4,428; IRR 1.14, 95% CI: 0.69-1.88). Similar results were obtained in models adjusting for lung cancer risk as estimated by the PLCO²⁰¹² model, except that ACO now also had a similar lung cancer risk with GOLD-U (IRR 1.51, 95% CI: 0.83-2.75). Patients with ACO did not differ to patients with COPD or GOLD-U in regards to lung cancer subtype, histological grade, tumor size or clinical stage.

Conclusion: Patients with ACO have an increased independent risk of lung cancer that appears to be similar to those with COPD and higher than the risk of asthmatic smokers. This suggests that asthmatic patients who demonstrate spirometric obstruction on baseline pulmonary function have a clinically substantial lung cancer risk, and should be screened with equal intensity as patients with COPD.

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Pulmonary Function Test Parameters Correlation With Apnea Hypopnea Index in Patients with Obstructive Sleep Apnea

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Purpose: We aimed to assess the association between physiologic and dynamic changes of pulmonary system with the diagnosis of obstructive sleep apnea (OSA) to establish a better understanding of disease process and to improve the diagnosis process.

Methods: We conducted a retrospective cohort study of patients who had pulmonary function test and polysomnography in file in Cleveland Clinic data base. Specifically, we included adult patients 18+ years who underwent PFT and sleep study within one year period and with stable BMI. We excluded patients with diaphragmatic injury, external spine deformities, and any co-Morbidities causing hypoxia. We extracted patient's demographic data as well as reported measures of Expiratory Reserved Volume (ERV), Forced Vital Capacity (FVC), Forced Expiratory Volume (FEV1), Total Lung Capacity (TLC), Diffusion Capacity (DLCO), Vital Capacity (VC), and Apnea Hypopnea Index (AHI). Univariate and multivariate logistic regression model with backward elimination method analysis was conducted to assess the correlation between each of the clinical features and the diagnosis of OSA.

Results: We included a total of, 286 patients (median (range) age = 62.0 (24.0-87.0), of which 163 (57.2%) females, and 122 (42.8%) males) were included in this study. For OSA, Univariate analysis revealed that BMI ≥ 30 ($p < 0.0001$), Age ≥ 54 year ($p = 0.0006$), $HCO_3 \geq 25.5$ mmol/L ($p = 0.0027$), ERV < 0.64 L ($p < 0.0001$), FVC $< 82\%$ ($p = 0.0010$), TLC $< 86\%$ ($p < 0.0001$), VC $< 82\%$ ($p = 0.0192$) were significantly associated with OSA. Using the a cut-off value of 0.64 L determined by ROC and Youden index, ERV had a sensitivity of 78.8% and a specificity of 65.6% to identify OSA. Multivariate logistic regression model showed that BMI, and age were the most important factors associated with OSA. Patients with BMI < 30 were less likely to have OSA compared to patients BMI ≥ 30 (OR = 0.05, 95% CI [0.023, 0.12] $p < 0.0001$); Patients with age < 54 year had lower chance to have OSA compared to patients with age ≥ 54 year (OR = 0.30, 95% CI [0.14, 0.61] $p = 0.0479$); Patients with FVC $< 82\%$ were more likely to have OSA compared to patients with FVC $\geq 82\%$ (OR = 3.8, 95% CI [1.65, 9.13] $P = 0.0019$).

Conclusions: Impaired lung physiology parameters such as ERV and FVC are significantly associated with OSA. ERV > 0.64 L has an acceptable sensitivity of 78.8% however lower specificity of 65.6% to identify OSA. BMI > 30 and age > 54 year associated with higher risk of OSA, as already known from the literature. More studies are needed to validate PFT as screening tool for sleep disorder, and assess progression and reversibility of PFT defect along with treatment of OSA.

Clinical Implications: Physiological data from PFTs are very important for evaluation of lung disease and following natural progression. There are significant body of evidence showing that PFT parameters can also be used to understand, and evaluate sleep disorder severity, and aid in diagnosis.

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Onset of Effect Questionnaire (OEQ) for Patients with Chronic Obstructive Pulmonary Disease: A Qualitative Evaluation

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Introduction: Two Onset of Effect Questionnaire (OEQ) items have demonstrated reliability and validity in asthma patients; however, this 5-item patient-reported outcome measure has not been evaluated in chronic obstructive pulmonary disease (COPD). This study evaluated the content validity (i.e., relevance and understandability) of the OEQ in patients with COPD.

Methods: One-on-one qualitative interviews were conducted with COPD patients recruited from 4 US-based clinical sites. The concept elicitation portion included open-ended questions to understand the COPD patient experience of being able to feel their medication begin to work. The cognitive interview portion included completion of the OEQ and assessment of the items, response options, and instructions. Findings were stratified based on disease severity as measured by the COPD Assessment Tool (CAT) and medication class.

Results: The 44 participants (54.5% female; mean age 66 years, range: 47-82) represented a range of CAT scores: < 10 (N=3), 11-20 (N=17), 21-30 (N=20), and > 30 (N=4). Most participants (72.7%; n=32) reported being able to feel their medication working, using phrases such as breathing better/easier, chest feeling less tight/heavy, and feeling their airways opening. Three of the 5 OEQ items (feel medication work, feel medication work right away, satisfied with how quickly medication works) were relevant and understood as intended. Similar results were observed across CAT scores and medication classes.

Conclusions: The content validity of 3 OEQ items was supported among COPD patients. Next steps involve an evaluation of the reliability and construct validity of the OEQ items in COPD patients.

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Quantifying Symptomatic Patients' Preferences for Maintenance Inhaler Therapies: Discrete Choice Experiment

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Rationale: Available maintenance therapies for asthma and chronic obstructive pulmonary disease (COPD) include inhaled corticosteroids (ICS), long-acting beta agonists (LABA), and long-acting muscarinic antagonists (LAMA) alone or in combination. This study assessed patients' preferences for different attributes of these maintenance therapies.

Methods: US patients with symptomatic asthma taking ICS/LABA or with symptomatic COPD aged ≥ 40 years in GOLD categories B, C, or D participated in an online discrete choice experiment (DCE) survey. Treatment attributes included in the DCE were selected based on patient focus groups, a literature review, and expert clinical advice. Multinomial logit models were used to estimate marginal utilities describing the relative value of changing from a reference to a non-reference level. $P < 0.05$ was considered statistically significant.

Results: The DCE survey was completed by 810 patients with asthma (61.7% male; mean \pm SD age 48.4 \pm 15.2 years) and 1,147 patients with COPD (57.5% male; mean \pm SD age 59.4 \pm 10.1 years). Patients with asthma most valued faster onset of action for symptom relief (from 30 to 5 min), followed by a reduction in yearly exacerbations (from 3 to 1). Patients with COPD considered changes in these two attributes to be of similar importance. Both patient groups were willing to accept an extra exacerbation in exchange for a 15-min faster onset of action. Patients with asthma were more willing to accept a slower onset of action if the risk of osteoporosis decreased from 6% to 4% than patients with COPD (10.8 min for asthma vs. 7.1 min for COPD). Patients with COPD would accept a slower onset of action of 13.5 min to decrease the risk of pneumonia from 20% to 10%. To obtain a pressurized metered-dose inhaler instead of a dry powder inhaler, asthma patients were more willing to accept slower onset of action than patients with COPD (8.1 min for asthma vs. 3.6 min for COPD). Both patient groups valued once-daily over twice-daily dosing, more precise dose counters, and non-capsule priming methods over single-use capsules, but to a lesser extent than the previously mentioned attributes.

Conclusion: For patients with asthma or COPD, the most important attributes of their maintenance therapies were faster onset of action for symptom relief and reduced number of exacerbations. Safety and convenience also affected patients' preferences for treatment attributes.

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Real-World Patterns and Implications of Short-acting Beta-Agonist Use Among Adolescent and Adult Patients with Asthma

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Rationale: Guidelines suggest assessing short-acting beta agonist (SABA) use as one measure for determining asthma control.^{1,2} Real-world utilization of rescue medications and associated asthma morbidity are not well described.

Methods: IBM[®] MarketScan[®] Research Databases of administrative claims dated 9/30/2014-9/30/2016 for US asthma patients aged ≥ 12 years receiving SABA were evaluated. Patients were indexed on earliest SABA claim and required to have 12 months of continuous eligibility both pre- and post-index, asthma diagnosis in pre-period through 30 days post-index, and either an additional SABA or ≥ 1 controller fill(s) post-period. SABA fills post-index (including index fill) were delineated corresponding to guideline-described¹ levels of control: Low SABA Group: index fill only, Well-controlled; Medium: 2-3 fills, Not Well-Controlled; High: 4+ fills, Very Poorly Controlled. Within-group disease severity (class/strength of prescribed controller²) and morbidity (severe exacerbations: hospitalization, emergency visits, or outpatient systemic corticosteroid bursts) were assessed. Group differences were analyzed via ANOVA and chi-square (significance: $P < 0.05$).

Results: 172,573 patients were included: 63.8% women; mean \pm SD age: 43.6 \pm 18.9 years; mean SABA fills/12-months post-index: 3.10 \pm 2.80, median: 2 (range: 1-44). Of the population, 27% were Low SABA group (1 fill), 46% Medium (2.35 \pm 0.58 fills), and 27% High (6.52 \pm 3.43 fills). Distribution of maintenance treatment steps differed between SABA groups, with GINA 4/5² used by the highest proportion of patients in all 3 groups. Overall, controller possession ratio was 60% and differed between groups (Low SABA, 54%; Medium, 60%; High, 68%). Mean exacerbation rate/person/12-months post-index was 0.77 \pm 1.30. Exacerbation rate and proportion of the population within each SABA group having an exacerbation increased progressively with increasing SABA use: Low SABA group, 0.55 \pm 1.00, 33.9%; Medium, 0.74 \pm 1.20, 40.9%; High 1.05 \pm 1.62, 47.5%. 59% of patients had no exacerbations, 22.3% had 1, and 18.4% had ≥ 2 , with mean SABA fills differing significantly between these 3 groups: 0 exacerbations, 2.90 \pm 2.63 fills; 1 exacerbation, 3.06 \pm 2.70; ≥ 2 exacerbations, 3.78 \pm 3.29.

Conclusion: SABA utilization and associated morbidity vary among asthmatics, and exacerbations occur regardless of level of controller therapy. All SABA groups demonstrated suboptimal maintenance medication possession; even among low SABA users 1/3 of patients experienced exacerbations, increasing to nearly 50% in the highest SABA group. New reliever/controller strategies may be needed that address airway inflammation at the time of symptom worsening with the goal of reducing exacerbation risk.

¹NHLBI. NAEP Expert Panel Report 3: Guidelines for the Diagnosis and Management of Asthma. 2007.

²GINA. Global Strategy for Asthma Management and Prevention. 2018.

Funding: AstraZeneca

Forced Vital Capacity in Patients With Idiopathic Pulmonary Fibrosis: Visit-to-Visit Variability and the Role of 6-Minute Walk Distance to Validate Changes

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Rationale: Disease progression in idiopathic pulmonary fibrosis (IPF) is monitored by forced vital capacity (FVC) decline. In individuals with IPF, visit-to-visit variability in FVC measurements can create uncertainty in clinical decision-making. This analysis of pooled data from Phase III clinical trials examined variability in FVC across 3-month follow-up visits and evaluated concurrent changes in 6-minute walk distance (6MWD).

Methods: Patients randomized to placebo in ASCEND (Study 016; NCT01366209) and CAPACITY (Studies 004 and 006; NCT00287716 and NCT00287729) and all patients randomized to interferon gamma-1b or placebo in GIPF-001 (NCT00047645) were analyzed for changes in pre-bronchodilator FVC (mL). Changes in 6MWD were examined in ASCEND and CAPACITY data.

Results: In 954 patients, 3966 total observations of 3-month change in FVC (mL) were analyzed; 41.3% of changes were improvements (≥ 0 mL), while 58.7% were declines (< 0 mL). Absolute 3-month changes in FVC of ≥ -100 mL to < 0 mL (26.8%) and ≥ 0 mL to < 100 mL (23.3%) were most frequent. In patients with available 6MWD data and any 3-month decline in FVC (1321 observations), a relative decline in FVC (mL) $> 6\%$ was more likely to be followed by further FVC decline if associated with a concurrent decreased ($\leq -5\%$) vs. stable ($> -5\%$ to $< 5\%$) or improved 6MWD ($> 5\%$).

Conclusions: Variability in FVC over 3-month intervals in patients with IPF was substantial. These findings highlight the need to consider other functional measures such as 6MWD in concert with FVC to predict meaningful changes in disease progression in individual patients with IPF.

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Consistent effect of nintedanib in patients with IPF and degrees of impairment in gas exchange

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Introduction: The two 52-week INPULSIS trials investigated nintedanib versus placebo in patients with IPF, FVC $\geq 50\%$ predicted and DLco 30–79% predicted. The 24-week INSTAGE trial investigated nintedanib plus sildenafil versus nintedanib alone in patients with IPF and DLco $\leq 35\%$ predicted. We compared the effects of nintedanib in the INPULSIS and INSTAGE trials.

Methods: The rate of decline in FVC over 24 weeks, the proportion of patients who had a confirmed or suspected idiopathic acute exacerbation over 24 weeks, and deaths over 24 weeks were analyzed descriptively in patients who received nintedanib alone in the INPULSIS and INSTAGE trials and placebo in the INPULSIS trials.

Results: 638 and 423 patients received nintedanib and placebo, respectively, in INPULSIS; 136 patients received nintedanib alone in INSTAGE. Rates of FVC decline were -52.3 and -102.8 mL/24 weeks in patients treated with nintedanib and placebo, respectively, in INPULSIS, and -66.7 mL/24 weeks in patients treated with nintedanib alone in INSTAGE. Confirmed/suspected idiopathic acute exacerbations occurred in 0.6% and 2.1% of patients treated with nintedanib and placebo, respectively, in INPULSIS, and 3.7% of patients treated with nintedanib alone in INSTAGE. Deaths occurred in 2.0% and 1.9% of patients treated with nintedanib and placebo, respectively, in INPULSIS, and 11.0% of patients treated with nintedanib alone in INSTAGE.

Conclusions: Based on data from the INSTAGE and INPULSIS trials, nintedanib appeared to have a similar effect on FVC decline over 24 weeks in patients with IPF irrespective of gas exchange impairment.

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The lung function profile of patients with COPD receiving once-daily tiotropium/olodaterol versus twice-daily fluticasone propionate/salmeterol in: ENERGITO 2 clinical trial

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INTRODUCTION: In the European ENERGITO trial, once-daily tiotropium/olodaterol (T/O) was superior to twice-daily fluticasone propionate/salmeterol (FP/SAL) at improving forced expiratory volume in 1 second (FEV₁) area under the curve 0–12 hours (AUC_{0–12h}) response and FEV₁ AUC_{0–24h} response after 6 weeks' treatment in patients with moderate-to-severe chronic obstructive pulmonary disease (COPD).

METHODS: ENERGITO 2 (NCT03240575), a longer, 12-week, randomized, double-blind, parallel-group trial evaluated lung function after treatment with T/O 5/5 μg versus FP/SAL 500/100 μg in US patients with moderate-to-severe COPD. The primary endpoint was FEV₁ AUC_{0–24h} change from baseline.

RESULTS: Adjusted mean (SE) FEV₁ AUC_{0–24h} response was 0.174 L (0.019 L) for T/O (n=145) and 0.122 L (0.019 L) for FP/SAL (n=138) after 12 weeks' treatment; the treatment difference (0.052 L) did not reach statistical significance (95% confidence interval [CI] -0.001–0.105; P=0.0543). However, the corresponding forced vital capacity curve for treatment effect showed a significant treatment difference: 0.151 L (95% CI 0.064–0.237; P=0.0007). 55% of patients received long-acting bronchodilator or inhaled corticosteroids prior to enrollment. Use of rescue medication was not recorded. A gender/smoking history imbalance between treatment arms was identified. Meta-analysis with ENERGITO data using a fixed-effects model found a statistically significant improvement in FEV₁ AUC_{0–24h} response with T/O (P<0.0001).

CONCLUSIONS: Once-daily T/O in moderate-to-severe COPD patients provided lung function improvements, compared with twice-daily FP/SAL. The treatment difference for flow parameters was lower than expected, however for volume (indicating impact on air-trapping), results were significant, in favor of T/O.

Funding: Boehringer Ingelheim

Treatment patterns in patients with idiopathic pulmonary fibrosis (IPF): data from the IPF-PRO Registry

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Introduction: Two antifibrotic medications, nintedanib and pirfenidone, were approved for treatment of IPF in the US in October 2014. Patterns of antifibrotic drug use in clinical practice have not been well described.

Methods: The IPF-PRO Registry enrolled patients with IPF that was diagnosed or confirmed at the enrolling center in the past 6 months. Data from patients enrolled from 5 June 2014 to 4 March 2018 were used to determine antifibrotic medication use at enrollment and first follow-up. Patients with documented medication use prior to or ≤ 3 months after enrollment were "treated" at enrollment; others were "untreated". Patients with documented medication use between 3 and 8 months after enrollment were "treated" at follow-up; others were "untreated".

Results: At enrollment, 551 (70.5%) of 782 eligible patients were treated. Among 534 patients treated at enrollment who had follow-up data, 94.0% remained treated at follow-up. Among 172 patients untreated at enrollment who had follow-up data, 29.7% had started treatment at follow-up. Younger age, lower FVC % predicted, oxygen use with activity, worse self-rated health based on the Short Form-12 or St George's Respiratory Questionnaire score, referral to the enrolling center by a pulmonologist, and having a diagnosis of IPF prior to enrollment were significantly associated with being treated at enrollment.

Conclusions: Most patients in the IPF-PRO Registry were receiving an approved medication for IPF at enrollment. By some measures, treated patients had more severe disease than untreated patients at time of enrollment.

Funding: Boehringer Ingelheim
The IPF-PRO Registry is coordinated by DCRI

Respiratory phenotypes and outcomes in a community-based cohort: Findings from the prospective MURDOCK COPD observational study

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Introduction: Chronic obstructive pulmonary disease (COPD) management in clinical practice may differ from Global Initiative for Chronic Obstructive Lung Disease (GOLD) recommendations. We evaluated outcomes in participants with COPD and novel phenotypes, including Preserved Ratio Impaired Spirometry (PRISm) and smokers with respiratory symptoms (SRS)—outside of GOLD definitions—in a community-based cohort.

Methods: The MURDOCK COPD Study (NCT02838108) enrolled participants aged ≥ 40 years with a ≥ 10 pack-year smoking history and COPD (forced expiratory volume in 1 second [FEV₁]/forced vital capacity [FVC] < 0.70), PRISm (preserved FEV₁/FVC with FEV₁ $< 80\%$), or SRS (preserved FEV₁/FVC, FVC $\geq 80\%$, and COPD Assessment Test™ score ≥ 10). Self-reported exacerbations were ascertained at 6-month intervals. The study was terminated prematurely.

Results: Among 448 enrolled participants (COPD, n=254; PRISm, n=73; SRS, n=112; PRISm+SRS, n=9), the median pack-year history was 35.0; 43% were current smokers. Participants with COPD tended to be older and white, whereas the PRISm and SRS groups had a higher percentage of black participants and a higher body mass index. Among COPD participants, 19.7% were GOLD 1, 55.5% GOLD 2, 21.7% GOLD 3, and 3.1% GOLD 4; 26.0% were GOLD A, 60.6% GOLD B, 0% GOLD C, and 13.4% GOLD D. At 6-month follow-up (n=218), 16.6%, 10.5%, and 7.5% of participants in the COPD, PRISm, and SRS groups, respectively, reported moderate or severe respiratory exacerbations.

Conclusions: We observed demographic differences among participants with COPD, PRISm, and SRS in this community-based cohort. Exacerbations occurred at clinically relevant frequencies even among participants not meeting formal COPD diagnostic criteria.

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The Pharmacokinetics and Relative Bioavailability of Mepolizumab 100 mg Liquid Formulation Administered Subcutaneously to Healthy Participants: A Randomized Trial

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Introduction: A mepolizumab liquid formulation delivered via a single-use prefilled autoinjector (AI) or prefilled syringe (PFS) has been approved. This study compared the pharmacokinetic (PK), safety and pharmacodynamic (PD) profiles of the liquid and lyophilized formulations.

Methods: In this open-label, randomized, parallel-group, single-dose study, healthy participants received (1:1:1) mepolizumab (100 mg SC) in a PFS or AI, or as a reconstituted lyophilized product. Injection site was randomized 1:1:1 to upper arm, abdomen, or thigh. Primary endpoints were maximum plasma concentration (C_{max}), area under the concentration-time curve from time zero (pre-dose) to last time (AUC_[0-1]), and AUC from time zero to infinity (AUC_[0-∞]). Secondary endpoints included additional PK parameters and safety. PD effect on blood eosinophil count was an exploratory objective.

Results: 244 participants received mepolizumab. Primary and secondary PK parameters were comparable across the groups; 90% confidence intervals for primary endpoint treatment ratios (PFS or AI versus lyophilized) were within the conventional bioequivalence bounds (0.80, 1.25). In all groups, mepolizumab exposure was similar across the injection sites. The incidence of on-treatment adverse events ranged 29%–38%; there was a low incidence (5%) of anti-drug antibodies (none neutralizing). The effect on blood eosinophils was similar across groups.

Conclusions: After one dose, the PK profile of the mepolizumab liquid formulation administered via PFS or AI was statistically comparable to the lyophilized formulation, with a similar safety profile. Exposure was similar between injection sites. Treatments resulted in a similar effect on blood eosinophils.

Funding: GSK (Study 204958; NCT03014674)

Comparative Efficacy of Umeclidinium/Vilanterol, Umeclidinium and Salmeterol in Symptomatic Patients with Chronic Obstructive Pulmonary Disease Free of Inhaled Corticosteroids: The EMAX Trial

François Maltais, Leif Bjermer, Edward Kerwi³, Claus Vogelmeier⁴, Michael L Watkins, Lee Tombs, Ian Naya, Isabelle Boucrot, David A. Lipson, Chris Compton, Paul Jones, on behalf of the EMAX study group.

Introduction: Long-acting β_2 -agonist/long-acting muscarinic antagonist combination therapy may improve symptoms versus monotherapy; however, comparator trials have not excluded patients using inhaled corticosteroids (ICS) or stepping down from combination therapy. The Early MAXimization of bronchodilation for improving chronic obstructive lung disease (COPD) stability (EMAX) trial compared umeclidinium/vilanterol (UMEC/VI), UMEC, and salmeterol (SAL) in symptomatic ICS-free patients with low exacerbation risk.

Methods: This 24-week, double-blind, parallel-group study randomized patients 1:1:1 to UMEC/VI 62.5/25 mcg once daily, UMEC 62.5 mcg once daily, or SAL 50 mcg twice daily. Primary endpoint was trough forced expiratory volume in 1 second (FEV₁) at Week 24. Secondary endpoints included inspiratory capacity, forced vital capacity, and patient-reported outcomes including transition dyspnea index, Evaluating Respiratory Symptoms-COPD, St George's Respiratory Questionnaire, COPD assessment test score, and Subject Global Rating of Change in COPD Severity. Rescue albuterol use, risk of first moderate/severe exacerbation and adverse events (AEs) were also captured.

Results: At baseline, the intent-to-treat population (N=2425 [UMEC/VI=812; UMEC=804; SAL=809]) had a mean post-bronchodilator FEV₁ predicted of 55% and 16% had 1 moderate COPD exacerbation in the past year. UMEC/VI provided significantly greater improvements in trough FEV₁ (vs UMEC: 66 mL [95% confidence interval (CI): 43, 89]; vs SAL: 141 mL [95% CI: 118, 164]; $P < 0.001$) and all other spirometry measures versus UMEC or SAL at Week 24. UMEC/VI also provided significant ($P < 0.05$) improvements in 8/11 and 10/11 symptom severity and quality of life assessments compared with UMEC and SAL, respectively. Patients receiving UMEC/VI had a significantly reduced risk of moderate/severe exacerbations compared with SAL (36% risk reduction; $P < 0.001$), but not UMEC (19% risk reduction, $P = 0.114$). Incidence of AEs was similar between treatments.

Conclusion: Once-daily UMEC/VI provides consistent improvements in lung function and symptoms compared with UMEC and SAL in ICS-free low exacerbation risk symptomatic patients with COPD.

Funding: GSK (study 201749/NCT03034915).

Mepolizumab prefilled autoinjector and prefilled syringe real world use: the patient experience

Evitt LA, Follows R, Bentley JH, Williams W, Shalhoub H, Celone M

Introduction: Mepolizumab is currently administered by health care professionals (HCPs) in-clinic as a reconstituted lyophilized powder. A prefilled autoinjector (AI) and prefilled syringe (PFS) containing mepolizumab have been approved to enable at-home, self-administration.

Methods: Two open-label, single-arm Phase IIIa studies evaluated real-world use (RWU) of mepolizumab administered via an AI (N=159) and PFS (N=56) in patients aged ≥ 12 years with severe eosinophilic asthma. Mepolizumab (100mg) was administered subcutaneously by the patient/caregiver every 4 weeks for ≤ 12 weeks. Dose 1 and 3 (Weeks 0 and 8) were self-administered in-clinic (observed); Dose 2 (Week 4) was self-administered at home (unobserved). Quantitative questionnaires were completed by all patients; a subset (AI, n=25; PFS, n=6) also completed a semi-structured, qualitative telephone exit-interview. Interview questions covered experience, comfort and confidence levels in using the devices, and views on the instructions for use and training.

Results: For both the AI and PFS, most patients ($\geq 98\%$) were satisfied with the training and reported feeling very/extremely confident ($\geq 90\%$) in self-administration; confidence improved over time. Most patients were satisfied with the devices ($\geq 96\%$), found them very/extremely easy to use ($\geq 82\%$) and would recommend them to other patients with asthma ($\geq 98\%$). In patients who had previously received mepolizumab, most preferred self-administration over HCP-administration (96%); convenience was the main reason for this preference.

Conclusions: These RWU studies indicate that both the AI and PFS devices provide a convenient, easy route of mepolizumab administration for patients; self-administration was preferred by those who had previously received mepolizumab in-clinic.

Funding: GSK [studies: 204959/NCT03099096; 205667/NCT03021304]

Baseline Characteristics of Phase 3 Randomized Controlled Trials of Omalizumab in Chronic Rhinosinusitis with Nasal Polyps

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Introduction: Chronic rhinosinusitis with nasal polyps (CRSwNP) is characterized by Type 2 immune reaction and has been shown to respond to omalizumab, an anti-IgE monoclonal antibody. We describe the baseline characteristics of patients from two large replicate Phase 3 trials of omalizumab (POLYP 1 [NCT03280550], POLYP 2 [NCT03280537]).

Methods: Two randomized, double-blind, placebo-controlled trials (24-week treatment) included CRSwNP patients inadequately controlled despite daily intranasal corticosteroid therapy. Eligible patients had persistent bilateral nasal polyps with a total nasal polyp score (NPS) $\geq 5/8$ ± asthma following a 5-week run-in period on intranasal mometasone 200µg BID and were randomized to omalizumab or placebo with background mometasone. Co-primary endpoints were change from baseline to Week 24 in average daily nasal congestion score (NCS, eDiary) and NPS (endoscopy). Secondary endpoints included patient-reported outcomes and adverse event monitoring.

Results: Patients enrolled in POLYP 1 (n=138) and POLYP 2 (n=127) exhibited severe nasal polyps and symptoms. From pooled results, mean (SD) NCS (2.4 [0.7], range 0-3), NPS (6.3 [1.0], range 0-8) and Sino-Nasal Outcome Test-22 (61.0 [20.5], range 0-110) scores were consistent with substantial CRSwNP-related impairment in patients' health-related quality of life. Most patients were male (64.5% overall) and had comorbid asthma (58.1%).

Conclusions: Two global replicate pivotal trials of omalizumab in nasal polyps enrolled patients with evidence of severe CRSwNP, consistent with a prior single-center study of omalizumab. These patients are experiencing impaired control despite intranasal corticosteroid therapy.

Funding: Genentech

Effects of Omalizumab on Blood Eosinophil Numbers in Patients with Allergic Asthma

Nicola A. Hanania, Jonathan Corren, Cecile Holweg, Tmirah Haselkorn, Ming Yang, Robert C. Lyon, Ahmar Iqbal, Thomas Casale

Introduction: Omalizumab reduces exacerbations in patients with moderate-to-severe allergic asthma, with a more pronounced response observed with higher baseline eosinophils and asthma severity. We examined omalizumab-associated changes in eosinophil levels by baseline blood eosinophil levels and asthma severity.

Methods: Post-hoc analysis assessed the longitudinal effects of omalizumab on eosinophils by baseline eosinophil levels (<150, 150-299, 300-399, and ≥ 400 cells/µL) and asthma severity (history of emergency asthma treatment or hospitalization, and LABA use [yes/no], and above/below median % predicted FEV₁) in three Phase III placebo-controlled omalizumab trials. Data from IA05 (steroid stable phase, ages 6-11; n=562) were available for baseline, Week 5 and 13 and pooled data from INNOVATE and EXTRA (ages 12-75; n=1094) for baseline, Week 12/16 and 28/32.

Results: Median baseline eosinophil levels were similar for omalizumab and placebo-treated groups in all subgroups examined. Omalizumab reduced eosinophils more than placebo in patients with baseline eosinophils >150 cells/µL. The largest median [IQR] reductions were observed in patients with ≥ 400 cells/µL by Week 5 for IA05 (-200 [300] vs -100 [400] cells/µL) and Week 12/16 for INNOVATE/EXTRA (-200 [280] vs -100 [340] cells/µL) for omalizumab vs placebo-treated patients and were maintained to study end. Reductions in eosinophils were similar between asthma severity subgroups. Efficacy and safety were not evaluated in this analysis.

Conclusion: Omalizumab reduced blood eosinophil levels across several baseline cut-points, with the greatest reductions in patients with the highest eosinophil levels. Reductions were small but consistently larger compared to placebo in both severe and less severe patients.

Funding: Genentech

Dupilumab Improved Asthma Control and Health-Related Quality of Life in Patients With Oral-Corticosteroid-Dependent Severe Asthma in the Phase 3 LIBERTY ASTHMA VENTURE Study

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Introduction: Dupilumab, a fully human monoclonal antibody, blocks the shared receptor component for interleukin (IL)-4 and IL-13, drivers of type 2 inflammation. In the phase 3 LIBERTY ASTHMA VENTURE study (NCT02528214), add-on dupilumab 300mg q2w vs placebo reduced oral corticosteroid (OCS) maintenance dose and severe asthma exacerbation rate and improved pre-bronchodilator FEV₁ in patients with OCS-dependent severe asthma. This pre-specified analysis assessed the effect of dupilumab on asthma control (AC) and health-related quality of life (HRQoL) in these patients.

Methods: AC was assessed by 5-item Asthma Control Questionnaire (ACQ-5) with scores ranging from 0 (controlled) to 6 (severely uncontrolled). HRQoL was assessed by Asthma Quality of Life Questionnaire (AQLQ), where higher scores (range 1-7) indicate better HRQoL. Changes from baseline were analyzed using mixed-effect models with repeated measures.

Results: In the dupilumab and placebo groups, mean baseline ACQ-5 scores were 2.42 and 2.58, and AQLQ scores 4.38 and 4.31. With dupilumab, ACQ-5 rapidly improved (Week 2, LS mean change from baseline: -0.57, $P=0.002$ vs placebo), further improved at Week 12 (-1.01, $P=0.001$ vs placebo), and stabilized through Week 24 (-1.05, $P=0.002$ vs placebo). AQLQ LS mean scores improved from baseline by 0.76 and 0.89 at Week 12 ($P=0.14$ vs placebo) and Week 24 ($P=0.008$ vs placebo) respectively. The most frequent treatment-emergent adverse event in dupilumab-treated patients (vs placebo) was eosinophilia (14% vs 1%); injection-site reactions also occurred (9% vs 4%).

Conclusions: Dupilumab vs placebo significantly improved AC and HRQoL in patients with OCS-dependent severe asthma. Dupilumab was generally well tolerated.

Funding: Sanofi Regeneron

Dupilumab Reduces Severe Exacerbations and Improves Lung Function in Patients With Late-Onset, Uncontrolled, Moderate-to-Severe Asthma Enrolled in the LIBERTY ASTHMA QUEST Study

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Introduction: Dupilumab, a fully human monoclonal antibody, blocks the shared receptor component for interleukin (IL)-4/IL-13, key drivers of type 2 inflammation. In the phase 3 LIBERTY ASTHMA QUEST study (NCT02414854), add-on dupilumab 200mg/300mg every 2 weeks vs placebo significantly reduced severe asthma exacerbations, improved pre-bronchodilator FEV₁ and quality-of-life measures in patients with uncontrolled, moderate-to-severe asthma. This post-hoc analysis assessed dupilumab efficacy in patients with late-onset asthma (LOA; age >40 years) and baseline post-bronchodilator FEV₁/forced vital capacity [FVC] ratio <0.7 (suggesting fixed airway obstruction [FAO]) or ≥ 0.7 .

Methods: Annualized rate of severe exacerbations during the 52-week treatment period, change from baseline in pre- and post-bronchodilator FEV₁ (L) and pre-bronchodilator FEV₁/FVC ratio at Weeks 12 and 52 were assessed.

Results: Dupilumab 200/300mg vs placebo reduced annualized rate of severe exacerbations in patients with LOA with FAO (-68.8%/-75.7%; both $P<0.0001$) and without FAO (-55.1%/-50.7%; both $P<0.05$). At Week 12, pre- and post-bronchodilator FEV₁ and FEV₁/FVC ratio improved in dupilumab-treated patients with LOA and FAO ($P<0.05$ vs placebo, either or both doses); similar improvements were observed at Week 52 (200mg: pre- and post-bronchodilator FEV₁ $P<0.05$; 300mg: pre-bronchodilator FEV₁ $P=0.09$, post-bronchodilator FEV₁ $P=0.06$). LOA patients without FAO had more modest improvements in pre-bronchodilator FEV₁ at Weeks 12 and 52 than those with FOA ($P=0.05$). The most frequent adverse event in dupilumab-treated patients (vs placebo) was injection-site reaction (15%/18% vs 5%/10%).

Conclusions: Dupilumab significantly reduced severe exacerbation rates in patients with LOA with or without FAO, and improved lung function in patients with LOA and FAO.

Funding: Sanofi Regeneron

Dupilumab Reduces Severe Exacerbations and Improves Lung Function Regardless of Baseline Bronchodilator Reversibility in Patients With Uncontrolled Moderate-to-Severe Asthma Enrolled in the LIBERTY ASTHMA QUEST Study

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Introduction: Dupilumab, a fully human monoclonal antibody, blocks the shared receptor component for interleukin (IL)-4 and IL-13, key drivers of type 2 inflammation. In the phase 3 LIBERTY ASTHMA QUEST study (NCT02414854), add-on dupilumab 200 mg or 300 mg every 2 weeks (q2w), vs placebo, significantly reduced severe asthma exacerbations, improved pre-bronchodilator forced expiratory volume in 1 second (FEV₁), and improved quality-of-life measures in patients with uncontrolled, moderate-to-severe asthma. This post-hoc analysis assessed the effect of dupilumab by baseline bronchodilator reversibility.

Methods: All patients had baseline bronchodilator reversibility $\geq 12\%$ and ≥ 200 mL in FEV₁ following β_2 -agonist administration. The population median (20.89%) was used to divide bronchodilator FEV₁ into reversibility-high (RH) and -low (RL) subgroups. Severe exacerbations during the 52-week treatment period, change from baseline in pre- and post-bronchodilator FEV₁, and pre-bronchodilator FEF_{25-75%} at Weeks 12 and 52 were assessed.

Results: Dupilumab 200/300 mg q2w vs placebo reduced severe exacerbations in RL (-41.9%/ -58.5%; $P=0.002/P<0.0001$) and RH subgroups (-52.6%/ -26.8%; $P<0.0001/P=0.06$). In both subgroups, dupilumab q2w vs placebo improved both pre- and post-bronchodilator FEV₁ (ranges 0.07–0.28 L and 0.07–0.27 L, respectively; $P\leq 0.05$ for all) at Weeks 12 and 52. In both subgroups, dupilumab q2w vs placebo improved FEF_{25-75%} at Weeks 12 and 52 (range 0.10–0.25 L/s; $P<0.05$ for all), except for a non-significant Week 12 improvement for the RL subgroup (0.07 L/s; $P=0.12$). The most frequent adverse event in dupilumab-treated patients (vs placebo) was injection-site reactions (15%/18% vs 5%/10%).

Conclusions: Dupilumab reduced severe exacerbations and improved lung function in uncontrolled, moderate-to-severe asthma patients with low- and high-baseline post-bronchodilator FEV₁ reversibility.

Funding: Sanofi Regeneron

Dupilumab Improves Lung Function and Reduces Severe Exacerbation Rate in Patients with Uncontrolled, Moderate-to-Severe Asthma With or Without Comorbid Allergic Rhinitis: Results from the Phase 3 LIBERTY ASTHMA QUEST Study

William W. Busse, Jorge F. Maspero, Nicola A. Hanania, J. Mark FitzGerald, Linda B. Ford, Megan S. Rice, Paul Rowe, Heribert Staudinger, Nikhil Amin, Neil M. H. Graham, Ariel Teper

Introduction: Dupilumab, a fully human monoclonal antibody, blocks the shared receptor component for interleukin (IL)-4 and IL-13, key drivers of type 2 inflammation. In the phase 3 LIBERTY ASTHMA QUEST study (NCT02414854), add-on dupilumab 200/300 mg every 2 weeks (q2w), vs placebo, significantly reduced severe asthma exacerbations, improved pre-bronchodilator FEV₁, and improved quality-of-life measures in patients with uncontrolled, moderate-to-severe asthma. This post-hoc analysis assessed the effect of dupilumab in patients with or without comorbid allergic rhinitis (AR).

Methods: The effect of add-on dupilumab 200mg/300mg or matched placebo q2w on the annualized rate of severe exacerbations and FEV₁ was assessed in asthma patients with (1,207/1,902) and without (695/1,902) a self-reported medical history of comorbid AR.

Results: Baseline characteristics of patients with and without AR were generally similar. The annualized rate of severe exacerbations was reduced (vs placebo) with dupilumab 200mg q2w (relative risk with AR: 0.606 [95%CI, 0.451–0.814]; $P=0.0009$; without AR: 0.406 [95%CI, 0.273–0.605]; $P<0.0001$) with similar results for 300mg q2w. FEV₁ was improved at Week 12 with dupilumab 200mg (LS mean difference vs placebo with AR: 0.14 L [95%CI, 0.07–0.21]; $P<0.0001$; without AR: 0.13 L [95%CI, 0.05–0.21]; $P=0.0025$) and sustained to Week 52 (both with/without AR: $P<0.0001$), with similar results at Week 52 for 300mg q2w. Overall, the most common adverse event in dupilumab-treated patients (vs placebo) was injection-site reactions (15%/18% vs 5%/10%).

Conclusions: Dupilumab significantly improved FEV₁ and reduced annual severe exacerbation rates in patients with uncontrolled asthma, with and without comorbid AR.

Funding: Sanofi Regeneron

The Effect of Baseline Rescue Medication Use on Lung Function and Patient-reported Outcomes in Patients with COPD Treated with Nebulized Glycopyrrolate in the GOLDEN 3 and 4 Studies

James F. Donohue, Ayca Ozol-Godfrey, Thomas Goodin, Shahin Sanjar

Introduction: Rescue medication use to alleviate respiratory symptoms is common among patients with chronic obstructive pulmonary disease (COPD) and increases with disease severity. The effect of different levels of baseline rescue medication was explored in COPD patients treated with glycopyrrolate (GLY) 25 mcg twice daily delivered by the eFlow® closed system nebulizer (PARI GmbH, Starnberg, Germany).

Methods: Pooled GLY and placebo data (n=861) from replicate 12-week studies in patients with moderate-to-very-severe COPD were grouped into quartiles generated by baseline rescue medication use; defined as the average number of puffs per day during the run-in period. The following endpoints were assessed: change from baseline in trough forced expiratory volume in one second (FEV₁); St. George's Respiratory Questionnaire (SGRQ) and responders, and EXacerbations of COPD Tool-Respiratory Symptoms (EXACT-RS) total scores.

Results: The median puffs/day (range) of rescue medication use in each quartile were: <Q1: 0.1 (0, 0.9); Q1-<Q2: 1.8 (1.0, 2.7); Q2-<Q3: 3.9 (2.7, 5.2); \geq Q3: 6.8 (5.2, 14.1). Increased rescue medication use was observed in both treatment groups in patients on a background of long-acting β_2 -agonists (LABA) and inhaled corticosteroids (ICS) (LABA: <Q1: 22.9%, Q1-<Q2: 25.2%, Q2-<Q3: 33.3%, \geq Q3: 40.2%; ICS: <Q1: 22.3%, Q1-<Q2: 23.8%, Q2-<Q3: 30.8%, \geq Q3: 38.1%). Improvements in trough FEV₁ with GLY at Week 12 were greatest in the <Q1 subgroup, with a trend towards smaller improvements with increased baseline rescue medication use. SGRQ and EXACT-RS total scores improved with GLY treatment with greater improvement seen with increased baseline rescue medication use. GLY was well tolerated; the incidence of adverse events (AEs) and serious AEs was similar across the different rescue medication use quartiles.

Conclusions: Nebulized GLY was associated with lung function and PRO improvements in moderate-to-very-severe COPD patients using rescue medication, LABAs and ICS more frequently at baseline.

Funding: Sunovion Pharmaceuticals Inc.

Improvement in Lung Function and Patient-reported Outcomes in Patients with COPD with Comorbid Anxiety and Depression Receiving Nebulized Glycopyrrolate in the GOLDEN 3 and 4 Studies

Nicola A. Hanania, Ayca Ozol-Godfrey, Michael Tocco, Thomas Goodin, Shahin Sanjar

Introduction: Depression and anxiety are common comorbidities in patients with chronic obstructive pulmonary disease (COPD). These patients are known to have worse patient-reported-outcomes, but limited data are available on their response to bronchodilator therapy. Physiologic and symptomatic responses were evaluated in moderate-to-very-severe COPD patients with anxiety and depression following treatment with glycopyrrolate (GLY) 25 mcg twice daily delivered by the eFlow® closed system nebulizer (PARI GmbH, Starnberg, Germany).

Methods: Pooled GLY and placebo data (n=861) from replicate 12-week studies were grouped into mood disorder ≥ 6 months prior to and ongoing at the first study treatment (MD; depression and anxiety; n=156) or no mood disorder (NMD; n=705) subgroups. GLY and placebo endpoints were compared for: placebo-adjusted change from baseline in trough forced expiratory volume in 1 second (FEV₁); St. George's Respiratory Questionnaire (SGRQ), and EXacerbations of COPD Tool-Respiratory Symptoms (EXACT-RS) total scores.

Results: Patients with comorbid MD were younger, predominantly female and current smokers. Treatment with GLY resulted in numerical improvements in the mean trough FEV₁, SGRQ and EXACT-RS total scores compared to placebo, in both subgroups. The mean response in FEV₁ was higher in the NMD subgroup (0.107 L \pm 0.016 vs 0.047 L \pm 0.036). Improvements in SGRQ and EXACT-RS following GLY treatment were observed in both MD vs NMD patients (SGRQ: -3.16 \pm 2.03 vs -3.34 \pm 0.63; EXACT-RS: -2.81 \pm 0.83 vs -0.72 \pm 0.40). Overall, nebulized GLY was generally well tolerated.

Conclusions: GLY treatment was generally associated with improvements in quality of life (SGRQ) and symptoms (EXACT-RS) in patients with COPD and MD as well as patients with NMD, even though the change in lung function was more pronounced in the latter. These findings suggest that comorbid mood disorder may be an important clinical phenotype associated with a differential response profile to bronchodilator therapy.

Funding: Sunovion Pharmaceuticals Inc.

Use of a Comorbidity Count to Assess the Prevalence of Comorbidities in the GOLDEN 3 and 4 Randomized Clinical Trials in Patients with Moderate-to-very-severe COPD

Sanjay Sharma, Thomas Goodin, Ayca Ozol-Godfrey, Shahin Sanjar

Introduction: COPD patients have multiple coexisting comorbidities, affecting quality of life, morbidity and mortality. The prevalence of comorbidities in COPD is unclear, as most randomized clinical trials (RCTs) either exclude or do not characterize comorbidities. Comorbidity prevalence was explored in two RCTs of glycopyrrolate 25 mcg and 50 mcg twice daily, delivered by the eFlow® closed system nebulizer (PARI GmbH, Starnberg, Germany), compared with placebo.

Methods: Pooled Data (n=1,293) from replicate, 12-week studies in patients with moderate-to-very-severe COPD was analyzed to quantify comorbidities using a published comorbidity count method (Putcha et al). The methodology included comorbidities that were present in at least 3% of the cohort. For this analysis, the same comorbidities were included. Patients were grouped as having <3 comorbidities (Group A; n=439) or ≥3 comorbidities (Group B; n=854).

Results: Most patients (66%) had at least three comorbidities. Baseline demographics of Group A and B were similar in age, pack-years and FEV₁ % predicted, while Group A had a higher prevalence of males and current smokers. Group B had a significantly higher prevalence of cardiovascular disease risk factors and heart disease. Depression and anxiety were also significantly more prevalent in Group B (depression [46.8% vs 8.7%]; anxiety [37.0% vs 5.9%]). The median baseline SGRQ total score was also higher in Group B (50.20 vs 46.48).

Conclusion: A comorbidity count demonstrated that most COPD patients in the studies had multiple comorbidities. Group B patients had a higher prevalence of cardiovascular disease risk factors and heart disease, and worse baseline SGRQ scores, despite having similar baseline lung function and smoking exposure. The comorbidity count is a simple method to quantify comorbidities in a COPD RCT population with broad airflow limitation inclusion criteria. These findings represent important clinical phenotypes and highlight the importance of comorbidities in the management of COPD.

Funding: Sunovion Pharmaceuticals Inc.

Effect of Metabolic Syndrome Status on Lung Function and Patient-reported Outcomes in Patients with COPD Receiving Nebulized Glycopyrrolate in the GOLDEN 3 and 4 Studies

Brian Carlin, Gary T Ferguson, Ayca Ozol-Godfrey, Thomas Goodin,³ Shahin Sanjar

Purpose: Concurrent chronic obstructive pulmonary disease (COPD) and metabolic syndrome (MetS) represent an important clinical phenotype based on overlapping symptomatology. The effect of MetS in COPD patients was assessed following treatment with nebulized glycopyrrolate (GLY; administered via eFlow® closed system nebulizer).

Methods: Posthoc analyses were performed on pooled, lung function, patient reported outcome (PRO); and safety data by MetS status from patients treated with placebo, GLY 25 and 50 mcg twice daily in two 12-week studies (GOLDEN 3 and 4; N=1293). Patients with MetS were characterized as having ≥3 of hypertension, hyperlipidemia, diabetes, body mass index >30 kg/m² risk factors. The results are presented for the FDA approved GLY 25 mcg dose.

Results: At baseline, the MetS group had increased BMIs, more ex-smokers, higher incidences of CV risk factors and MetS specific risk factors were 2-14 times higher versus non-MetS. At 12-weeks, GLY produced significant ($p<0.001$), clinically important improvements [MetS (0.121 L); non-MetS (0.083 L)] in trough forced expiratory volume in 1 second (FEV₁). In the non-MetS group, significant improvements occurred in the St George's Respiratory Questionnaire (MetS: -2.28, $p=0.157$; non-MetS: -3.71, $p<0.001$) and EXAcerbations of COPD Tool-Respiratory Symptoms (MetS: 0.42, $p=0.574$; non-MetS: -1.61, $p<0.001$) total scores. Incidence of adverse events (AEs and SAEs) were lower in patients treated with GLY versus placebo regardless of MetS status.

Conclusions: GLY was well-tolerated, significantly improved lung function regardless of MetS status; while significant PRO improvements occurred in non-MetS patients. These results highlight the importance of comorbidities on bronchodilator responses in COPD patients.

Funding: Sunovion Pharmaceuticals Inc.

Effect of Gender on Lung Function and Patient-reported Outcomes in Patients with COPD Receiving Nebulized Glycopyrrolate in the GOLDEN 3 and 4 Studies

Jill Ohar, Ayca Ozol-Godfrey, Thomas Goodin, Shahin Sanjar

Introduction: The impact of gender on lung function and patient-reported outcomes was assessed in patients with moderate-to-very-severe COPD treated with glycopyrrolate (GLY; via eFlow® closed system nebulizer [PARI GmbH, Starnberg, Germany]) 25 mcg twice daily.

Methods: Data from the replicate, 12-week phase 3 GOLDEN 3 (NCT02347761) and GOLDEN 4 (NCT02347774) studies were pooled (N=861) to compare GLY with placebo by gender.

Results: A greater proportion of men had high cardiovascular risk (67.7% vs 59.9%), and used background long-acting beta₂-agonists (33.8% vs 27.6%) or inhaled corticosteroids (31.2% vs 27.1%). Baseline trough FEV₁ was numerically lower and baseline SGRQ total score was numerically higher in women compared with men, while baseline EXACT-RS total scores were similar across genders (Table). GLY led to significant, clinically important placebo-adjusted improvements in trough FEV₁ regardless of gender (men: 0.086 L ±0.019; women: 0.102 L ±0.022). Patients treated with GLY reported significant placebo-adjusted improvements in SGRQ total score, although the improvement was numerically higher in women. Placebo-adjusted EXACT-RS improved in both genders, only women experienced a significant improvement. GLY was well tolerated; the incidence of adverse events was numerically lower in men (placebo: 51%; GLY: 40%) than women (placebo: 54%; GLY: 48%).

Conclusions: Nebulized GLY therapy resulted in significant placebo-adjusted improvements in lung function and SGRQ outcomes, regardless of gender; only women reported a significant improvement in EXACT-RS total score. Despite women with COPD tending to report greater symptoms than men, the effect of nebulized GLY was equivalent in both genders.

Funding: Sunovion Pharmaceuticals Inc.

Efficacy and Safety of Revefenacin in Patients With Chronic Obstructive Pulmonary Disease (COPD) Is Not Age Dependent: A Post Hoc Subgroup Analysis of Three Phase 3 Trials

Sanjay Sethi, James F. Donohue, Mia Barnes, Edmund J. Moran, Chris N. Barnes, Glenn Crater

Introduction: Revefenacin (REV), a once-daily (QD), long-acting muscarinic antagonist delivered via standard jet nebulizer, was approved for the maintenance treatment of COPD. We present post hoc efficacy and safety data from three phase 3 trials in patients with COPD receiving 175-µg REV by subgroup (<65 years, 65–75 years, >75 years).

Methods: Patients received 175-µg REV, 88-µg REV, or placebo (PBO) QD in the 12-week 0126 and 0127 trials and 175-µg REV, 88-µg REV or tiotropium (TIO) 18 µg QD in the 52-week 0128 trial. Efficacy endpoints included the least-squares mean changes of trough forced expiratory volume in 1 second (FEV₁) from baseline to day 85 (0126, 0127). The safety profile was characterized over 52 weeks (0126, 0127, 0128).

Results: There were significantly greater increases in trough FEV₁ from baseline for REV than PBO across all subgroups (all p values <0.022). The safety profiles of REV and TIO were generally similar and consistent across all subgroups. Patients on REV in the >75 years subgroup had fewer adverse events (AEs) than TIO or PBO. Patients in the 65–75 and >75 years PBO subgroups had more AEs leading to permanent discontinuation than REV and TIO. The most reported AE across all treatment arms in the subgroups was worsening/exacerbation of COPD. Serious AEs were comparable between treatments across subgroups; mortality was low.

Conclusions: This post hoc analysis demonstrated that REV and TIO had similar and consistent safety profiles across all subgroups. REV provided consistent benefits in FEV₁ versus PBO across all subgroups.

Funding: Theravance Biopharma US, Inc

Safety and Efficacy of Revefenacin for Nebulization in Patients With Chronic Obstructive Pulmonary Disease (COPD) Taking Concomitant Long-Acting β -Agonist (LABA) or Inhaled Corticosteroid (ICS)/LABA

Sanjay Sethi, James F. Donohue, Gary T. Ferguson, Chris N. Barnes, Glenn D. Crater

Introduction: Revefenacin, a once-daily long-acting muscarinic receptor antagonist administered via standard jet nebulizer, is indicated for maintenance treatment of patients with COPD. Here, we present safety and efficacy results for revefenacin in a subgroup of patients using a LABA-containing medication (LABA alone or LABA/ICS combination; LABA subgroup).

Methods: Data were taken from two 12-week replicate (NCT02512510, NCT02459080) and one 52-week (NCT02518139) randomized, controlled, phase 3 trials. Patients received placebo or 175- μ g revefenacin in the 12-week studies, and 18- μ g tiotropium or 175- μ g revefenacin in the 52-week study. Safety data were pooled across the trials. The efficacy endpoint was least squares (LS) mean change from baseline in 24-hour trough forced expiratory volume in 1 second (tFEV₁) on day 85 for the 12-week studies combined.

Results: Overall, 43% of patients were using concurrent LABA or ICS/LABA combination. Patients in the LABA subgroup had more severe disease at baseline and reported a higher incidence of adverse events (AEs; 50.2% vs 37.5%). The incidence of serious (46.7% vs 34.1%) and antimuscarinic-related (2.5% vs 1.4%) AEs was higher in the LABA than non-LABA subgroup for all treatments. COPD worsening/exacerbation was the most common AE (non-LABA, 11.8%; LABA, 25.0%). Revefenacin produced significant improvements in day 85 tFEV₁ versus placebo ($p < 0.0001$) in the non-LABA (LS mean difference [standard error], 151 [21] mL) and LABA (139 [29] mL) subgroups in the pooled 12-week studies.

Conclusions: Revefenacin was well tolerated and produced greater improvements from baseline in tFEV₁ than placebo among patients with COPD taking LABA-containing medication.

Funding: Theravance Biopharma US, Inc.

Efficacy of Revefenacin by Nebulization and Tiotropium by Handihaler[®] in Patients With Chronic Obstructive Pulmonary Disease (COPD) and Suboptimal Peak Inspiratory Flow Rates (sPIFR)

Donald A. Mahler, Jill A. Ohar, Chris N. Barnes, Edmund J. Moran, Srikanth Pendyala, Glenn D. Crater

Introduction: Some patients with COPD and sPIFR cannot use dry powder inhalers (DPIs) effectively as they cannot generate sufficient inspiratory flow against the resistance of a DPI. These patients may benefit from nebulized therapies. We compared the efficacy of two long-acting muscarinic antagonists—revefenacin for nebulization versus dry powder tiotropium—in patients with COPD and sPIFR (<60 L/min).

Methods: This was a randomized, double-blind, double-dummy, 28-day, phase 3b study. Patients with moderate to very severe COPD and sPIFR received 175- μ g revefenacin via standard jet nebulizer or 18- μ g tiotropium via Handihaler[®]. The primary endpoint was the change from baseline trough forced expiratory volume in 1 second (tFEV₁) on day 29.

Results: We enrolled 206 patients with mean (standard deviation) age, 65 (8) years; percent predicted FEV₁, 37 (16)%; PIFR, 45 (12) L/min. Revefenacin improved tFEV₁ from baseline in the intent-to-treat (ITT) population, but the difference versus tiotropium was not significant (least squares [LS] mean difference [standard error], 17.0 [22.4] mL, $p = 0.45$). In a prespecified analysis of patients with FEV₁ <50% predicted, revefenacin improved tFEV₁ (LS mean difference, 49.1 [21.8] mL; nominal $p = 0.02$) and forced vital capacity (103.5 [48.9]; nominal $p = 0.03$) versus tiotropium. More patients achieved >100 mL increase in FEV₁ with revefenacin than tiotropium in the ITT (41.6% vs 34.4%) and FEV₁ <50% predicted (41.4% vs 25.7%) populations.

Conclusion: Revefenacin for nebulization did not produce significant improvements in tFEV₁ versus dry powder tiotropium in the ITT population, but improved lung function significantly in patients with FEV₁ <50% predicted and sPIFR.

Funding: Theravance Biopharma US, Inc.

Workflow Mapping of Nebulized COPD Therapy in Inpatient and Long-term Care (LTC) Settings in the US: a Precursor to an Observational Time and Motion (T&M) Study

Erwin De Cock, Grace Leung, Grant Maclaine, Hemal Shah, Brooks Kuhn

Background: The economic burden of COPD is substantial with US medical costs projected to rise to \$49 billion by 2020. Standard of care for inpatient and LTC residents requiring COPD pharmacotherapy includes nebulized SABA, SAMA, or SABA+SAMA. There is a lack of understanding of healthcare professional (HCP) time dedicated to nebulized COPD therapy administration. Workflow mapping was performed as a precursor to an observational T&M study.

Methods: A survey was designed to understand (1) center characteristics and pharmacologic COPD therapy, (2) SABA (albuterol) and SABA+SAMA (DuoNeb[®]) nebulization workflow, and (3) estimated time per nebulization. Two HCPs, from inpatient and LTC settings respectively, completed the survey and were interviewed.

Results: DuoNeb is the main choice for short-term therapy. Workflow appeared consistent across settings and bronchodilators. Consecutive tasks performed by respiratory therapists (inpatient) or nurses (LTC) included: (1) collect nebulized drug, (2) collect materials, (3) pre-nebulization assessment, (4) add medication to reservoir, (5) nebulization, (6) clean/discard/store materials, (7) post-nebulization assessment, (8) record-keeping. Minor inconsistencies included the need or not for pre- and post-nebulization assessment, and process for cleaning/discarding/storing materials. Estimated minutes per nebulization for DuoNeb and albuterol were 13 and 27 (inpatient), and 21 and 37 (LTC).

Conclusions: Nebulization workflow appears highly standardized and is expected to consume substantial HCP time. This research confirmed the suitability of the T&M method to accurately quantify HCP time. IRB approval was obtained for the ongoing T&M study, data from which may reveal efficiencies to be gained from nebulized COPD therapies with less frequent dosing regimens.

Funding: Theravance Biopharma US, Inc.,

Reduction in the risk of all-cause mortality with fluticasone furoate/umeclidinium/vilanterol compared to umeclidinium/vilanterol in IMPACT including previously missing or censored vital status data

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Introduction: The IMPACT trial (NCT02164513, CTT116855) demonstrated a statistically significant and clinically relevant reduction in the risk of on-treatment all-cause-mortality (ACM), and ACM including off-treatment data, comparing fluticasone furoate/umeclidinium/vilanterol (FF/UMEC/VI) with UMEC/VI. However, 574 subjects (5.5%) were censored from the original analysis including off-treatment data because of incomplete vital status information at Week 52, suggesting the mortality reduction finding could be fragile. We evaluated ACM following collection of additional vital status data.

Methods: IMPACT (N=10,355) was a 52-week phase III, double-blind, multicenter trial comparing single-inhaler triple therapy FF/UMEC/VI versus FF/VI or UMEC/VI dual therapy (randomized 2:2:1). Time to ACM was a prespecified endpoint. Additional vital status data collection and subsequent analyses were performed post-hoc.

Results: The IMPACT trial demonstrated a 42.1% reduction in the risk of on-treatment ACM (95% CI: 11.9, 61.9; $p = 0.011$), and a 28.6% reduction in the risk of ACM (95% CI: 1.0, 48.6; $p = 0.043$) including off-treatment data, in the intent-to-treat population, comparing FF/UMEC/VI with UMEC/VI. Additional data collection now provides data for 99.6% of the population (42 subjects censored) and identified an additional 27 off-treatment deaths which are included in the analyses. The on-treatment findings are not affected by this data collection and these analyses. There were 98 deaths (2.36%) on FF/UMEC/VI, 109 (2.64%) on FF/VI and 66 (3.19%) on UMEC/VI. For patients randomized to FF/UMEC/VI, the hazard ratio for death was 0.89 (11% reduction; 95% CI 0.67, 1.16; $p = 0.387$) versus FF/VI, and 0.72 (27.7% reduction; 95% CI 0.53, 0.99; $p = 0.042$) versus UMEC/VI, using a Cox proportional hazards model. Sensitivity analyses supported the findings.

Conclusions: Once-daily single-inhaler triple therapy with FF/UMEC/VI reduced the risk of all-cause-mortality compared to UMEC/VI in a large patient population with symptomatic COPD and a history of exacerbations. These results confirm the robustness of the originally reported findings.

Funding: GSK (study CTT116855, NCT02164513).

Improvements in exacerbation rates with single inhaler triple therapy versus dual ICS/LABA therapy in patients with advanced chronic obstructive pulmonary disease (COPD): subgroup analyses of the Phase III FULFIL study

Emma Hilton, Noushin Brealey, Ruby Birk, Chang-Qing Zhu, Gerard J. Criner, Mark T. Dransfield, David Halpin, David A. Lomas, David A. Lipson

Introduction: FULFIL demonstrated statistically significant improvements in lung function and health-related quality of life, and reduced exacerbation rates with once-daily fluticasone furoate/umeclidinium/vilanterol (FF/UMEC/VI) 100µg/62.5µg/25µg administered using an ELLIPTA® inhaler compared with twice-daily budesonide/formoterol (BUD/FOR) 400µg/12µg using Turbuhaler® in patients with symptomatic COPD at risk of exacerbations. The safety profile of FF/UMEC/VI reflected that of the components. Herein we present *post-hoc* subgroup analyses of exacerbation rates by prior COPD medication class, disease severity and exacerbation history during FULFIL.

Methods: In the intent-to-treat (ITT; 24 weeks) population, mean annual exacerbation rate, FF/UMEC/VI versus BUD/FOR ratios, and annual exacerbation rates reductions were calculated for subgroups by: prior COPD medication class (inhaled corticosteroid (ICS)+long-acting beta agonists (LABA); BUD/FOR; ICS+LABA+long-acting muscarinic antagonists (LAMA); LAMA; tiotropium; LAMA+LABA); disease severity (forced expiratory volume in 1 second (FEV₁)<50% predicted, no moderate/severe exacerbation; FEV₁<50%, ≥1 moderate/severe exacerbation; FEV₁≥50-≤80%, ≥2 moderate or ≥1 severe exacerbations); and exacerbation history (0/1 moderate; ≥2 moderate; or ≥1 severe exacerbation).

Results: Up to Week 24 (ITT population), FF/UMEC/VI versus BUD/FOR improved mean annual exacerbation rate (range, 63-24%) in all prior medication subgroups, except LAMA+LABA (annual exacerbation rate reduction, -44%) and improved mean annual exacerbation rates in all disease severity (range, 45-27%) and exacerbation prior history (range, 57-27%) subgroups. Statistical significance of the FF/UMEC/VI:BUD/FOR ratio was observed for subgroups: prior medication class ICS+LABA (0.37; 95% confidence interval [CI] 0.20-0.71; p=0.003) and ICS+LAMA+LABA (0.53; 95% CI 0.33-0.87; p=0.012); disease severity FEV₁<50% and ≥1 moderate/severe exacerbation (0.55; 0.34-0.89; p=0.015); exacerbation history 0/1 prior moderate exacerbation (0.62; 0.44-0.87; p=0.005) and ≥1 prior severe exacerbation (0.43; 0.22-0.86; p=0.017).

Conclusion: Improvements in mean annual exacerbation rates with once-daily FF/UMEC/VI compared with twice-daily BUD/FOR were observed in all patients regardless of disease severity or exacerbation history and all prior COPD medication class subgroups except for LAMA+LABA.

Funding: GSK (NCT02345161; CTT116853)

Efficacy and tolerability of the fixed-dose combinations acclidinium/formoterol, glycopyrronium/indacaterol and umeclidinium/vilanterol for the treatment of chronic obstructive pulmonary disease in daily practice – results of the non-interventional DETECT study

Plate T and Beier J

Introduction: The DETECT study compared the efficacy and tolerability of three approved long-acting muscarinic antagonist/long-acting β₂-agonist (LAMA/LABA) fixed-dose combinations (FDCs) for the treatment of chronic obstructive pulmonary disease (COPD) in real-world clinical practice conditions.

Methods: DETECT was a prospective, non-randomized, 12-month, observational study to assess the effectiveness of acclidinium/formoterol (ACL/FOR, twice daily), glycopyrronium/indacaterol (GLY/IND, once daily.) and umeclidinium/vilanterol (UMEC/VIL, once daily) FDC treatments in patients with COPD who had been switched to LAMA/LABA FDC within the last three months or had planned to switch. Forced expiratory volume in one second (FEV₁), forced vital capacity (FVC), quality of life (COPD Assessment Test [CAT]), early morning COPD symptoms and adverse events (AEs) were assessed.

Results: In total, 3,653 patients were enrolled (ACL/FOR, 2,121 patients; GLY/IND, 1,056 patients; UMEC/VIL, 476 patients). No differences in baseline characteristics were observed between treatment groups. After 15 months FEV₁ and FVC were significantly improved across treatments (ACL/FOR, 0.09 L/0.10 L, respectively; GLY/IND, 0.06 L/0.05 L, respectively; UMEC/VIL 0.12 L/0.10 L respectively). CAT scores decreased over 15 months, indicating a reduction in COPD severity (ACL/FOR, -4.17; GLY/IND, -3.66; UMEC/VIL, -4.06) and early morning COPD symptoms were significantly reduced across all treatment groups. The incidence of AEs was comparable across treatment groups (ACL/FOR, 13.3%; GLY/IND, 13.2%; UMEC/VIL, 12.7%).

Conclusion: ACL/FOR, GLY/IND and UMEC/VIL provided similar clinical benefits in lung function, and COPD symptoms reduction in this broad cohort of patients with COPD under routine medical practice conditions. All three LAMA/LABA FDC treatments were equally well-tolerated

Funding: Circassia

Acclidinium Bromide Treatment in Patients Receiving Beta-Blockers: Effects on MACE, Moderate/Severe COPD Exacerbations, and Lung Function in Patients with Moderate-to-Very-Severe COPD and CV Risk Factors (ASCENT-COPD)

Chapman KR, Wise RA, Scirica BM, Bhatt DL, Daoud SZ, Lythgoe D, Garcia-Gil E

Rationale: ASCENT-COPD, Phase IV, double-blind, parallel-group study assessing the effects of acclidinium on cardiovascular (CV) safety and exacerbations in patients with moderate-to-very-severe COPD and CV risk factors. This post-hoc analysis evaluated the effect of acclidinium in patients receiving beta-blockers at baseline versus those who were not.

Methods: Patients were randomized to acclidinium or placebo for up to 36 months. Outcomes: Time to first MACE (on-study), all-cause mortality; moderate/severe COPD exacerbation rate during the first year (on-treatment) and time to first moderate/severe COPD exacerbation (on-treatment) and change from baseline in morning trough FEV₁ from Week 4-52 (on-treatment).

Results: At baseline, 35.4% patients used beta-blockers. The effect of acclidinium treatment vs placebo on MACE (HR 1.01 vs 0.80; p=0.483) and all-cause mortality (HR 1.13 vs 0.89; p=0.352) did not differ between beta-blocker users and non-users respectively. Acclidinium delayed time to first moderate/severe COPD exacerbation in both groups and reduced the exacerbation rate vs placebo 25% for beta-blocker users and 21% for non-users with no differential treatment effect (interaction p = 0.753). Morning trough FEV₁ improved from baseline with acclidinium versus placebo at all visits with beta-blocker users deriving a greater benefit from acclidinium treatment than non-users, on average (99 mL [95% CI 76, 122] and 69 mL [95% CI 52, 86], respectively, interaction p=0.041).

Conclusions: In COPD patients with CV risk factors, acclidinium did not increase risk of MACE or all-cause mortality, while reducing the rate of moderate/severe exacerbations and prolonging the time to first exacerbation irrespective of beta-blocker use. However, improvements in lung function were significantly better with acclidinium in patients using beta blockers concurrently.

Funding: Circassia

Acclidinium Bromide Added to a Long-Acting β₂-Agonist (LABA) + Inhaled Corticosteroid (ICS): A Post-Hoc Analysis of Exacerbations and Lung Function from the ASCENT-COPD study.

Wise RA, Chapman KR, Daoud SZ, Asmus MJ, Garcia GIL E

Rationale: ASCENT-COPD was a Phase-IV, double-blind, parallel-group study assessing the effects of acclidinium on cardiovascular (CV) safety and exacerbations in patients with moderate-to-very-severe COPD and CV risk factors. This post-hoc analysis evaluated the effect of acclidinium in patients receiving LABA+ICS.

Methods: Patients were randomized 1:1 to inhale acclidinium 400µg or placebo twice daily for up to 36 months. The moderate/severe exacerbation rate over 12-months and change from baseline in trough FEV₁ at week 52 were evaluated in patients receiving concomitant LABA+ICS.

Results: At baseline 2,200 (61%) patients received LABA+ICS (acclidinium arm: N=1,097 ; placebo arm: N=1,103). The moderate/severe exacerbation rate per patient per year in patients receiving concomitant LABA+ICS was significantly reduced with acclidinium versus placebo (RR [95% CI]: 0.77 [0.66, 0.90], p<0.001) and was comparable with reductions observed in the overall population (RR [95% CI]: 0.78 [0.68, 0.89], p<0.001). The change from baseline in trough FEV₁ at week 52 in patients receiving concomitant LABA+ICS significantly improved with acclidinium (mean change + 55mL) versus placebo (mean change -30mL) [mean difference +85mL, p<0.001] and was comparable with FEV₁ change for acclidinium over placebo in the overall population [mean difference +84mL, p<0.001].

Conclusion: The reduced rate of moderate/severe exacerbations and improved lung function seen with acclidinium 400µg twice daily versus placebo was significant and similar in magnitude in patients using background LABA+ICS as compared to those who were not.

Funding: Circassia

Pharmacokinetic (PK) Evaluation of Amikacin Liposome Inhalation Suspension (ALIS) in Patients With Treatment-Refractory Nontuberculous Mycobacterial (NTM) Lung Disease

C Rubino, NJ Onufrak, DE Griffith, K Mange, K Winthrop

Introduction: ALIS is FDA approved as part of a combination antibacterial regimen for adults with treatment-refractory *Mycobacterium avium* complex lung disease and limited or no treatment options. A population PK (PopPK) model was used to describe amikacin disposition in serum following ALIS administration by nebulizer and to compare systemic exposure in Japanese and white patients.

Methods: Data were pooled from PK substudies as part of TR02-112 (phase 2) and CONVERT (INS-212; phase 3) trials assessing ALIS efficacy and safety in adults with treatment-refractory NTM lung disease. In both trials, patients received either nebulized ALIS 590 mg once daily plus ongoing stable guideline-based treatment (GBT) or GBT alone. Serum amikacin C_{max} and AUC_{24} on day 1 and steady-state (day 168) were calculated from individual profiles fitted to candidate PopPK models. Summary statistics described urine and sputum concentrations.

Results: Patients (TR02-112, n=14; CONVERT, n=39) were Japanese (28/53) or white (25/53), with a median age of 63 years and a median body weight of 52.6 kg; most were female (85%). A total of 150 serum samples (TR02-112, n=111; CONVERT, n=39) and 23 urine samples (from TR02-112) were collected. Median AUC_{24} and C_{max} distributions were consistent at day 1 and steady-state, and between white and Japanese patients. On average, $\approx 7\%$ of the total ALIS dose was excreted unchanged in urine. In both studies, median sputum amikacin concentrations were lower predose (7.14-38.2 $\mu\text{g/mL}$) vs postdose (240-3185 $\mu\text{g/mL}$).

Conclusions: ALIS administration in patients with NTM resulted in high amikacin concentrations in sputum and low systemic exposure.

Funding: Insmed

Isolated Pulmonary Nodule Due to Acute Self Limiting Coccidioidomycosis
A. Gandhi, M. Akbik, E. Rojas, P. Bejarano, S. Aleyas;

Introduction: Pulmonary coccidioidomycosis is a fungal disease endemic to the desert regions of the southwestern US, Mexico, Central America and South America. The disease is caused by inhalation of spores of *Coccidioides* species. The infection is self-limited in 60% of cases. The diagnosis is established by direct visualization of mature spherules by using special stains or cultures from biologic specimens. Serologic testing of anticoccidioidal antibodies is used for diagnosis and treatment monitoring.

Case presentation: A 65 year old Caucasian female with past medical history significant for 10 pack year tobacco abuse was referred for evaluation of growing lung nodule. She is an avid traveler and enjoys golfing. About six months ago she had flu like illness which was treated with supportive care. Her symptoms progressed to productive cough, night sweats and fatigue. Her chest radiograph showed focal infiltrate which prompts an empiric antimicrobial course. Subsequently she noticed a skin rash described as a target lesion. Clinically she improved from her acute illness but her chest radiograph showed persistent abnormality hence she underwent a computed tomography scan which showed left upper lobe 2 cm round nodule and mediastinal lymphadenopathy. The positron emission tomography scan showed 1.5 SUV uptake within the nodule. Considering her recent acute illness, smoking history and recent travel to Arizona endemic fungal infections and malignancy were considered. She undergoes an elective bronchoscopy with lavage, endobronchial ultrasound guided transbronchial needle biopsy and electromagnetic navigational bronchoscopy which were unrevealing. Her serologic testing for coccidioidomycosis also returns negative. She underwent video assisted thoracoscopic wedge resection of the lung nodule which showed necrotizing granulomatous inflammation and large fungal organism suggestive of coccidioidomycosis. The fungal culture grew one colony of organism which was identified as *Coccidioides immitis* by DNA gene probe.

Discussion: Pulmonary involvement is categorized into acute, disseminated, and chronic forms, each with a spectrum of imaging findings. In patients with acute disease, the most common findings are lobar or segmental consolidation, multifocal consolidation, and nodules. Adenopathy and pleural effusions are also seen. Disseminated disease is rare and occurs in less than 1% of patients. The acute findings resolve in most patients, with chronic changes developing in approximately 5% of patients. Manifestations of chronic disease include residual nodules, chronic cavities, persistent pneumonia with or without adenopathy, pleural effusion and regressive changes. Patients with immunocompromised state and pregnant women may show severe, progressive, or disseminated disease.

Funding: none

Non-resolving Lobar Pneumonia: A case of Adenocarcinoma with Spread Through Air Spaces

Anneka Hutton MD, Sahar Takkouche MD, Vlad Voin MD, Navneet Kaur MD, Fernando Keller MD

Case presentation: A 79-year-old female with a 20 pack-year smoking history presented with dyspnea on exertion. She noted supine wheezing, but denied cough, fevers or weight loss. Physical examination revealed oxygen saturation of 97% on room air, no use of accessory muscles of respiration and clear lung fields. CBC was without leukocytosis or eosinophilia. CXR revealed right upper lobe consolidation; she was treated for community-acquired pneumonia without improvement. Infiltrate persistence was evident on CXR four weeks later; subsequent CT scan revealed a posterior right upper lobe consolidation with air bronchograms. ESR and CEA were elevated at 46 mm/hour and 37 ng/mL respectively. Bronchoalveolar lavage was negative for infection, malignant cells or endobronchial obstruction. Transbronchial biopsy revealed well-differentiated adenocarcinoma with Napsin A and TTF-1 positivity. Patient underwent lobectomy; pathology revealed lepidic predominant adenocarcinoma measuring 10.5 cm with lymph node positivity. Additionally, microscopy of surrounding tissue revealed noncontiguous tumor nests separate from the primary lesion, confirming spread through air spaces (STAS). Postoperatively her symptoms resolved; however, due to her IIIb stage, she was scheduled for palliative chemotherapy.

Discussion: While adenocarcinoma typically presents as a well-circumscribed peripheral lesion, cases of adenocarcinoma mimicking organizing pneumonia are well described. Pneumonic-adenocarcinoma can be radiologically indistinguishable from organizing pneumonia requiring a high degree of clinical suspicion to minimize diagnostic delay.¹⁻⁵ The consolidation of pneumonic-adenocarcinoma is multifactorial: caused by lepidic tumor growth along alveoli, mucin secretion and tumor shedding into alveoli, and reactive alveolitis.¹⁻⁶ Unlike post-obstructive cancer-associated pneumonia, there is no causative endobronchial lesion.^{4,7} Compared to well-circumscribed adenocarcinoma, complete resection in pneumonic-adenocarcinoma is more difficult, with resultant increased rate of recurrence and decreased rate of survival.^{1,8} Of additional concern is the potential for STAS, a unique pattern of invasion described in lung malignancy in which tumor cells spread beyond the primary tumor through airways. STAS is associated with a significantly increased rate of both local and distant recurrence and is increasingly recognized as a new pattern of tumor invasion. This poses a treatment concern as limited resection or lobectomy to remove the primary lesion may neglect remaining STAS tumor nests.⁹⁻¹¹ Due to prognostic significance of STAS in pulmonary adenocarcinoma, further evaluation of surgical intervention and treatment is required. Additionally, we urge the recognition of STAS as an aggressive invasive tumor behavior and unique method of metastasis.

Finding: none

A Rare Presentation of Broncho-pulmonary Kaposi's Sarcoma

Raiko Diaz, DO; Patricia Almeida, DO; Dionne Morgan, MD

Introduction: Kaposi's Sarcoma (KS) is one of the most common acquired immunodeficiency syndrome (AIDS) defining illnesses. The typical presentation of KS is diffuse cutaneous KS, but it may be seen with visceral involvement as well. It is rare for visceral involvement to occur without skin manifestation.

Discussion: A 67 yo African American male with history of subtotal colectomy was admitted for high ileostomy output. Physical exam was remarkable for cachexia and diffuse rhonchi on lung auscultation. No skin lesions were noted. Despite aggressive treatment he deteriorated and developed respiratory failure requiring mechanical ventilation. Chest CT showed bilateral consolidations. Fiber-optic bronchoscopy showed a violaceous, slightly raised lesion, in the trachea and left main bronchus. The lesion was suspicious for Kaposi's Sarcoma. Cultures were negative. HIV testing returned positive with a low CD4 count and high viral load. Patient unfortunately expired shortly after diagnosis.

KS is mainly a tumor of the skin and muco-cutaneous surfaces but it may affect other organs. Most cases of Broncho-Pulmonary Kaposi's Sarcoma (BPKS) present with muco-cutaneous involvement; in fact, only a few cases of isolated BPKS have been reported in the literature. Patients typically present with nonspecific symptoms as well as non-specific imaging findings. The study with the most diagnostic value is bronchoscopy. Lesions for BPKS appear as violaceous, raised lesions with increased vascularity; usually located in the proximal airways. Appearance of the lesion in a patient with known diagnosis of AIDS and CD4 cell count of less than 150 cells/ μL is enough for diagnosis. Biopsy of endobronchial lesion has a poor yield and is associated with significant risk of bleeding.

Results: Our case presents an unusual presentation of BPKS with no skin involvement. It emphasizes the importance of recognizing uncommon presentations of KS.

Funding: none

Organizing pneumonia as initial presentation of rheumatoid arthritis.

L Wulff, M Akbik, E Rojas, S Gillenwater, J Kaur, A Ghandi, S Palasamudram Shekar, M Gonzalez, L Smolley.

Case: We present a 33-year-old male who presented with an organizing pneumonia (OP). Imaging findings were consistent with this, and the diagnosis of OP was confirmed histologically. On further work-up found to have positive anti-cyclic citrullinated peptide (anti-CCP) antibodies consistent with a diagnosis of rheumatoid arthritis (RA). Several months after diagnosis he developed joint pain. Although OP can be frequently associated with RA, few cases have shown OP as the initial manifestation of RA.

A 33-year-old male with no significant past medical history and a family history of RA, who presented to an outside hospital with a chief complaint of shortness of breath. Recently he had two prior admissions and was treated for pneumonia with steroids and antibiotics. Imaging showed bilateral patchy pulmonary infiltrates. He underwent a lung biopsy which showed a patchy air-space filling process of fibroblasts and myofibroblasts along with inflammatory infiltrate of foamy macrophages and occasional eosinophils, consistent with an organizing pneumonia. He then presented to our institution for further evaluation. Upon presentation he was hemodynamically stable, afebrile and on room air. Physical exam with bilateral rhonchi. Chest X-ray showed bibasilar opacities with diffuse reticulonodular interstitial pattern. Computed tomography chest showed multifocal bilateral reticular and ground-glass opacities predominantly in a peribronchovascular distribution with associated bronchiolectasis. He was treated with prednisone 60mg daily and a prolonged taper. Three months later, with tapering of steroid, he developed a diffuse maculo-papular rash with migratory joint pains mainly in the hands and wrists. Extensive serological work-up revealed elevated anti-CCP 173 units (<20 units), consistent with a clinical presentation of RA. Interstitial lung disease (ILD) is a common extra-articular manifestation of rheumatoid arthritis. The presentation of RA-associated ILD (RA-ILD) can be heterogeneous, however most commonly associated with nonspecific interstitial pneumonia (NSIP), usual interstitial pneumonia (UIP) and OP. Clinically joint involvement and other symptoms of connective tissue disease usually precede lung involvement. However the pulmonary aspect rarely precedes the joint pain, and this can lead to delayed diagnosis. The delay in diagnosis can lead to significant morbidity as treatment is therefore also delayed. Therefore in patients with COP, idiopathic UIP and NSIP, anti-CCP antibodies should be measured to consider RA as a possible etiology even without joint involvement.

Funding: none

A Rare Case of Nocardia beijingensis Lung Abscess Presenting as a Solitary Pulmonary Mass

Christopher D'Angelo Co Author: Jeevna Kaur

Case: Nocardia beijingensis is a recently discovered species first isolated in China in 2001¹. There have only been a few cases reported in the United States (US)². Although nocardia species are considered opportunistic infections, about one third of patients infected are immunocompetent. In this case, we discuss a patient residing in the US with Nocardia beijingensis lung abscess that was initially suspected to be pulmonary neoplasm.

A 57 year old male with past medical history of Hypertension, Anxiety and a 20 pack year smoking history (quit 3 months prior) who presented to the emergency department with exertional dyspnea and pleuritic left upper chest pain for the past one month. He also endorsed a 20 pound unintentional weight loss and malaise. He had a chronic dry cough that was at baseline. He denied night sweats, fever, chills, sick contacts or recent international travel. He also denied contact with individuals who may have travelled outside of the US. Mentioned he worked on a golf course here in Florida as a groundskeeper.

Vitals on initial presentation were notable for tachycardia and tachypnea. Physical exam was notable for erythematous plaques on the dorsum of both hands. Lungs clear to auscultation bilaterally. Laboratory studies showed leukocytosis count and elevated inflammatory markers. Human immunodeficiency virus testing was non-reactive and Immunoglobulin testing was within normal limits.

CT scan of the chest showed a 3.8 x 2.5cm left lingular spiculated mass and mild hilar adenopathy. Given his history of smoking, weight loss and malaise, there was concern for malignancy. He mentioned that this "mass" was worked up previously, which included two CT guided needle biopsy which showed plasmocytic lymph cells, along with a bronchoscopy with biopsy. He was subsequently admitted for further workup.

Cardiothoracic surgery was consulted, and the patient underwent left upper lobectomy, video-assisted thoracoscopic surgery, and lymph node resection. The gross specimen was consistent with abscess. Intra-operative frozen section showed abscesses and benign anthracotic lymph node tissue. Culture results from the tissue sample grew Nocardia beijingensis. Subsequently, initial cultures obtained via bronchoscopy also came back positive after four weeks for Nocardia beijingensis by 16S rDNA gene sequencing. There was no evidence of malignancy and the patient was treated with six weeks of intravenous Ceftriaxone and Bactrim, and his symptoms improved.

When evaluating lung masses, it is important to include fungal cultures as part of the workup. What initially was deemed highly suspicious for primary lung neoplasm was found to be quite the contrary. Furthermore, the long incubation period of Nocardia from the bronchoscopy added to the diagnostic uncertainty of this case.

Given the patient's lack of any type of immunodeficiency, a symptomatic Nocardia beijingensis infection is indeed a rare finding and there are only a few reported cases in the United States. His physical exam findings, most notably the skin, and his occupation as a groundskeeper in contact with soil and fresh pond water, all pose diagnostic clues as to the nature of his infection, and stress the importance of paying attention to details throughout this interesting case.

Funding: none

A Rare Case of Adult-onset Severe Laryngomalacia

Jeevna Kaur, Christopher D'Angelo, Samantha Gillenwater, Sajive Aleyas, Ihab AlShelli

Introduction: Laryngomalacia (LM) is a congenital disorder resulting in decreased laryngeal tone and supraglottic collapse¹. Although common in pediatric populations, its presentation during adulthood is a rare occurrence. The following is a case of adult-onset severe LM masquerading as tracheal stenosis.

Case Report/ Clinical Case: A 56 year old female with a 40 pack year smoking history presented to emergency department with progressive dyspnea at rest and with exertion. Past medical history included asthma-chronic obstructive pulmonary disease (COPD) overlap syndrome (ACOS) on home oxygen and Bi-level non-invasive ventilation, obstructive sleep apnea (OSA), prior tracheostomy following pneumonia (decannulated after 9 months). Physical exam revealed diminished breath sounds bilaterally. She was initially treated for COPD exacerbation but was subsequently intubated for worsening hypercapnic respiratory failure. Bronchoscopy during intubation showed subglottic stenosis involving the second tracheal ring, thought to be a complication of previous tracheostomy. Electrocautery and balloon dilation were performed, and the patient was extubated after a few days. She was evaluated for stent placement but was deemed not to be a suitable candidate due to the proximal location of lesion.

Following extubation, the patient experienced persistent dyspnea with poor functional capacity. Neuromuscular disease workup was negative. She underwent laryngoscopy and bronchoscopy with ENT at bedside, without intubation, which revealed severe laryngomalacia with airway collapse at the level of the arytenoids, along with persistent subglottic stenosis. No significant dynamic airway collapse was appreciated. A plan was made for direct laryngoscopy and supraglottoplasty. However, due to the patient's multilevel obstruction with laryngomalacia as well as tracheal stenosis from significant tracheal granulation tissue, it was decided that the best management was tracheostomy.

Discussion: There have only been a handful of documented cases of LM in adults. It is distinct from intermittent laryngeal obstruction (ILO), a transient, reversible laryngeal dysfunction in response to environmental triggers². Cases of irreversible LM require surgical intervention (supraglottoplasty) for symptomatic relief, whereas in ILO conservative management may be effective³. In our patient, the case was complicated by concomitant tracheal stenosis, which would have made supraglottoplasty alone ineffective.

In the literature, LM is noted to be the most common cause of stridor in neonates, with only 10% of cases requiring surgical intervention. Late onset LM is a much less reported phenomenon. The most common presenting clinical symptom in older individuals is exercise intolerance, though our patient had persistent symptoms despite the level of activity. Conservative management of ACOS, gastroesophageal reflux and laryngoesophageal reflux are all noted to be unsuccessful. One prospective study showed supraglottoplasty relieved patient symptoms in each late-onset LM group and helped confirm LM as the source of disease⁴. It is unclear why some patients develop LM after infancy, as in our patient. There have been previously reported cases of late-onset or acquired LM being associated with neurologic injury and neuromuscular hypotonia.

Funding: none

Septic Shock Attributed to *Elizabethkingia meningosepticum* Bacteremia

Patricia Almeida, D.O., Raiko Diaz, D.O., Daniel Heller, M.D.

Introduction: *Elizabethkingia meningosepticum* is a gram-negative bacteria ubiquitously found in the environment. Its pathogenesis has most commonly been described in cases of neonatal meningitis¹. We report a case of *E. meningosepticum* bacteremia in an immunosuppressed patient, resulting in septic shock and multi-organ failure.

Case Description: A 79 year old Caucasian male with history of ischemic cardiomyopathy, paroxysmal atrial fibrillation, diabetes, stage III chronic kidney disease, and idiopathic thrombocytopenic purpura on chronic prednisone presented to our institution with altered mental status. Hemodynamics were notable for atrial fibrillation with rapid ventricular response and an adequate blood pressure. Physical exam was significant for confusion, bilateral lung crackles, +2 pitting edema of the lower extremities, and diffuse ecchymosis. Labs revealed lactic acidosis, thrombocytopenia, impaired renal function, and significant electrolyte derangements. Computed tomographies of the brain, chest, abdomen, and pelvis were negative for acute pathology. Despite being started on empiric cefepime and vancomycin, the patient rapidly progressed to septic shock requiring vasopressor support and intensive care monitoring. Initial blood cultures resulted in growth of gram-negative rods in all bottles, therefore, antimicrobial coverage was broadened to meropenem. On the second hospital day, blood cultures finalized with growth of *Elizabethkingia meningosepticum*, which was resistant to most antibiotics, including beta-lactams and aminoglycosides, and only sensitive to fluoroquinolones, tetracyclines, and rifampin. Urine culture grew 50,000 CFU/ml of extended-spectrum beta-lactamase *Klebsiella pneumoniae*, which was thought to represent colonization. In addition to meropenem, levofloxacin, doxycycline, and rifampin were started. The patient progressed to shock liver and anuric renal failure, necessitating hemodialysis. He had a prolonged hospital course, which was complicated by encephalopathy, worsening deconditioning, coagulopathy, and severe protein calorie malnutrition. He completed a ten day course of levofloxacin, doxycycline, and rifampin, with successful clearance of blood cultures. He was discharged to a long-term acute care facility after his twenty day hospitalization.

Discussion: *Elizabethkingia meningosepticum* is a gram-negative bacteria found in soil and water that has been implicated in cases of neonatal meningitis, and less commonly, nosocomial infections in immunocompromised hosts^{1,2}. *E. meningosepticum* is inherently resistant to antibiotics used for the empiric treatment of septic shock, therefore, prompt diagnosis is essential in order to effectively tailor antimicrobial coverage².

Funding: none

Breathing Outside Your Lungs: A case of an Extrathoracic Lung Herniation

Naveet Kaur MD, Angel Sanchez MD, Gagandeep Samra BS, Ralph Palumbo MD

Introduction: Extrathoracic lung herniation, a rare entity; can be congenital or acquired. Acquired lung herniations are further classified into: traumatic, pathologic and sporadic [1]. Sporadic lung herniation is a protrusion of lung parenchyma and pleural membranes beyond the confines of the thoracic cavity through an abnormal opening in the chest wall, diaphragm or mediastinum without preceding trauma or pathological process [2].

Case Presentation: A 71-year-old male with a past medical history of COPD and a stable right lung mass presented to the emergency department with a 3 day history of shortness of breath and left sided chest pain. Patient denied chest trauma. He was afebrile, tachycardic, tachypneic and hypotensive. Chest auscultation revealed decreased breath sounds in the left lower lobe. Laboratory data revealed: leukocytosis, D-dimer 0.73, BUN 36, creatinine 2.1, lactic acid 2.3. CXR revealed a large left pleural effusion. Chest CT with contrast revealed new loculated left pleural effusion with air bronchograms noted at the left lung base. 550cc of clear amber fluid was removed via thoracentesis. A diagnosis of left lower lobe pneumonia with parapneumonic effusion and possible empyema was made and treatment with clindamycin, levofloxacin and IV solumedrol was begun. A CXR two days after admission showed minimal decrease in loculated fluid with consolidation at the left lung base still present. The patient underwent left tube thoracostomy later and dornase alfa and intrapleural tPA was started for loculations. After receiving dornase alfa, 2 hours post intrapleural tPA, he immediately experienced worsening dyspnea, diaphoresis with 91% saturation on a non-rebreather. Right thoracic asymmetry was noted, with a soft, reducible mass corresponding with the region of swelling that increased in size with inspiration and decreased with expiration. CXR was negative, but CT Chest revealed lung herniation between the right anterior 3rd and 4th ribs with partial resection of the right anterior 4th rib. The patient was transferred to the ICU and started on high flow oxygen with conservative treatment.

Discussion: Extra thoracic lung herniations are relatively rare, and acquired ones may be due to trauma, pathology or sporadic. Sporadic herniations occur due to sudden increase in intrathoracic pressure seen with coughing, sneezing, blowing or heavy lifting [3]. COPD, is a predisposing factor as it decreases surfactant surface tension in the alveolar parenchyma causing hyperinflation [4]. Our patient had a history of COPD exacerbated with left lower lobe pneumonia, empyema and coughing in the setting of a previous right side surgery. Management of pulmonary hernias depend on symptoms, location and size.

Funding: none

Diffuse Pulmonary Lymphangiomatosis – a Rare Cause of Wheezing and NSIP

Andrew Daya, MD; Christine Girard, MD; Nydia Martinez, MD

Introduction: The lymphatic system plays a pivotal role in immunological and circulatory homeostasis. Disorders of the pulmonary lymphatic system occur in a variety of clinical settings, such as cancer, trauma, and in rare cases, congenital errors in lymphatic development. Lymphangiomatosis is a rare disorder defined by the presence of multiple lymphangiomas, which are focal proliferations of well differentiated lymphatic tissue, and is typically associated with other lymphatic related abnormalities. Lymphangiomatosis has been described at any age, however, frequently presents in late childhood. We report a rare case of wheezing due to lymphangiomatosis.

Case Report: A 42 year old gentleman presented to our clinic for evaluation of persistent wheezing. He initially presented with persistent fevers after an upper respiratory tract infection and was found to have bilateral infiltrates and a chyloous pericardial and pleural effusion. A wedge resection demonstrated interstitial lymphoplasmocytic infiltrates, peribronchiolar and interstitial lymphocytic aggregates with foci of emphysema, and immunohistochemical techniques failed to demonstrate LAM cells. He was given a diagnosis of lymphangiomatosis. He has no other notable past medical history. His family history is negative for asthma or atopy. He is a never smoker. His physical examination was notable for a pulse oximetry of 97% on room air, diffuse expiratory wheezing, and decreased breath sounds at the left base. Pulmonary function tests (PFT) show moderately severe obstruction without bronchodilator response with a mildly reduced diffusing capacity. CT imaging of the chest demonstrates mid to upper lung predominant bronchiectasis, architectural distortion, cystic spaces, bronchial wall thickening, ground glass and consolidative opacities, mild to moderate air trapping on expiratory imaging, and a loculated left pleural effusion. The CT imaging overall favored a nonspecific interstitial pneumonia (NSIP) pattern. The patient was placed on combined long acting beta agonist with inhaled corticosteroids and has had mild improvement in respiratory symptoms.

Discussion: Lymphangiomatosis is a rare congenital disorder. Thoracic and bone involvement are common. The combination of lytic bone lesions and chylothorax is clinically suggestive. This patient presented with wheezing to an outpatient clinic, highlighting an unusual cause of wheezing. Many patients with lymphangiomatosis experience wheeze and therefore may be misdiagnosed as asthma. Additionally, our patient had obstructive PFT's and air trapping on CT, further mimicking obstructive airway disease. Additionally, in this case, lymphangiomatosis was also presenting with an NSIP like pattern.

Funding: none

Use of Cardiopulmonary Bypass during cardiac arrest due to massive Pulmonary Thromboembolism.

Rajaganesh Rajagopalan , Sanjay Theodore

Case Summary: 53 year old Male was transferred to ICU following a cardiac arrest on POD 1 post open hernia repair. Chest compressions were ongoing during transport, CPR was continued per ACLS protocol, pulseless electrical activity was noted during rhythm checks. ROSC was achieved after 15 minutes of CPR. Bedside ECHO was done following ROSC, enlarged RV with paradoxical bowing of the interventricular septum into the left ventricle was noted. Patient went into PEA cardiac arrest again, diagnosis of massive Pulmonary Thromboembolism was considered, tPA was contraindicated due to recent abdominal surgery. CPR was continued for 15 more minutes without ROSC. Cardiac surgery was consulted for bedside ECMO cannulation and pulmonary artery thrombectomy. Femoro-femoral veno-arterial cannulation was performed, cardiopulmonary bypass was initiated. Patient was cooled to 35°C. Saddle pulmonary embolus was removed during exploration of the pulmonary artery. The patient was weaned off cardiopulmonary bypass in the OR after thrombectomy, and extubated 12 hours later. Patient did not have any neurological deficits and was subsequently discharged 48 hours later.

Conclusion: Bedside ECHO played a key role in the diagnosis of massive pulmonary thromboembolism when transfer for CT was not feasible. Cardiopulmonary bypass is an alternative to ECMO device for extra-corporal life support during CPR.

Funding: none

Real-World Biologic Medication Use in a Diverse Population of U.S., Specialist-Treated Adults with Severe Asthma: Results of CHRONICLE Study

Wendy C. Moore, Warner Carr, Bradley E. Chipps, Dennis K. Ledford, Njira Lugogo, Reynold A. Panettieri, Jr., Weily Soong, Jennifer Trevor, Laura Belton, Frank Trudo, Christopher S. Ambrose

Introduction: Several biologic therapies are now available in the United States for treatment of severe asthma (SA). However, few data reflect real-world use of individual biologic therapies by patients with SA treated by U.S. subspecialists.

Methods: The CHRONICLE Study is an ongoing, non-interventional, observational study of U.S. adults with SA treated by a diverse sample of U.S. allergists/immunologists or pulmonologists. Protocol-eligible patients are adults receiving biologics and/or maintenance systemic corticosteroids (mSCS), as well as those uncontrolled per ERS/ATS criteria while receiving high-dose inhaled corticosteroids with additional controllers (HD ICS+). For enrolled patients, sites reported details of any biologic therapy use within 12 months prior to enrollment, including start dates prior to the 12-month period. Use of individual biologic medications were summarized by time period for overall use, as well as initiations or terminations of a specific product. Biologic switches and concomitant use of anti-IgE and anti-IL-5/anti-IL-5R α biologic therapies were also summarized.

Results: Between 2/27/18 and 2/1/19, 89 sites evaluated 1,428 eligible patients; 936 patients enrolled, and 798 had all baseline forms completed. Of these patients, 557 had data regarding current or prior use of biologic therapies available for analysis. Anti-IgE (omalizumab) prevalence (51%) and anti-IL-5/anti-IL-5R α therapy prevalence (48%) were similar, with anti-IL-5/anti-IL-5R α most prevalent among biologic therapy initiations since December 2017. There were 10 concomitant uses of biologic therapies reported for 8 patients (1% of biologic therapy recipients). Overall, 43 biologic therapy switches were reported for 43 patients (8% of all biologic therapy recipients); 23 were between anti-IL-5 and anti-IL-5R α , 18 were inter-class (between anti-IgE and anti-IL-5/anti-IL-5R α) and 2 patients switched to dupilumab. The most common switch was from mepolizumab to benralizumab (n=17). The most commonly reported reasons for switching biologic treatments were asthma symptom worsening (n=14), medication was never effective (n=5), and medication effectiveness waned and is now ineffective (n=5).

Conclusions: In this sample of 557 U.S. patients with SA treated with biologic therapies by U.S. subspecialists, the most prevalent biologic therapy was omalizumab. However, anti-IL-5/anti-IL-5R α biologic treatments were predominant in those initiating therapy since December 2017. Switching most commonly occurred among anti-IL-5/anti-IL-5R α agents. Concomitant use of >1 biologic treatment occurs rarely. A limitation of these data is that sites were only required to report biologic therapy use that was ongoing in the 12 months prior to enrollment.

Funding: AstraZeneca

Change in Post-Bronchodilator FEV₁ for Patients with Severe Asthma with Eosinophilic Features Following Benralizumab Therapy

Sameer K. Mathur, Brian D. Modena, Hanneke Coumou, Amol P. Kamboj, Peter Barker, James Kreindler, James G. Zangrilli

Introduction: Benralizumab, an interleukin-5 receptor alpha-directed cytolytic monoclonal antibody, uniquely depletes blood and tissue eosinophils via enhanced antibody-dependent cell-mediated cytotoxicity. We examined whether benralizumab improves post-bronchodilator lung function for patient subgroups with severe asthma and eosinophilic features.

Methods: We assessed post-bronchodilator FEV₁ (post-FEV₁) for at-risk subgroups in a *post-hoc* analysis of pooled data from the Phase III SIROCCO (48 weeks; NCT01928771) and CALIMA (56 weeks; NCT01914757) trials. Subgroups were defined by previously identified predictors of enhanced benralizumab response: ≥ 3 exacerbations in prior year, baseline pre-bronchodilator forced vital capacity <65% of predicted (FVC <65%), adult-onset disease, and nasal polyposis. Subgroups were further classified by blood eosinophil counts (<300 vs. ≥ 300 cells/ μ L). All *p*-values were nominal.

Results: Improvements in post-FEV₁ for patients with ≥ 3 exacerbations in prior year, FVC <65%, adult-onset disease, or nasal polyposis were greater with benralizumab than placebo (by 170, 230, 150, and 330 mL, respectively; all *p*<0.0001). Patients with blood eosinophil counts ≥ 300 cells/ μ L and ≥ 3 exacerbations in prior year, FVC <65%, adult-onset disease, or nasal polyposis had greater improvements with benralizumab than placebo (by 190, 270, 180, and 310 mL, respectively; all *p*<0.005). Post-FEV₁ also improved with benralizumab vs. placebo for patients with blood eosinophil counts <300 cells/ μ L and ≥ 3 exacerbations in prior year (140 mL) or nasal polyposis (340 mL; both *p*<0.05).

Conclusions: At-risk patients with frequent exacerbation, poor baseline lung function, adult-onset disease, or nasal polyps who were treated with benralizumab had more clinically meaningful improvements in post-FEV₁ than those who received placebo. For these first three subgroups, the difference was more pronounced for patients with blood eosinophil counts ≥ 300 cells/ μ L. Although further investigation is needed, our data suggest that patients with these predictors and greater eosinophilic burdens may have improvements in airway physiology or remodeling following benralizumab treatment.

Funding: AstraZeneca

Patients Remaining Exacerbation-Free During Benralizumab Treatment Compared with Placebo: Analysis of Pooled Data from the SIROCCO and CALIMA Trials

Frank Trudo, Eugene R. Bleecker, J. Mark FitzGerald, Peter Barker, Viktoria Werkstrom, Sarang Rastogi, Ubaldo Martin

Introduction: Asthma exacerbations disrupt patients' daily activities and may result in emergency department (ED) visits or hospitalizations. Benralizumab is an anti-eosinophilic monoclonal antibody that significantly reduces asthma exacerbations, improves lung function, and alleviates symptoms for patients with severe, uncontrolled, eosinophilic asthma. We aimed to determine if benralizumab treatment also increases the percentage of exacerbation-free patients relative to placebo.

Methods: We pooled data from two Phase III trials, SIROCCO (NCT01928771; *Lancet*. 2016;388:2115–27) and CALIMA (NCT01914757; *Lancet*. 2016;388:2128–41). Patients in the pooled population were ≥ 12 years old, received high-dosage inhaled corticosteroids/long-acting β_2 -agonists, and had baseline blood eosinophils ≥ 300 cells/ μ L. In the SIROCCO and CALIMA trials, patients received benralizumab 30 mg every 4 weeks (Q4W; n=516), benralizumab 30 mg every 8 weeks (Q8W; first three doses every 4 weeks; n=506), or placebo (n=515). This analysis examined overall exacerbations and exacerbations requiring ED visits and/or hospitalizations over the course of both trials (SIROCCO: 48 weeks; CALIMA: 56 weeks).

Results: More patients were exacerbation-free with benralizumab Q4W (332 patients [64%]) and benralizumab Q8W (318 patients [63%]) than with placebo (254 patients [49%]); 98 patients (19%), 115 patients (23%), and 108 patients (21%), respectively, experienced one exacerbation. Two or more exacerbations were experienced by 86 (17%), 73 (14%), and 153 (30%) patients, respectively. The mean number of days with exacerbations per year was also less for benralizumab-treated patients (Q4W: 6.5 days; Q8W: 6.0 days) compared with placebo (11.6 days). Compared with placebo, fewer patients in the benralizumab Q4W and Q8W treatment groups experienced exacerbations that required ED visits or hospitalizations (44 [9%] and 38 [8%], respectively) than with placebo (57 [11%]).

Conclusions: Most benralizumab-treated patients were exacerbation-free throughout the SIROCCO and CALIMA studies, whereas about half of patients in the placebo group experienced exacerbations. Fewer than one-fifth of benralizumab-treated patients experienced >1 exacerbation during these trials, compared with almost one-third of those receiving placebo.

Clinical implications: By increasing patients' likelihood of remaining exacerbation-free, benralizumab improves patients' asthma control, lessens exacerbation-related loss of lung function, and reduces exposure to oral corticosteroids. Increasing exacerbation-free days could also decrease disease-related disruptions in patients' daily activities and potentially reduce health care costs associated with ED visits and hospitalizations.

Funding: AstraZeneca

Safety profile of nintedanib in patients with systemic sclerosis-associated interstitial lung disease (SSc-ILD) and idiopathic pulmonary fibrosis (IPF)

Kristin B. Highland, Oliver Distler, Martina Gahlemann, Arata Azuma, Toby M. Maher on behalf of the SENSIS trial investigators

Introduction: Nintedanib has been investigated in patients with SSc-ILD in the SENSIS trial and IPF in the two INPULSIS trials. These patient populations differ in age, sex, disease characteristics and comorbidities. The objectives of this analysis were to compare the safety and tolerability of nintedanib in patients with SSc-ILD and IPF.

Methods: Adverse events that occurred over 52 weeks of treatment in the SENSIS and INPULSIS trials were assessed descriptively in subjects who received ≥ 1 dose of trial drug.

Results: A total of 576 subjects were treated in the SENSIS trial (288 nintedanib; 288 placebo) and 1061 in the INPULSIS trials (638 nintedanib; 423 placebo). At baseline, mean (standard deviation) age was 54.0 (12.2) and 66.8 (8.0) years in SENSIS and INPULSIS, respectively. The proportion of males was 24.8% and 79.3%, respectively. Over 52 weeks, 19.4% and 10.8% of patients treated with nintedanib and placebo discontinued treatment in SENSIS, compared with 24.5% and 18.9% of patients treated with nintedanib and placebo in INPULSIS. Gastrointestinal adverse events were the most frequently reported adverse events with nintedanib and, as expected based on the underlying disease, were more frequent in patients with SSc-ILD than IPF in both treatment groups. Diarrhea adverse events were reported in 75.7% and 31.6% of patients treated with nintedanib and placebo in SENSIS, and 62.4% and 18.4% of patients treated with nintedanib and placebo in INPULSIS, respectively.

Conclusion: The safety and tolerability profile of nintedanib in patients with SSc-ILD is similar to that observed in patients with IPF.

Funding: Boehringer Ingelheim

Nintedanib reduced decline in forced vital capacity (FVC) across subgroups of patients with systemic sclerosis-associated interstitial lung disease (SSc-ILD): data from the SENSIS trial

Oliver Distler, Kristin B. Highland, Martina Gahlemann, Arata Azuma, Toby M. Maher on behalf of the SENSIS trial investigators

Introduction: In the SENSIS trial, nintedanib reduced the progression of SSc-ILD compared with placebo, as demonstrated by a significantly lower rate of decline in FVC over 52 weeks (primary endpoint). The objectives of this analysis were to assess the effect of nintedanib on the rate of decline in FVC in the SENSIS trial across pre-specified subgroups defined by baseline characteristics.

Methods: Patients with SSc-ILD with onset of first non-Raynaud symptom <7 years before screening and $\geq 10\%$ fibrosis of the lungs on a high-resolution computed tomography scan were randomized to receive nintedanib 150 mg bid or placebo double-blind. The annual rate of decline in FVC (mL/year) assessed over 52 weeks (primary endpoint) was analyzed in the overall population using a random coefficient regression model (with random slopes and intercepts) including anti-topoisomerase I antibody status, age, height, gender and baseline FVC as covariates. Analyses in subgroups by baseline characteristics included additional terms for treatment-by-subgroup and treatment-by-subgroup-by-time interaction.

Results: A total of 576 patients were treated (288 in each group). Most (75.2%) patients were female, 51.9% had diffuse cutaneous SSc, and 48.4% were taking mycophenolate at baseline. Mean (\pm standard deviation) age was 54.0 \pm 12.2 years and 21.4% of patients were aged ≥ 65 years. Nintedanib had a consistent effect on reducing the rate of FVC decline across pre-specified subgroups defined by baseline characteristics (*p*>0.05 for all treatment-by-time-by-subgroup interactions).

Conclusion: Nintedanib is effective at reducing ILD progression in a broad range of patients with SSc-ILD.

Funding: Boehringer Ingelheim

Characteristics of patients with progressive fibrosing interstitial lung disease (ILDs) in the INBUILD trial of nintedanib

Kevin R Flaherty, Athol U Wells, Emmanuelle Clerisme-Beaty, Vincent Cottin, Kevin K Brown on behalf of the INBUILD trial investigators

Introduction: Nintedanib is an intracellular inhibitor of tyrosine kinases that slows the rate of disease progression in patients with idiopathic pulmonary fibrosis (IPF). Non-clinical data suggest that nintedanib may inhibit the progression of lung fibrosis irrespective of the trigger.

Methods: The efficacy and safety of nintedanib in patients with non-IPF progressive fibrosing ILDs are being studied in the Phase III INBUILD trial. Eligible patients had features of diffuse fibrosing lung disease of >10% extent on high-resolution computed tomography (HRCT), forced expiratory volume (FVC) $\geq 45\%$ predicted, diffusing capacity of the lungs for carbon monoxide (DLco) ≥ 30 – $<80\%$ predicted, and met ≥ 1 of 4 protocol-defined criteria for ILD progression in the 24 months before screening, despite treatment with medications used to treat ILDs in clinical practice. Patients were randomized to receive nintedanib 150 mg bid or placebo double-blind for at least 52 weeks. The primary endpoint is the annual rate of decline in FVC (mL/year) assessed over 52 weeks.

Results: A total of 663 subjects in 15 countries were randomized and received ≥ 1 dose of trial medication. The most common diagnoses were hypersensitivity pneumonitis (25.5%), idiopathic nonspecific interstitial pneumonia (18.9%), unclassifiable idiopathic interstitial pneumonia (16.6%) and rheumatoid arthritis-associated ILD (13.1%). Mean (\pm standard deviation) age was 65.8 ± 9.8 years, FVC was $69.0 \pm 15.7\%$ predicted and DLco was $47.7 \pm 32.2\%$ predicted. Approximately half of the trial participants had a relative decline in FVC $\geq 10\%$ predicted in the 24 months before screening. Based on central review of HRCT scans, 410 patients (61.8%) had a usual interstitial pneumonia-like fibrotic pattern (based on INPULSIS trial criteria) and 253 (38.2%) patients had other fibrotic patterns.

Conclusions: The INBUILD trial will provide insights into the potential role of nintedanib in treating progressive fibrosing ILDs other than IPF.

Funding: Boehringer Ingelheim

The fevipiprant Phase IIIb systemic corticosteroid avoidance study: SHIELD

Klaus F. Rabe, Arnaud Bourdin, Roland Buhl, William W. Busse, John Strigkas, Chaitali Babanrao Pisal, Simone Hiltl, Claudia Mailaender, Sebastian Fucile, Pablo Altman

Introduction: Short courses of systemic corticosteroids (SCS) are widely used in asthma; however, they are associated with a significant risk of side effects. Fevipiprant, an oral, selective prostaglandin D₂ receptor antagonist, is in development for the treatment of patients with asthma. The Phase IIIb SHIELD study (NCT03629249) will assess the efficacy of two doses of fevipiprant versus placebo, both added to flexible background standard-of-care (SoC) therapy, in terms of reduction in total SCS dose in patients with severe asthma.

Methods: This 52-week, multicenter, double-blind, double-dummy, placebo-controlled, parallel-group study will randomize (1:1:1) patients (aged ≥ 18 years) with inadequately controlled severe asthma receiving Global Initiative for Asthma Step 4 SoC at baseline to oral once-daily fevipiprant (150 or 450 mg) or placebo on top of SoC. All patients will receive flexible SoC background therapy (high-dose inhaled corticosteroid/long-acting β_2 -agonist \pm long-acting muscarinic antagonist).

Results: Primary endpoint: Reduction in total SCS dose over 52 weeks in patients with severe asthma with high blood eosinophil counts (≥ 250 cells/ μ L) and in all patients with severe asthma. Relevant secondary endpoints: proportion of patients prescribed with biological therapy and time to first prescription; change in Asthma Control Questionnaire-5 and Asthma Quality of Life Questionnaire scores. Safety will be assessed in terms of adverse events, vital signs, electrocardiogram, and laboratory analysis.

Conclusions: Results of this study should provide evidence of the efficacy of fevipiprant in reducing SCS use in patients with severe asthma.

Funding: Novartis Pharma AG, Basel, Switzerland.

Long-term safety of fevipiprant in patients with asthma inadequately controlled on standard-of-care therapy: design of the Phase III SPIRIT study

Edward M. Kerwin, Motokazu Kato, Jorge F. Maspero, James M. Felsler, Bryan Boone, Mary Smolen, Sophia Wang, Barbara Knorr

Introduction: Fevipiprant is an oral, selective prostaglandin D₂ receptor antagonist that has been shown to reduce eosinophilic airway inflammation, resulting in improvements in lung function and symptoms in patients with asthma. Here, we present the design of the SPIRIT study (NCT03052517), which will assess the long-term safety of fevipiprant added to standard-of-care (SoC) therapy.

Methods: SPIRIT is a two-treatment-period, randomized, placebo-controlled, parallel-group study in patients (aged ≥ 12 years; N=1570) with moderate to severe asthma. Patients with asthma inadequately controlled (Asthma Control Questionnaire score ≥ 1.5) on Global Initiative for Asthma 2016 Steps 3, 4, and 5 SoC therapy will be randomized (3:3:1) to add-on therapy with once daily fevipiprant (150 or 450 mg), or placebo during both treatment periods (period 1: 52 weeks, double-blind; period 2: optional 104 weeks, single-blind). Patients who have (~ 1000) and have not (~ 570) completed a Phase III study of fevipiprant are eligible.

Results: The primary endpoints will be time to first: treatment-emergent (TE) adverse event (AE); TE serious AE; and TEAE leading to discontinuation in treatment period 1, and periods 1 and 2 combined. Secondary endpoints will be rate of patients with ≥ 1 TEAE and TE deaths or hospitalizations due to an asthma exacerbation in treatment period 1, and periods 1 and 2 combined.

Conclusions: Results will provide evidence for the long-term safety of add-on treatment with fevipiprant in patients with asthma inadequately controlled on SoC therapy.

Funding: The study was funded by Novartis Pharma AG, Basel, Switzerland.