P272 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

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Results from FULFIL have shown statistically significant improvements in lung function and health-related quality of life, and a reduction in exacerbation rates with once-daily fluticasone furoate/umeclidinium/vilanterol (FF/UMEC/VI) 100 µg/62.5 µg/25 µg administered using a single ELLIPTA® inhaler compared with twice-daily budesonide/formoterol (BUD/FOR) 400 µg/12 µg using the Turbuhaler® in patients with symptomatic COPD at risk of exacerbations. The safety profile of FF/UMEC/VI reflected that of the components (Lipson, et al. Am J Respir Crit Care Med. 2017). Herein we present *post-hoc* subgroup analyses of exacerbation rates by prior COPD medication class, disease severity and exacerbation history during FULFIL. In the intent-to-treat (ITT; 24 weeks) population, the 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; by disease severity, forced expiratory volume in 1 s (FEV₁) <50% predicted, no moderate/severe exacerbation; FEV₁ <50%, ≥1 moderate/severe exacerbation; FEV₁ ≥50–≤80%, ≥2 moderate or ≥1 severe exacerbations; and by exacerbation history, 0/1 moderate exacerbations; ≥2 moderate exacerbations; ≥1 severe exacerbation. Up to Week 24 in the ITT population, FF/UMEC/VI versus BUD/FOR improved the 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 (Table). Statistical significance of the FF/UMEC/VI:BUD/FOR ratio was observed for the 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) (Table). 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.

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Please refer to page A260 for declarations of interest in relation to abstract P272.

Abstract P272 Table 1 Mean annual exacerbation rates by subgroup (ITT population; up to Week 24)

Subgroup	FF/UMEC/VI 100/62.5/25 µg (n=911)		BUD/FOR 400/12 µg (n=899)		Reduction in annual exacerbation rate	
	n	rate	n	rate	%	(95% CI)
Prior medication						
ICS+LABA	266	0.10	258	0.27	63*	(29–80)
BUD+FOR	87	0.05	83	0.10	54	(–74–88)
ICS+LABA+LAMA	256	0.28	254	0.53	47*	(13–67)
LAMA alone	79	0.12	79	0.23	49	(–42–81)
TIO alone	65	0.15	67	0.20	24	(–125–74)
LAMA+LABA	100	0.38	83	0.26	–44	(–194–29)
Disease severity						
FEV ₁ <50%, no moderate/severe exacerbations	311	0.22	315	0.33	33	(–4–57)
FEV ₁ <50%, ≥1 moderate/severe exacerbation	299	0.22	290	0.41	45*	(11–66)
FEV ₁ ≥50–≤80%, ≥2 moderate/≥1 severe exacerbations	296	0.22	289	0.30	27	(–21–56)
Exacerbation history						
0/1 moderate	599	0.23	609	0.37	38*	(13–56)
≥2 moderate	308	0.01	283	0.02	27	(–20–55)
≥1 severe	185	0.12	200	0.29	57*	(14–78)

*Statistically significant difference for FF/UMEC/VI:BUD/FOR ratio; CI, confidence interval; ICS, inhaled corticosteroid; ITT, intent-to-treat; LABA, long-acting beta agonists; LAMA, long-acting muscarinic antagonists; TIO, tiotropium.

P273 ASSOCIATION OF INCIDENT PNEUMONIA AND EXACERBATIONS WITH EXTRA-FINE TRIPLE THERAPY IN ONE SINGLE INHALER IN COPD PATIENTS: A POST-HOC ANALYSIS FROM TRILOGY AND TRINITY STUDIES

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Rationale Efficacy and safety of extra-fine fixed triple combination of beclomethasone dipropionate, formoterol fumarate, and glycopyrronium bromide (BDP/FF/GB; 100/6/12.5 mcg, two actuations BID via pMDI; ‘fixed triple’) has been recently demonstrated in two phase III trials. Fixed triple has shown superiority in improving lung function and reducing moderate/severe exacerbations versus BDP/FF (Fostair 100/6 mcg, two actuations BID via pMDI; TRILOGY – Singh et al. Lancet 2016; 388: 963–73) and versus tiotropium (18 mcg one inhalation OD via DPI; TRINITY – Vestbo et al. Lancet 2017; 389: 1919–29). Increase in pneumonia risk associated with ICS containing medications is a known class effect. The risk/benefit balance of extra-fine fixed triple was evaluated by comparing variations in pneumonia and exacerbation events.

Methods Information on moderate/severe exacerbations and confirmed pneumonia was extracted from TRINITY and TRILOGY. A frequency plot was generated considering days in the study versus cumulative number of events.

Results In TRILOGY study, the number of recorded events was 288 exacerbations (rate: 0.448 exacerbations per patient

per year) versus 25 pneumonias (rate: 0.039 events per patient per year) with fixed triple and 353 exacerbations (0.565) versus 18 pneumonias (0.029) with Fostair (figure 1A). In TRINITY study, the number of events was 485 exacerbations (0.472) versus 30 pneumonias (0.029) with fixed triple and 569 exacerbations (0.583) versus 20 pneumonias (0.020) with tiotropium (figure 1B). Overall, treatment with fixed triple therapy reduced exacerbations by 65 events compared to Fostair (adjusted rate ratio: 0.773, $p=0.005$) and by 84 events compared to tiotropium (0.801, $p=0.003$). No fatal pneumonias occurred in TRILOGY while 5 pneumonias led to death in TRINITY (1 with fixed triple versus 4 with tiotropium). All pneumonias were classified as non-related to treatment.

Conclusions This analysis confirms that, in two independent populations of COPD patients treated with an ICS containing extrafine fixed triple combination, the number of incident pneumonia remains very small compared to that of moderate/severe exacerbations. The benefit observed in reducing the absolute number of exacerbations outweighs the increase observed in absolute number of pneumonias, thus confirming the positive risk benefit balance of extrafine fixed triple in severe/very severe COPD patients.

Please refer to page A260 for declarations of interest in relation to abstract P273.

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COMPARISON OF THE INITIATION OF COPD TREATMENT WITH LICENSED FDC ICS/LABA TREATMENTS IN TERMS OF DISEASE CONTROL AND COST EFFECTIVENESS

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Several fixed-dose combination inhaled corticosteroid (FDC ICS/LABA) inhalers are licensed for chronic obstructive pulmonary disease (COPD) in the UK. This study compares effectiveness of Fostair 100/6 (BDP/FOR) metered dose inhaler (MDI) against other licensed FDC ICS/LABAs, namely; Seretide Accuhaler 500 (FP/SAL) dry powder inhaler (DPI) and Symbicort Turbohaler 200/6 and 400/24 DPI (BUD/FOR) in a patient group with recent exacerbations and poor lung function. A historical cohort study using data extracted from the Optimum Patient Care Research Database. Patients with diagnostic read codes for COPD, smoking history, age ≥ 35 years, postdose FEV₁ percent predicted $< 55\%$, ≥ 1 previous long acting bronchodilator ever, and ≥ 1 previous exacerbation in the 18 months prior initiation of FDC ICS/LABA therapy. The observation period consisted of one year after the initiation of FDC ICS/LABA for follow up and one year prior for patient characterisation. Patients were excluded if they switched or halted ICS/LABA treatment during the 1 year follow up period. The primary outcome was the proportion of patients with ≥ 1 exacerbation. The non-inferiority margin was defined as 20%. Patients were directly matched 1:1 on categorised age, smoking status, FEV₁ percent predicted and exacerbations. Mean total costs consisting of medication/resource costs were

compared between treatment arms after adjusting for confounders. Out of the patients prescribed BDP/FOR ($n=537$) and 537 FP/SAL ($n=537$), the median age was 70 and 69 respectively and 41.7% were current smokers. In the BDP/FOR ($n=540$) and BUD/FOR ($n=540$) comparison, the median age was 70 and 69 respectively, and 42% were current smokers. The risk of ≥ 1 exacerbation in BDP/FOR group was non-inferior during the year following the initiation of ICS/LABA compared to FP/SAL (OR 0.89, 95% CI: 0.67–1.19) or BUD/FOR (OR 0.79, 95% CI: 0.58–1.08). Cost was significantly lower for BDP/FOR versus FP/SAL (adjusted mean £730.0 versus £850.1 respectively, $p<0.001$) and lower for BDP/FOR versus BUD/FOR (adjusted mean £732.4 versus £757.2 respectively, $p=0.054$). Treatment with BDP/FOR is non-inferior in terms of exacerbation risk and is additionally associated with a lower point estimate of exacerbation risk, a lower cost compared to FP/SAL and BUD/FOR, and a lower ICS dose compared to FP/SAL.

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COMPARING CLINICALLY RELEVANT IMPROVEMENT WITH UMECLIDINIUM/VILANTEROL AND TIOTROPIUM/ OLODATEROL IN SYMPTOMATIC COPD: A RANDOMISED NON-INFERIORITY CROSSOVER TRIAL

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Introduction and Objectives Here we report the Results of the first direct comparison of the once-daily fixed-dose long-acting muscarinic antagonist/long-acting β_2 -agonist (LAMA/LABA) combinations umeclidinium/vilanterol (UMEC/VI) 62.5/25 mcg and tiotropium/olodaterol (TIO/OLO) 5/5 mcg in patients with chronic obstructive pulmonary disease (COPD).

Methods This randomised, 2-period crossover study (204990, NCT02799784) included inhaled corticosteroid-free patients with COPD, a modified Medical Research Council dyspnoea score ≥ 2 , forced expiratory volume in 1 s (FEV₁)/forced vital capacity ratio of < 0.70 and post-salbutamol FEV₁ 50%–70% predicted. Patients were randomised to UMEC/VI (62.5/25 mcg once daily) via an ELLIPTA dry powder inhaler followed by TIO/OLO 5/5 mcg (2 puffs once daily) via a RESPIMAT inhaler (each for 8 weeks with an interim 3 week washout period), or *vice versa*. The primary endpoint was change from baseline (CFB) in trough FEV₁ at Week 8 with a non-inferiority (NI) margin of -50 mL in the per protocol (PP) population. Additional outcomes included inspiratory capacity (IC), rescue medication use and ease of inhaler use (assessed using a six-point questionnaire). Adverse events (AEs) were also assessed.

Results 236 patients (mean age 64.4 years, 60% male) were included in the intent-to-treat (ITT) population and 227 in the PP population. The primary endpoint of CFB in trough FEV₁ at Week 8 confirmed NI of UMEC/VI vs TIO/OLO (175 mL vs 122 mL; least squares mean difference 53 mL [95% confidence interval: 26, 80]; $p<0.001$; PP population) and demonstrated superiority in the ITT population (Table). Patients receiving UMEC/VI were significantly more likely to achieve clinically meaningful improvements (≥ 100 mL) in trough FEV₁ at Weeks 4 and 8 vs TIO/OLO, and showed significant improvements at Weeks 4 and 8 in IC and rescue medication use (Table). The