EFFICACY AND SAFETY OF ONCE-DAILY SINGLE-INHALER TRIPLE THERAPY (FLUTICASONE FUROATE/UMECLIDINIUM/VILANTEROL (FF/UMEC/VI) VERSUS FF/VI IN PATIENTS WITH INADEQUATELY CONTROLLED ASTHMA: A DOUBLE-BLIND, RANDOMISED, PHASE IIIA TRIAL (CAPTAIN STUDY)

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SUMMARY

Background

Despite inhaled corticosteroid/long-acting β_2-agonist (ICS/LABA) therapy, 30–50% of patients with moderate/severe asthma remain inadequately controlled. We investigated safety/efficacy of single-inhaler fluticasone furoate/umeclidinium/vilanterol (FF/UMEC/VI) for such patients with/without exacerbation histories.

Methods

Phase IIIA, double-blind, parallel-group study conducted 16 December, 2016 to 31 August, 2018. 322 centres across 15 countries randomised adults with inadequately controlled asthma despite ICS/LABA to once-daily FF/VI or FF/UMEC/VI via Ellipta dry powder inhaler. Endpoints: change from baseline in clinic trough forced expiratory volume in 1 second (FEV_1) at Week 24 (primary); annualised moderate/severe asthma exacerbation rate (key secondary). Exploratory analyses of biomarkers of type 2 airway inflammation on treatment response were also performed.

Findings

2439 patients were randomised: FF/VI (100/25 µg [n=407]; 200/25 µg [n=406]) or FF/UMEC/VI (100/31·25/25 µg [n=405]; 100/62·5/25 µg [n=406]; 200/31·25/25 µg [n=404]; 200/62·5/25 µg [n=408]) (three randomised in error). Mean (95% confidence interval) improvements in FEV_1 change from baseline for FF/UMEC/VI 100/62·5/25 versus FF/VI 100/25 and 200/62·5/25 µg versus 200/25 µg were 110 mL (66, 153; p<0·001) and 92 mL (49, 135; p<0·001), respectively. Adding UMEC 31·25 µg to FF/VI produced similar improvements. Non-statistically significant reductions in moderate/severe exacerbation rates were observed for FF/UMEC 62·5 µg/VI versus FF/VI (pooled analysis), with rates lower in FF 200- versus FF 100 µg-containing treatment groups. Effects of higher dose FF but not UMEC were greater in patients with higher baseline blood eosinophil count and exhaled nitric oxide. Occurrence of adverse events was similar across treatment groups (range, n [%]: 210 [52%]–258 [63%]). Of three deaths, one was considered study drug related.

Interpretation

In patients with uncontrolled moderate/severe asthma on ICS/LABA, adding UMEC improved lung function and led to reductions in moderate/severe exacerbations. Single-inhaler FF/UMEC/VI is an effective and safe treatment option for such patients.

Funding

GSK study number 205715, Clinicaltrials.gov identifier NCT02924688

RESEARCH IN CONTEXT

Evidence before this study

Despite adherence to ICS/LABA therapy, 30–50% of patients with asthma remain symptomatic and poorly controlled, indicating a clear unmet need in asthma management. Triple therapy – the combination of inhaled corticosteroid/long-acting muscarinic antagonist/long-acting β_2-agonist (ICS/LAMA/LABA) – administered via multiple inhalers improves lung function and reduces exacerbation rates in patients with asthma. Two recent trials in which patients with asthma received ICS/LAMA/LABA twice daily via a single inhaler resulted in positive impacts on lung function and exacerbation rates. These studies all enrolled patients with uncontrolled asthma on ICS/LABA and a history of a severe exacerbation in the preceding year, thus excluding a large proportion of patients whose main clinical problem is poor symptom control. Single-inhaler triple therapy (FF/UMEC/VI) is widely approved as a once-daily treatment for chronic obstructive pulmonary disease; however, to date, no studies have investigated its use in asthma. Asthma studies also need to better characterise patients who may respond to such therapy in order to precisely select their treatments based on the underlying problem.

Added value of this study

Relative to other studies investigating triple therapy in asthma, our inclusion criteria were intentionally broadened to capture the heterogeneity of uncontrolled asthma seen in real-world clinical practice, with no requirement for a history of exacerbations. As the study included both approved doses of FF/VI, direct comparisons of major treatment options for patients uncontrolled on ICS/LABA therapy can be made (i.e. adding a LAMA and/or increasing the ICS dose). UMEC improves lung function and symptom control when added to both FF/VI doses. Our study also demonstrates a dose response for improvement in forced expiratory volume in 1 second (FEV_1) and exacerbation reduction by increasing the FF dose in either FF/VI or FF/UMEC/VI. Greater effects from increasing the FF dose were observed in patients with elevated baseline blood eosinophils and fractional exhaled nitric oxide (FeNO); this was not the case for the addition of UMEC. These differential treatment responses indicate that a personalised, biomarker-directed approach to asthma care may result in better treatment outcomes.

Implications of all the available evidence

The results of this large, randomised Phase IIIA trial confirm that adding a second long-acting bronchodilator, UMEC, to FF/VI dual therapy via a single inhaler administered once daily improves lung function in patients with poorly controlled asthma on ICS/LABA. This is also the first single-inhaler triple therapy asthma study to report treatment outcomes by underlying type 2

inflammatory markers. Adding UMEC appears to improve FEV_1 independently of blood eosinophils and FeNO. In contrast, following an increase in FF dose, greater improvements in lung function and reductions in exacerbations are seen with increasing blood eosinophil counts and FeNO. Findings from this study may aid clinicians' selection of the most appropriate inhaled treatment based on patients' clinical problem(s) being addressed, and the type and severity of the underlying airway inflammation.

INTRODUCTION

Inhaled corticosteroid/long-acting β_2-agonist (ICS/LABA) combination therapy is recommended for patients with asthma who are inadequately controlled with ICS monotherapy along with as-needed bronchodilation.[1] However, 30–50% of such patients remain symptomatic and poorly controlled on ICS/LABA, even when treatment adherence is optimal.[2-5] In addition, between 10% and 25% of patients at Step 3 or higher in the Global Initiative for Asthma guidelines[1] experience an exacerbation within 1 year.[6,7] Therefore, the unmet need for effective step-up treatments after ICS/LABA in symptomatic patients both with and without an exacerbation history remains. Furthermore, although biologics are effective for reducing severe exacerbations in patients with high type 2 inflammation, they are generally less consistent in improving lung function and symptoms.[8] Studies comparing ICS with other treatments are needed for patients with low type 2 inflammation. To address these unmet needs, the Clinical study in Asthma Patients receiving Triple therapy in A single INhaler (CAPTAIN) investigated the efficacy and safety of the single-inhaler triple combination of fluticasone furoate/umeclidinium/vilanterol (FF/UMEC/VI) in patients with uncontrolled asthma on medium-high dose ICS/LABA. To explore the potential for a treatable traits approach to inhaled therapy, we also assessed whether the effects of increasing FF dose or adding UMEC on lung function and exacerbations were related to baseline type 2 airway inflammation biomarkers.

METHODS

Study design

CAPTAIN was a Phase IIIA, randomised, double-blind, 24–52-week, active-controlled, parallel-group, multinational, multicentre study (registered: 5 October, 2016), evaluating once-daily FF/UMEC/VI (100/31·25/25 µg; 100/62·5/25 µg; 200/31·25/25 µg; 200/62·5/25 µg) versus FF/VI (100/25 µg; 200/25 µg) in patients with uncontrolled asthma despite maintenance ICS/LABA therapy (Figure 1). The study was conducted in accordance with the Declaration of Helsinki, International Conference on Harmonisation Good Clinical Practice and applicable country-specific regulatory requirements. The protocol received approval from applicable central or local institutional review boards or independent ethics committees. Written informed consent was obtained from all patients before participation.

Patients

Eligible patients were adults (≥18 years of age) with inadequately controlled asthma symptoms (Asthma Control Questionnaire [ACQ]-6 score ≥1·5; documented healthcare contact or documented temporary change in asthma therapy for acute asthma symptoms within 1 year prior to screening)

despite requiring maintenance therapy with daily ICS/LABA for ≥12 consecutive weeks prior to pre-screening, with no changes to therapy allowed in the 6 weeks immediately prior to pre-screening (including no changes to a stable ICS dose of >250 µg/day fluticasone propionate [FP] or equivalent) (Figure 1). Additionally, patients were required to demonstrate a best pre-bronchodilator morning forced expiratory volume in 1 second (FEV_1) of ≥30–<85% of predicted normal value and airway reversibility (defined as an increase in FEV_1 of ≥12% and ≥200 mL 20–60 minutes following 4 inhalations of salbutamol) at screening (Figure 1).

Patients with a chronic obstructive pulmonary disease (COPD) diagnosis, including those meeting criteria for COPD at screening, or concurrent respiratory disorders, including pneumonia and pneumonia risk factors, were excluded. Current smokers and former smokers with a smoking history of ≥10 pack years were also excluded (Supplementary Table 1).

Patients were required to meet further criteria at the end of the 3-week run-in period before entering the 2-week stabilisation period, and at the end of stabilisation period prior to randomisation (Figure 1 and Supplementary Table 1). Patients who prematurely discontinued treatment were encouraged to provide data for the duration of the study (post-treatment data).

Run-in and stabilisation

Regardless of ICS dose at screening, eligible patients received twice-daily open-label FP/salmeterol (FP/SAL) 250/50 µg combination therapy via DISKUS dry powder inhaler (DPI) during the 3-week run-in period and open-label FF/VI 100/25 µg once daily via the Ellipta DPI during the subsequent 2-week stabilisation period. Trough FEV_1 was measured following a ≥24-hour washout after the last dose of ICS/LABA at each visit of run-in and stabilisation.

Randomisation and masking

Patients who met the randomisation criteria were randomly assigned (1:1:1:1:1:1) to one of six treatment arms (Figure 1). Central-based randomisation was used to allocate treatments. Patients were assigned to a double-blind treatment group in accordance with randomisation schedules generated by a validated computerised system. Randomisation was stratified across each of the six treatment arms by pre-study ICS treatment dosage (medium [>250–500 µg FP daily or equivalent] or high [>500 µg FP daily or equivalent])[1] at study entry.

Procedures

The study had a variable treatment period, with all patients completing a minimum of 24 weeks of treatment, and patients randomised during the initial recruitment period continuing further up to 36

or a maximum of 52 weeks (Figure 1). All randomised treatments were administered via the Ellipta DPI. Temporary treatment for the management of exacerbations and rescue medication were provided as detailed in the Supplementary Material. Blood eosinophils were measured at screening and exhaled nitric oxide at randomisation using NIOX MINO.

eDiary and home spirometry data were recorded twice daily at home with the use of an AM3 device which was provided to patients at screening (see Supplementary Material for details).

The occurrence of adverse events (AEs) and serious AEs (SAEs) was documented by the investigators throughout the study, along with data on duration and severity.

Endpoints

The primary efficacy endpoint was change from baseline in clinic trough FEV_1 at Week 24. The key secondary endpoint was the annualised rate of moderate/severe asthma exacerbations (up to Week 52). Moderate asthma exacerbations were defined as deterioration in either asthma symptoms or lung function, or increased rescue bronchodilator use, that required a physician-directed temporary change in maintenance treatment in order to prevent it from becoming a severe exacerbation.[9,10] Severe exacerbations were defined as a hospitalisation or emergency department visit due to asthma requiring systemic corticosteroids, or asthma deterioration requiring systemic corticosteroid use (or doubling of the current maintenance systemic corticosteroid dose) for ≥3 days.

All other endpoints reported here are listed in Table 1.

Statistical and data analysis

The intent-to-treat (ITT) population comprised all randomised patients (except any randomised in error) and was used for all efficacy and safety analyses.

Sample size calculations are detailed in the Supplementary Material.

For clinic FEV_1, the baseline measurement was the last acceptable measurement prior to the start of randomised treatment. Baseline patient-reported outcome (PRO) scores were determined at randomisation (Visit 3).

For the primary analysis of spirometry endpoints, each FF/UMEC/VI dose was compared with the corresponding dose of FF/VI to measure the additional effect of UMEC. For the primary analysis of non-spirometry endpoints, data from the FF/UMEC/VI arms for each UMEC dose were pooled and compared with pooled FF/VI data to increase the power and precision of the analysis.

All pooled and unpooled treatment comparisons reported are listed in Table 1. A step-down closed-testing hierarchy was employed to account for multiplicity across UMEC doses and efficacy endpoints, whereby inference for a test in the pre-defined hierarchy is dependent upon statistical significance having been achieved for the previous tests (Supplementary Figure 1). All analyses for tests carried out after the hierarchy was broken, and analyses not included in the hierarchy, were considered descriptive and were not adjusted for multiplicity.

Further detail on all analyses, including subgroup analyses by baseline eosinophil counts and fractional exhaled nitric oxide (FeNO), are included in the Supplementary Materials.

The study was not overseen by a data-monitoring committee. The study was registered with ClinicalTrials.gov: NCT02924688.

Role of the funding source

This study was funded by GlaxoSmithKline. The funders of the study had a role in study design, data analysis, data interpretation, and writing of the report. The corresponding author had full access to all data and final responsibility to submit for publication. Ellipta and DISKUS are trademarks owned by or licensed to the GSK group of companies.

Protocol available online: https://s3.amazonaws.com/ctr-gsk-7381/205715/a18b7932-13cc-4ddc-b5b7-2e0cc41376e2/846e29f6-19ca-4c32-9b10-1cac5ecc8d2d/gsk-205715-protocol-redact-v2.pdf

RESULTS

The study was conducted in 322 centres across 15 countries and randomised 2439 patients from 16 December, 2016 to 31 August, 2018. Three patients were randomised in error and thus 2436 patients were included in the ITT population, of which 2274 (93·3%) completed the study (Figure 2). In this variable treatment duration study, 1097 patients (52% of the ITT population) continued in the study beyond 24 weeks, with 547 (22% of the ITT population) completing 36 weeks and 550 (23%) completing 52 weeks. Duration of time in reporting period for moderate/severe exacerbations is summarised in Supplementary Tables 2 and 3.

Baseline demographics and disease characteristics were generally similar across treatment arms (Table 2). At screening, mean (standard deviation [SD]) % predicted pre-bronchodilator FEV_1 was 58·48 (12·79), 67% of patients were on medium-dose ICS, and 63% had experienced an exacerbation in the last year requiring oral corticosteroids and/or hospitalisation.

The provision of FP/SAL 250/50 µg twice daily for 3 weeks followed by once-daily FF/VI 100/25 µg for 2 weeks during the run-in and stabilisation phases, respectively, was associated with a mean (SD)

improvement in pre-bronchodilator clinic FEV_1 of 287 (356·4) mL (Supplementary Figure 2A), and a mean (SD) ACQ-7 total score reduction of 0·674 (0·7053) points, exceeding the minimal clinically important difference (MCID) of 0·5[11] (Supplementary Figure 2B). Similar improvements were observed on ACQ-6 (Table 2). Despite these improvements, patients still had impaired lung function and asthma control at randomisation: mean (SD) % predicted pre-bronchodilator FEV_1 68·18 (14·76); mean (SD) ACQ-7 score 2·12 (0·702) and ACQ-6 score 1·87 (0·734) (Table 2).

Addition of UMEC 62·5 µg to FF 100 µg/VI and FF 200 µg/VI resulted in mean (95% confidence interval [CI]) improvements of 110 [66, 153] mL and 92 [49, 135] mL from baseline in clinic trough FEV_1 at Week 24 (Figure 3A). These increases were statistically significant, and therefore the primary endpoint was met.

Improvements were also observed following addition of UMEC 31·25 µg to both FF 100 µg/VI and FF 200 µg/VI (96 [52, 139] mL and 82 [39, 125] mL, respectively) (Figure 3A). These findings were supported by pooled analysis of trough FEV_1 for each UMEC dose (Supplementary Figure 3A) and were seen from Week 4 and were sustained over the course of the study (Supplementary Figure 2A). Unpooled and pooled analysis of change from baseline in FEV_1 3 hours post-dose also supported these findings (Figure 3B and Supplementary Figure 3B).

During the variable 24–52-week treatment period, 688 (28%) patients experienced a moderate/severe asthma exacerbation, and 1075 individual events were reported. Of these events, 51% met the definition of a severe exacerbation. In the pooled analysis, addition of UMEC 62·5 µg to FF/VI resulted in a 13% (95% CI: -5·2, 28·1) reduction in the annualised rate of moderate/severe exacerbations (Figure 4A). As the step-down closed-testing hierarchy was broken here, all subsequent analyses were considered descriptive and not controlled for multiplicity. No reduction in the annualised rate of moderate/severe exacerbations was observed with the addition of UMEC 31·25 µg to FF/VI (Figure 4A).

Pre-specified unpooled analyses were also conducted. A numerically lower annualised rate of moderate/severe exacerbations was observed in the FF/UMEC/VI 100/62·5/25 µg group compared with both the FF/UMEC/VI 100/31·25/25 and FF/VI 100/25 µg groups (0·68, 0·76, and 0·87, respectively) (Figure 4B). Compared with FF/VI 100/25 µg, the annualised rate was reduced by 21·8% (95% CI: -1·1, 39·5) in the FF/UMEC/VI 100/62·5/25 µg group and 12·0% (95% CI: -13·3, 31·6) in the FF/UMEC/VI 100/31·25/25 µg group. In contrast, no additional reductions were observed when UMEC 62·5 or 31·25 µg was added to FF/VI 200/25 µg (Figure 4B).

The rate of severe exacerbations was generally low and similar across all pooled treatment groups (Supplementary Table 4). However, the rates of severe exacerbations were lower in the unpooled FF 200 µg-containing treatment groups (mean [95% CI] range: 0·23 [0·17, 0·30]–0·26 [0·20, 0·34]) than the FF 100 µg-containing treatment groups (mean [95% CI] range: 0·38 [0·30, 0·49]–0·41 [0·32, 0·52]) (Supplementary Table 5).

Of the 529 moderate exacerbations, 85% were characterised by symptom deterioration, of which approximately half (47%) also had either a deterioration in lung function, increase in short-acting β_2-agonist use or both. Only 11% of moderate exacerbations were characterised by a deterioration in lung function alone (Supplementary Table 6). The addition of UMEC did not alter the duration of either moderate or severe exacerbations (Supplementary Table 7).

For mean change from baseline to Week 24 in ACQ-7 score, improvements (decreases) exceeding the MCID of 0·5 points were observed in all pooled treatment groups (Table 3). Adding UMEC to FF/VI resulted in small, dose-related improvements compared with FF/VI (Table 3). Improvements in ACQ-7 were seen as early as Week 4, and were sustained throughout the study (Supplementary Figure 2B).

ACQ-7 responder rates (defined as change greater than or equal to the MCID) were also dose-related (63%, 58%, and 55% for FF/UMEC 62·5 µg/VI, FF/UMEC 31·25 µg /VI, and FF/VI, respectively), and favoured FF/UMEC 62·5 µg/VI over FF/VI with an odds ratio of 1·43 (95% CI: 1·16, 1·76) (Table 3, Supplementary Figure 4A). Analysis of ACQ-7 responder rates in unpooled data supported the pooled analyses at both FF doses (Supplementary Figure 5).

Pooled analysis of ACQ-5 responder rates, encompassing only patient-reported symptoms and impact, were consistent with the pooled analysis of ACQ-7 (Supplementary Figure 4B).

All pooled treatment groups demonstrated mean improvements (decreases) in St George's Respiratory Questionnaire (SGRQ) total score at Week 24 compared with baseline in excess of the MCID of 4 points; however, there were no differences between treatment groups (Table 3). Pooled analysis of SGRQ responders (defined as change greater than or equal to the MCID) showed a numerical improvement for the FF/UMEC 62·5/VI group only versus FF/VI (Table 3).

Pooled analysis of change from baseline in rescue medication use and rescue-free days are presented in Supplementary Table 9. Small changes on both endpoints were observed in all treatment groups; rescue medication use was low at baseline in all groups.

Doubling the FF dose in FF/VI and FF/UMEC/VI resulted in marked reductions in the annualised rate of both moderate/severe and severe exacerbations, and modest improvements in FEV_1 (Table 4). Effects on PROs were minimal with the increased FF dose (Table 4).

The relationship between type 2 biomarkers of airway inflammation (blood eosinophils and FeNO) and the effect of either doubling FF dose or adding UMEC 62·5 µg to FF/VI on change from baseline in FEV_1 at Week 24 and annualised rate of moderate/severe exacerbations is shown in Figure 5 (performed post hoc). Corresponding unpooled analyses are shown in Supplementary Figures 6 and 7 (pre-specified for FF/UMEC/VI 100/62·5/25, FF/UMEC/VI 200/62·5/25 and FF/VI 200/25 µg treatment arms only).

To assess the increase in ICS dose, all FF 100 µg-containing treatment groups were pooled and compared with the pooled FF 200 µg-containing treatment groups. Doubling the FF dose had a greater effect in patients with higher blood eosinophils and FeNO for both treatment outcomes (Figure 5A). Conversely, the addition of UMEC 62·5 µg led to an improvement in FEV_1 across the range of blood eosinophil and FeNO levels, with a suggestive trend towards a greater reduction in moderate/severe exacerbations at the lower range of these biomarkers (Figure 5B).

A categorical analysis (performed post hoc) of treatment effect by combined baseline type 2 inflammatory markers supported these findings. Patients with FeNO <20 parts per billion (ppb) and blood eosinophils <150 cells/µL (low type 2 inflammatory biomarker group) had a 23 [-38, 84] mL mean [95% CI] improvement from baseline in trough FEV_1 and 12·4% (95% CI: -29·5, 40·8) reduction in moderate/severe exacerbations in the FF 200 µg-containing groups (n=211) compared with FF 100 µg-containing groups (n=194) (Table 5). In contrast, of patients in the high type 2 inflammatory biomarker group (FeNO >50 ppb and blood eosinophils ≥300 cells/µL) there was a 127 [20, 233] mL mean [95% CI] increase in FEV_1 and 65·2% (95% CI: 29·6, 82·8) reduction in moderate/severe exacerbations when comparing FF 200 µg-containing groups (n=71) with FF 100 µg-containing groups (n=67) (Table 5). Unpooled analyses of treatment outcomes by combined baseline biomarkers of type 2 inflammation are presented in Supplementary Table 11. The proportion of patients experiencing a severe exacerbation in the low type 2 inflammatory biomarker group was similar for FF 200 µg and FF 100 µg (14% [29 of 211] and 12% [24 of 194]), respectively (Supplementary Table 12). In contrast, for the high type 2 inflammatory biomarker group, a smaller proportion of patients receiving FF 200 µg (13% [9 of 71]) had a severe exacerbation than those receiving FF 100 µg (33% [22 of 67]).

The proportion of patients experiencing AEs was similar across treatment groups. The proportions of on-treatment drug-related AEs were also broadly similar between treatment groups, ranging from

4% to 7%, of which 2 events were serious (Table 6). The most commonly reported AEs were nasopharyngitis (range: 13% to 15%), headache (range: 5% to 9%), and upper respiratory tract infection (range: 3% to 6%). The most commonly reported AEs of special interest (AESI) was dry mouth/drying of the airway secretions, which was driven by the number of patients with nasopharyngitis. The incidence of all AESIs was similar across all groups, including anticholinergic syndrome, cardiovascular effects (including tachycardias), and infective pneumonia (Supplementary Table 13).

There were 3 deaths (2 in the FF/UMEC/VI 100/31·25/25 µg group [pulmonary embolism and hypertrophic cardiomyopathy] and 1 in the FF/VI 200/25 µg group [circulatory collapse]), of which one (pulmonary embolism) was considered as related to study drug by the investigator.

DISCUSSION/CONCLUSIONS

FF/UMEC/VI is widely approved as once-daily treatment for COPD, but it is not yet approved for use in asthma. The Phase IIIA CAPTAIN study was specifically designed to evaluate the effects of adding UMEC to FF/VI in a single-inhaler triple therapy on the most common clinical problems faced by patients with moderate/severe uncontrolled asthma on ICS/LABA.

This study extends the body of evidence for triple therapy[12] to a broad population with moderate-to-severe asthma, both with and without a history of exacerbations, characterised by airflow limitation and poor symptom control. There was no upper age limit or requirement for onset of disease before 40 years of age and patients with a wide range of lung function values were eligible. As we recruited adults both with and without a history of a severe exacerbation in the previous year, the results are relevant for a broad range of patients in clinical practice and provide an understanding of the benefit:risk profile of FF/UMEC/VI, including the optimal UMEC dose. For the first time, the influence of baseline biomarkers of type 2 airway inflammation (blood eosinophils and FeNO) was assessed for stepped-up inhaled therapies, allowing us to determine if these biomarkers might help in clinical decision making.

Improvements in FEV_1 were noted for both UMEC doses on a background of high- and low-dose FF/VI in the overall population. The reduction in the annualised rate of moderate/severe exacerbations on a background of FF/VI 100/25 was dose dependent for UMEC 31·25 and 62·5 µg (12% and 22%, respectively), and potentially clinically meaningful for UMEC 62·5 µg. However, when the FF dose was maximised no additional reduction was seen with the addition of UMEC in the overall population. The annualised rate of severe exacerbations was similar between pooled treatment groups, suggesting that any treatment effect of UMEC on moderate/severe exacerbations was driven by a reduction in moderate exacerbations only.

Moderate exacerbations in this study were considered to be significant events based on the requirement for the physician to assess the patient and determine that additional therapy was warranted, as per the American Thoracic Society/European Respiratory Society joint statement.[9] This requirement was not made in other triple-therapy asthma studies such as TRIGGER/TRIMARAN[13], where the rate of moderate exacerbations alone with ICS/LABA was higher (1·72 [95% CI: 1·58, 1·87]) than the combined rate of moderate and severe events in CAPTAIN (0·70 [0·61, 0·80]). The similarity in the duration of moderate and severe exacerbations in CAPTAIN, and the finding that 85% of the events were characterised by a deterioration in symptoms, provide further support that moderate exacerbations are clinically important events. Although relevant literature is limited, moderate exacerbations have been shown to be more frequent than severe events in the general asthma population.[14,15] In addition, individually these events have been shown to place a burden on healthcare systems, with one analysis showing that moderate exacerbations have higher mean unit costs than non-hospitalised severe exacerbations.[15] Our study also differs from TRIGGER, TRIMARAN, and tiotropium studies where reductions in severe exacerbations were observed with the addition of LAMA.[13,16] This is likely due to differences in study populations and design, including no requirement to enrol patients with a history of severe exacerbation prior to screening and a variable treatment duration following randomisation where only 23% of patients completed 52 weeks in the study.

In contrast to the addition of UMEC, which mainly improved lung function and ACQ, the major effect of doubling FF dose was to reduce both moderate and severe exacerbations. These findings are generally consistent with published data comparing a higher dose ICS with the addition of a LABA to low-dose ICS, where increased ICS dose had a greater impact on severe exacerbations than the addition of the long-acting bronchodilator, while LABA was more effective at improving FEV_1, non-severe exacerbations and symptoms.[17] These differential effects indicate that bronchodilators and increased dose of anti-inflammatory therapies modify clinical problems differently, presumably by targeting different pathways.

The reduction in moderate/severe exacerbations was apparent when UMEC was added to a background of FF/VI 100/25 but not 200/25, suggesting that adding UMEC may be an alternative strategy to increasing ICS dose, particularly in patients with low type 2 inflammatory biomarkers, which is a population with a particular unmet need. This view is supported by the different relationship between the effects of UMEC and higher dose FF and baseline biomarkers of type 2 inflammation. As previously demonstrated with tiotropium,[18] the addition of a LAMA improved FEV_1 independently of blood eosinophils; in addition, we found no clear relationship between efficacy of UMEC and baseline FeNO. In contrast, the effect of increasing the dose of FF on trough FEV_1 and moderate/severe exacerbations was greater with increasing blood eosinophil counts and FeNO. The

relationship was particularly noteworthy for the combined measure of blood eosinophils and FeNO, and severe exacerbations. The proportion of patients on FF 100 µg having a severe exacerbation was nearly three times higher in patients with baseline blood eosinophils ≥300 cells/µl and FeNO >50 ppb compared with patients with baseline blood eosinophils <150 cells/µl and FeNO <20 ppb. This relationship was not seen in patients on FF 200 µg indicating that the higher FF dose reduces the excess risk of severe exacerbations associated with type 2 inflammation.[19] These findings are consistent with observations in COPD[20] and in patients with mild asthma,[21] and suggest that raised biomarkers of type 2 inflammation are a marker of increased risk of severe exacerbations and an increased likelihood of a response to more intensive corticosteroid treatment across the range of obstructive airway diseases. Collectively, these findings suggest that a precision medicine approach targeting treatment according to desired outcome and type 2 inflammatory biomarker status would lead to more effective and economic use of inhaled treatments.

Dose-related improvements in ACQ measures were observed when UMEC was added to FF/VI. These improvements were observed from Week 4, were sustained throughout the study, and were also seen on ACQ-5, indicating that these patient-centric measures were not driven by improvements in lung function alone. Importantly, and as seen with lung function, these improvements in asthma control were observed on a background of both doses of FF/VI, supporting the clinical utility of both FF doses in the triple therapy. These data align with the emerging treatable traits paradigm[22] for asthma in which bronchodilators are preferential to ICS for the treatment of airflow limitation and associated symptoms. For these clinical problems, our results also demonstrate that the bronchodilator effects of a β_2-agonist and muscarinic receptor antagonist are complementary.

Although UMEC 62·5 µg consistently showed better effects on clinical outcomes than UMEC 31·25 µg, particularly moderate exacerbations and the proportion of ACQ responders, safety profiles were similar. No new or unexpected safety findings were identified; addition of UMEC to FF/VI did not have a negative impact on either the type or incidence of AEs, including AESIs and AEs leading to withdrawal, showing that triple therapy was well tolerated in these populations. Additionally, there was no evidence of a safety signal from doubling FF dose; cardiovascular events (including tachycardias) were similar across treatment groups and reports of pneumonia were low in all groups, with no increase in pneumonia occurrence linked to increased ICS dose. Of three deaths on the study, one was considered by the investigator to be related to the study drug. The cause of death was pulmonary embolism, and the patient had been receiving medication for concurrent arterial hypertension.

Strengths of this study include the 5-week pre-randomisation period where standardised medication was provided, as well as the use of a potent comparator (FF/VI) in the treatment period. Both features helped to demonstrate how optimising ICS/LABA therapy may improve outcomes. Improvements in asthma control in all treatment groups continued post-randomisation and illustrate the ongoing challenge of asthma studies to show substantial differences between ICS-containing treatments in patient-reported measures of symptoms and health-related quality of life.[23] As both FF/VI and FF/UMEC/VI were administered by the Ellipta DPI, the effect of UMEC was measured in a controlled way on top of the improvements gained in the pre-randomisation phases. Further, we were able to directly compare all treatment options for patients who were previously uncontrolled on medium-high dose ICS/LABA in a single study.

The main limitation of this study was the low rate of exacerbations, likely due to the potent anti-inflammatory effects of FF[24] and a lower risk population, which differed from the assumptions behind the power calculations. This potentially limited the opportunity to fully assess the impact of the addition of UMEC on exacerbations, and the break in the statistical hierarchy meant all other analyses were considered descriptive. For the analysis of biomarker-based outcomes, baseline eosinophil counts and FeNO levels were measured at different times prior to randomisation, and the size of the subgroups and variability in data limit our ability to draw definitive conclusions. Lastly, inconsistencies in the treatment effect of adding UMEC to FF 100 µg- and FF 200 µg-containing treatment groups in the unpooled analysis of moderate and severe exacerbations may have implications on the validity of pooling the data. As such, the pooled comparisons for measuring the effect of adding UMEC for biomarker-based outcomes require further research.

In conclusion, there remains a need for additional treatments when medium-to-high dose ICS/LABA does not achieve adequate asthma control, including in patients who may benefit from but have not yet started biologics and those not eligible for biologics (i.e. low type 2) who have limited treatment options. We have shown that once-daily single-inhaler FF/UMEC/VI reduces airflow obstruction and improves asthma control, effectively reducing risk for patients whose asthma is inadequately controlled on ICS/LABA, with no additional safety concerns. The effects of adding UMEC and increasing FF differed by outcome measure and also by biomarkers of type 2 airway inflammation. The implication of this observation is that different treatable traits are associated with different treatment outcomes and that a targeted, precision medicine-type approach may result in more effective use of add-on inhaled therapy in this patient population.

CONTRIBUTORS

The authors meet criteria for authorship as recommended by the International Committee of Medical Journal Editors, take responsibility for the integrity of the work as a whole, contributed to the writing and reviewing of the manuscript, and have given final approval for the version to be published. All authors had full access to the data in this study and take complete responsibility for the integrity of the data and accuracy of the data analysis. DE, HAMK, IDP, and NB were involved in the conception and design of the study and the data analysis and interpretation. AP, JO, MT, SP, ZB, and GB were involved in the data analysis and interpretation. AF, L-PB, NAH, NS, and RN were involved in the acquisition of data and data analysis and interpretation. EK, LAL, and GP were involved in the conception and design of the study, acquisition of data and the data analysis and interpretation.

DECLARATION OF INTERESTS

ZB, NB, DE, AF, NS, and MT are employees of GSK and hold stocks or shares in GSK; GP is an employee of GSK and holds stocks or shares in GSK and Novartis; SP and LAL were employees of GSK at the time of study and own stocks in GSK; L-PB has received research grants for participation in multicentre clinical research trials and support for research projects from AstraZeneca, Boehringer Ingelheim, Boston Scientific, GSK, Hoffman La Roche, Merck, Novartis, Ono Pharma, Sanofi, and Takeda. L-PB has also received fees for consulting and advisory boards, conference fees, and support for participation in conferences and meetings from AstraZeneca, GSK, Merck, Metapharm, Novartis, and Takeda, and non-profit grants for the production of educational materials from AstraZeneca, Boehringer Ingelheim, GSK, Merck, and Novartis; NAH reports receiving personal fees from AstraZeneca, Genentech, Sanofi Genzyme, GSK, Mylan, Novartis, and Regeneron for serving as an advisor or consultant. He also received research support from AstraZeneca, Boehringer Ingelheim, Novartis, Sanofi Genzyme, Genentech, and GSK; HAMK has received research/educational grants and served on advisory boards for Boehringer Ingelheim, GSK, and Novartis, and has served on advisory boards for Chiesi, AstraZeneca, and Fluidda; EK is an employee of Crisor LLC Research and has served on advisory boards, speaker panels, or received travel reimbursement from Amphastar, AstraZeneca, Boehringer Ingelheim, Cipla, Chiesi, Forest, GSK, Mylan, Novartis, Pearl, Sunovion, Teva, and Theravance. He has also conducted multicentre clinical research trials for approximately 40 pharmaceutical companies; RN is a non-paid instructor and clinical professor at the University of Colorado Health Sciences Center, and he was an employee of Asthma and Allergy Associates, P.C. and research center at the time of the study. He received speaker's fees and honoraria for advisory boards for GSK and Boehringer Ingelheim; JO has served on adjudication committees/data and

safety monitoring boards for AstraZeneca, GSK, Novartis, and Sanofi/Regeneron, and has received grants/personal fees from GSK; AP has received research grants and personal fees from AstraZeneca, Chiesi, GSK, Menarini, and Teva, and personal fees from Boehringer Ingelheim, Edmond Pharma, Mundipharma, Novartis, Sanofi, and Zambon; GB has received speaker's fees from and served on advisory boards for AstraZeneca, Boehringer Ingelheim, Chiesi, GSK, Novartis, and Teva. He has served on advisory boards for Sanofi; IDP is an employee of the University of Oxford. He has received research grants, speaker fees, fees for advisory boards and travel expenses for attending international meetings/advisory boards from Chiesi and Afferent. He has received speaker's honoraria, travel expenses and honoraria for attending advisory boards from AstraZeneca, Boehringer Ingelheim, GSK and Teva. IDP has also received speaker fees/fees for advisory boards from Circassia, Knopp, Merck, Mundipharma, Novartis, Roche/Genentech and Sanofi/Regeneron.

DATA SHARING

Anonymised individual participant data and study documents can be requested for further research from www.clinicalstudydatarequest.com.

ACKNOWLEDGEMENTS

The authors would like to thank Susannah Hammond, David Walpole, Christine Broderick, Shoaib Muhammad, and Kenneth Cooper for their help in the operationalisation and oversight of the study. They would also like to thank Eric Bateman, Wei Wu, and Shuying Yang for advising on the study design, and Ben Hartley for his contributions to statistical analyses. NIOX MINO is a trademark of Circassia AB (Sweden). AM3 is a trademark of eResearch Technology Inc.). Editorial support in the form of preparation of the first draft based on input from all authors, and collation and incorporation of author feedback to develop subsequent drafts was provided by Chloe Stevenson, MSci, of Fishawack Indicia, and was funded by GSK.

TABLES AND FIGURES

Table 1. Efficacy endpoints, safety assessments and treatment comparisons

Efficacy endpoints
Primary
Change from baseline in clinic trough FEV_1 at Week 24
Key secondary
Annualised rate of moderate/severe asthma exacerbations
Other secondary
Change from baseline in clinic FEV_1 at 3 hours post-dose at Week 24 Change from baseline in SGRQ total score[25,26] at Week 24 Change from baseline in ACQ-7* total score[27,28] at Week 24 Change from baseline in E-RS: Asthma total score[29,30] at Weeks 21–24 (not reported here)
Additional endpoints reported
Annualised rate of severe asthma exacerbations Percent of patients meeting a responder threshold of ≥0·5 points improvement (decrease) from baseline for ACQ-7 and ACQ-5 at Week 24 Change from baseline in daily rescue medication over the first 24 weeks of treatment Change from baseline in % rescue-free days over the first 24 weeks of treatment
Subgroup analyses†
Fractional polynomial modelling was carried out to investigate treatment response on trough FEV_1 at Week 24 and annualized rate of moderate/severe exacerbation based on eosinophils and FeNO at baseline, considered as continuous variables. Trough FEV_1 at Week 24, annualised rates of moderate/severe exacerbations, and proportion of patients experiencing a severe exacerbation were considered by the following categories: • Baseline blood eosinophil categories (<150, 150–<300, ≥300 cells per µL) • Baseline FeNO (<20, 20–50, >50 ppb) • Baseline blood eosinophils AND FeNO combined categories (eosinophils <150 cells per µL AND FeNO <20 ppb, eosinophil ≥300 cells per µL AND FeNO >50 ppb, any other pattern of eosinophil and FeNO)
Safety assessments
Incidence and types of AEs, SAEs including deaths, and AESIs ECG measurements, vital signs, and clinical laboratory parameters

Comparisons to measure treatment effects of ICS and UMEC
Lung function endpoints; unpooled comparisons (pre-specified)
FF/UMEC/VI 100/62·5/25 µg vs FF/VI 100/25 µg
FF/UMEC/VI 200/62·5/25 µg vs FF/VI 200/25 µg
FF/UMEC/VI 100/31·25/25 µg vs FF/VI 100/25 µg
FF/UMEC/VI 200/31·25/25 µg vs FF/VI 200/25 µg
Non-lung function endpoints; pooled comparisons[‡] (pre-specified)
Pooled FF 100+200 µg/UMEC 62·5 µg/VI versus pooled FF 100+200 µg/VI
Pooled FF 100+200 µg/UMEC 31·25 µg/VI versus pooled FF 100+200 µg/VI
Comparisons to measure additional effects of increasing ICS dose (pre-specified)[§]
FF/VI 200/25 µg vs FF/VI 100/25 µg
FF/UMEC/VI 200/62·5/25 µg vs FF/UMEC/VI 100/62·5/25 µg
FF/UMEC/VI 200/31·25/25 µg vs FF/UMEC/VI 100/31·25/25 µg
Comparisons to measure effect of increasing ICS dose in relation to baseline blood eosinophil and FeNO (post hoc)
Pooled FF/VI 200/25 µg + FF 200 µg/UMEC 31·25+62·5 µg/VI vs pooled FF/VI 100/25 µg + FF 100 µg/UMEC 31·25+62·5 µg/VI
Comparisons to measure effect of adding UMEC in relation to baseline blood eosinophil and FeNO (post hoc)
Pooled FF 100+200 µg/UMEC 62·5 µg/VI vs pooled FF 100+200 µg/VI

*Asthma control was assessed using the ACQ-7. ACQ-7 assesses seven attributes of disease control, relating to symptoms and impacts (also included in ACQ-5) assessed by patient questionnaire, rescue medication use (also included in ACQ-6), and lung function (assessed by FEV_1 % predicted).[11]

[†]All subgroup analyses were performed post hoc with the exception of the continuous analyses of eosinophil and FeNO subgroups on unpooled data from FF/UMEC/VI 100/62·5/25, FF/UMEC/VI 200/62·5/25 and FF/VI 200/25 µg treatment arms which were pre-specified.

[‡]For non-lung function endpoints, it was assumed that, for a given dose of UMEC, a similar magnitude of effect would be observed in the treatment comparison of FF/UMEC/VI and FF/VI for FF 100 µg- and FF 200 µg-containing treatments. Therefore, to increase the power and precision of the primary analysis of the non-lung function endpoints, it was pre-specified that the data from the two FF/UMEC/VI arms for each fixed UMEC dose were pooled and compared with pooled data from the two FF/VI arms.

[§]Pre-specified for primary, key secondary and secondary endpoints, as well as any other endpoints related to secondary endpoints.

ACQ, Asthma Control Questionnaire; AE, adverse event; AESI, adverse event of special interest; FEV_1, forced expiratory volume in 1 second; ECG, electrocardiogram; E-RS: asthma, Evaluating Respiratory Symptoms: asthma; FeNO, fractional exhaled nitric oxide; FF, fluticasone furoate; ICS, inhaled

corticosteroids; ppb, parts per billion; SAE, serious adverse event; SGRQ, St George's Respiratory Questionnaire; UMEC, umeclidinium; VI, vilanterol.

Table 2. Baseline demographics and clinical characteristics (ITT)

		FF/VI 100/25 µg (N=407)	FF/UMEC/VI 100/31·25/25 µg (N=405)	FF/UMEC/VI 100/62·5/25 µg (N=406)	FF/VI 200/25 µg (N=406)	FF/UMEC/VI 200/31·25/25 µg (N=404)	FF/UMEC/VI 200/62·5/25 µg (N=408)	Total (N=2436)
Baseline demographics								
Age, years, mean (SD)		53·3 (13·03)	51·7 (13·27)	52·9 (13·39)	53·9 (13·30)	53·5 (13·12)	53·7 (12·50)	53·2 (13·11)
Male, n (%)		153 (38%)	143 (35%)	158 (39%)	154 (38%)	164 (41%)	150 (37%)	922 (38%)
BMI (kg/m^2), mean (SD)		29·3 (6·08)	29·1 (6·80)	29·2 (6·65)	29·4 (6·29)	29·4 (7·07)	29·7 (6·93)	29·4 (6·64)
Pre-study ICS – medium-dose*, n (%)		268 (66%)	275 (68%)	274 (67%)	263 (65%)	268 (66%)	273 (67%)	1621 (67%)
Number of exacerbations requiring oral corticosteroids and/or hospitalisation in previous 12 months, n (%)	0	144 (35%)	160 (40%)	160 (39%)	157 (39%)	147 (36%)	124 (30%)	892 (37%)
	1	198 (49%)	185 (46%)	179 (44%)	196 (48%)	192 (48%)	216 (53%)	1166 (48%)
	≥2	65 (16%)	60 (15%)	67 (17%)	53 (13%)	65 (16%)	68 (17%)	378 (16%)
Disease duration, years, mean (SD)		20·4 (15·03)	21·5 (15·28)	20·8 (15·70)	20·7 (14·53)	21·1 (15·14)	22·3 (16·15)	21·2 (15·31)
Former smokers, n (%)		69 (17%)	78 (19%)	81 (20%)	69 (17%)	80 (20%)	93 (23%)	470 (19%)
Smoking pack years, mean (SD)		4·2 (2·66)	3·7 (2·70)	4·7 (2·74)	3·4 (2·33)	4·9 (2·79)	4·5 (2·91)	4·3 (2·74)
Geometric mean (SD of log) blood eosinophils (cells/µl) (screening)		n=394 233 (0·91)	n=395 228 (0·10)	n=399 236 (0·91)	n=398 222 (0·94)	n=397 225 (1·03)	n=403 225 (0·92)	n=2386 228 (0·95)

Geometric mean (SD of log) fractional exhaled nitric oxide, ppb (randomisation)	n=374 19·8 (0·65)	n= 372 18·6 (0·64)	n=377 20·6 (0·68)	n=373 21·2 (0·65)	n=386 18·9 (0·64)	n=380 19·2 (0·67)	n=2262 19·7 (0·66)
Disease characteristics at screening							
Pre-bronchodilator FEV_1, mL, mean (SD)	n=402 1733 (582)	n=405 1750 (540)	n=404 1756 (598)	n=401 1722 (599)	n=404 1714 (573)	n=407 1732 (613)	n=2423 1734 (584)
Pre-bronchodilator FEV_1, %predicted, mean (SD)	n=402 58·24 (13·061)	n=405 58·80 (11·728)	n=404 58·76 (12·741)	n=401 58·66 (13·169)	n=404 57·43 (12·699)	n=407 58·98 (13·255)	n=2423 58·48 (12·787)
Post-bronchodilator FEV_1/FVC, mean (SD)	n=406 0·65 (0·107)	n=405 0·67 (0·115)	n=404 0·66 (0·109)	n=405 0·66 (0·116)	n=403 0·66 (0·120)	n=407 0·66 (0·115)	n=2430 0·66 (0·114)
ACQ-7 score, mean (SD)	n=401 2·77 (0·589)	n=400 2·81 (0·604)	n=403 2·77 (0·618)	n=404 2·81 (0·630)	n=401 2·80 (0·601)	n=401 2·78 (0·605)	n=2410 2·79 (0·608)
ACQ-6 score, mean (SD	n=406 2·48 (0·610)	n=405 2·53 (0·643)	n=406 2·49 (0·653)	n=406 2·53 (0·662)	n=403 2·50 (0·650)	n=407 2·51 (0·652)	n=2433 2·51 (0·645)
Reversibility to salbutamol, %[†] mean (SD)	n=402 29·52 (18·068)	n=405 30·55 (17·618)	n=402 30·16 (18·302)	n=400 29·44 (18·293)	n=403 29·98 (18·084)	n=406 29·88 (18·445)	n=2418 29·92 (18·122)
Disease characteristics at randomisation							
Pre-bronchodilator FEV_1, mL, mean (SD)	n=405 2008 (681)	n=401 2073 (675)	n=402 2073 (678)	n=405 1987 (674)	n=401 2011 (667)	n=406 1984 (693)	n=2420 2023 (678)
Pre-bronchodilator FEV_1, %predicted[†], mean (SD)	n=405 67·37 (15·193)	n=401 69·59 (14·160)	n=402 69·54 (14·687)	n=405 67·62 (14·749)	n=401 67·24 (14·129)	n=406 67·73 (15·470)	n=2420 68·18 (14·760)
ACQ-7 score, mean (SD)	n=396 2·14 (0·668)	n=399 2·11 (0·729)	n=400 2·10 (0·726)	n=397 2·13 (0·734)	n=396 2·15 (0·707)	n=395 2·10 (0·647)	n=2383 2·12 (0·702)
ACQ-6 score, mean (SD)	n=405	n=404	n=404	n=405	n=399	n=404	n=2421

	1·88 (0·691)	1·88 (0·755)	1·87 (0·745)	1·88 (0·769)	1·90 (0·755)	1·85 (0·690)	1·87 (0·734)
SGRQ, mean (SD)	n=405 39·12 (16·557)	n= 402 38·80 (18·279)	n=403 38·43 (18·342)	n=404 40·03 (18·291)	n=399 40·94 (18·787)	n=404 39·97 (16·939)	n=2417 39·54 (17·883)

*Medium-dose defined as >250 to ≤500 µg/day FP (or equivalent).

†Patients were required to meet the threshold for reversibility (defined as post-bronchodilator increase in FEV_1 of ≥12% and ≥200 mL).

ACQ-6, Asthma Control Questionnaire; BMI, body mass index; FEV_1, forced expiratory volume in 1 second; FF, fluticasone furoate; FP, fluticasone propionate; FVC, forced vital capacity; ICS, inhaled corticosteroid; ITT, intent-to-treat; ppb, parts per billion; SD, standard deviation; UMEC, umeclidinium; SGRQ, St George's Respiratory Questionnaire; VI, vilanterol.

Table 3. Pooled analysis of change from baseline in patient-reported outcomes at Week 24 (ITT)

	FF/VI (N=813)	**FF/UMEC 31·25 µg/VI (N=809)**	**FF/UMEC 62·5 µg/VI (N=814)**
ACQ-7 score			
Change from baseline			
Patients with analysable data at Week 24 (n)	745	746	761
LS mean (95% CI) change from baseline	-0·678 (-0·725, -0·630)	-0·734 (-0·781, -0·687)	-0·767 (-0·813, -0·720)
Treatment difference vs FF/VI (95% CI) p-value	Reference	-0·057 (-0·124, 0·010) 0·094	-0·089 (-0·156, -0·023) 0·008
Responders			
Responders*, n/N (%)	436/793 (55)	464/795 (58)	498/795 (63)
Odds ratio vs FF/VI (95% CI) p-value	Reference	1·15 (0·94, 1·42) 0·179	1·43 (1·16, 1·76) <0·001
SGRQ total score			
Change from baseline			
Patients with analysable data at Week 24 (n)	766	753	777
LS mean (95% CI) change from baseline	-11·39 (-12·35, -10·42)	-10·29 (-11·26, -9·32)	-11·69 (-12·64, -10·73)
Treatment difference vs FF/VI (95% CI) p-value	Reference	1·10 (-0·27, 2·47) 0·115	-0·30 (-1·66, 1·05) 0·662
Responders			
Responders†, n/N (%)	535/809 (66)	505/801 (63)	555/807 (69)
Odds ratio vs FF/VI (95% CI) p-value	Reference	0·86 (0·69, 1·06) 0·149	1·14 (0·92, 1·42) 0·224

*Defined as ≥0·5-point improvement from baseline.

†Defined as ≥4-point improvement from baseline.

Analysis of unpooled data for change from baseline and responder data in ACQ-7 and SGRQ are reported in Supplementary Table 8.

Note: p-values are not adjusted for multiplicity.

ACQ, Asthma Control Questionnaire; CI, confidence interval; FF, fluticasone furoate; ITT, intent-to-treat; LS, least squares; SGRQ, St George's Respiratory Questionnaire; UMEC, umeclidinium; VI, vilanterol.

Table 4. Effect of increasing ICS dose on lung function, exacerbations and patient-reported outcomes (ITT)

	FF/VI 200/25 µg (N=406) vs FF/VI 100/25 µg (N=407)	**FF/UMEC/VI 200/31·25/25 µg (N=404) vs FF/UMEC/VI 100/31·25/25 µg (N=405)**	**FF/UMEC/VI 200/62·5/25 µg (N=408) vs FF/UMEC/VI 100/62·5/25 µg (N=406)**
Mean change from baseline in clinic trough FEV_1 at Week 24; mL (95% CI)	51 (8, 95)	37 (-6, 81)	34 (-9, 77)
Mean change from baseline in clinic FEV_1 3 hours post-dose at Week 24; mL (95% CI)	36 (-8, 81)	36 (-8, 81)	44 (0, 87)
Reduction in annualised rate of moderate/severe exacerbations; % (95% CI)	34·6 (14·8, 49·8)	20.0 (-4·4, 38·7)	19·1 (-6·4, 38·5)
ACQ-7 responder rate at Week 24; odds ratio (95% CI)	1·34 (1·00, 1·79)	1·13 (0·83, 1·51)	1·08 (0·80, 1·45)
SGRQ responder rate at Week 24; odds ratio (95% CI)	1·21 (0·89, 1·63)	1·05 (0·78, 1·41)	0·99 (0·73, 1·35)
Reduction in annualised rate of severe exacerbations; % (95% CI)	32·2 (2·1, 53)	34.0 (4·7, 54·3)	44.1 (19·1, 61·4)

ACQ, Asthma Control Questionnaire; CI, confidence interval; FEV_1, forced expiratory volume in 1 second; FF, fluticasone furoate; ICS, inhaled corticosteroids; ITT, intent-to-treat; SGRQ; St George's Respiratory Questionnaire UMEC; umeclidinium, VI; vilanterol.

Table 5. Pooled analysis of the effect of a combined measure of biomarkers of type 2 airway inflammation on treatment outcomes (ITT) (unpooled analysis presented in Supplementary Table 11)

Endpoint	Treatment	Low type 2 inflammatory biomarkers (eosinophils <150 cells/µl, and FENO <20 ppb)	Medium type 2 inflammatory biomarkers (all other patients with an eosinophil and FeNO measurement)	High type 2 inflammatory biomarkers (eosinophils ≥300 cells/µl, and FeNO >50 ppb)
Effect of increasing FF dose				
Mean treatment difference in trough FEV_1 at Week 24, mL (95% CI)	Pooled FF/VI 200/25 µg + FF 200 µg/UMEC 31·25+62·5 µg/VI (n=203, 797, 69) vs pooled FF/VI 100/25 µg + FF 100 µg/UMEC 31·25+62·5 µg/VI (n=185, 796, 59)	23 (-38, 84)	44 (15, 74)	127 (20, 233)
Percent reduction in annualised rate of moderate/severe exacerbations (95% CI)	Pooled FF/VI 200/25 µg + FF 200 µg/UMEC 31·25+62·5 µg/VI (n=211, 838, 71) vs pooled FF/VI 100/25 µg + FF 100 µg/UMEC 31·25+62·5 µg/VI (n=194, 836, 67)	12·4 (-29·5, 40·8)	21·2 (5·0, 34·7)	65·2 (29·6, 82·8)
Effect of adding UMEC 62·5 µg				
Mean treatment difference in trough FEV_1 at Week 24, mL (95% CI)	FF/UMEC 62·5 µg/VI (n=131, 543, 42)	100 (24, 177)	95 (59, 131)	82 (-52, 216)

	vs FF/VI (n=118, 534, 40)			
Percent reduction in annualised rate of moderate/severe exacerbations (95% CI)	FF/UMEC 62·5 µg/VI (n=133, 568, 44) vs FF/VI n=119, 565, 43)	36.6 (-3.1, 61.0)	5.7 (-18.3, 24.9)	26.6 (-89.6, 71.6)

n= patients with analysable data for low, medium, and high type 2 inflammatory marker groups (at Week 24 for FEV_1).

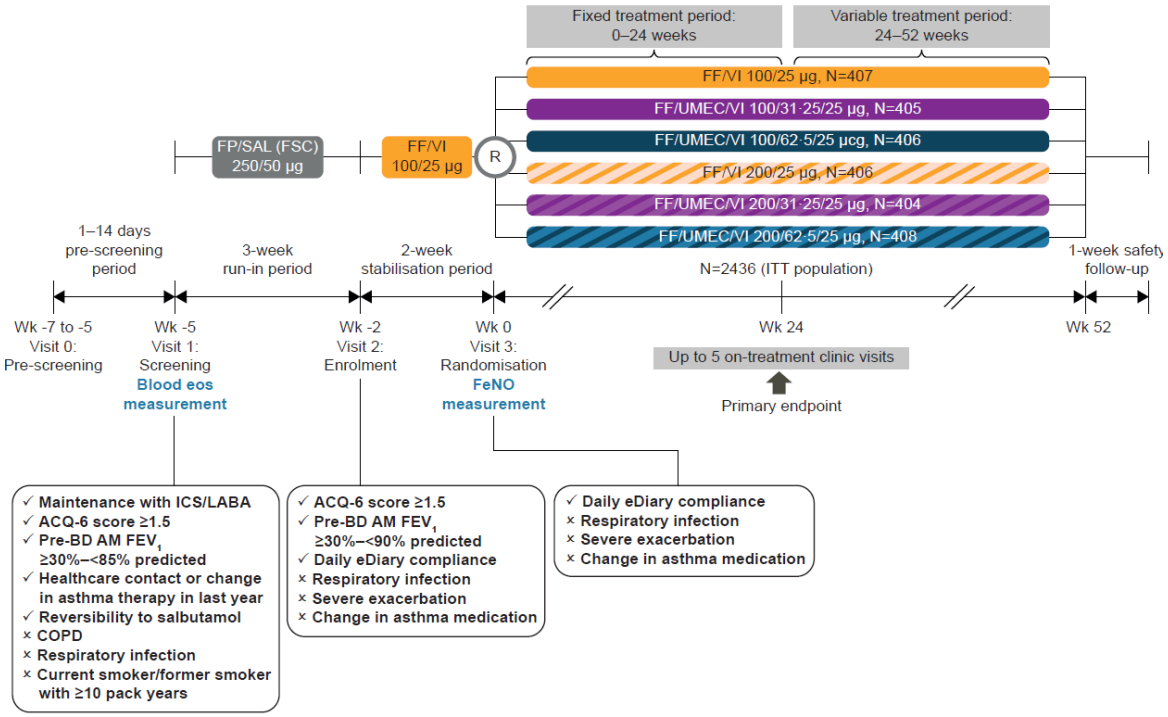
CI, confidence interval; FeNO, fractional exhaled nitric oxide; FEV_1, forced expiratory volume in 1 second; FF, fluticasone furoate; ppb, parts per billion; UMEC, umeclidinium; VI, vilanterol.

Table 6. On-treatment AEs occurring in any treatment group (ITT)

	FF/VI 100/25 µg N=407	FF/UMEC/VI 100/31·25/25 µg N=405	FF/UMEC/VI 100/62·5/25 µg N=406	FF/VI 200/25 µg N=406	FF/UMEC/VI 200/31·25/25 µg N=404	FF/UMEC/VI 200/62·5/25 µg N=408
AEs, n (%)	258 (63)	232 (57)	239 (59)	210 (52)	233 (58)	217 (53)
AEs occurring in ≥3% of patients, n (%)						
Nasopharyngitis	63 (15)	56 (14)	60 (15)	53 (13)	51 (13)	51 (13)
Headache	30 (7)	31 (8)	36 (9)	23 (6)	27 (7)	19 (5)
Upper respiratory tract infection	21 (5)	24 (6)	15 (4)	13 (3)	15 (4)	19 (5)
Bronchitis	14 (3)	18 (4)	15 (4)	19 (5)	17 (4)	22 (5)
Back pain	16 (4)	12 (3)	13 (3)	6 (1)	14 (3)	9 (2)
Respiratory tract infection viral	11 (3)	17 (4)	10 (2)	7 (2)	12 (3)	9 (2)
Influenza	13 (3)	12 (3)	15 (4)	9 (2)	8 (2)	6 (1)
Pharyngitis	8 (2)	10 (2)	9 (2)	14 (3)	11 (3)	9 (2)
Treatment-related AEs, n (%)	21 (5)	16 (4)	29 (7)	17 (4)	20 (5)	19 (5)
SAEs, n (%)	25 (6)	18 (4)	23 (6)	21 (5)	23 (6)	21 (5)
MACE (broad focus), n (%)	5 (1)	3 (<1)	4 (<1)	2 (<1)	3 (<1)	3 (<1)
AEs leading to study treatment discontinuation, n (%)	11 (3)	5 (1)	7 (2)	5 (1)	6 (1)	3 (<1)
AEs leading to death, n (%)	0	2 (<1)	0	1 (<1)	0	0

AE, adverse event; FF, fluticasone furoate; ITT, intent-to-treat; MACE, major adverse cardiovascular event; SAE, serious adverse event; UMEC, umeclidinium; VI, vilanterol.

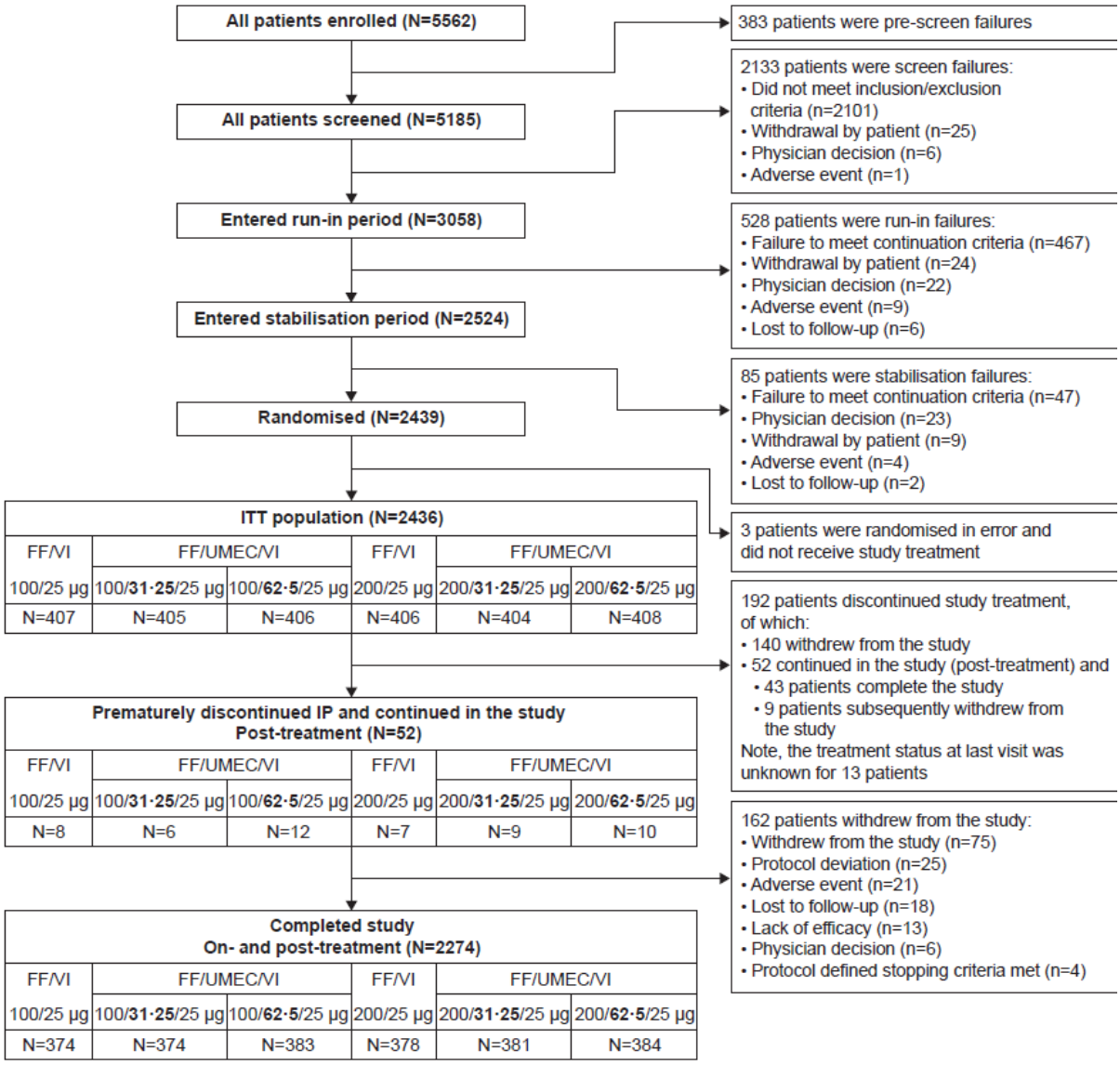
Figure 1. Study design



The study was conducted in five phases: **Pre-screening period:** 1–14 days (Visit 0); patients provided consent and continued to receive pre-study asthma treatments; **Screening/run-in period:** 3 weeks (Visit 1); patients who met the eligibility inclusion criteria at Visit 1 entered the run-in period during which their current ICS/LABA therapy was replaced with open-label FP/SAL 250/50 µg twice daily for 3 weeks via the DISKUS DPI, as well as rescue medication as needed. The purpose of the run-in period was to assess eligibility, washout patient's current asthma therapy and confirm inadequate asthma control on regular medium dose ICS/LABA; **Enrolment/stabilisation period**: 2 weeks (Visit 2); patients who met the enrolment criteria at Visit 2 received FF/VI 100/25 µg once daily via the Ellipta DPI inhaler until randomisation. The purpose of the stabilisation period was to allow subjects to become accustomed to Ellipta DPI and collect baseline data for daily diary-related endpoints; **Randomisation/treatment**: ≥24–≤52 weeks (Visits 3–8); patients who met the randomisation criteria were randomised (1:1:1:1:1:1) to receive one of six study treatments at Visit 3; **Follow-up**: Safety telephone contact or clinic visit was conducted 1 week after the end of the treatment period. Full inclusion and exclusion criteria at screening, enrolment and randomisation are presented in Supplementary Table 1.

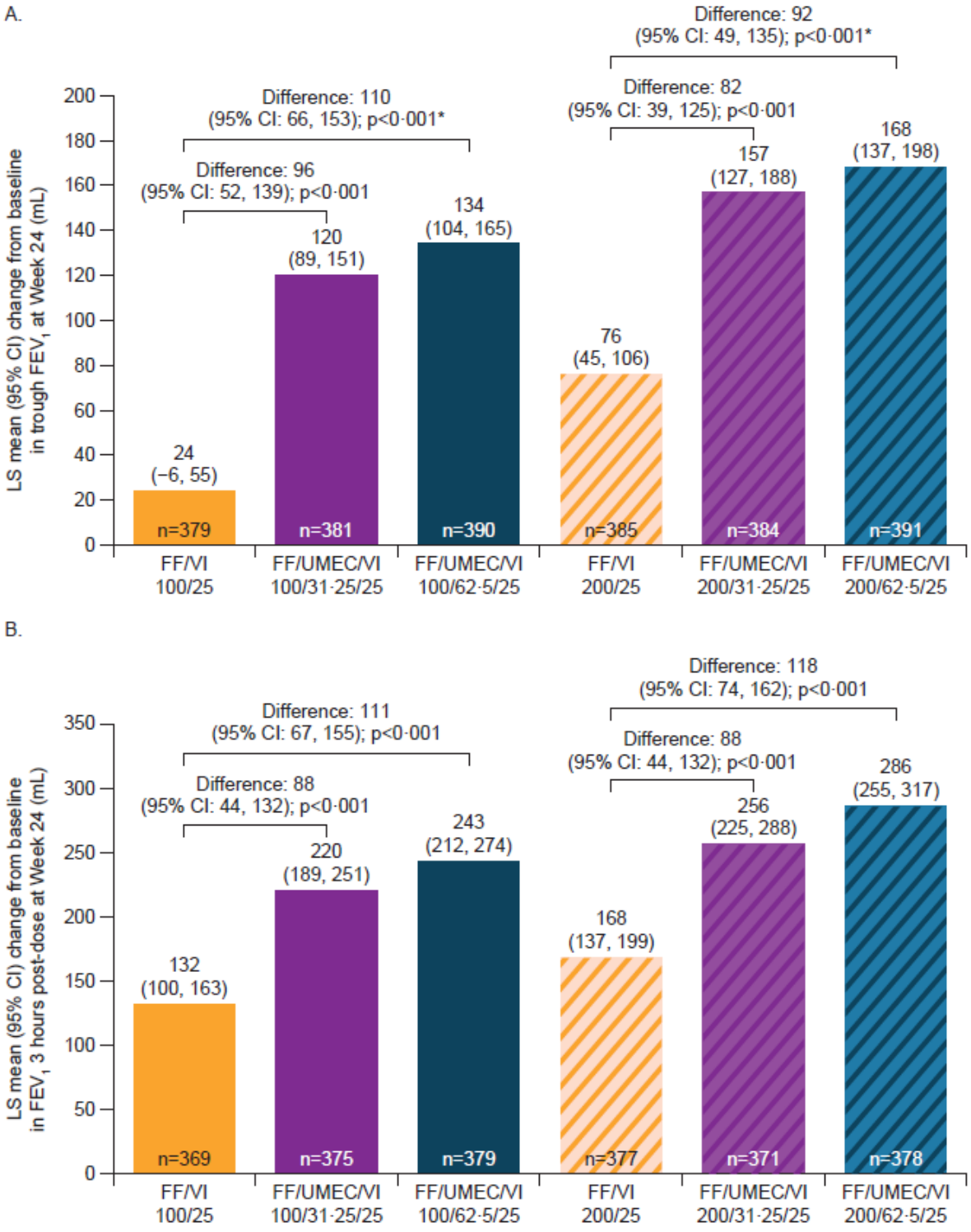
ACQ, asthma control questionnaire; BD, bronchodilator; DPI, dry powder inhaler; FF, fluticasone furoate; FP/SAL, fluticasone/salmeterol combination; FSC, FP/SAL combination; IP, investigational product; ICS, inhaled corticosteroid; LABA, long-acting β_2-agonist; UMEC, umeclidinium, VI, vilanterol.

Figure 2. Trial profile



FF, fluticasone furoate; IP, investigational product; ITT, intent-to-treat; UMEC, umeclidinium, VI, vilanterol.

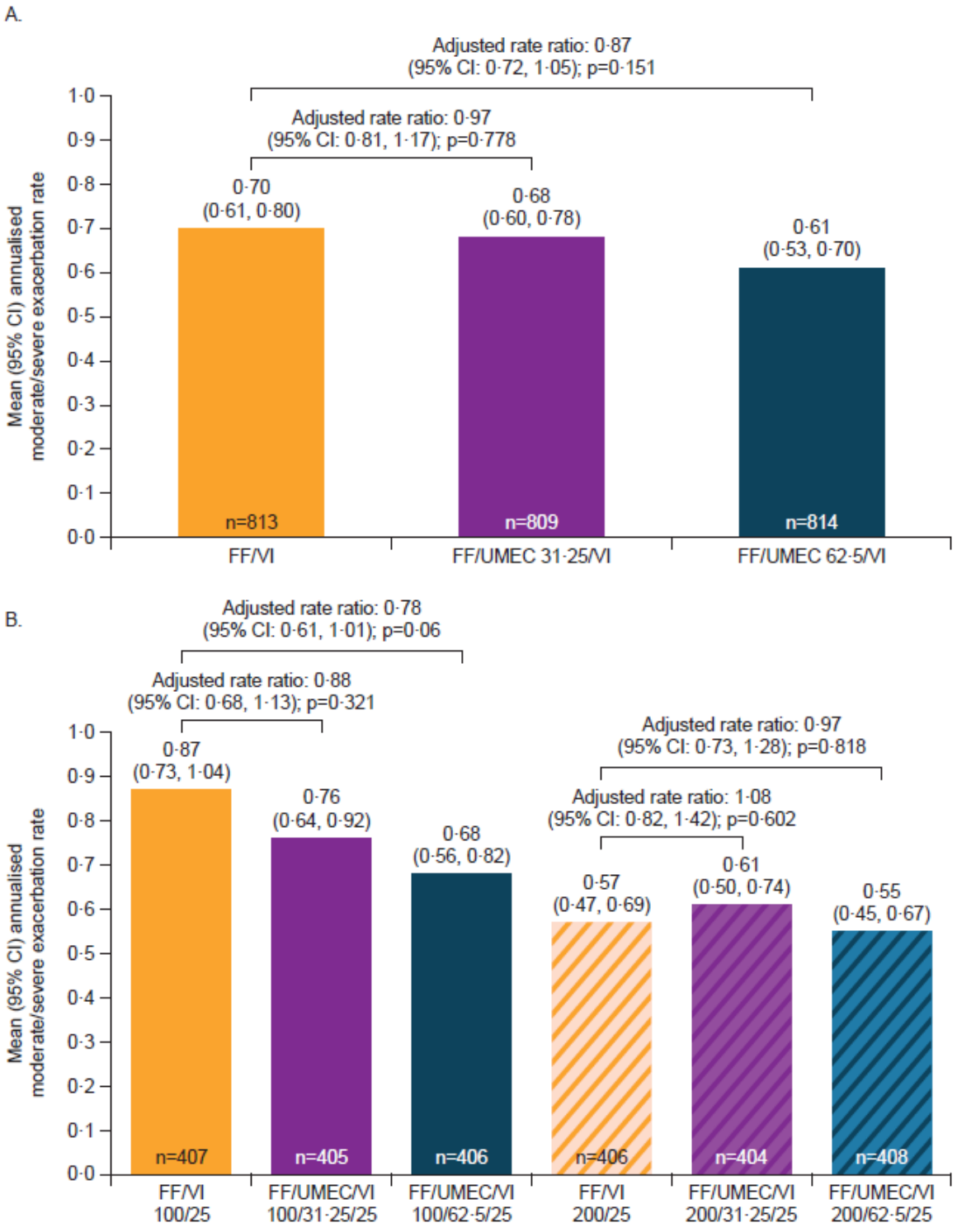
Figure 3. Unpooled analysis of LS mean change from baseline in (A) clinic trough FEV_1 and (B) clinic FEV_1 3 hours post-dose at Week 24 (ITT)



Note: p-values were not adjusted for multiplicity unless marked with an asterisk. All doses are µg.

CI, confidence interval; FEV_1, forced expiratory volume in 1 second; FF: fluticasone furoate; ITT, intent-to-treat; LS: least squares; UMEC: umeclidinium; VI: vilanterol.

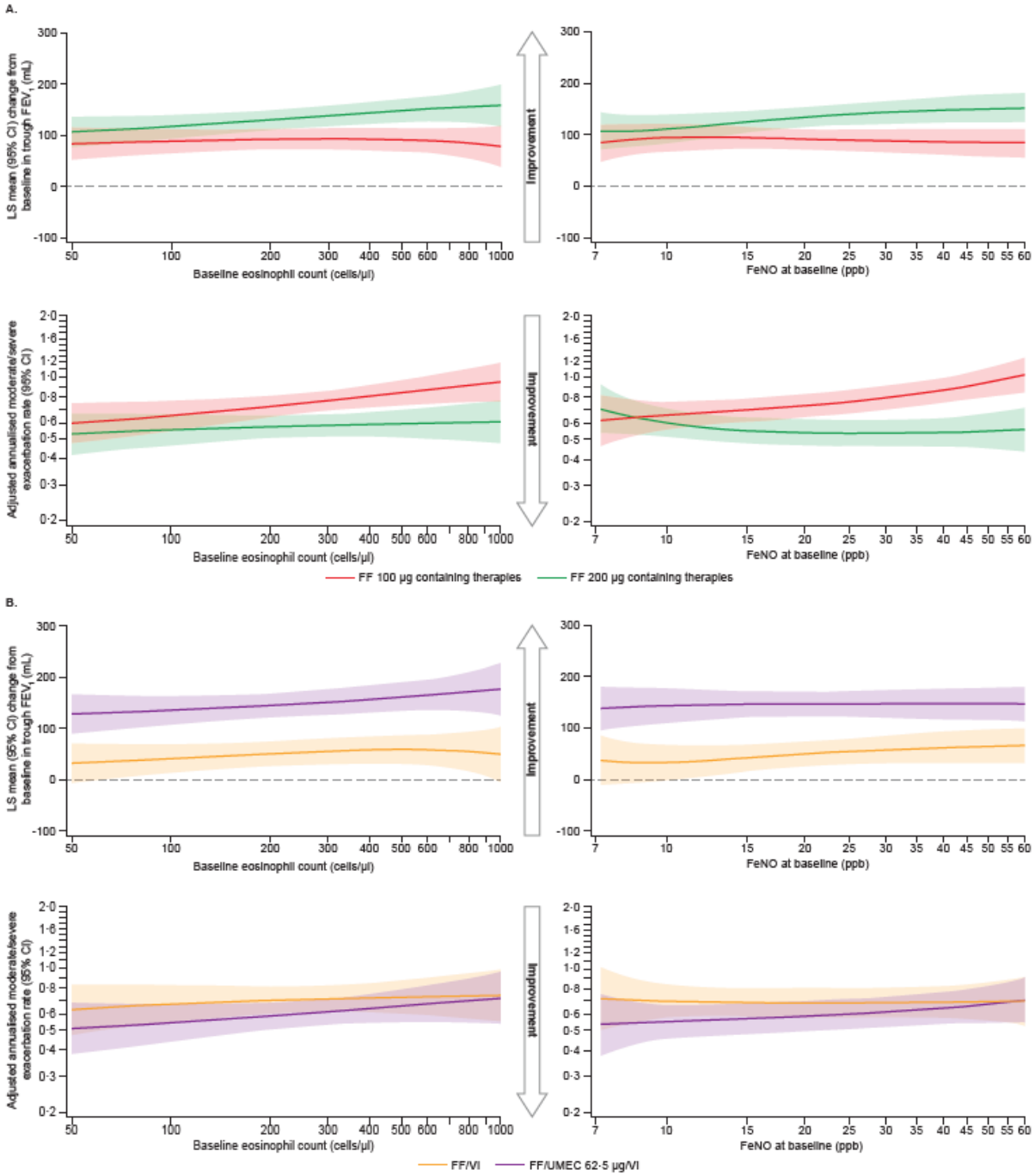
Figure 4. (A) Pooled and (B) unpooled analysis of mean annualised rate of moderate/severe exacerbations (ITT)



Note: p-values were not adjusted for multiplicity. All doses are µg.

CI, confidence interval; ITT, intention-to-treat; FF: fluticasone furoate; UMEC: umeclidinium; VI: vilanterol.

Figure 5. Pooled analysis of the relationship between baseline type 2 inflammatory markers (blood eosinophils and FeNO) and the effects of (A) doubling FF dose and (B) adding UMEC on trough FEV_1 and moderate/severe exacerbation rates (ITT)



Results from the pooled analysis by eosinophil/FeNO quartiles are described separately in Supplementary Table 10.

Best fitting FP models from 36 pre-defined models presented. Further details are presented in the Supplementary Material.

FeNO, fractional exhaled nitric oxide; FEV_1, forced expiratory volume in 1 second; FF, fluticasone furoate; FP, fractional polynomial; LS, least squares; ppb, parts per billion; UMEC, umeclidinium; VI, vilanterol.

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