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Original article

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**INTREPID: Single- vs multiple-inhaler triple therapy for COPD in usual clinical practice**

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**Take Home Message**

Once-daily single-inhaler treatment with FF/UMEC/VI resulted in greater improvements in health status and lung function compared with non-ELLIPTA multiple-inhaler triple therapy in patients with COPD in a usual clinical practice setting.

Running head: Single- vs multiple-inhaler triple therapy in COPD

**Target journal:** ERJ Open Research

## Abstract

### Introduction

Real-world trial data comparing single- with multiple-inhaler triple therapy (MITT) in COPD patients are currently lacking. The effectiveness of once-daily single-inhaler fluticasone furoate/umeclidinium/vilanterol (FF/UMEC/VI) and MITT were compared in usual clinical care.

### Methods

INTREPID was a multicentre, randomised, open-label, phase IV effectiveness study comparing FF/UMEC/VI 100/62.5/25μg via the ELLIPTA inhaler with a clinician's choice of any approved non-ELLIPTA MITT in usual COPD clinical practice in five European countries. Primary endpoint was proportion of COPD Assessment Test (CAT) responders (≥2-unit decrease in CAT score from baseline) at Week 24. Secondary endpoints in a subpopulation included change from baseline in forced expiratory volume in 1 second ($FEV_1$) and percentage of patients making ≥1 critical error in inhalation technique at Week 24. Safety was also assessed.

### Results

3092 patients were included (FF/UMEC/VI N=1545; MITT N=1547). The proportion of CAT responders at Week 24 was significantly greater with FF/UMEC/VI versus non-ELLIPTA MITT (odds ratio: 1.31; 95% confidence interval [CI]: 1.13, 1.51; $p<0.001$) and mean change from baseline in $FEV_1$ was significantly greater with FF/UMEC/VI (77mL vs 28mL; treatment difference [95% CI] 50mL [26, 73]; $p<0.001$). The percentage of patients with ≥1 critical error in inhalation technique was low in both groups (FF/UMEC/VI 6%, non-ELLIPTA MITT 3%). Safety profiles, including incidence of pneumonia serious adverse events, were similar between treatments.

**Conclusions**

In a usual clinical care setting, treatment with once-daily single-inhaler FF/UMEC/VI resulted in significantly more patients gaining health status improvement and greater lung function improvement versus non-ELLIPTA MITT.

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## Introduction

Triple therapy with inhaled corticosteroid (ICS), long-acting $\beta_2$-agonist (LABA) and long-acting muscarinic antagonist (LAMA) for chronic obstructive pulmonary disease (COPD) has traditionally required use of multiple inhalers, sometimes several times per day [1]. However, patients' persistence and adherence with COPD medication administered via multiple inhalers have been shown to be worse than with therapy administered via a single inhaler [2, 3]. Reducing the number of inhalers required and frequency of use should improve treatment persistence and adherence, which could in turn improve clinical effectiveness and patient outcomes [4, 5]. Fewer inhalers and reduced treatment complexity has previously been highlighted as a preferred treatment strategy for patients with COPD [6, 7]. The use of multiple inhalers has also been associated with more frequent errors in inhaler technique compared with therapy administered via a single inhaler [8]. This may result in worse symptom control, as shown in observational studies [9, 10], and the Global Initiative for Chronic Obstructive Lung Disease (GOLD) report recommends that inhaler technique and adherence be checked regularly as part of routine follow-up and before changing treatment [11].

Single-inhaler triple therapy (SITT) is a recent development for COPD treatment and could provide a more practical option for patients [1, 12]. In conventional randomised controlled trials (RCTs), SITT with fluticasone furoate/umeclidinium/vilanterol (FF/UMEC/VI) has shown significant reductions in moderate/severe exacerbation rates and significant improvements in lung function and health status compared with dual therapy with FF/VI, UMEC/VI or budesonide/formoterol [13, 14]. Recent RCT results indicate that FF/UMEC/VI SITT may provide more sustained lung function benefit compared with budesonide/formoterol plus tiotropium multiple-inhaler triple therapy (MITT) [15]. However, evidence from controlled studies supporting the superiority of single-inhaler combination

therapy versus multiple-inhaler therapy on health status and symptoms is needed [16]. Conventional double-blind RCTs include highly selected patient populations, involve using dummy inhalers and are conducted in highly controlled environments which may limit the applicability of the results to routine clinical care [17-19].

Effectiveness studies provide real-world context to complement conventional RCTs as they enrol patients more representative of those prescribed treatment in routine care, do not involve dummy inhalers [20] and allow physicians and patients to prescribe and take their medication as they would in usual care settings. The Salford Lung Study demonstrated the effectiveness of once-daily FF/VI single-inhaler therapy over usual care in a COPD population [21]. However, data are lacking with respect to health status benefits of SITT versus MITT in COPD in usual clinical care settings.

The INTREPID (**IN**vestigation of **TR**elegy **E**ffectiveness: Usual **P**ract**I**ce **D**esign) study was designed to build on the effectiveness data obtained in the Salford Lung Study to investigate the impact of SITT with FF/UMEC/VI versus MITT on health status over 24 weeks in a usual clinical care setting across multiple sites in five European countries.

## Materials and methods

### Study design

INTREPID (GSK study 206854; NCT03467425) was a multicentre, randomised, open-label, phase IV effectiveness study comparing once-daily single-inhaler FF/UMEC/VI delivered by the ELLIPTA inhaler with any licenced non-ELLIPTA MITT in patients with COPD in a usual clinical practice setting. The trial protocol has been described previously [22]. The primary objective was to evaluate the effectiveness of FF/UMEC/VI versus non-ELLIPTA MITT on health status in patients with COPD after 24 weeks of treatment.

Patients were randomised 1:1 to receive either once-daily FF/UMEC/VI 100/62.5/25 µg or continue with their usual twice-daily triple therapy regimen (ICS+LAMA+LABA) administered via multiple non-ELLIPTA inhalers (non-ELLIPTA MITT). Patients on dual therapy at screening, who the clinician deemed in need of triple therapy, were stepped up at randomisation. Randomisation was stratified based on previous treatment (ICS+LABA, LAMA+LABA or ICS+LAMA+LABA) and recruitment of patients on prior dual therapy was not to exceed a combined total of approximately 50% for each country. Patients continued to use short-acting $\beta_2$-agonist therapy as required.

The inclusion and exclusion criteria were minimal [22]; details are provided in the **Supplementary Appendix.**

This trial was conducted at 147 centres in the UK, Germany, the Netherlands, Spain and Sweden from April 2018 to October 2019 in usual care settings. It was carried out in accordance with Good Clinical Practice guidelines under the provisions of the Declaration of Helsinki and received approval from local institutional review boards or independent ethics committees. All patients provided signed informed consent.

To minimise deviations from usual care and impact on normal patient behaviour, patients were managed by their clinician in accordance with usual care practice and only two study visits were mandated: screening/randomisation (Visit 1) and study end (Visit 2; Week 24; **Figure 1**).

In total, 3000 patients were required to obtain sufficient power to assess the primary outcome but only approximately 1520 patients were required to assess secondary outcomes [22]. Therefore, in order to minimise disruption to usual care, spirometry data were only collected in Germany and the UK. Critical errors in inhalation technique were also only assessed in patients enrolled at centres within the countries participating in spirometry assessment and

only if an appropriate error checklist was available for all of the inhalers they were using. Details on the production and validation of the error checklists have been published previously [22].

**Effectiveness Outcomes**

The primary endpoint was proportion of responders based on the CAT at Week 24. A clinically meaningful response was defined as a decrease in CAT score of ≥2 units from baseline [23]. Secondary endpoints included change from baseline in forced expiratory volume in 1 second ($FEV_1$) and percentage of patients making ≥1 critical error in inhalation technique at Week 24.

In addition, an exploratory treatment comparison of FF/UMEC/VI versus non-ELLIPTA MITT was performed for the primary outcome by prior medication strata. Details of the analysis populations and statistical analyses are provided in the **Supplementary Appendix**. In brief, the proportion of CAT responders was analysed in the intent-to-treat (ITT) population using a logistic regression model with treatment as an explanatory variable and covariates of baseline CAT score, number of exacerbations in the prior year, actual prior medication use strata, and country. For analysis of the primary endpoint using the primary estimand, patients who modified their randomised treatment, changed pulmonary rehabilitation status or started oxygen therapy were considered as non-responders. CAT data for patients who discontinued randomised treatment without receiving another COPD maintenance therapy during the study were used if available (**Supplementary Table S1**). Missing Week 24 CAT data was imputed using multiple imputation based on the randomised treatment arm characteristics assuming missing at random (MAR) (**Supplementary Table S1**). Three supportive estimands were defined for the primary endpoint, with different strategies for handling intercurrent events or events leading to missing data (**Supplementary**

**Table S1**). Details of the statistical analyses for the secondary outcomes and the exploratory analysis of the primary outcome can be found in the **Supplementary Appendix**.

### Safety Assessments

Adverse event (AE) recording was limited to treatment-related AEs, serious AEs (SAEs) and AEs leading to study treatment discontinuation or study withdrawal. Serious AEs of special interest (AESI), i.e. SAEs which have specified areas of interest for FF, VI or UMEC or the overall COPD population, were also collected.

## Results

### Trial Population

Of the 3109 patients who underwent randomisation, 3092 patients were included in the ITT population, and 1545 and 1547 patients were randomised to FF/UMEC/VI and non-ELLIPTA MITT, respectively. Within the ITT population, 910 patients randomised to FF/UMEC/VI and 904 patients randomised to non-ELLIPTA MITT were included in the $FEV_1$ population. The critical error population included 691 patients from the FF/UMEC/VI randomised ITT population and 267 patients from the non-ELLIPTA MITT randomised ITT population (**Figure 2**).

Overall, 2991 patients (97%) completed the trial, with 2615 patients (85%) completing the trial while receiving the treatment components to which they were randomised. During the first 8 weeks of treatment rates of discontinuation of randomised treatment were higher with FF/UMEC/VI compared with non-ELLIPTA MITT but were then comparable over the next 16 weeks (**Figure 2, Supplementary Figure S1**). Demographic characteristics at screening were similar between the two treatment groups. Prior to study entry, 80% of patients were receiving triple therapy, 12% were receiving LAMA+LABA and 8% were receiving ICS+LABA maintenance therapy (**Table 1, Supplementary Table S2**).

**Primary and Secondary Efficacy Analyses**

The odds of being a CAT responder at Week 24 were significantly greater in patients receiving FF/UMEC/VI compared with those receiving non-ELLIPTA MITT (OR: 1.31; 95% confidence interval [CI]: 1.13, 1.51; p<0.001; **Figure 3**). Mean (standard deviation [SD]) CAT score at Week 24 was 18.0 (8.0) and 19.1 (7.9) in the FF/UMEC/VI and non-ELLIPTA MITT arms, respectively. Mean (SD) change from baseline in CAT score at Week 24 in FF/UMEC/VI and non-ELLIPTA MITT arms was -2.8 (6.3) and -1.3 (6.0), and median (interquartile range) was -3.0 (-7.0, 1.0) and -1.0 (-5.0, 3.0), respectively. A significantly greater proportion of CAT responders were seen with FF/UMEC/VI over non-ELLIPTA MITT across all three supportive estimands (**Supplementary Table S3**). In patients receiving triple therapy prior to randomisation the odds of being a CAT responder at Week 24 were significantly greater with FF/UMEC/VI versus non-ELLIPTA MITT. The same was found for patients who had stepped up to triple therapy from ICS/LABA. In patients who had stepped up to triple therapy from LAMA+LABA, there was a numerical improvement in favour of FF/UMEC/VI but this was not statistically significant (**Figure 4**).

In the $FEV_1$ population, the mean change from baseline in $FEV_1$ (trough and non-trough values) at Week 24 was significantly greater with FF/UMEC/VI versus non-ELLIPTA MITT (**Table 2**).

In the critical error population, there was no statistically significant difference in the percentage of patients with ≥1 critical error in inhalation technique at Week 24 (6% in the FF/UMEC/VI group, 3% in the non-ELLIPTA MITT group; OR [95% CI]: 1.99 [0.87, 4.53]; p=0.103). Similar results were seen in the supportive estimand (**Supplementary Table S4**). Moderate/severe exacerbation rates are summarised in **Supplementary Table S5.**

**Safety Profile**

On-randomised treatment AEs occurred in 250 (16%) and 151 (10%) of patients receiving FF/UMEC/VI and non-ELLIPTA MITT, respectively (**Table 3**). Of these, 9% in the FF/UMEC/VI arm and 3% in the non-ELLIPTA MITT arm were considered treatment-related in the opinion of the investigator. The only treatment-related AE occurring in >1% of patients was dyspnoea (**Supplementary Table S6**). On randomised treatment AEs leading to study withdrawal, SAEs, fatal SAEs and serious AESIs are described in **Table 3**. No new safety findings associated with the use of an ICS, a LAMA, or a LABA in combination were seen. The on-study safety profile is described in **Supplementary Table S7.**

## Discussion

In this effectiveness trial, in patients with COPD in routine care settings, FF/UMEC/VI SITT resulted in a significantly greater proportion of patients gaining clinically meaningful improvements in health status compared with non-ELLIPTA MITT. In the $FEV_1$ population, larger improvements in lung function were also seen in patients receiving FF/UMEC/VI compared with those receiving non-ELLIPTA MITT. Similar benefits on health status were seen whether patients had previously been on triple therapy or were stepped up from dual therapy. These results provide compelling evidence of the benefits of FF/UMEC/VI SITT compared with non-ELLIPTA MITT on both health status and lung function in routine care and support simplification of COPD treatment regimens.

The significantly increased odds of achieving a clinically relevant CAT response with FF/UMEC/VI compared with non-ELLIPTA MITT reported in this study, show that more patients can achieve an improvement in health status with single-inhaler FF/UMEC/VI versus multiple-inhaler regimens. Numerical differences in odds in favour of FF/UMEC/VI versus non-ELLIPTA MITT were seen regardless of therapy prior to study entry. The health status result is further supported by the spirometry data demonstrating significantly greater

improvements in lung function in patients receiving FF/UMEC/VI compared with non-ELLIPTA MITT.

The proportion of patients making ≥1 critical error in inhalation technique at Week 24 was low in both treatment arms, with no statistical difference between arms. To assess critical errors, patients had to be capable of withholding their COPD maintenance medication prior to the study visit, remember to do so and be using devices for which validated technique checklists were available. Only a small proportion of patients met these criteria, limiting our ability to analyse this endpoint. The main reasons patients were not assessed were: not omitting their morning dose, forgetting to bring their inhaler for the visit, or using one or more devices without an assessment checklist. This last point largely explains the difference in population sizes as all patients randomised to FF/UMEC/VI were using the ELLIPTA device, which had an assessment checklist, while only a subset of patients in the non-ELLIPTA MITT arm would have been using inhalers that all had a checklist. Furthermore, although participating clinicians were offered training on the assessment of inhaler technique, their ability to perform this accurately was not assessed. It is important to note that no selection of patients based on their inhaler technique was conducted at screening and this low critical error rate may be due to patients having had extensive previous experience of using their inhaler. The low critical error rate contrasts with other studies where error rates have generally been higher, although the ELLIPTA inhaler has previously been associated with low critical error rates compared to other inhalers in patients with COPD [10, 24, 25].

Discontinuation rates with randomised treatment were higher with FF/UMEC/VI compared with non-ELLIPTA MITT during the first 8 weeks of treatment but were comparable over the next 16 weeks. This may be attributed to device familiarity. Patients randomised to the non-ELLIPTA MITT arm were likely to have been using their devices for many years, whereas patients randomised to FF/UMEC/VI would have been unfamiliar with the new ELLIPTA

device and switched back to devices they were more familiar with or were more competent at using [26]. As the supportive estimands were consistent with the primary estimand, the difference in discontinuation rates within the first 8 weeks is unlikely to have affected the primary endpoint. However, the significant effects observed for the primary endpoint may not solely be a consequence of the single- versus multiple-inhaler regimen but may also reflect the different molecules and frequency of dosing.

The incidence of treatment-related AEs, and AEs leading to study withdrawal was higher in patients receiving FF/UMEC/VI compared with non-ELLIPTA MITT. This was not unexpected as the open-label nature of the trial is likely to have introduced a potential bias in the reporting of more AEs for a new treatment compared with standard of care options [27]. However, it should be noted that treatment-related AEs and AEs leading to study withdrawal occurred in <1% patients across most preferred terms. Overall the incidence of SAEs and serious AESI, including cardiovascular effects and pneumonia serious AESIs, was low, and unsurprisingly, as all patients received triple therapy, was comparable across treatment arms. These data add confidence to the evidence from conventional RCTs that FF/UMEC/VI has a similar safety profile to non-ELLIPTA MITT including when used by a much broader group of patients in the usual clinical care setting.

Effectiveness studies are designed to test the benefit and risk of interventions when used in routine care settings so that results generated are applicable and generalisable to usual clinical care populations. Compared with conventional RCTs, effectiveness studies allow, by design, more heterogeneity in study elements such as patient populations, permitted additional therapeutics, delivery of care (e.g. general versus specialist services; involvement of respiratory nurses) and patterns of medication use. Consequently, effectiveness studies are at risk of being unable to detect small differences in outcomes due to the dilution of treatment effects that can occur in heterogeneous populations [18, 28]. The magnitude of the

differences in health status, supported by the lung function improvement, observed in INTREPID is therefore particularly meaningful.

Some limitations of this study should be considered. The minimal intervention design of INTREPID and the fact that study treatments were prescribed by the treating physician as per usual clinical practice meant that it was not possible to measure adherence. Similarly, additional measures that affect patients with COPD and that are modified by pharmacological treatments were not assessed in order to minimise intervention, including exercise tolerance and dyspnoea. The pragmatic nature of the study meant that it was simple in design, but the decision to only include two clinic visits meant that collection of data was restricted to just these two timepoints. More timepoints would have allowed a more complete picture of concordance with the various treatment regimens and more measurements of health status, but would have deviated more from usual care. The short length of the study combined with the study population size meant that exacerbation rate could not be compared, however the annualised rates in both arms were low. Another potential limitation was that critical errors could only be assessed for devices for which an assessment form was available, and if patients remembered to withhold medication prior to the second assessment visit and bring their inhaler(s) with them. If this study was to be conducted again, we would reconsider the most effective way of assessing critical errors. Improvements in CAT score were observed in both treatment groups, which could be attributed to the open-label study design and a potential Hawthorne effect [29]; however, despite this, improvements in health status were observed in more patients randomised to FF/UMEC/VI compared with those randomised to non-ELLIPTA MITT.

The study has a number of key strengths. It is the first to evaluate SITT effectiveness over MITT in a usual clinical care setting in multiple countries. Previous studies have been double-blind, double-dummy studies that did not permit investigation of possible benefits

such as improved adherence or reduced number of devices. INTREPID compared SITT with MITT without dummy placebo inhalers, and is therefore more reflective of the usual clinical care setting. The study entry criteria were primarily focused on physicians' management strategies; any patients requiring triple therapy could be enrolled and the lack of strict inclusion/exclusion criteria ensured that patients enrolled were representative of patients with COPD requiring triple therapy in the general population. The study protocol also permitted patients to change treatment regimen at the discretion of their physician, mirroring clinical practice. The study was designed to align the 'usual care' to that of all countries in which the study was conducted, allowing examination of therapeutic effectiveness in accordance with the heterogeneity seen in everyday clinical practice and across different country healthcare systems. Complexity and interventions were kept to a minimum to avoid impact on physician and patient behaviour that may have influenced results. This means that although compromises were made to maintain the usual care setting, INTREPID still collected robust clinical data, allowing treatment superiority to be demonstrated.

In conclusion, single-inhaler FF/UMEC/VI therapy in a usual clinical care setting resulted in more patients achieving significant and clinically meaningful improvements in health status and significant improvements in lung function compared with non-ELLIPTA MITT, with a similar safety profile. The pragmatic design of INTREPID extends understanding of the effectiveness of FF/UMEC/VI beyond RCT settings. For the first time the benefits of SITT versus MITT in patients with highly symptomatic COPD have been confirmed in a routine care setting.

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**Declaration of interests**

Chris Compton, Elaine Irving, Afisi S. Ismaila, Neil Martin, Dawn Midwinter, Maggie Tabberer and Sally Worsley are GSK employees and hold stock/shares in GSK. Afisi S. Ismaila is also an unpaid part-time Professor at McMaster University. David M.G. Halpin has received personal fees from AstraZeneca, Boehringer Ingelheim, Chiesi, GSK, Novartis, Pfizer and Sanofi; and non-financial support from Boehringer Ingelheim and Novartis. Kai-Michael Beeh has received personal and/or institutional compensation for clinical research, consulting, lecturing fees from AstraZeneca, Boehringer Ingelheim, GSK, Novartis, Menarini/Berlin Chemie and Chiesi; consulting and lecturing fees from Sanofi and Elpen; and consulting fees from Sterna. Janwillem W.H. Kocks has received grants, personal fees and non-financial support from AstraZeneca, Boehringer Ingelheim and GSK; grants and personal fees from Chiesi Pharmaceuticals and Novartis; and research grants from MundiPharma and TEVA. All personal fees were paid to the institutions. Jose M. Marin has received speakers fees from AstraZeneca, Chiesi and Menarini; and has been a speaker and advisory committee member for GSK. Neil G. Snowise is a former employee and shareholder of GSK, hold shares in Vectura and is a visiting senior lecturer at King's College London. ELLIPTA is owned by or licensed to the GSK Group of Companies.

**Data availability**

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

## Author contributions

The authors meet criteria for authorship as recommended by the International Committee of Medical Journal Editors. 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. David M.G. Halpin, Sally Worsley, Neil G. Snowise, Chris Compton, Dawn Midwinter, Afisi S. Ismaila, Elaine Irving and Maggie Tabberer contributed to study conception and design. David M.G. Halpin, Jose M. Marin, Janwillem W.H. Kocks and Kai-Michael Beeh contributed to the acquisition of data. David M.G. Halpin, Sally Worsley, Neil G. Snowise, Chris Compton, Dawn Midwinter, Afisi S. Ismaila, Janwillem W.H. Kocks, Jose M. Marin, Kai-Michael Beeh, Maggie Tabberer and Neil Martin contributed to data analysis and interpretation. All authors contributed to the writing and reviewing of the manuscript and have given final approval for the version to be published.

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## Figure Legends

### Figure 1: Study design

*Where available, peripheral blood eosinophil counts were collected using the historical value closest to the patient's consenting visit and no later than 36 months prior to Visit 1. †Patients were asked, if possible, to withhold short-acting $\beta_2$-agonists or short-acting anticholinergics for ≥4 hours and not to take either their SITT or MITT until after the clinic visit at Week 24 to enable measurement of trough $FEV_1$. If this was not possible or had not been done $FEV_1$ was still measured. ‡Safety information was collected at all scheduled or usual care visits recorded in the electronic case report form. BEC, blood eosinophil count; CAT, COPD assessment test; COPD, chronic obstructive pulmonary disease; $FEV_1$, forced expiratory volume in 1 second; FF, fluticasone furoate; MITT, multiple-inhaler triple therapy; R, randomisation; UMEC, umeclidinium; VI, vilanterol.

### Figure 2: Patient disposition

*Patients may have been excluded for multiple reasons. For those withdrawing from the study or randomised treatment only one primary reason is recorded. A patient completed randomised study treatment if they did not prematurely discontinue randomised study treatment and attended Visit 2 (Week 24). A patient who continued on all components of the randomised treatment and added additional medication to their maintenance treatment were considered as modifying their randomised treatment (intercurrent event) but were not considered to have prematurely discontinued from randomised treatment. †One patient who withdrew >1 day after randomisation and did not take any study medication was included in the ITT population. $FEV_1$, forced expiratory volume in 1 second; FF, fluticasone furoate; ITT, intent-to-treat; MITT, multiple-inhaler triple therapy; UMEC, umeclidinium; VI, vilanterol

**Figure 3: Proportion of CAT responders at Week 24**

Missing CAT scores were imputed using multiple imputation based on the randomised treatment arm characteristics assuming MAR. Data labels above bars are n (%). CAT, COPD Assessment Test; CI, confidence interval; COPD, chronic obstructive pulmonary disease; FF, fluticasone furoate; MAR, missing at random; MITT, multiple-inhaler triple therapy; OR, odds ratio; SD, standard deviation; UMEC, umeclidinium; VI, vilanterol. Response is defined as a CAT score ≥2 units below baseline.

**Figure 4: Proportion of CAT responders at Week 24 by prior medication strata**

CAT, COPD Assessment Test; CI, confidence interval; COPD, chronic obstructive pulmonary disease; $FEV_1$, forced expiratory volume in 1 second; FF, fluticasone furoate; MITT, multiple-inhaler triple therapy; OR, odds ratio; UMEC, umeclidinium; VI, vilanterol

**Tables**

**Table 1: Patient Characteristics at Screening (ITT Population)**

| Characteristic | FF/UMEC/VI (N=1545) | Non-ELLIPTA MITT (N=1547) | Total (N=3092) |
|---|---|---|---|
| **Age, mean (SD) years** | 67.8 (8.78) | 67.8 (8.59) | 67.8 (8.68) |
| **Male, n (%)** | 837 (54) | 818 (53) | 1655 (54) |
| **BMI, mean (SD) kg/m$^2$** | n=1536 | n=1538 | n=3074 |
| | 27.84 (5.93) | 28.05 (6.05) | 27.95 (5.99) |
| **COPD exacerbation history in the prior 12 months, n (%)** | | | |
| **Moderate** | | | |
| 0 | 409 (26) | 405 (26) | 814 (26) |
| 1 | 639 (41) | 645 (42) | 1284 (42) |
| ≥2 | 497 (32) | 497 (32) | 994 (32) |
| **Severe** | | | |
| 0 | 1349 (87) | 1361 (88) | 2710 (88) |
| 1 | 155 (10) | 139 (9) | 294 (10) |
| ≥2 | 41 (3) | 47 (3) | 88 (3) |
| **Moderate/severe** | | | |
| 0 | 363 (23) | 361 (23) | 724 (23) |
| 1 | 615 (40) | 610 (39) | 1225 (40) |
| ≥2 | 567 (37) | 576 (37) | 1143 (37) |
| **CAT score, mean (SD)** | n=1543 | n=1547 | n=3090 |
| | 20.8 (6.76) | 20.5 (6.62) | 20.7 (6.69) |
| **Peripheral blood eosinophil count, n (%)*** | n=605 | n=572 | n=1177 |
| <150 cells/µL | 208 (34) | 223 (39) | 431 (37) |
| ≥150 cells/µL | 397 (66) | 349 (61) | 746 (63) |
| **Actual prior medication use strata, n (%)** | | | |
| ICS + LAMA + LABA | 1226 (79) | 1235 (80) | 2461 (80) |
| ICS + LABA | 126 (8) | 126 (8) | 252 (8) |
| LABA + LAMA | 192 (12) | 183 (12) | 375 (12) |
| Missing† | 1 (<1) | 3 (<1) | 4 (<1) |

*Historical eosinophil were recorded as the most recent measure taken within the previous 36 months. †Actual strata is considered missing if the combination of maintenance treatments taken in the 14 days prior to randomisation do not meet any of the three defined strata groups. BMI, body mass index; CAT, COPD Assessment Test; COPD, chronic obstructive pulmonary disease; FF, fluticasone furoate; ICS, inhaled corticosteroid; ITT, intent-to-treat, LABA, long acting $\beta_2$-agonist; LAMA, long acting muscarinic receptor antagonist; MITT, multiple-inhaler triple therapy; SD, standard deviation; UMEC, umeclidinium; VI, vilanterol.

**Table 2: Change from baseline in $FEV_1$ and trough $FEV_1$ at Week 24**

| Outcome | FF/UMEC/VI Population (N=910) | MITT Population (N=904) | FF/UMEC/VI versus MITT |
|---|---|---|---|
| **$FEV_1$*** | | | |
| n | 691 | 675 | 50 (26, 73); p<0.001 |
| LS mean (95% CI), mL | 1446 (1425, 1467) | 1396 (1375, 1418) | |
| LS mean change from baseline (95% CI), mL | 77 (57, 98) | 28 (6, 49) | |
| **Trough $FEV_1$** | | | |
| n | 301 | 292 | 53 (9, 96); p=0.017 |
| LS mean (95% CI), mL | 1498 (1462, 1534) | 1445 (1404, 1486) | |
| LS mean change from baseline (95% CI)†, mL | 100 (64, 135) | 47 (6, 88) | |

*Data includes both trough and non-trough values; †Patients with imputed $FEV_1$, n=82 (FF/UMEC/VI), n=115 (non-ELLIPTA MITT). Trough $FEV_1$ is defined as the $FEV_1$ value recorded while patients have withheld COPD maintenance, short-acting $\beta_2$-agonist and short-acting muscarinic receptor antagonist treatment. For COPD maintenance treatments taken once-daily, $FEV_1$ was considered as Trough if the patient withheld the LABA and LAMA components of the maintenance treatment for ≥16 hours. For COPD maintenance treatments taken twice-daily, $FEV_1$ was considered as Trough if the patient withheld the LABA and LAMA components of the maintenance treatment for ≥8 hours. CI, confidence interval; $FEV_1$, forced expiratory volume in 1 second; FF, fluticasone furoate; LS mean, least squares mean; MITT, multiple-inhaler triple therapy; SD, standard deviation; UMEC, umeclidinium; VI, vilanterol.

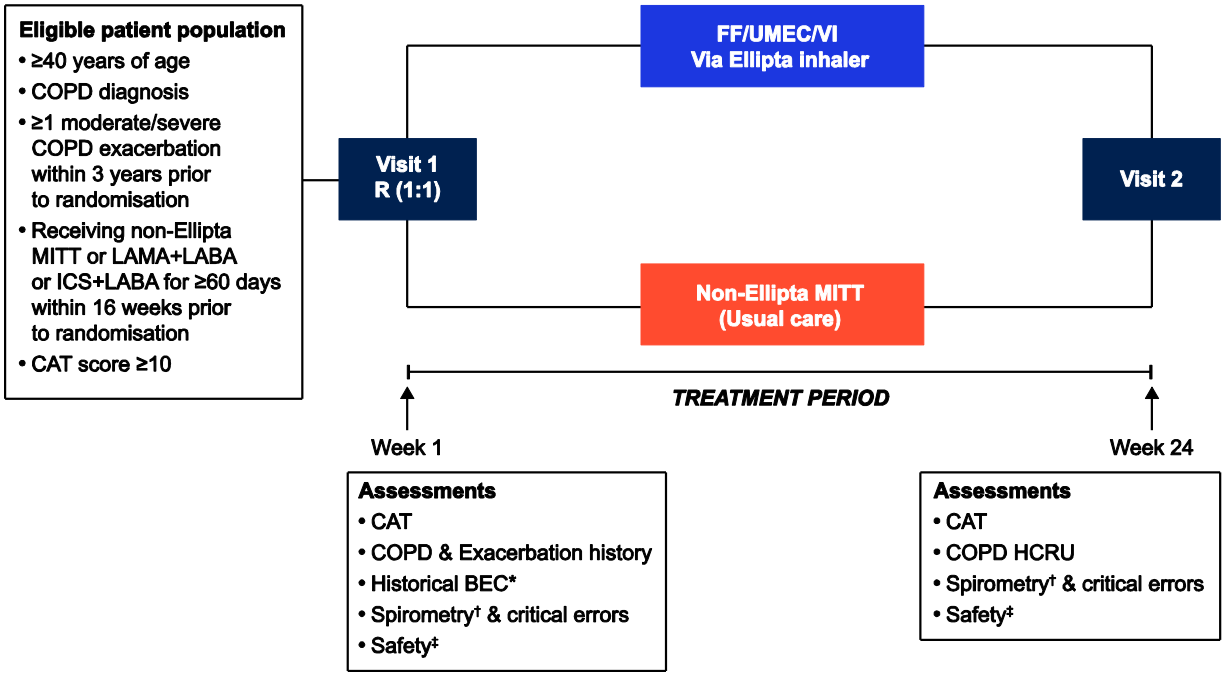
**Table 3: Incidence of on-randomised treatment AEs***

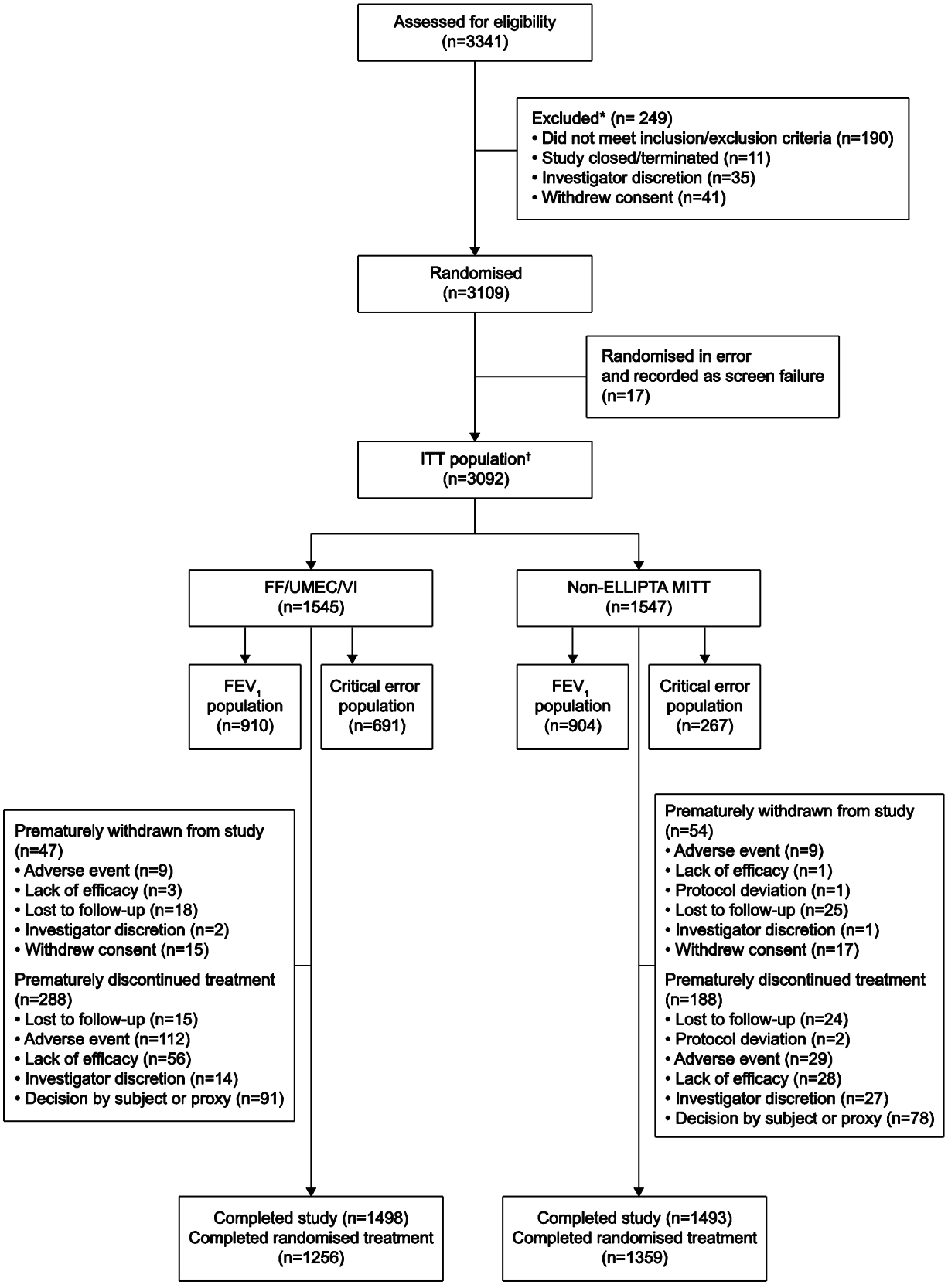
| | **FF/UMEC/VI (N=1545)** | | **Non-ELLIPTA MITT (N=1547)** | |
|---|---|---|---|---|
| Total duration at risk (patient-years) | 636.7 | | 685.8 | |
| | n (%) | Rate [#] | n (%) | Rate [#] |
| Any AE | 250 (16) | 590.6 [376] | 151 (10) | 322.2 [221] |
| Any treatment-related AE | 145 (9) | 329.8 [210] | 44 (3) | 77.3 [53] |
| Any AE leading to study withdrawal | 115 (7) | 279.6 [178] | 32 (2) | 70.0 [48] |
| Any SAE | 114 (7) | 257.6 [164] | 114 (7) | 255.2 [175] |
| Any treatment-related SAE | 13 (<1) | 20.4 [13] | 6 (<1) | 10.2 [7] |
| Any fatal SAE | 8 (<1) | 20.4 [13] | 8 (<1) | 23.3 [16] |
| Any treatment-related fatal SAE | 0 | 0 | 0 | 0 |
| Serious AESIs | | | | |
| Cardiovascular effects | 29 (2) | 55.0 [35] | 23 (1) | 39.4 [27] |
| Decreased BMD and associated fractures | 6 (<1) | 9.4 [6] | 4 (<1) | 7.3 [5] |
| Infective pneumonia | 27 (2) | 44.0 [28] | 32 (2) | 46.7 [32] |
| LRTI excluding infective pneumonia | 7 (<1) | 11.0 [7] | 10 (<1) | 14.6 [10] |

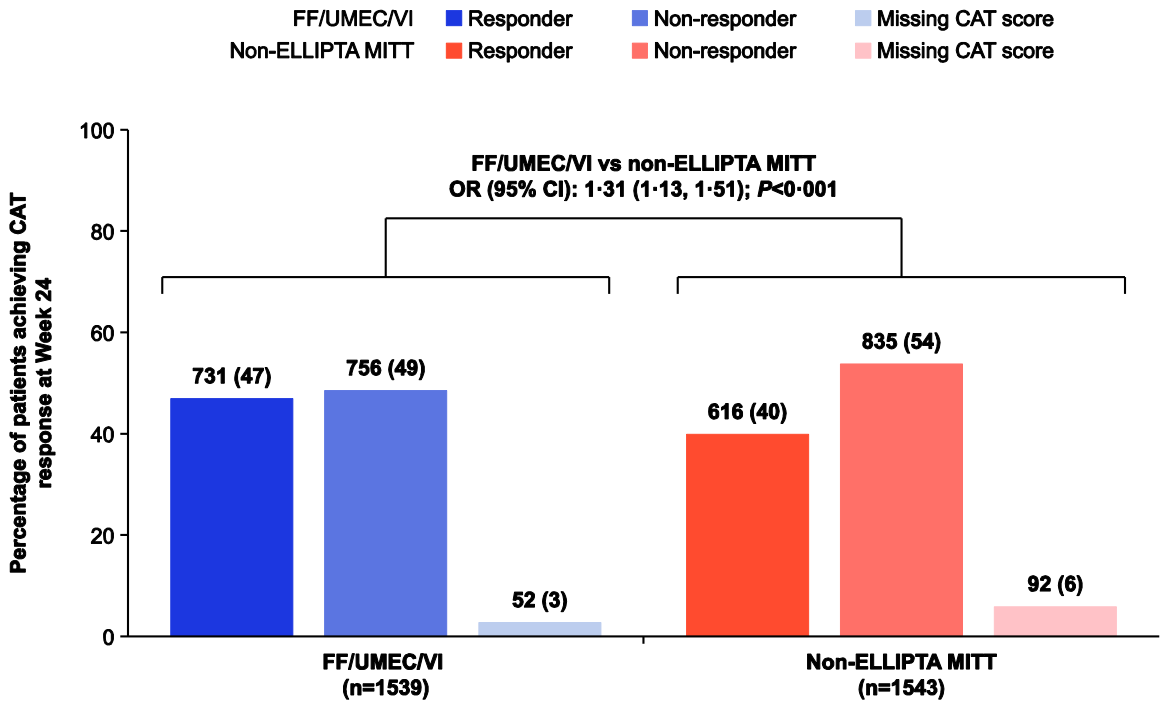
*The recording of AEs was limited to treatment-related AEs, SAEs and AEs leading to study treatment discontinuation or study withdrawal. Refer to Supplementary Tables S6 and S7 for further details.

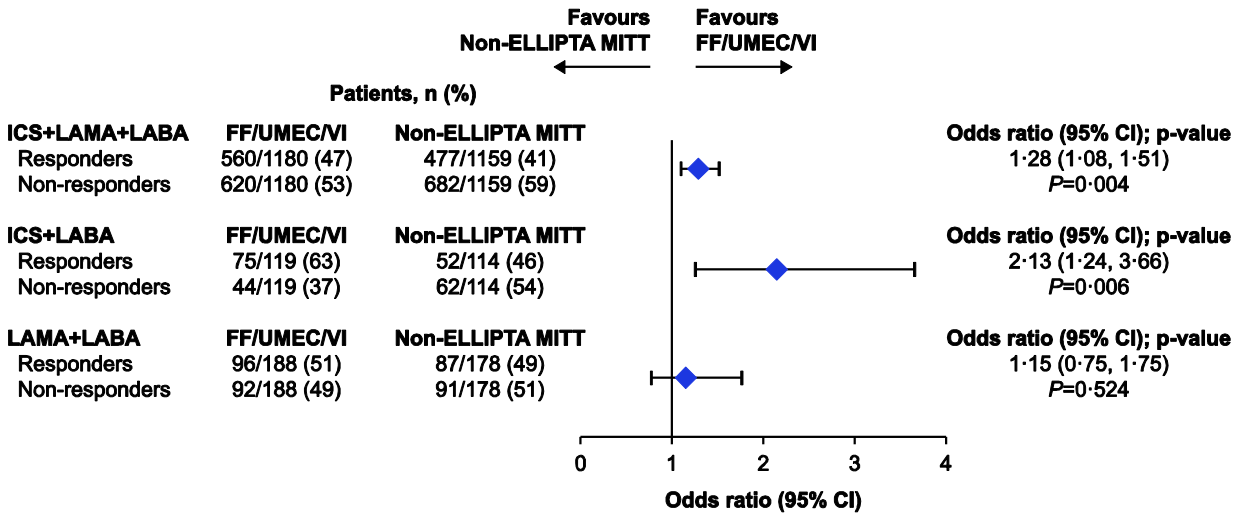
Rate is event rate per 1000 patient-years, calculated as the number of events x 1000, divided by the total duration at risk.

#, number of events; AE, adverse event; AESI, adverse event of special interest; BMD, bone mineral density; FF, fluticasone furoate; LRTI, lower respiratory tract infection; SAE, serious adverse event; UMEC, umeclidinium; VI, vilanterol.


Eligible patient population
• ≥40 years of age
• COPD diagnosis
• ≥1 moderate/severe COPD exacerbation within 3 years prior to randomisation
• Receiving non-Ellipta MITT or LAMA+LABA or ICS+LABA for ≥60 days within 16 weeks prior to randomisation
• CAT score ≥10
Visit 1
R (1:1)
FF/UMEC/VI
Via Ellipta inhaler
Non-Ellipta MITT
(Usual care)
Visit 2
TREATMENT PERIOD
Week 1
Week 24
Assessments
• CAT
• COPD & Exacerbation history
• Historical BEC*
• Spirometry† & critical errors
• Safety‡
Assessments
• CAT
• COPD HCRU
• Spirometry† & critical errors
• Safety‡


Assessed for eligibility (n=3341)
Excluded* (n= 249)
• Did not meet inclusion/exclusion criteria (n=190)
• Study closed/terminated (n=11)
• Investigator discretion (n=35)
• Withdrew consent (n=41)
Randomised (n=3109)
Randomised in error and recorded as screen failure (n=17)
ITT population† (n=3092)
FF/UMEC/VI (n=1545)
Non-ELLIPTA MITT (n=1547)
FEV1 population (n=910)
Critical error population (n=691)
FEV1 population (n=904)
Critical error population (n=267)
Prematurely withdrawn from study (n=47)
• Adverse event (n=9)
• Lack of efficacy (n=3)
• Lost to follow-up (n=18)
• Investigator discretion (n=2)
• Withdrew consent (n=15)
Prematurely discontinued treatment (n=288)
• Lost to follow-up (n=15)
• Adverse event (n=112)
• Lack of efficacy (n=56)
• Investigator discretion (n=14)
• Decision by subject or proxy (n=91)
Prematurely withdrawn from study (n=54)
• Adverse event (n=9)
• Lack of efficacy (n=1)
• Protocol deviation (n=1)
• Lost to follow-up (n=25)
• Investigator discretion (n=1)
• Withdrew consent (n=17)
Prematurely discontinued treatment (n=188)
• Lost to follow-up (n=24)
• Protocol deviation (n=2)
• Adverse event (n=29)
• Lack of efficacy (n=28)
• Investigator discretion (n=27)
• Decision by subject or proxy (n=78)
Completed study (n=1498)
Completed randomised treatment (n=1256)
Completed study (n=1493)
Completed randomised treatment (n=1359)


FF/UMEC/VI
Responder
Non-responder
Missing CAT score
Non-ELLIPTA MITT
Responder
Non-responder
Missing CAT score
FF/UMEC/VI vs non-ELLIPTA MITT
OR (95% CI): 1·31 (1·13, 1·51); P<0·001
Percentage of patients achieving CAT response at Week 24
100
80
60
40
20
0
731 (47)
756 (49)
52 (3)
616 (40)
835 (54)
92 (6)
FF/UMEC/VI
(n=1539)
Non-ELLIPTA MITT
(n=1543)


Favours Non-ELLIPTA MITT
Favours FF/UMEC/VI
Patients, n (%)
ICS+LAMA+LABA
FF/UMEC/VI
Non-ELLIPTA MITT
Odds ratio (95% CI); p-value
Responders
560/1180 (47)
477/1159 (41)
1·28 (1·08, 1·51)
Non-responders
620/1180 (53)
682/1159 (59)
P=0·004
ICS+LABA
FF/UMEC/VI
Non-ELLIPTA MITT
Odds ratio (95% CI); p-value
Responders
75/119 (63)
52/114 (46)
2·13 (1·24, 3·66)
Non-responders
44/119 (37)
62/114 (54)
P=0·006
LAMA+LABA
FF/UMEC/VI
Non-ELLIPTA MITT
Odds ratio (95% CI); p-value
Responders
96/188 (51)
87/178 (49)
1·15 (0·75, 1·75)
Non-responders
92/188 (49)
91/178 (51)
P=0·524
0
1
2
3
4
Odds ratio (95% CI)

# Supplementary Materials

## Single- vs multiple-inhaler triple therapy for COPD in usual clinical practice: the INTREPID trial

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**Online Data Supplement**

### Materials and methods

#### Inclusion and exclusion criteria

Briefly, eligible patients were ≥40 years of age with physician-diagnosed symptomatic COPD (COPD Assessment Test [CAT] score ≥10), who had been receiving a non-ELLIPTA maintenance therapy (ICS+LAMA+LABA MITT, or LAMA+LABA or ICS+LABA dual therapy) for ≥16 weeks prior to randomisation; and had a history of ≥1 COPD exacerbation requiring treatment with systemic or oral corticosteroids, antibiotics and/or hospitalisation in the 3 years prior to randomisation. Patients receiving dual therapy at the time of study entry were required to be considered by their physician as needing a step-up to triple therapy and the reason clearly documented. It was advised that patients enrolled to the study who were already receiving triple therapy for COPD and randomised to the non-ELLIPTA MITT arm continued on their existing therapy. Patients randomised to FF/UMEC/VI started this as a new therapy. In line with usual care, at the start of the study, and whenever patients were issued with a prescription for a new COPD maintenance treatment, the physician or their delegate were asked, at their discretion, to train the patient on the correct use of their inhaler(s).

**Analysis Populations**

The intent-to-treat (ITT) population included all randomised patients, excluding those randomised in error. The $FEV_1$ population included all members of the ITT population for whom a spirometry assessment was performed at any of Visit 1 or Visit 2. The critical error population included all members of the ITT population for whom a critical error assessment was performed at Visit 2. Patients who were not using an inhaler for which an error checklist was available or who did not have assessments for all unique inhalers they were using at Visit 2 were not included in this population. Additionally, patients who had not withheld their inhaled medication prior to assessment at Visit 2 were not included as they were unable to dose again for the assessment.

The following study phases were defined: on-randomised treatment, post randomised treatment and on-study (**Supplementary Figure S2**). A patient was defined as being in the on-randomised treatment phase from the start of randomised treatment to the date they modified or stopped any component of their randomised treatment. If the patient modified their randomised treatment regimen with a change of their COPD maintenance therapy and did not stop any other component, then the end of the randomised treatment phase was considered as the day before the modification took place. The post randomised treatment phase was defined as the time following the on-randomised treatment phase to the end of the study. Patients were defined as being on-study from the date of randomisation to the end of the study. Intercurrent events that occur after treatment initiation and preclude the observation, or affect the interpretation, of the endpoint data and thus affect the estimation of treatment effect were considered to be: treatment modification (patients who modified their randomised treatment with the addition, or changing, of at least one of the components of their maintenance therapy), treatment discontinuation (patients who stopped all components of their randomised treatment and did not start any alternative maintenance treatment),

change in pulmonary rehabilitation status and starting oxygen therapy for the first time (**Supplementary Table S1**).

**Statistical Analysis**

Statistical analyses were performed using Statistical and Analysis Software (SAS) Version 9.4. Sample size calculations were performed based on the results from two recent studies: the Salford Lung Study COPD [21], and a RCT comparing ELLIPTA single-inhaler triple therapy and non-ELLIPTA dual therapy [13]. The proportion of CAT responders in the non-ELLIPTA MITT arm at Week 24 was assumed to be 35% and an odds ratio (OR) of 1.3 was assumed in order to reject the null hypothesis that there is no difference in the proportion of CAT responders at Week 24 between FF/UMEC/VI and non-ELLIPTA MITT. As the previous studies had low drop-out rates, the dropout rate for INTREPID was assumed to be approximately 13.5%. Overall, taking these aspects into consideration, it was estimated that the INTREPID target enrolment for a 1:1 randomisation between treatment arms should be 3000 patients [22].

Change from baseline in $FEV_1$ was analysed using an analysis of covariance (ANCOVA) model with treatment as an explanatory variable and covariates of baseline $FEV_1$, actual prior medication use strata, country, and timing of spirometry. Change from baseline in trough $FEV_1$ was analysed using an ANCOVA model with treatment as an explanatory variable and covariates of baseline trough $FEV_1$, actual prior medication use strata, and country. The analysis of the proportion of patients making at least one critical error was performed using a logistic regression model with covariates of treatment group, actual prior medication use strata and country. Further details on the handling of intercurrent events and missing data are described in **Supplementary Table S1**.

The analysis of proportion of CAT responders by prior medication strata was performed using a separate logistic regression model for each subgroup with covariates of treatment

group, baseline CAT score, number of exacerbations in the prior year and country. The analysis of this estimand, intercurrent events and missing data is described in **Supplementary Table S1**.

**Table S1. Strategies for handling intercurrent events or events leading to missing data for the primary and supportive estimands**

| | Intercurrent events | | | | Missing data | | Patients with multiple imputed data, n (%)* |
|---|---|---|---|---|---|---|---|
| **Estimand** | **Randomised treatment discontinuation** | **Randomised treatment modification** | **Pulmonary rehabilitation** | **Oxygen therapy** | **Study withdrawal** | **Week 24 CAT score not available** | |
| ***CAT score at Week 24 primary estimand*** | | | | | | | |
| Treatment policy × composite | Week 24 CAT score data used regardless of event (treatment policy) | Considered as non-responders (composite) | Considered as non-responders (composite) | Considered as non-responders (composite) | Missing Week 24 CAT score imputed based on randomised treatment (assumes MAR) | Missing Week 24 CAT score imputed based on randomised treatment (assumes MAR) | FF/UMEC/VI: 52<br>Non-ELLIPTA MITT: 92 |
| ***CAT score at Week 24 supportive estimand 1*** | | | | | | | |
| Treatment policy × composite | Week 24 CAT score data used regardless of event (treatment policy) | Week 24 CAT score data used regardless of event (treatment policy) | Week 24 CAT score data used regardless of event (treatment policy) | Week 24 CAT score data used regardless of event (treatment policy) | Considered as non-responders (composite) | Considered as non-responders (composite) | |
| ***CAT score at Week 24 supportive estimand 2*** | | | | | | | |
| Treatment policy × composite | Week 24 CAT score data used regardless of event (treatment policy) | Considered as non-responders (composite) | Week 24 CAT score data used regardless of event (treatment policy) | Week 24 CAT score data used regardless of event (treatment policy) | Missing Week 24 CAT score imputed based on randomised treatment (assumes MAR) | Missing Week 24 CAT score imputed based on randomised treatment (assumes MAR) | FF/UMEC/VI: 52<br>Non-ELLIPTA MITT: 93 |
| ***CAT score at Week 24 supportive estimand 3*** | | | | | | | |

| | | | | | | | |
|---|---|---|---|---|---|---|---|
| Hypothetical | Ignore actual Week 24 CAT score. Assume MAR and impute Week 24 CAT score as if the intercurrent event did not occur | Ignore actual Week 24 CAT score. Assume MAR and impute Week 24 CAT score as if the intercurrent event did not occur | Ignore actual Week 24 CAT score. Assume MAR and impute Week 24 CAT score as if the intercurrent event did not occur | Ignore actual Week 24 CAT score. Assume MAR and impute Week 24 CAT score as if the intercurrent event did not occur | Missing Week 24 CAT score imputed assuming MAR and impute value as if patient did not withdraw early from the study | Missing Week 24 CAT score imputed assuming MAR and impute value as if patient did have an available value at Week 24 | FF/UMEC/VI: 336<br>Non-ELLIPTA MITT: 264 |
| ***Change from baseline in $FEV_1$ at Week 24 primary estimand*** | | | | | | | |
| Treatment policy | Week 24 $FEV_1$ data used regardless of event (treatment policy) | Week 24 $FEV_1$ data used regardless of event (treatment policy) | Week 24 $FEV_1$ data used regardless of event (treatment policy) | Week 24 $FEV_1$ data used regardless of event (treatment policy) | Missing Week 24 $FEV_1$ was not imputed | Missing Week 24 $FEV_1$ was not imputed | |
| ***Change from baseline in trough $FEV_1$ at Week 24 primary estimand*** | | | | | | | |
| Treatment policy | Week 24 trough $FEV_1$ data used regardless of event (treatment policy) | Week 24 trough $FEV_1$ data used regardless of event (treatment policy) | Week 24 trough $FEV_1$ data used regardless of event (treatment policy) | Week 24 trough $FEV_1$ data used regardless of event (treatment policy) | Missing Week 24 trough $FEV_1$ imputed based on randomised treatment (assumes MAR) | Missing Week 24 trough $FEV_1$ imputed based on randomised treatment (assumes MAR) | FF/UMEC/VI: 82<br>Non-ELLIPTA MITT: 115 |
| ***Critical error at Week 24 primary estimand*** | | | | | | | |
| Hypothetical | N/A | Any inhaler error assessment data following randomised treatment modification included in the analysis if the | N/A | N/A | No imputation performed for the missing data | No imputation performed for the missing data | |

| | | | | | | | |
|---|---|---|---|---|---|---|---|
| | | new maintenance therapy uses the same devices as the randomised therapy. Data treated as missing if devices used are different to the randomised treatment devices or not being assessed in the study (i.e. checklist not available) | | | | | |
| ***Critical error at Week 24 supportive estimand*** | | | | | | | |
| Treatment policy | N/A | Any inhaler error assessment data following randomised treatment modification included in the analysis regardless of inhaler device used (treatment policy) | N/A | N/A | No imputation performed for the missing data. Inhaler error assessment data collected at the early withdrawal visit to be used in the analysis | No imputation performed for the missing data | |
| ***CAT responders by prior medication strata*** | | | | | | | |

| | | | | | | | |
|---|---|---|---|---|---|---|---|
| Treatment policy × composite | Week 24 CAT score data used regardless of event (treatment policy) | Considered as non-responders (composite) | Considered as non-responders (composite) | Considered as non-responders (composite) | Missing Week 24 CAT score was not imputed | Missing Week 24 CAT score was not imputed | |

[*]Data is imputed for the analysis using multiple imputation methods based on the randomised treatment arm characteristics and assuming MAR.

CAT, COPD Assessment Test; COPD, chronic obstructive pulmonary disease; $FEV_1$, forced expiratory volume in 1 second; MAR, missing at random.

**Table S2. Patient characteristics at screening ($FEV_1$ and critical error populations)**

| Characteristic | FF/UMEC/VI | Non-ELLIPTA MITT | Total |
|---|---|---|---|
| ***$FEV_1$ population*** | N=910 | N=904 | N=1814 |
| **Age, mean (SD) years** | 67.7 (8.78) | 67.4 (8.64) | 67.6 (8.71) |
| **Male, n (%)** | 501 (55) | 476 (53) | 977 (54) |
| **BMI ($kg/m^2$), mean (SD)** | n=906<br>28.08 (6.19) | n=901<br>28.19 (6.28) | n=1807<br>28.14 (6.24) |
| **Post-bronchodilator $FEV_1$, mL, mean (SD)** | n=825<br>1474 (565.3) | n=827<br>1462 (584.0) | n=1652<br>1468 (574.6) |
| ***Critical Error population*** | N=691 | N=267 | N=958 |
| **Age, mean (SD) years** | 67.5 (8.80) | 67.2 (8.94) | 67.4 (8.84) |
| **Male, n (%)** | 386 (56) | 137 (51) | 523 (55) |
| **BMI ($kg/m^2$), mean (SD)** | n=687<br>28.10 (6.03) | n=265<br>27.92 (6.22) | n=952<br>28.05 (6.08) |

BMI, body mass index; CAT, COPD Assessment Test; COPD, chronic obstructive pulmonary disease; FF, fluticasone furoate; ICS, inhaled corticosteroid; ITT, intent-to-treat, LABA, long acting $\beta_2$-agonist; LAMA, long acting muscarinic receptor antagonist; MITT, multiple-inhaler triple therapy; SD, standard deviation; UMEC, umeclidinium; VI, vilanterol

**Table S3. CAT responders at Week 24 (supportive estimands)**

| CAT response status | FF/UMEC/VI (N=1545) | Non-ELLIPTA MITT (N=1547) | OR (95% CI), FF/UMEC/VI vs MITT |
|---|---|---|---|
| **n** | 1539 | 1543 | |
| **Supportive estimand 1** | | | |
| Responders | 847 (55) | 683 (44) | 1.54 (1.33, 1.78); p<0.001 |
| Non-responders | 692 (45) | 860 (56) | |
| **Supportive estimand 2** | | | |
| Responders | 746 (48) | 630 (41) | 1.31 (1.13, 1.51); p<0.001 |
| Non-responders | 741 (48) | 820 (53) | |
| Patients with imputed CAT score | 52 (3) | 93 (6) | |
| **Supportive estimand 3** | | | |
| Responders | 731 (47) | 615 (40) | 1.65 (1.40, 1.94); p<0.001 |
| Non-responders | 472 (31) | 664 (43) | |
| Patients with imputed CAT score | 336 (22) | 264 (17) | |

For definitions of supportive estimands refer to **Table S1**. As patients with missing CAT scores are subject to multiple imputation methods they cannot be categorised explicitly as responders or non-responders and have been reported as an additional category in these analyses. CAT, COPD Assessment Test, CI, confidence interval; COPD, chronic obstructive pulmonary disease; FF, fluticasone furoate; MITT, multiple-inhaler triple therapy; OR, odds ratio; UMEC, umeclidinium; VI, vilanterol. Analyses performed using a logistic regression model with covariates of treatment group, baseline CAT score, number of exacerbations in the prior year, actual prior medication use strata and country.

**Table S4. Proportion of patients making ≥1 critical error in inhaler technique at Week 24 (supportive estimand)**

| Outcome | FF/UMEC/VI (N=691) | Non-ELLIPTA MITT (N=267) | OR (95% CI), FF/UMEC/VI vs MITT |
|---|---|---|---|
| Patients with ≥1 critical error | 40 (6) | 9 (3) | 1.80 (0.86, 3.78); |
| Patients with no critical error | 651 (94) | 258 (97) | p=0.119 |

For definition of supportive estimand refer to **Table S1**. CI, confidence interval; FF, fluticasone furoate; MITT, multiple-inhaler triple therapy; OR, odds ratio; UMEC, umeclidinium; VI, vilanterol. Analysis performed using a logistic regression model with covariates of treatment group, actual prior medication use strata and country.

**Table S5. On-randomised treatment moderate/severe exacerbations.**

| | FF/UMEC/VI (N=1545) | Non-ELLIPTA MITT (N=1547) |
|---|---|---|
| **Total number of moderate/severe exacerbations per patient, n (%)** | | |
| n | 1544 | 1547 |
| 0 | 1118 (72) | 1096 (71) |
| 1 | 324 (21) | 334 (22) |
| ≥2 | 102 (7) | 117 (8) |
| **Annualised moderate/severe exacerbation rate, mean (SD)*** | 1.2 (3.65) | 1.1 (5.57) |

*Annualised moderate/severe exacerbation rate was calculated as [number of on-randomised treatment exacerbations / time on randomised treatment (in days)] multiplied by 365.25. One ITT subject withdrew from the study prior to starting randomised study treatment and therefore is excluded from the on-randomised treatment summary.

FF, fluticasone furoate; MITT, multiple-inhaler triple therapy; SD, standard deviation; UMEC, umeclidinium; VI, vilanterol.

**Table S6: On-randomised treatment AE profile by Preferred Term***

| | FF/UMEC/VI (N=1545) | | Non-ELLIPTA MITT (N=1547) | |
|---|---|---|---|---|
| Total duration at risk (patient-years) | 636.7 | | 685.8 | |
| | n (%) | Rate [#] | n (%) | Rate [#] |
| Any AE | 250 (16) | 590.6 [376] | 151 (10) | 322.2 [221] |
| Chronic obstructive pulmonary disease | 38 (2) | 62.8 [40] | 28 (2) | 42.3 [29] |
| Dyspnoea | 33 (2) | 51.8 [33] | 5 (<1) | 7.3 [5] |
| Pneumonia | 26 (2) | 42.4 [27] | 30 (2) | 43.7 [30] |
| Any treatment-related AE† | 145 (9) | 329.8 [210] | 44 (3) | 77.3 [53] |
| Dyspnoea | 29 (2) | 45.5 [29] | 3 (<1) | 4.4 [3] |
| Any AE leading to study treatment discontinuation or study withdrawal | 115 (7) | 279.6 [178] | 32 (2) | 70.0 [48] |
| Dyspnoea | 28 (2) | 44.0 [28] | 1 (<1) | 1.5 [1] |
| Chronic obstructive pulmonary disease | 18 (1) | 28.3 [18] | 2 (<1) | 2.9 [2] |
| Cough | 11 (<1) | 17.3 [11] | 1 (<1) | 1.5 [1] |
| Headache | 11 (<1) | 17.3 [11] | 1 (<1) | 1.5 [1] |
| Arthralgia | 7 (<1) | 11.0 [7] | 0 (0) | 0 [0] |
| Fatigue | 5 (<1) | 7.9 [5] | 0 (0) | 0 [0] |
| Pneumonia | 4 (<1) | 6.3 [4] | 4 (<1) | 5.8 [4] |
| Dysphonia | 4 (<1) | 6.3 [4] | 1 (<1) | 1.5 [1] |
| Malaise | 3 (<1) | 4.7 [3] | 1 (<1) | 1.5 [1] |
| Oropharyngeal pain | 3 (<1) | 4.7 [3] | 1 (<1) | 1.5 [1] |
| Increased bronchial secretion | 3 (<1) | 4.7 [3] | 0 (0) | 0 [0] |
| Wheezing | 3 (<1) | 4.7 [3] | 0 (0) | 0 [0] |
| Tachycardia | 3 (<1) | 4.7 [3] | 0 (0) | 0 [0] |
| Dysgeusia | 2 (<1) | 3.1 [2] | 1 (<1) | 1.5 [1] |
| Chest discomfort | 2 (<1) | 3.1 [2] | 0 (0) | 0 [0] |
| Discomfort | 2 (<1) | 3.1 [2] | 0 (0) | 0 [0] |
| Exercise tolerance decreased | 2 (<1) | 3.1 [2] | 0 (0) | 0 [0] |
| Oedema peripheral | 2 (<1) | 3.1 [2] | 0 (0) | 0 [0] |
| Influenza | 2 (<1) | 3.1 [2] | 0 (0) | 0 [0] |
| Tremor | 2 (<1) | 3.1 [2] | 0 (0) | 0 [0] |
| Palpitations | 2 (<1) | 3.1 [2] | 0 (0) | 0 [0] |
| Gastroesophageal reflux disease | 2 (<1) | 3.1 [2] | 0 (0) | 0 [0] |
| Nausea | 2 (<1) | 3.1 [2] | 0 (0) | 0 [0] |
| Oral pain | 2 (<1) | 3.1 [2] | 0 (0) | 0 [0] |
| Vision blurred | 2 (<1) | 3.1 [2] | 0 (0) | 0 [0] |
| Acute myocardial infarction | 1 (<1) | 1.6 [1] | 2 (<1) | 2.9 [2] |
| Pruritus | 1 (<1) | 1.6 [1] | 2 (<1) | 2.9 [2] |
| Infective exacerbation of chronic obstructive airways disease | 0 (0) | 0 [0] | 2 (<1) | 2.9 [2] |

| | | | | |
|---|---|---|---|---|
| Any SAE | 114 (7) | 257.6 [164] | 114 (7) | 255.2 [175] |
| Pneumonia | 26 (2) | 42.4 [27] | 30 (2) | 43.7 [30] |
| Chronic obstructive pulmonary disease | 26 (2) | 44.0 [28] | 28 (2) | 42.3 [29] |

Specific AEs are reported if they occurred in ≥1% of patients in any treatment arm (AE, treatment-related AEs, SAEs) or in >1 patient in any treatment arm (AEs leading to study treatment discontinuation or study withdrawal). *The recording of AEs was limited to treatment-related AEs, SAEs and AEs leading to study treatment discontinuation or study withdrawal.

†AEs were defined as treatment-related according to the judgment of the study investigators. Rate is event rate per 1000 patient-years, calculated as the number of events x 1000, divided by the total duration at risk.

#, number of events; AE, adverse event; FF, fluticasone furoate; MITT, multiple-inhaler triple therapy; SAE, serious adverse event; UMEC, umeclidinium; VI, vilanterol.

**Table S7: On -study AE profile***

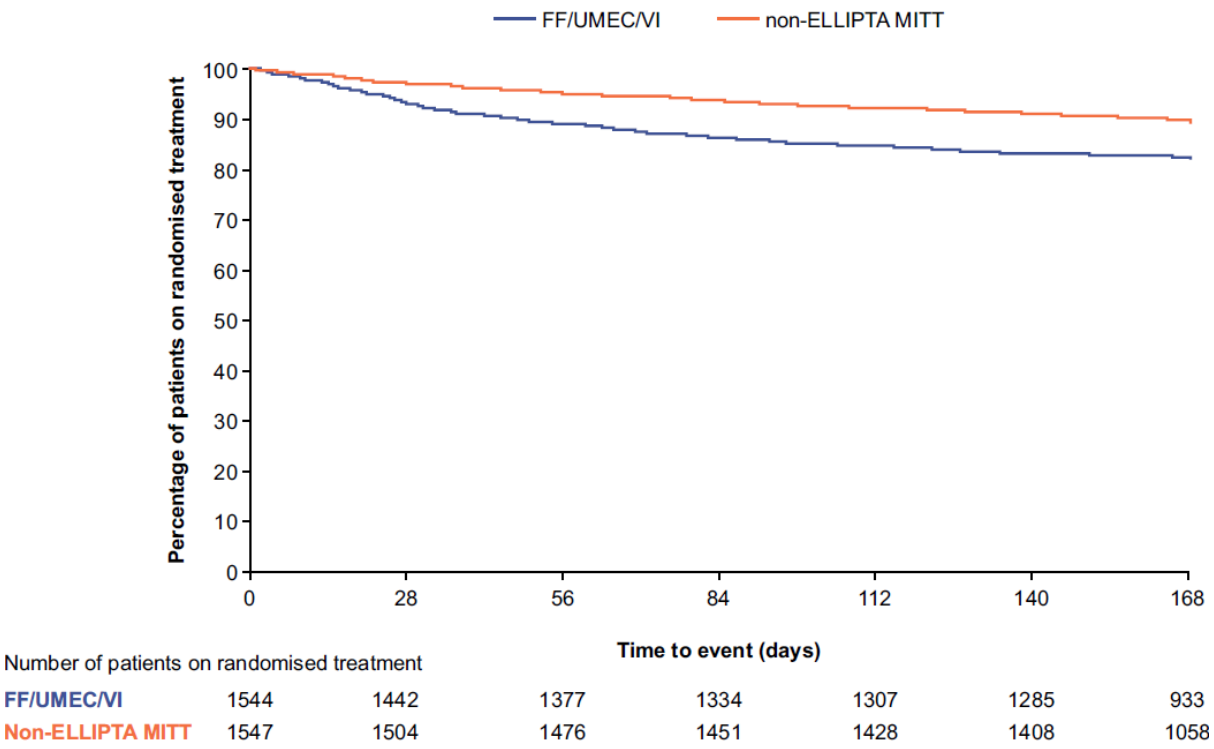
| | **FF/UMEC/VI (N=1545)** | | **Non-ELLIPTA MITT (N=1547)** | |
|---|---|---|---|---|
| Total duration at risk (patient-years) | 724.6 | | 729.9 | |
| | n (%) | Rate [#] | n (%) | Rate [#] |
| Any AE | 265 (17) | 579.6 [420] | 163 (11) | 348.0 [254] |
| Any SAE | 134 (9) | 277.4 [201] | 125 (8) | 279.5 [204] |

*The recording of AEs was limited to treatment-related AEs, SAEs and AEs leading to study treatment discontinuation or study withdrawal.

Rate is event rate per 1000 patient-years, calculated as the number of events x 1000, divided by the total duration at risk.

#, number of events; AE, adverse event; FF, fluticasone furoate; MITT, multiple-inhaler triple therapy; SAE, serious adverse event; UMEC, umeclidinium; VI, vilanterol.

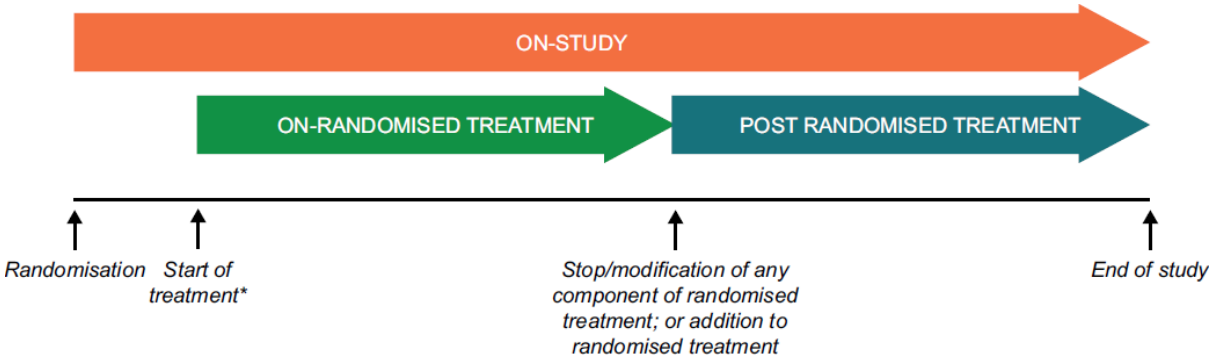
**Figure S1: Kaplan-Meier Plot of Time to Premature Discontinuation of Randomised Treatment (ITT Population)**




| Number of patients on randomised treatment | | | | | | | |
|---|---|---|---|---|---|---|---|
| FF/UMEC/VI | 1544 | 1442 | 1377 | 1334 | 1307 | 1285 | 933 |
| Non-ELLIPTA MITT | 1547 | 1504 | 1476 | 1451 | 1428 | 1408 | 1058 |

Kaplan-Meier estimate of time to premature discontinuation of randomised treatment. Patients are represented from their randomised treatment start date to the date of discontinuation from any randomised treatment component (or date of death) regardless of any prior modification to treatment pathway. Patients that completed the randomised treatment period per protocol were censored at the earliest date of completion of randomised treatment and Day 169. Patients who had not discontinued any component of their randomised treatment but had modified their treatment pathway by adding additional maintenance medication were considered to have completed in this output. One ITT patient withdrew from the study prior to starting randomised study treatment and therefore was excluded from this output. FF, fluticasone furoate; ITT, intent-to-treat; MITT, multiple-inhaler triple therapy; UMEC, umeclidinium; VI, vilanterol.

**Figure S2 INTREPID study phases**




*Start of on-randomised treatment usually occurred in parallel with randomisation, although in some instances the start of treatment occurred after randomisation