Supplementary Materials

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

David M. G. Halpin MD, Sally Worsley MSc, Afisi S. Ismaila PhD, Kai-Michael Beeh MD,
Dawn Midwinter MSc, Janwillem W. H. Kocks MD, Elaine Irving PhD, Jose M. Marin MD,
Neil Martin MD, Maggie Tabberer MSc, Neil G. Snowise BM BCh, Chris Compton MD

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 FEV₁ 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

| Estimand | Intercurrent events | Missing data | Patients with multiple imputed data, n (%) |
|----------|---------------------|--------------|-------------------------------------------|
|          | 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 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) | Considered as non-responders (composite) | Considered as non-responders (composite) |
| FF/UMEC/VI: 52 Non-ELLIPTA MITT: 92 |
| **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 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 |
| --- | --- | --- | --- | --- | --- | --- |
| **Change from baseline in FEV₁ at Week 24 primary estimand** | Treatment policy | Week 24 FEV₁ data used regardless of event (treatment policy) | Week 24 FEV₁ data used regardless of event (treatment policy) | Week 24 FEV₁ data used regardless of event (treatment policy) | Week 24 FEV₁ data used regardless of event (treatment policy) | Missing Week 24 FEV₁ was not imputed | Missing Week 24 FEV₁ was not imputed |
| **Change from baseline in trough FEV₁ at Week 24 primary estimand** | Treatment policy | Week 24 trough FEV₁ data used regardless of event (treatment policy) | Week 24 trough FEV₁ data used regardless of event (treatment policy) | Week 24 trough FEV₁ data used regardless of event (treatment policy) | Week 24 trough FEV₁ data used regardless of event (treatment policy) | Missing Week 24 trough FEV₁ imputed based on randomised treatment (assumes MAR) | Missing Week 24 trough FEV₁ imputed based on randomised treatment (assumes MAR) |
| **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 | No imputation performed for the missing data | No imputation performed for the missing data |

| FF/UMEC/VI: 336 | Non-ELLIPTA MITT: 264 | FF/UMEC/VI: 82 | Non-ELLIPTA MITT: 115 |
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**
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\textsubscript{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        | n=901            | n=1807      |
|                                | 28.08 (6.19) | 28.19 (6.28)     | 28.14 (6.24)|
| Post-bronchodilator FEV$_1$, mL, mean (SD) | n=825 | n=827 | n=1652 |
|                                | 1474 (565.3) | 1462 (584.0)     | 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        | n=265            | n=952       |
|                                | 28.10 (6.03) | 27.92 (6.22)     | 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 β$_2$-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); p=0.119    |
| Patients with no critical error| 651 (94)           | 258 (97)                 |                               |

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.

| Total number of moderate/severe exacerbations per patient, n (%) | FF/UMEC/VI (N=1545) | Non-ELLIPTA MITT (N=1547) |
|---------------------------------------------------------------|----------------------|--------------------------|
| 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                     |
| Any AE                           | 250 (16)            | 151 (10)                  |
|   Rate [#]                       | 590.6 [376]         | 322.2 [221]               |
| Chronic obstructive pulmonary disease | 38 (2)              | 28 (2)                    |
|   Dyspnoea                       | 33 (2)              | 5 (<1)                    |
|   Pneumonia                      | 26 (2)              | 30 (2)                    |
| Any treatment-related AE†         | 145 (9)             | 44 (3)                    |
|   Dyspnoea                       | 29 (2)              | 3 (<1)                    |
| Any AE leading to study treatment discontinuation or study withdrawal | 115 (7)             | 32 (2)                    |
|   Dyspnoea                       | 28 (2)              | 1 (<1)                    |
| Chronic obstructive pulmonary disease | 18 (1)              | 2 (<1)                    |
|   Cough                          | 11 (<1)             | 1 (<1)                    |
|   Headache                       | 11 (<1)             | 1 (<1)                    |
|   Arthralgia                     | 7 (<1)              | 0 (0)                     |
|   Fatigue                        | 5 (<1)              | 0 (0)                     |
|   Pneumonia                      | 4 (<1)              | 4 (<1)                    |
|   Dysphonia                      | 4 (<1)              | 1 (<1)                    |
|   Malaise                        | 3 (<1)              | 1 (<1)                    |
|   Oropharyngeal pain             | 3 (<1)              | 1 (<1)                    |
|   Increased bronchial secretion  | 3 (<1)              | 0 (0)                     |
|   Wheezing                       | 3 (<1)              | 0 (0)                     |
|   Tachycardia                    | 3 (<1)              | 0 (0)                     |
|   Dysgeusia                      | 2 (<1)              | 1 (<1)                    |
|   Chest discomfort               | 2 (<1)              | 0 (0)                     |
|   Discomfort                     | 2 (<1)              | 0 (0)                     |
|   Exercise tolerance decreased   | 2 (<1)              | 0 (0)                     |
|   Oedema peripheral              | 2 (<1)              | 0 (0)                     |
|   Influenza                      | 2 (<1)              | 0 (0)                     |
|   Tremor                         | 2 (<1)              | 0 (0)                     |
|   Palpitations                   | 2 (<1)              | 0 (0)                     |
|   Gastroesophageal reflux disease | 2 (<1)              | 0 (0)                     |
|   Nausea                         | 2 (<1)              | 0 (0)                     |
|   Oral pain                      | 2 (<1)              | 0 (0)                     |
|   Vision blurred                 | 2 (<1)              | 0 (0)                     |
|   Acute myocardial infarction    | 1 (<1)              | 2 (<1)                    |
|   Pruritus                       | 1 (<1)              | 2 (<1)                    |
|   Infective exacerbation of chronic obstructive airways disease | 0 (0)              | 2 (<1)                    |

*AE: Adverse Event; FF/UMEC/VI: Fife/Umec/VI; Non-ELLIPTA MITT: Non-ELLIPTA Modified Intent To Treat.
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)

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