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 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 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 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 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 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 28.08 (6.19)	n=901 28.19 (6.28)	n=1807 28.14 (6.24)
Post-bronchodilator FEV_1, mL, mean (SD)	n=825 1474 (565.3)	n=827 1462 (584.0)	n=1652 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 28.10 (6.03)	n=265 27.92 (6.22)	n=952 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			1.54 (1.33, 1.78); p<0.001
Responders	847 (55)	683 (44)	
Non-responders	692 (45)	860 (56)	
Supportive estimand 2			1.31 (1.13, 1.51); p<0.001
Responders	746 (48)	630 (41)	
Non-responders	741 (48)	820 (53)	
Patients with imputed CAT score	52 (3)	93 (6)	
Supportive estimand 3			1.65 (1.40, 1.94); p<0.001
Responders	731 (47)	615 (40)	
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*

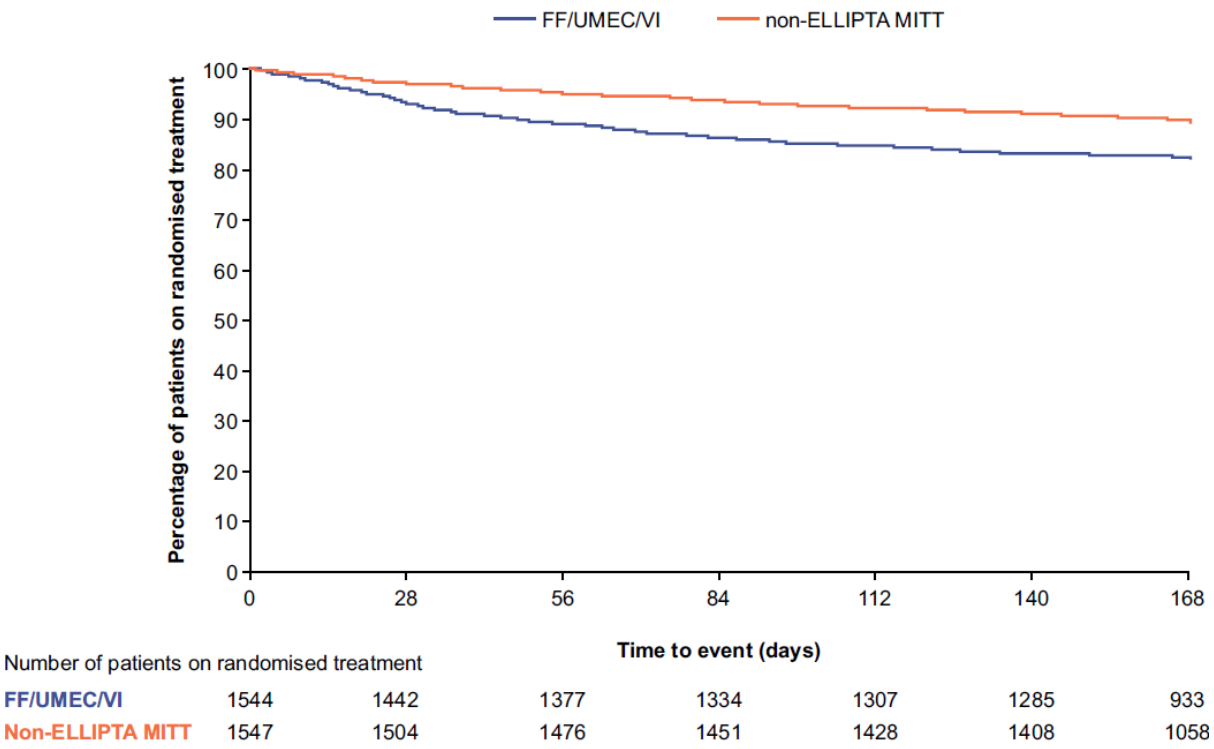
	FF/UMEC/VI (N=1545)		**Non-ELLIPTA MITT (N=1547)**	
Total duration at risk (patient-years)	724.6		729.9	
	n (%)	Rate [#]	n (%)	Rate [#]
Any AE	265 (17)	579.6 [420]	163 (11)	348.0 [254]
Any SAE	134 (9)	277.4 [201]	125 (8)	279.5 [204]

*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.

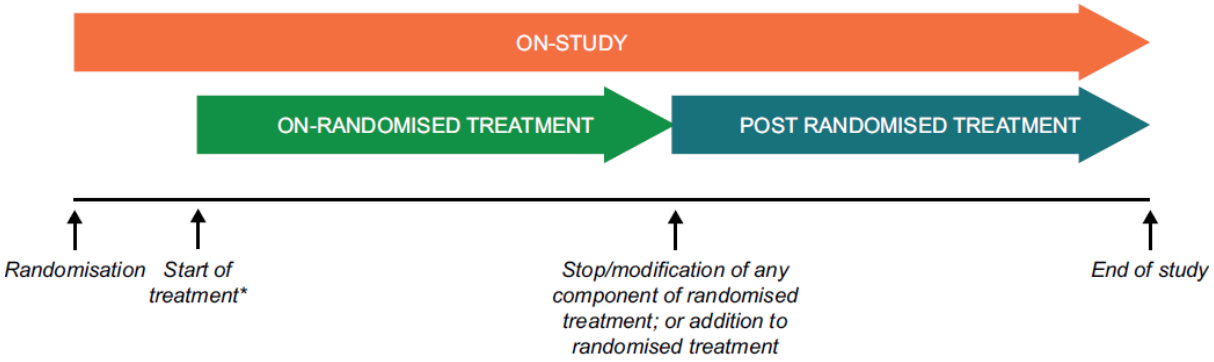
Figure S1: Kaplan-Meier Plot of Time to Premature Discontinuation of Randomised Treatment (ITT Population)



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