ORIGINAL RESEARCH

Cost-Effectiveness of Single- versus Multiple-Inhaler Triple Therapy in a UK COPD Population: The INTREPID Trial

David MG Halpin [1], Robyn Kendall [2], Soham Shukla [3], Alan Martin [4], Dhvani Shah [5], Dawn Midwinter [6], Kai M Beeh [7], Janwillem WH Kocks [8–11], Paul W Jones [12], Chris Compton [12], Nancy A Risebrough [13], Afisi S Ismaila [3,14]

[1]University of Exeter Medical School, College of Medicine and Health, University of Exeter, Exeter, UK; [2]ICON Health Economics, ICON plc, Vancouver, BC, Canada; [3]Value Evidence and Outcomes, GSK, Collegeville, PA, USA; [4]Value Evidence and Outcomes, GSK, Uxbridge, UK; [5]ICON Health Economics, ICON plc, New York, NY, USA; [6]Biostatistics, GSK, Brentford, UK; [7]Insaf Respiratory Research Institute, Wiesbaden, Germany; [8]General Practitioners Research Institute, Groningen, the Netherlands; [9]Observational and Pragmatic Research Institute, Singapore; [10]Groningen Research Institute Asthma and COPD (GRIAC), University of Groningen, University Medical Center Groningen, Groningen, the Netherlands; [11]Department of Pulmonology, University of Groningen, University Medical Center Groningen, Groningen, the Netherlands; [12]Global Respiratory Franchise, GSK, Brentford, UK; [13]ICON Health Economics, ICON plc, Toronto, ON, Canada; [14]Department of Health Research Methods, Evidence, and Impact, McMaster University, Hamilton, ON, Canada

Correspondence: David MG Halpin, University of Exeter Medical School, College of Medicine and Health, University of Exeter, Exeter, EX1 2LU, UK, Tel +44 01392 201178, Email d.halpin@nhs.net

Purpose: The 24-week INTREPID trial demonstrated the clinical benefits of once-daily single-inhaler triple therapy (SITT) with fluticasone furoate, umeclidinium, and vilanterol (FF/UMEC/VI) versus non-ELLIPTA multiple-inhaler triple therapy (MITT) in patients with symptomatic chronic obstructive pulmonary disease (COPD). This analysis assessed the cost-effectiveness of FF/UMEC/VI versus non-ELLIPTA MITT for the treatment of symptomatic COPD from a United Kingdom (UK) National Health Service (NHS) perspective.

Patients and Methods: The analysis was conducted using the validated GALAXY COPD disease progression model. Baseline characteristics, treatment effect parameters (forced expiratory volume in 1 second and St. George's Respiratory Questionnaire score [derived from exploratory COPD Assessment Test score mapping]), and discontinuation data from INTREPID were used to populate the model. UK healthcare resource and drug costs (2020 British pounds) were applied, and costs and outcomes were discounted at 3.5%. Analyses were conducted over a lifetime horizon from a UK NHS perspective. Model outputs included exacerbation rates, total costs, life years (LYs), quality-adjusted LYs (QALYs) and incremental cost-effectiveness ratio per QALY. Sensitivity analyses were conducted to assess the robustness of the results by varying parameter values and assumptions.

Results: Over a lifetime horizon, FF/UMEC/VI provided an additional 0.174 (95% confidence interval [CI]: 0.024, 0.344) LYs (approximately 2 months), and 0.253 (95% CI: 0.167, 0.346) QALYs (approximately 3 months), at a cost saving of £1764 (95% CI: −£2600, −£678) per patient, compared with non-ELLIPTA MITT. FF/UMEC/VI remained the dominant treatment option, meaning greater benefits at lower costs, across all scenario and sensitivity analyses.

Conclusion: Based on this analysis, in a UK setting, FF/UMEC/VI would improve health outcomes and reduce costs compared with non-ELLIPTA MITT for the treatment of patients with symptomatic COPD. SITT may help to reduce the clinical and economic burden of COPD and should be considered by physicians as a preferred treatment option.

Keywords: chronic obstructive pulmonary disease, cost-effectiveness, health technology assessment, pragmatic, real-world, triple therapy

Introduction

Chronic obstructive pulmonary disease (COPD) is associated with a substantial economic burden, making it one of the most costly inpatient conditions treated by the United Kingdom National Health Service (UK NHS).[1] In 2017, the total cost to the healthcare system was estimated to be £1.9 billion.[2] Pharmacological management of chronic, stable COPD

primarily aims to improve symptoms and quality of life, optimize lung function, reduce exacerbations, and improve exercise tolerance.[3] The Global Initiative for Chronic Obstructive Lung Disease (GOLD) and the National Institute for Health and Care Excellence (NICE) clinical guidelines provide pharmacologic treatment algorithms for patients with COPD based on their symptoms and exacerbation history.[3,4]

Current GOLD guidelines recommend initial COPD maintenance therapy with a long-acting muscarinic antagonist (LAMA) or a long-acting β₂-agonist (LABA). For patients who continue to experience symptoms despite initial maintenance therapy, an escalation to dual therapy (LAMA+LABA or LABA with an inhaled corticosteroid [ICS]) is suggested. A further escalation to triple therapy (LAMA+LABA+ICS) is recommended for patients who continue to experience symptoms or have a high risk of exacerbation, despite receiving dual therapy.[3] Current NICE guidelines advise an escalation to dual therapy (LAMA+LABA or LABA+ICS) for patients with COPD who remain symptomatic despite initial treatment with a short-acting bronchodilator. A further escalation to triple therapy is then recommended for patients receiving LABA+ICS whose symptoms continue to adversely impact their quality of life, or for patients taking either LABA+ICS or LAMA+LABA who experience a severe exacerbation (requiring hospitalization) or ≥2 moderate exacerbations within 1 year.[4]

Triple therapy has previously required the use of multiple inhalers; however, multiple inhaler use is associated with poorer persistence and adherence, and an increased potential for critical inhaler errors compared with the use of single inhalers.[5–7] Poor treatment adherence and errors in inhalation technique are associated with increased exacerbations, more hospitalizations, and higher healthcare costs in patients with COPD.[8–11]

In 2017, single-inhaler triple therapy (SITT) with fluticasone furoate, umeclidinium, and vilanterol (FF/UMEC/VI; GSK, Brentford, Middlesex, UK) was approved for the long-term maintenance treatment of patients with COPD in the UK. Patients treated with FF/UMEC/VI in a randomized controlled trial (RCT) had fewer moderate or severe exacerbations compared with patients receiving dual therapy with FF/VI, UMEC/VI, or budesonide/formoterol.[12,13]

Whilst RCTs are crucial in demonstrating initial efficacy and safety of a drug, real-world pragmatic study designs are important for evaluating the effectiveness of a drug in usual clinical practice.[14] The controlled environment of a traditional RCT can help limit variability between groups and reduce confounding; however, patients are more likely to be adherent to their medication, because of monitoring, and have better control over comorbid conditions, potentially limiting the generalizability of the results in a real-world setting.[14] Many RCTs also include comparator therapies representing different treatment steps or pharmacological regimens; in practice, a direct comparison between similar treatment regimens may be more relevant.

The pragmatic INTREPID trial investigated the clinical benefits of once-daily FF/UMEC/VI (100/62.5/25 µg) delivered using a single ELLIPTA™ (GSK, Brentford, Middlesex, UK) inhaler versus continuing therapy with non-ELLIPTA multiple-inhaler triple therapy (MITT) for patients with symptomatic COPD in usual clinical practice.[15] Over a 24-week period, FF/UMEC/VI resulted in greater improvements in health status and lung function versus non-ELLIPTA MITT.

Previous economic analyses have found FF/UMEC/VI to be a cost-effective option versus dual therapies.[16–19] However, these studies were performed using data obtained from a more strictly defined patient population (ie more stringent inclusion criteria regarding disease severity) and in a more controlled setting (ie data collected from traditional RCTs). Therefore, although the internal validity of the result is high, application to the real-world patient population is more limited. The pragmatic INTREPID trial, whilst randomized, included a wider variety of patients to reflect the general COPD population and there were minimal interventions in addition to usual care.

The objective of this analysis was to assess the cost-effectiveness of FF/UMEC/VI single ELLIPTA inhaler therapy compared with non-ELLIPTA MITT for the treatment of symptomatic COPD patients with a history of exacerbation from a UK NHS perspective in a real-world setting, using data from the INTREPID trial.

Materials and Methods
Study Design
The analysis was conducted using the validated GALAXY COPD disease progression model,[20–23] adapted using patient characteristics and treatment effects from the INTREPID study and UK resource utilization and healthcare costs. The

GALAXY model uses linked risk equations to model associations between patient characteristics, treatment effects, progression, and outcomes.[21]

Model Inputs

The clinical data used in the model were based upon INTREPID trial data (ClinicalTrials.gov identifier: NCT03467425). Details of the INTREPID study design, patient population, and results have been published previously.[15,24] In brief, the study enrolled patients requiring triple therapy aged ≥40 years with a physician-confirmed diagnosis of COPD, a COPD Assessment Test (CAT) score of ≥10 at screening, and who had previously received non-ELLIPTA MITT or dual therapy with ICS/LABA, or LAMA/LABA as maintenance therapy continually for ≥16 weeks prior to randomization. Eligible patients also had a history of ≥1 COPD exacerbation requiring treatment with systemic or oral corticosteroids, antibiotics, and/or hospitalization in the 3 years prior to randomization. Patients were studied over 24 weeks and had only two mandated study visits: the first for screening/randomization and the second at the end of the study (week 24). The primary endpoint of INTREPID was the proportion of CAT responders (≥2-unit decrease in CAT score from baseline) at week 24.

Baseline covariates required by the GALAXY model are shown in Table 1. Pooled baseline characteristics from the intent-to-treat (ITT) population of INTREPID were used in the model. Characteristics of the ITT population at baseline are shown in Table S1. The mean age of the population was 67.8 years, 46.5% of patients were female, and 76.6% had experienced ≥1 moderate or severe exacerbation in the previous 12 months. Baseline forced expiratory volume in 1 second (FEV_1)% predicted was 54.1%.

Treatment effect parameters included in the model were change from baseline in FEV_1, absolute change from baseline in SGRQ score, and discontinuation data (for the first year only). As 52-week discontinuation data were not available from INTREPID (which was a 24-week study), 24-week discontinuation data (18.64% vs 12.15% for the FF/UMEC/VI

Table 1 Model Inputs for Patient Characteristics (ITT Population, INTREPID Trial)

Parameter	Pooled Characteristics (n=3092)
Age, years, mean (SD)	67.8 (8.7)
Female sex, n (%)	46.5
BMI low, %	10.1
BMI medium, %	56.9
BMI high, %	33.0
Any cardiovascular comorbidity, %	45.5
Any other comorbidity, %	27.1
History of exacerbation (≥1), %	76.6
mMRC score ≥2, %	46.6
Current smokers, %	35.0
Height, cm, mean (SD)	168.2 (9.3)
Number of exacerbations in the previous year, mean	1.50
Number of moderate exacerbations in the previous year, mean	1.30
Number of severe exacerbations in the previous year, mean	0.20
Starting SGRQ score, mean	54.9
Starting FEV_1% predicted, mean (SD)	54.1 (18.53)

Abbreviations: BMI, body mass index; cm, centimeter; FEV_1, forced expiratory volume in 1 second; ITT, intent-to-treat; mMRC, modified Medical Research Council; SD, standard deviation; SGRQ, St George's Respiratory Questionnaire.

and non-ELLIPTA MITT cohorts, respectively) were applied for the first year. In the model, patients who discontinued their initial treatment (FF/UMEC/VI or non-ELLIPTA MITT) switched to alternate maintenance treatment combinations. Treatment effect parameters observed in the INTREPID trial and used in the model are shown in Table 2. For baseline parameters that were not available directly from INTREPID trial data (fibrinogen level, modified Medical Research Council [mMRC] dyspnea scale score, SGRQ score, and 6-minute walk test [6MWT] score), estimates were made using risk equations or analogous data collected in the trial, as has been done previously (Appendix S1).[16,17] SGRQ scores were not collected in the INTREPID trial; for the base-case analysis, exploratory regression equations were used to convert INTREPID trial-observed CAT scores into SGRQ scores using data from the IMPACT trial[25] (ClinicalTrials.gov identifier: NCT02164513; Appendix S1, Table S2).

Model Assumptions

It was assumed that the INTREPID trial population was representative of the UK COPD population likely to receive triple therapy in routine clinical practice. Treatment effect was considered to remain constant over time while patients were still receiving FF/UMEC/VI treatment, and the efficacy of subsequent treatment (for patients who discontinued their initial treatment) was assumed to be the same as that of the reference treatment (non-ELLIPTA MITT) for the remaining duration of the analysis. In the base-case, treatment discontinuation after the first year was assumed to be 0% for both treatment arms (different assumptions were tested in scenario analyses). Finally, as the INTREPID study was not designed to investigate whether SITT was associated with a decreased exacerbation rate versus MITT, the model efficacy input for relative risk of moderate and severe exacerbation reductions was set to parity (ie the model assumed no difference between treatment arms for moderate and severe exacerbation treatment effects at the starting point). Therefore, any predicted effects on exacerbations are an indirect effect of differences in treatment effect (change in FEV_1 and SGRQ score) between the two arms over time. This conservative assumption was validated by clinical experts.

Utilities

Quality-adjusted life years (QALYs) were calculated by translating predicted SGRQ scores to a utility value for each cycle, using a published, validated algorithm.[26] Incremental cost-effectiveness ratios (ICERs) were calculated by dividing incremental costs by incremental QALYs.

Table 2 Treatment Effects Observed in the INTREPID Trial (at 24 Weeks)

	FF/UMEC/VI (n=1545)	Non-ELLIPTA MITT (n=1547)
Health status		
CAT score, mean (SD)	18.0 (7.98)	19.1 (7.89)
CAT score, CFB, mean (SD)	−2.8 (6.31)	−1.3 (6.05)
CAT responders[a], n (%)	731 (47)	616 (40)
FF/UMEC/VI vs non-ELLIPTA MITT responders OR (95% CI); p value		1.31 (1.13, 1.51); <0.001
Mean CAT score difference (95% CI); p value		−1.40 (−1.80, −1.00); <0.001
FF/UMEC/VI vs non-ELLIPTA MITT calculated SGRQ score, difference in CFB		−1.76
Lung function[b]	n=301	n=292
Adjusted mean trough FEV_1, L (SE)	1.50 (0.02)	1.45 (0.02)
Adjusted mean trough FEV_1 CFB, L (SE)	0.10 (0.02)	0.05 (0.02)
FF/UMEC/VI vs non-ELLIPTA MITT mean difference CFB, L (95% CI); p value		0.05 (0.01, 0.10); 0.017

Notes: [a]≥2-unit decrease in CAT score from baseline; [b]Due to the sample size required, spirometry data were only collected in a subset of patients, which in turn minimized the disruption to usual care. Trough FEV_1 was a further subset, as spirometry data were not required to be trough in the INTREPID trial.
Abbreviations: CAT, COPD Assessment Test; CFB, change from baseline; CI, confidence interval; FEV_1, forced expiratory volume in 1 second; FF, fluticasone furoate; L, liter; MITT, multiple inhaler triple therapy; OR, odds ratio; SD, standard deviation; SE, standard error; SGRQ, St. George's Respiratory Questionnaire; UMEC, umeclidinium; VI, vilanterol.

Costs

UK healthcare resource utilization and drug costs were applied, and costs and outcomes were discounted at 3.5%. The daily weighted average cost of subsequent therapy for FF/UMEC/VI and non-ELLIPTA MITT was based on the re-normalized percentage of patients receiving each class of treatment (Table S3). Medication costs were obtained from the British National Formulary[27] and are shown in Table S4. Weighted average MITT costs were calculated using market data for the three most commonly prescribed ICS/LABA and LAMA drugs in the UK. For healthcare costs, three health states were defined, based on three categories of COPD severity defined by lung function (moderate to severe [FEV_1% predicted 80–50%], severe [FEV_1% predicted <50% to 30%], and very severe [FEV_1% predicted <30%]). The model calculated the proportion of the cohort in each health state in each cycle and appropriate annual costs were applied. Events (moderate and severe exacerbations) were costed individually (Table S5). Health state and exacerbation costs were sourced from literature and publicly available data. Resource utilization estimates and unit costs for health care items in each health state were obtained from a published NICE economic model report.[28] Resource use costs were inflated to 2020 values using Consumer Price Index data obtained from the Office of National Statistics.[29]

Analyses

Analyses were conducted over a lifetime horizon and from a UK NHS perspective in accordance with NICE guidance.[30] Model outputs included disaggregated direct costs for maintenance and exacerbation (COPD medications and non-drug costs), total direct costs, cumulative total exacerbations (moderate and severe), average annual exacerbations per patient per year, total life years (LYs) gained, and total QALYs gained.

Scenario Analyses

Scenario analyses were performed to examine the impact of assumptions, and model settings on the base-case results. Scenario analyses included patient loss of productivity incurred by sick leave, estimated as the gross lost value during time absent from usual activities (although a patient may be unemployed or retired, they may still be unable to carry out usual activities and may need to hire help); the use of alternative time horizons (5 years and 10 years); the use of discounted rates for costs and benefits (0% and 5%); exclusion of treatment discontinuation rates in the first year; treatment discontinuation rates for subsequent years were the same as those in the first year (18.64% and 12.15% for the FF/UMEC/VI and non-ELLIPTA MITT cohorts, respectively); and the use of other slopes and intercept values for regression equations to convert CAT scores into SGRQ scores (eg exploratory regression equations derived using FULFIL trial data; Appendix S1).

Sensitivity Analyses

Sensitivity analyses were conducted to assess the robustness of the results by varying parameter values and assumptions. One-way sensitivity analyses were conducted on baseline covariate values that were not available from INTREPID (fibrinogen level, 6MWT, mMRC dyspnea scale score, and SGRQ score) and FF/UMEC/VI treatment effects (difference in change from baseline in FEV_1 and SGRQ; Appendix S1, Table S6). Probabilistic sensitivity analyses examined the impact of uncertainty around input parameters. These were conducted with random sampling from distributions assigned to input parameters over 5000 Monte Carlo simulations. Input parameters were risk equation coefficients, incremental change from baseline in FEV_1, difference in change from baseline in SGRQ score, proportion of patients discontinuing treatment in the first and subsequent years, and the distribution of subsequent treatments after discontinuation. Risk equation coefficients were included in the probabilistic analysis via Cholesky decomposition.

Results
Base-Case Analyses

Over a lifetime horizon, FF/UMEC/VI provided an additional 0.174 LYs (95% confidence interval [CI]: 0.024, 0.344), and 0.253 QALYs (95% CI: 0.167, 0.346), at a cost saving of £1764 (95% CI: −£2600, −£678) per patient (Table 3). This

Table 3 Base-Case Results (FF/UMEC/VI versus Non-ELLIPTA MITT)

Deterministic (Lifetime)	FF/UMEC/VI	Non-ELLIPTA MITT	Incremental, Mean (95% CI)
Cumulative number of exacerbations over timeframe			
Moderate	8.783	8.777	0.006
Severe	2.720	2.789	−0.069
Total	11.504	11.567	−0.063
Severe exacerbations PPPY	0.302	0.316	−0.014
Total exacerbations PPPY	1.278	1.311	−0.032
Outcome at end of timeframe			
Accumulated LYs (undiscounted)	9.000	8.825	0.174 (0.024, 0.344)
Accumulated QALYs	4.382	4.129	0.253 (0.167, 0.346)
ICER (QALY)			Dominant
Costs at end of timeframe			
Accumulated total costs	£13,031	£14,795	−£1764 (−£2600, −£678)
Drug costs	£4221	£5123	−£902
Total non-drug costs	£8810	£9672	−£862

Abbreviations: CI, confidence interval; FF, fluticasone furoate; ICER, incremental cost-effectiveness ratio; LY, life year; MITT; multiple-inhaler triple therapy; PPPY, per person per year; QALY, quality-adjusted life year; UMEC, umeclidinium; VI, vilanterol.

was a result of both lower drug costs (incremental: −£902), and lower non-drug costs (ie lower healthcare resource utilization; incremental: −£862) with FF/UMEC/VI compared with MITT. Hence, FF/UMEC/VI was the dominant treatment option. The model suggested that patients receiving FF/UMEC/VI would have a numerically lower exacerbation rate compared with those receiving MITT over a lifetime, but the difference between the two treatment groups was extremely small (−0.063).

Scenario Analyses

FF/UMEC/VI remained the dominant treatment option (greater benefits at lower cost) compared with non-ELLIPTA MITT across all scenario analyses (Table 4). Cost savings were highest (−£2108) for the scenario in which treatment discontinuation was excluded, and lowest (−£1006) for the scenario in which 24-week treatment discontinuation data were applied for the first and subsequent years. Incremental cost savings using a 5-year and 10-year time horizon were −£1438 and −£1728, respectively (base-case: −£1764).

Sensitivity Analyses

FF/UMEC/VI was the dominant treatment option across all sensitivity analyses (Table S7). Cost savings were highest (−£2097) when FEV_1 upper CI was used in the one-way sensitivity analyses, and cost savings were lowest (−£1374) when baseline SGRQ was increased by 25% relative to the base-case value.

Probabilistic Sensitivity Analyses

FF/UMEC/VI was less costly across all simulations and remained dominant (showed higher QALYs) across the majority of the simulations (99% of 5000 simulations; Figure 1). The net benefit acceptability curve demonstrated that at a willingness to pay a threshold of £20,000 per QALY, the probability that FF/UMEC/VI was cost-effective was 100% (Figure 2).

Discussion

This analysis demonstrated that SITT with FF/UMEC/VI is associated with an improvement in QALYs, together with lower drug costs, compared with MITT in patients with COPD experiencing symptoms and exacerbations despite MITT

Table 4 Scenario Analyses (FF/UMEC/VI versus Non-ELLIPTA MITT)

Scenario	Incremental LYs	Incremental QALYs	Incremental Costs	ICER/QALY
Base-case	0.174	0.253	−£1764	Dominant
Time horizon 5 years	0.017	0.112	−£1438	Dominant
Time horizon 10 years	0.073	0.195	−£1728	Dominant
Discount rate 0%	0.174	0.315	−£1991	Dominant
Discount rate 5%	0.174	0.233	−£1679	Dominant
Discontinuation in first and subsequent years	0.060	0.124	−£1006	Dominant
Discontinuation excluded	0.214	0.308	−£2108	Dominant
Include patient productivity costs	0.174	0.253	−£1896	Dominant
Regression for CAT/SGRQ conversion based on IMPACT baseline and change from baseline	0.174	0.202	−£1764	Dominant
Regression for CAT/SGRQ conversion based on FULFIL baseline	0.173	0.263	−£1760	Dominant

Abbreviations: CAT, COPD Assessment Test; COPD, chronic obstructive pulmonary disease; FF, fluticasone furoate; ICER, incremental cost-effectiveness ratio; LY, life year; MITT; multiple-inhaler triple therapy; QALY, quality-adjusted life year; SGRQ, St. George's Respiratory Questionnaire; UMEC, umeclidinium; VI, vilanterol.

or dual therapy, using UK resource and cost data. ICERs for the base-case, sensitivity, and scenario analyses were dominant (greater benefit and lower costs) for FF/UMEC/VI, strongly suggesting that it is a cost-effective treatment option compared with MITT for symptomatic COPD patients with a history of exacerbation.

The cost savings observed with FF/UMEC/VI in this analysis are in part attributed to lower drug unit costs, as well as lower healthcare resource utilization, which is an effect of the long-term benefit of FF/UMEC/VI on change from

◆ FF/UMEC/VI vs non-Ellipta MITT
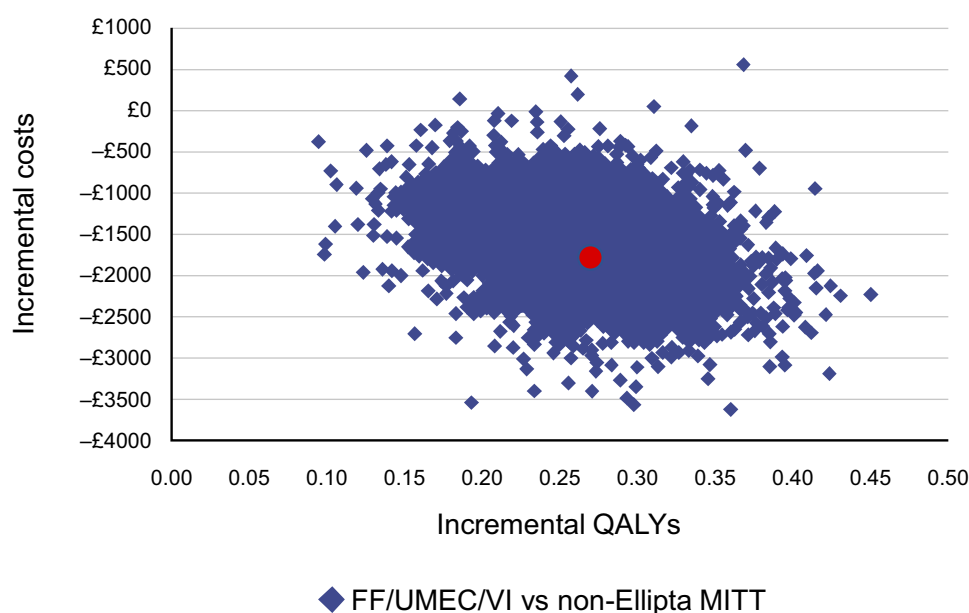
Figure 1 Incremental cost-effectiveness plane (FF/UMEC/VI versus non-ELLIPTA MITT).
Notes: The red dot represents the mean ICER.
Abbreviations: FF, fluticasone furoate; ICER, incremental cost-effectiveness ratio; MITT, multiple-inhaler triple therapy; QALY, quality-adjustedlife year; UMEC, umeclidinium; VI, vilanterol.
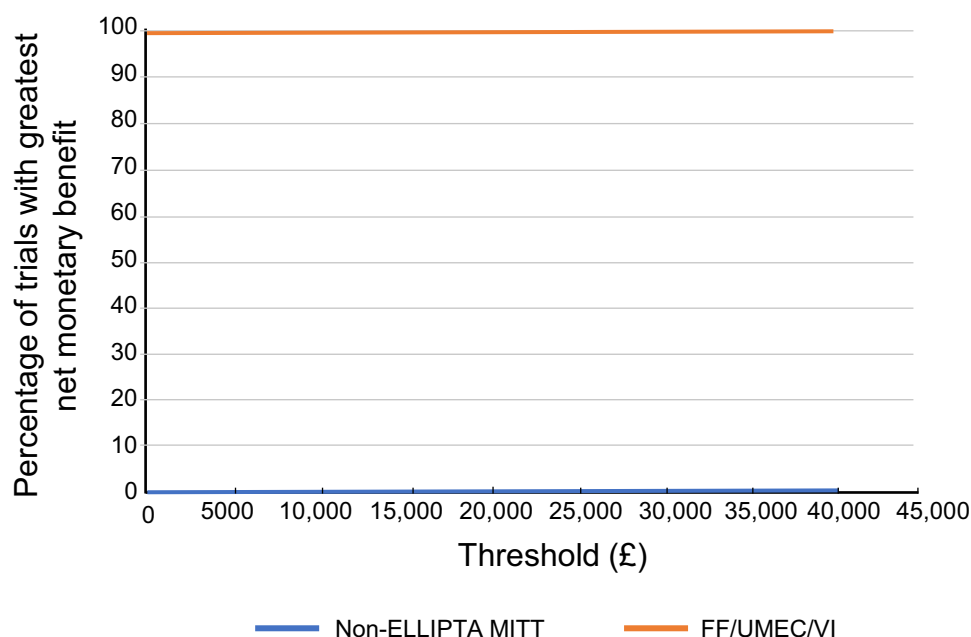
Figure 2 Net benefit acceptability curve (FF/UMEC/VI versus non-ELLIPTA MITT).
Abbreviations: FF, fluticasone furoate; MITT, multiple-inhaler triple therapy; UMEC, umeclidinium; VI, vilanterol.

baseline in FEV_1 and SGRQ score (ie reduced costs due to fewer exacerbations and symptoms). FF/UMEC/VI has been shown in previous economic analyses to be a cost-effective option compared with dual therapies in patients with COPD.[16–19] The question remains whether delivering triple therapy via a single inhaler may be more effective or cost-effective than delivering via multiple inhalers.

Previous studies have reported that critical inhalation errors are more likely among patients receiving MITT compared with patients receiving SITT,[6] and that multiple-inhaler therapy is associated with poorer treatment adherence and persistence compared with single-inhaler therapy.[5] Therefore, simplification of treatment regimen for patients with COPD would be expected to result in improved health outcomes and lower health costs.[9–11] In an effectiveness study comparing treatment with FF/VI via an ELLIPTA inhaler versus continuing treatment with existing therapy, FF/VI was associated with reduced rates of moderate-to-severe exacerbations, improved health status, and reduced costs compared with usual care as part of the Salford Lung Study.[31] This study set the standard for future pragmatic trials such as INTREPID.[14]

The use of data from the pragmatic INTREPID trial is a major strength of this cost-effectiveness analysis. Pragmatic study designs allow the participation of a broader range of patients, including those who would often be excluded from traditional RCTs, as well as minimizing study interventions that could influence patients' behavior. The results are therefore expected to be more representative of the patient population and treatment effects commonly encountered in real-world practice and have a wider applicability in a routine clinical setting. Of note, pneumonia events were not considered in this analysis. The rates of pneumonia reported in INTREPID were low and were comparable between treatment arms (approximately 2% per arm). Therefore, the inclusion of pneumonia-associated costs would not result in any significant incremental cost difference. Further to this, all patients in INTREPID received ICS therapy; as ICS therapy is associated with an increased risk of pneumonia,[32] inclusion of pneumonia events would be most relevant in analyses comparing treatment regimens with and without an ICS.

This analysis assumed no reduction in exacerbation rate with SITT, which may have underestimated the clinical benefit of SITT. If SITT does have a beneficial effect on exacerbation compared with MITT, then the cost-effectiveness of SITT would be greater than observed. As exacerbations and hospitalizations are major cost drivers in COPD, the lack of exacerbation data due to the short follow-up is a limitation of the current analysis. This analysis does have some further limitations that should be considered. First, some input data required by the model were not collected in the INTREPID trial and instead were estimated from risk equations/analogous data. However, one-way sensitivity analyses

exploring a range of values for these estimated parameters did not affect the conclusions of the analysis. SGRQ scores were not available from INTREPID trial data and were instead predicted from CAT scores by exploratory regression equations developed using baseline data from the IMPACT trial. In sensitivity analyses using SGRQ scores predicted from CAT scores by exploratory regression equations developed using FULFIL trial data, and also in analyses varying input SGRQ score plus and minus 25% relative to the base-case, FF/UMEC/VI remained the dominant treatment option, corroborating this approach. Discontinuation data at 52 weeks were not available as INTREPID was a 24-week trial. Therefore, 24-week discontinuation data were used at the end of the first year. Discontinuation rates were highest during the first 8 weeks of the INTREPID trial and therefore we believe this approach was acceptable Sensitivity analyses of discontinuation data demonstrated that ICERs did not differ significantly from the base-case results. Finally, data collected from different countries were pooled to generate the group means in the model. It is possible that there may have been differences between different countries or health systems, although this limitation is common to such analyses.

Conclusions

According to the GALAXY COPD model in a UK setting, SITT with FF/UMEC/VI would improve health outcomes and reduce costs compared with non-ELLIPTA MITT for the treatment of symptomatic COPD patients with a history of exacerbation. Therefore, SITT may help to reduce the clinical and economic burden of COPD from a UK NHS perspective and should be considered by physicians as a preferred treatment option.

Abbreviations

µg, microgram; 6MWT, 6-minute walk test; BMI, body mass index; CAT, COPD Assessment Test; CI, confidence interval; cm, centimeter; COPD, chronic obstructive pulmonary disease; dL, deciliter; FEV_1, forced expiratory volume in 1 second; FF, fluticasone furoate; GOLD, Global Initiative for Chronic Obstructive Lung Disease; ICER, incremental cost-effectiveness ratio; ICS, inhaled corticosteroid; ITT, intent-to-treat; L, liter; LABA, long-acting β_2-agonist; LAMA, long-acting muscarinic antagonist; LY, life year; m, meter; MITT, multiple-inhaler triple therapy; mL, milliliter; mMRC, modified Medical Research Council; NHS, National Health Service; NICE, National Institute for Health and Care Excellence; OR, odds ratio; PPPY, per person per year; QALY, quality-adjusted life year; RCT, randomized controlled trial; SD, standard deviation; SE, standard error; SGRQ, St George's Respiratory Questionnaire; SITT, single-inhaler triple therapy; UK, United Kingdom; UMEC, umeclidinium; VI, vilanterol.

Data Sharing Statement

Anonymized individual participant data and study documents for the INTREPID trial can be requested for further research from www.clinicalstudydatarequest.com.

Ethics Approval and Informed Consent

Ethics committee approval and patient informed consent were not required for this analysis. The analysis was conducted using patient characteristics and treatment effects from a previously published study; therefore, no direct patient contact or primary collection of individual patient data were required.

Acknowledgments

The abstract of this paper was presented at the 2021 European Respiratory Society Congress as a conference talk. (Robyn Kendall, Soham Shukla, Alan Martin, Dhvani Shah, Dawn Midwinter, Isabelle Boucot, Nancy Risebrough, Paul Jones, Chris Compton, Afisi Ismaila. Cost-effectiveness of single- vs multiple-inhaler triple therapy in a UK COPD population: INTREPID trial. European Respiratory Society – 31st Annual Congress. 2021). Available from https://erj.ersjournals.com/content/58/suppl_65/OA78. DOI 10.1183/13993003.congress-2021.OA78

Author Contributions

All authors made a significant contribution to the work reported, whether that was in the conception, study design, execution, acquisition of data, analysis and interpretation, or in all these areas; took part in drafting, revising, or critically reviewing the manuscript; gave final approval of the version to be published; have agreed on the journal to which the article has been submitted; and agree to be accountable for all aspects of the work.

Funding

Disclosure

CC, PWJ, ASI, DM, AM, and SS are employees of GSK and/or hold stocks/shares in GSK. ASI is also an unpaid faculty member at McMaster University, Hamilton, ON, Canada. Current affiliation details for CC and PWJ: General Medicines Therapy Area, GSK, Brentford, UK. Current affiliation details for AM: Value Evidence and Outcomes, GSK, Brentford, UK.

RK, DS, and NAR are employees of ICON; ICON received funding from GSK to conduct the analysis.

DMGH reports personal fees from Aerogen, AstraZeneca, and CSL Behring, personal fees and non-financial support from Boehringer Ingelheim, personal fees from Chiesi and GSK, personal fees and non-financial support from Novartis, and personal fees from Pfizer and Sanofi.

JWHK reports grants, personal fees, and non-financial support from AstraZeneca, Boehringer Ingelheim, and GSK, grants and personal fees from Chiesi Pharmaceuticals and TEVA, non-financial support and grants from Mundi Pharma, personal fees from MSD and COVIS pharma, grants from Valneva, and holds 72.5% of shares in the General Practitioners Research Institute. KMB and/or the institution he represents have in the past 5 years received compensation for services on advisory boards or consulting activities from AstraZeneca, Berlin Chemie, Boehringer Ingelheim, Chiesi, Elpen, GSK, MSD, Mundipharma, Novartis, Pohl Boskamp, Sanofi, and Teva; compensation for speaker activities in scientific meetings supported by AstraZeneca, Berlin Chemie, Boehringer Ingelheim, Chiesi, Elpen, ERT, GSK, Novartis, Pfizer, Pohl Boskamp, Sanofi, and Teva; and compensation for design and performance of clinical trials from AstraZeneca, Boehringer Ingelheim, GSK, Novartis, Parexel, Pearl Therapeutics, Teva, and Sterna Biologicals.

References

1. NICE. Health and social care directorate. Quality standards and indicators. Briefing paper; 2015. Available from: https://www.nice.org.uk/guidance/qs10/documents/briefing-paper. Accessed August 2, 2021.
2. Trueman D, Woodcock F, Hancock E, British Lung Foundation. Estimating the economic burden of respiratory illness in the UK; 2017. Available from: https://www.blf.org.uk/policy/economic-burden. Accessed August 2, 2021.
3. GOLD. 2020 report; 2020. Available from: https://goldcopd.org/. Accessed August 2, 2021.
4. NICE. NICE guideline - chronic obstructive pulmonary disease in over 16s: diagnosis and management; 2019. Available from: https://www.nice.org.uk/guidance/ng115. Accessed August 2, 2021.
5. Yu AP, Guerin A, Ponce de Leon D, et al. Therapy persistence and adherence in patients with chronic obstructive pulmonary disease: multiple versus single long-acting maintenance inhalers. *J Med Econ*. 2011;14(4):486–496. doi:10.3111/13696998.2011.594123
6. van der Palen J, Moeskops-van Beurden W, Dawson CM, et al. A randomized, open-label, single-visit, crossover study simulating triple-drug delivery with Ellipta compared with dual inhaler combinations in patients with COPD. *Int J Chron Obstruct Pulmon Dis*. 2018;13:2515–2523. doi:10.2147/COPD.S169060
7. Sulku J, Bröms K, Högman M, et al. Critical inhaler technique errors in Swedish patients with COPD: a cross-sectional study analysing video-recorded demonstrations. *NPJ Primary Care Respir Med*. 2021;31(1):5. doi:10.1038/s41533-021-00218-y
8. Brennan V, Mulvey C, Costello RW. The clinical impact of adherence to therapy in airways disease. *Breathe*. 2021;17(2):210039. doi:10.1183/20734735.0039-2021
9. van Boven JF, Chavannes NH, van der Molen T, Rutten-van Molken MP, Postma MJ, Vegter S. Clinical and economic impact of non-adherence in COPD: a systematic review. *Respir Med*. 2014;108(1):103–113. doi:10.1016/j.rmed.2013.08.044
10. Molimard M, Raherison C, Lignot S, et al. Chronic obstructive pulmonary disease exacerbation and inhaler device handling: real-life assessment of 2935 patients. *Eur Respir J*. 2017;49(2):1601794. doi:10.1183/13993003.01794-2016
11. Kocks JWH, Chrystyn H, van der Palen J, et al. Systematic review of association between critical errors in inhalation and health outcomes in asthma and COPD. *NPJ Primary Care Respir Med*. 2018;28(1):43. doi:10.1038/s41533-018-0110-x

12. Lipson DA, Barnhart F, Brealey N, et al. Once-daily single-inhaler triple versus dual therapy in patients with COPD. *N Engl J Med*. 2018;378 (18):1671–1680. doi:10.1056/NEJMoa1713901

13. Lipson DA, Barnacle H, Birk R, et al. FULFIL trial: once-daily triple therapy for patients with chronic obstructive pulmonary disease. *Am J Respir Crit Care Med*. 2017;196(4):438–446. doi:10.1164/rccm.201703-0449OC

14. Albertson TE, Murin S, Sutter ME, Chenoweth JA. The Salford Lung Study: a pioneering comparative effectiveness approach to COPD and asthma in clinical trials. *Pragmatic Observational Res*. 2017;8:175–181. doi:10.2147/POR.S144157

15. Halpin DMG, Worsley S, Ismaila AS, et al. INTREPID: single- versus multiple-inhaler triple therapy for COPD in usual clinical practice. *ERJ Open Res*. 2021;7(2):00950–02020. doi:10.1183/23120541.00950-2020

16. Ismaila AS, Risebrough N, Schroeder M, et al. Cost-effectiveness of once-daily single-inhaler triple therapy in COPD: the IMPACT trial. *Int J Chron Obstruct Pulmon Dis*. 2019;14:2681–2695. doi:10.2147/COPD.S216072

17. Schroeder M, Benjamin N, Atienza L, et al. Cost-effectiveness analysis of a once-daily single-inhaler triple therapy for patients with chronic obstructive pulmonary disease (COPD) using the FULFIL trial: a Spanish perspective. *Int J Chron Obstruct Pulmon Dis*. 2020;15:1621–1632. doi:10.2147/COPD.S240556

18. Fenwick E, Martin A, Schroeder M, et al. Cost-effectiveness analysis of a single-inhaler triple therapy for COPD in the UK. *ERJ Open Res*. 2021;7 (1):00480–2020. doi:10.1183/23120541.00480-2020

19. Schroeder M, Shah D, Risebrough N, et al. Cost-effectiveness analysis of a single-inhaler triple therapy for patients with advanced chronic obstructive pulmonary disease (COPD) using the FULFIL trial: a UK perspective. *Respir Med*. 2019;1:100008.

20. Exuzides A, Colby C, Briggs AH, et al. Statistical modeling of disease progression for chronic obstructive pulmonary disease using data from the ECLIPSE study. *Med Decis Making*. 2017;37(4):453–468. doi:10.1177/0272989X15610781

21. Briggs AH, Baker T, Risebrough NA, et al. Development of the Galaxy chronic obstructive pulmonary disease (COPD) model using data from ECLIPSE: internal validation of a linked-equations cohort model. *Med Decis Making*. 2017;37(4):469–480. doi:10.1177/0272989X16653118

22. Tabberer M, Gonzalez-McQuire S, Muellerova H, et al. Development of a conceptual model of disease progression for use in economic modeling of chronic obstructive pulmonary disease. *Med Decis Making*. 2017;37(4):440–452. doi:10.1177/0272989X16662009

23. Risebrough NA, Briggs A, Baker TM, et al. Validating a model to predict disease progression outcomes in patients with COPD. *Value Health*. 2014;17(7):A560–561. doi:10.1016/j.jval.2014.08.1852

24. Worsley S, Snowise N, Halpin DMG, et al. Clinical effectiveness of once-daily fluticasone furoate/umeclidinium/vilanterol in usual practice: the COPD INTREPID study design. *ERJ Open Res*. 2019;5(4):00061–02019. doi:10.1183/23120541.00061-2019

25. Jones P, Shukla S, Tombs L, et al. Predicting SGRQ score based on CAT score: post-hoc analysis of the IMPACT trial. Paper presented at: European Respiratory Society Congress; 2021; Barcelona, Spain.

26. Starkie HJ, Briggs AH, Chambers MG, Jones P. Predicting EQ-5D values using the SGRQ. *Value Health*. 2011;14(2):354–360. doi:10.1016/j.jval.2010.09.011

27. BNF. British National Formulary; 2020. Available from: https://bnf.nice.org.uk/. Accessed September 28, 2022. 15, 2021.

28. NICE. Chronic obstructive disease in over 16s: diagnosis and management. Economic model report; 2018. Available from: https://www.nice.org.uk/guidance/ng115/documents/economic-report. Accessed September 15, 2021.

29. ONS. Office of National Statistics (ONS). Consumer price index; 2020. Available from: https://www.ons.gov.uk/economy/inflationandpriceindices/timeseries/l522/mm23. Accessed September 15, 2021.

30. NICE. Guide to the methods of technology appraisal; 2013. Available from: https://www.nice.org.uk/process/pmg9/resources/guide-to-the-methods-of-technology-appraisal-2013-pdf-2007975843781. Accessed August 2, 2021.

31. Bakerly ND, Browning D, Boucot I, et al. The impact of fluticasone furoate/vilanterol on healthcare resource utilisation in the Salford Lung Study in chronic obstructive pulmonary disease. *Ther Adv Respir Dis*. 2021;15:17534666211001013. doi:10.1177/17534666211001013

32. Singh S, Amin AV, Loke YK. Long-term use of inhaled corticosteroids and the risk of pneumonia in chronic obstructive pulmonary disease: a meta-analysis. *Arch Intern Med*. 2009;169(3):219–229. doi:10.1001/archinternmed.2008.550