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ORIGINAL RESEARCH

Cost-Effectiveness of Single-Inhaler Versus Multiple-Inhaler Triple Therapy in COPD: A German Healthcare Perspective

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Purpose: The INTREPID trial showed that once-daily single-inhaler triple therapy (SITT) using fluticasone furoate, umeclidinium, and vilanterol (FF/UMEC/VI) offers clinical benefits versus non-ELLIPTA multiple-inhaler triple therapy (MITT) for the management of chronic obstructive pulmonary disease (COPD) in real-world clinical practice. This analysis evaluated the cost-effectiveness of SITT with FF/UMEC/VI versus non-ELLIPTA MITT for treating symptomatic COPD from a German healthcare perspective.

Patients and Methods: Data from the INTREPID trial, including baseline characteristics, treatment effects (forced expiratory volume in 1 second and St. George's Respiratory Questionnaire score [derived from exploratory COPD assessment test score mapping]), and discontinuation rates, along with German healthcare resource and drug costs (2023 Euros), were used to populate the GALAXY COPD model. The analysis was conducted over a lifetime horizon, with outcomes including life years (LYs), quality-adjusted LYs (QALYs), and incremental cost-utility ratios. The robustness of the analysis was assessed using scenario, one-way sensitivity, and probabilistic analyses.

Results: Improved lifetime outcomes were predicted for FF/UMEC/VI versus non-ELLIPTA MITT, providing additional LYs of 0.174 (95% range: 0.065, 0.322) and QALYs of 0.261 (0.186, 0.346) per patient, together with cost savings of €2,850 (€3,517, €2,220). Additionally, patients receiving FF/UMEC/VI were predicted to experience a reduction in exacerbations (−0.063), highlighting its dominance as the preferred treatment option. These findings remained consistent across one-way sensitivity, scenario, and probabilistic analyses, highlighting the robustness of FF/UMEC/VI as a cost-effective solution for COPD management in Germany.

Conclusion: FF/UMEC/VI offers clinical benefits and cost savings compared with non-ELLIPTA MITT, suggesting that it may reduce the burden of COPD in Germany and warranting consideration as a preferred treatment option by physicians.

Keywords: chronic obstructive pulmonary disease, cost-effectiveness, Germany, fluticasone furoate/umeclidinium/vilanterol, single-inhaler triple therapy, multiple-inhaler triple therapy

Introduction

Chronic obstructive pulmonary disease (COPD) is the third leading cause of death globally and the seventh foremost contributor to global health burdens, as assessed by disability-adjusted life years (LYs).[1] In Germany, the prevalence of COPD is 6.3% and 5.1%, respectively, among men and women aged 45–64 years, and 12.5% and 11%, respectively, among men and women aged ≥65 years,[2] and is expected to increase sharply over the coming years.[3] By 2050, an estimated 49.5 million Europeans are projected to be impacted, with Germany bearing the highest burden.[3] Beyond its health impact, COPD imposes a significant economic burden, representing 0.19% of Germany's gross domestic product,[4]

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with direct costs estimated at €7,847 per patient per year and productivity losses estimated at €5,735 per patient per year in 2019.[5] Additionally, COPD often triggers feelings of hopelessness and social isolation, leading to reduced physical activity and increased sedentary behavior, which are associated with more severe depressive symptoms.[6] The worsened dyspnea in patients with COPD having depression exacerbates social isolation and worsens physical inactivity, further diminishing their health-related quality of life (HRQoL).[7]

In 2005, Germany introduced a nationwide disease management program (DMP) aimed at reducing costs and improving health outcomes for patients with COPD. Although participants in the DMP experienced lower mortality and morbidity rates, treatment costs increased.[8] A real-world, register-based cohort study (AvoidEx) involving 250,723 German COPD patients revealed that, over 3 years follow-up, 35.9% of those without initial exacerbations had experienced an exacerbation compared to 59.1% for one moderate exacerbation, 58.1% for one severe exacerbation, and 84.1% for two or more moderate/severe exacerbations in patients with initial exacerbations.[9] This data emphasizes the progressive nature of this disease and the substantial cost burden associated with it, especially due to severe exacerbations that frequently lead to extended hospital stays for COPD patients.

Triple therapy, typically delivered via multiple inhalers, is associated with lower adherence and persistence rates compared with single-inhaler use in European countries.[10,11] The Global Initiative of Chronic Obstructive Lung Disease (GOLD) recommends a single inhaler over multiple inhalers, potentially because of its reduced susceptibility to handling errors, greater convenience, and improved effectiveness.[12] A retrospective analysis of German national claims data, in patients with COPD, found significantly higher rates of adherence and persistence with single-inhaler triple therapy (SITT) compared to multiple-inhaler triple therapy (MITT).[13]

In 2017, a combination therapy of fluticasone furoate, umeclidinium, and vilanterol (FF/UMEC/VI) via a single ELLIPTA™ inhaler (GSK, Brentford, Middlesex, UK) was approved for the long-term maintenance treatment of patients with COPD in Germany.[14] Previous evaluations of cost-effectiveness (CE), in Canada, UK and Spain, have shown FF/UMEC/VI to be a cost-effective option compared with FF/VI, UMEC/VI, and budesonide/formoterol dual therapies.[15–17] These analyses were based on data from randomized controlled trials. The INTREPID trial demonstrated the clinical benefits of FF/UMEC/VI compared with non-ELLIPTA MITT in a real-world clinical setting.[18] A study using data from the INTREPID trial, concluded that FF/UMEC/VI is a dominant treatment (more effective and less costly) compared with non-ELLIPTA MITT from a UK National Health Service perspective.[19]

Considering the burden of COPD in Germany, it is important to understand how the effects of available treatments could impact health and economic outcomes. A CE analysis of FF/UMEC/VI single ELLIPTA inhaler therapy versus non-ELLIPTA MITT was conducted for the treatment of symptomatic patients with COPD having a history of exacerbation from a German healthcare perspective in a real-world setting using the INTREPID trial data.

Materials and Methods

This post-hoc analysis from the INTREPID study aimed to estimate the incremental cost utility (cost per quality-adjusted life year [QALY] gained) of initiating once-daily FF/UMEC/VI (100 µg/62.5 µg/25 µg) versus non-ELLIPTA MITT for treating symptomatic patients with COPD having a history of exacerbation using data from the INTREPID trial. This analysis used GALAXY, a well-established and validated model of COPD progression,[20,21] built in Microsoft Excel®, which was tailored to incorporate patient characteristics and treatment effects observed in the INTREPID trial population as well as German healthcare costs. The INTREPID study complies with the Declaration of Helsinki.

Model Inputs

The clinical data used in this model were derived from the INTREPID trial (ClinicalTrials.gov identifier: NCT03467425), the details of which have been previously published.[18,22] In brief, the INTREPID trial was a 24-week, randomized, open-label, parallel-group, multicenter study that enrolled patients with COPD aged ≥40 years with a history of treatment with systemic/oral corticosteroids, antibiotics, and/or hospitalization for at least one COPD exacerbation within 3 years before randomization. Additionally, they were required to have been receiving non-ELLIPTA maintenance therapy continuously for at least 16 weeks before randomization. The primary endpoint of the study was the impact of COPD on quality of life, as measured using the COPD assessment test (CAT) at 24 weeks.

The baseline characteristics of the intent-to-treat (ITT) population in the INTREPID trial have been previously published.[19] The model was parameterized with the pooled baseline characteristics of the target patient population across the comparator arms, as well as the treatment effects and discontinuation rates for the interventions. The mean age of the trial population was 67.8 years, and 46.5% of patients were female. Moreover, 76.6% of the patients had experienced at least one moderate/severe exacerbation in the previous year, and the overall baseline percent predicted forced expiratory volume in 1 second (FEV_1%) was 54.1%.[19] Table 1 presents the treatment effect parameters included in the model. Baseline St. George's Respiratory Questionnaire (SGRQ) values were not available from the INTREPID trial; however, CAT scores were observed and documented as a measure of patients' quality of life. The mapping algorithm developed by Jones et al (2021)[23] using data from a post hoc analysis of the IMPACT trial[24] was also used to convert baseline CAT scores and treatment effects into SGRQ scores. Details of CAT/SGRQ conversion and derivation of baseline modified Medical Research Council (mMRC) scores, fibrinogen levels, 6-minute walk test (6MWT), and baseline SGRQ, which were also not directly measured in the INTREPID trial, are provided in Appendix S1.

Model Assumptions

The INTREPID trial population was deemed representative of the German COPD population likely to receive FF/UMEC/VI or non-ELLIPTA MITT. In the analysis, the treatment effect was considered ongoing (persistent) and maintained at a consistent level over time while patients remained on treatment with FF/UMEC/VI or the comparator. In this analysis, all other outcomes were assumed to be consistent and projected based on a 24-week study. In the base case, treatment discontinuation was only modeled for the first year; for subsequent years, it was assumed to be 0% for both treatment arms. In the base case analysis, the discontinuation rate during the first year was 18.64% for the FF/UMEC/VI group compared with 12.15% for the non-ELLIPTA MITT group (unpublished data). The frequency of adverse events leading to treatment discontinuation was captured in the data describing discontinuation and was not modeled separately. In this model, all patients who discontinued their initial treatment (FF/UMEC/VI or non-ELLIPTA MITT) during the first year were switched to subsequent treatments. Additionally, the efficacy of the subsequent treatment was assumed to be the same as that of the reference treatment (non-ELLIPTA MITT) for patients discontinuing either non-ELLIPTA MITT or FF/UMEC/VI for the remaining duration of the analysis.

Table 1 Treatment Effects Observed in the INTREPID Trial (ITT Population, at 24 weeks)

	FF/UMEC/VI (N=1,545)	Non-ELLIPTA MITT (N=1,547)
Health status[a]		
CAT score	18.0 (7.98)	19.1 (7.89)
CAT score change from baseline	−2.8 (6.31)	−1.3 (6.04)
CAT responders[b], n (%)	731 (47%)	616 (40%)
FF/UMEC/VI vs column		
Responders OR (95% CI); p-value		1.31 (1.13, 1.51); <0.001
Mean score difference (95% CI); p-value		−1.40 (−1.80, −1.00); <0.001
Lung function		
Trough FEV_1, L	1.440 (0.53)	1.391 (0.59)
Trough FEV_1 change from baseline, L	0.073 (0.20)	0.015 (0.23)
FF/UMEC/VI vs column		
Mean difference (95% CI); p-value		0.050 (0.02, 0.07); <0.001

Notes: Data are expressed as mean (SD) unless otherwise stated. [a]CAT treatment effect was converted to an SGRQ treatment effect for the model, which was converted to an SGRQ-c treatment effect; [b]≥2-unit decrease in CAT score from baseline.

Abbreviations: CAT, COPD assessment test; CI, confidence interval; COPD, chronic obstructive pulmonary disease; FEV_1, forced expiratory volume in 1 second; FF/UMEC/VI, fluticasone furoate, umeclidinium bromide, and vilanterol; ITT, intent-to-treat; MITT, multiple-inhaler triple therapy; N, total number of patients; n, number of patients in each category; OR, odds ratio; SD, standard deviation; SGRQ, St. George's Respiratory Questionnaire; SGRQ-c, St. George's Respiratory Questionnaire for COPD patients.

Utilities

QALYs were determined by converting the predicted SGRQ score for each annual model cycle to a utility value using a published algorithm.[25] In the present analysis, data gathered over the 24 weeks were used as input parameters for the annual model cycle and projected over a lifetime.

Costs

Medication costs were obtained from the Rote Liste[26] (Table S1), with calculations based on dose, pack size, and cost per pack used to determine the daily cost. The cost of non-ELLIPTA MITT was derived as the weighted average cost of treatments within each class using the German market share data (unpublished data). Similarly, the daily cost of subsequent treatment after discontinuation of either FF/UMEC/VI or non-ELLIPTA MITT was determined based on the weighted average cost within each treatment class, adjusted according to the renormalized percentage of patients receiving treatment (Table S1). Estimates for healthcare resource utilization for each of the model health states and exacerbation events were sourced from a published National Institute for Health and Care Excellence (NICE) economic model report[27] (2018; Table S2). Costs were derived from German-based sources, including Rote Liste[26] and ARTZ & WIRSCHAFT.[28] All costs were inflated to 2023 values using the Consumer Price Index obtained from the Federal Statistical Office in Germany.[29] A scenario analysis was conducted to test the effect of including resource utilization estimates from a German paper published by Price et al (2011)[30] that applied the same unit costs as in the base case analysis (Table S2). Indirect costs included productivity losses due to sick leave, estimated using the human capital approach, which broadly calculated the gross value loss during time away from usual activities.[31] According to the INTREPID trial, the average duration of moderate exacerbations and severe exacerbations was 12.2 days (standard error [SE] 0.42) and 15.8 days (SE 1.36) across both treatment arms. These durations were assumed to equate to the number of days absent from usual activities. The cost per day absent was calculated based on the average German earnings of €181.20 per day, as reported by Destatis Statistisches Bundesamt in April 2022.[32]

Analysis

The analysis was conducted over a lifetime horizon (the time point where survival reached 0% in the model) and by using a 3.0% discount rate (for costs and benefits) in the base case, as recommended by the Institute for Quality and Efficiency in Health Care guidelines[33] because of the chronic nature of COPD. Model outputs included cumulative exacerbation rates (both moderate and severe) per person per year, LYs, QALYs, and total and disaggregated direct costs, encompassing COPD medications and nondrug costs. Incremental cost-utility ratios were calculated by dividing the incremental costs by the incremental QALYs.

Scenario, one-way sensitivity, and probabilistic analyses were conducted to test the robustness of the model results. Scenario analyses were performed to examine the impact of alternative populations, assumptions, and model settings on the base case model results. One-way sensitivity analyses were conducted on baseline covariate values that were not available from the INTREPID data (fibrinogen level, 6MWT, mMRC dyspnea scale, and SGRQ score) and FF/UMEC/VI treatment effects on SGRQ response and FEV_1.[19] Probabilistic analyses were conducted to assess the impact of uncertainty for the input parameters. This involved 5,000 simulations using random sampling (from the distributions assigned to the input parameters and other variables).

Results

Base Case Analyses

Over a lifetime horizon, FF/UMEC/VI was predicted to offer notable benefits over non-ELLIPTA MITT, providing additional 0.174 LYs and 0.261 QALYs, with cost savings of €2,850 (Table 2). These additional LYs and QALYs were largely attributable to the favorable treatment effects of FF/UMEC/VI on the FEV_1 and SGRQ scores (derived from the CAT score). Consequently, compared with non-ELLIPTA MITT, FF/UMEC/VI emerged as a dominant treatment option, offering favorable clinical outcomes at a lower cost.

Table 2 Base Case Results: Comparison of FF/UMEC/VI and Non-ELLIPTA MITT Costs (2023 Euros)

Deterministic (Lifetime)	FF/UMEC/VI	Non-ELLIPTA MITT	Incremental
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
Moderate exacerbations PPPY	0.976	0.995	−0.019
Severe exacerbations PPPY	0.302	0.316	−0.014
Total exacerbations PPPY	1.278	1.311	−0.032
Outcomes at end of timeframe			
Accumulated LYs (undiscounted)	9.000	8.825	0.174
Accumulated QALYs	4.477	4.217	0.261
Costs at end of timeframe (€)			
Accumulated costs total	24,039.15	26,889.04	−2,849.90
Drug costs	9,415.10	11,655.27	−2,240.17
Total nondrug costs	14,624.05	15,233.77	−609.72
Incremental results			
Incremental cost (€)			−2,850
Incremental QALYs			0.261
ICER (QALY)			Dominant

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

Scenario Analyses

Across all scenarios, FF/UMEC/VI exhibited dominance, ie, greater effectiveness and lower costs, compared with non-ELLIPTA MITT (Table 3). The highest cost savings of €3,205 (with incremental QALYs of 0.315) were observed in the scenario in which the discount rate was set at 0%. Conversely, the lowest cost savings of €1,650 (with incremental QALYs of 0.126) were noted in the scenario where the 24-week treatment discontinuation data were applied for the first and subsequent years. These findings emphasize the robustness of FF/UMEC/VI as a preferred treatment choice over non-ELLIPTA MITT across various scenarios, with notable variations in cost savings depending on specific scenario settings.

One-Way Sensitivity Analyses

FF/UMEC/VI consistently emerged as the dominant treatment option (Table 4) across all sensitivity analyses. The greatest cost savings of €3,034 were observed when utilizing the upper value of the confidence interval for the FEV_1 treatment effect.

Table 3 Scenario Analyses: FF/UMEC/VI Vs Non-ELLIPTA MITT Costs (2023 Euros)

Scenario	Incremental QALYs	Incremental Costs (€)	ICER/ QALY
Base case	0.261	−2,850	**Dominant**
Time horizon 5 years	0.113	−1,910	**Dominant**
Time horizon 10 years	0.199	−2,676	**Dominant**
Discount rate 0%	0.315	−3,205	**Dominant**
Discount rate 5%	0.233	−2,651	**Dominant**
Discontinuation in the first and subsequent years	0.126	−1,650	**Dominant**
Discontinuation excluded	0.261	−2,850	**Dominant**
Include patient productivity costs	0.261	−3,071	**Dominant**
Price 2011 resource utilization	0.261	−2,671	**Dominant**

Abbreviations: FF/UMEC/VI, fluticasone furoate, umeclidinium bromide, and vilanterol; ICER, incremental cost-effectiveness ratio; MITT, multiple-inhaler triple therapy; QALY, quality-adjusted life year.

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Table 4 One-Way Sensitivity Analyses: FF/UMEC/VI Vs Non-ELLIPTA MITT Costs (2023 Euros)

Analysis	Incremental LYs	Incremental QALYs	Incremental Costs (€)	ICER/ QALY
Base case	0.174	0.261	−2,850	**Dominant**
Baseline parameters				
Fib lower CI using ECLIPSE data	0.180	0.263	−2,855	**Dominant**
Fib upper CI using ECLIPSE data	0.174	0.259	−2,837	**Dominant**
6MWT lower CI using ECLIPSE data	0.174	0.260	−2,849	**Dominant**
6MWT upper CI using ECLIPSE data	0.175	0.261	−2,857	**Dominant**
mMRC −25%	0.181	0.264	−2,869	**Dominant**
mMRC +25%	0.176	0.258	−2,822	**Dominant**
SGRQ −25%	0.191	0.256	−2,912	**Dominant**
SGRQ +25%	0.165	0.262	−2,629	**Dominant**
Treatment effects (difference in change from baseline)				
FEV_1 lower CI	0.090	0.229	−2,636	**Dominant**
FEV_1 upper CI	0.261	0.292	−3,034	**Dominant**
SGRQ −25% (converted to SGRQ-c)	0.174	0.212	−2,850	**Dominant**
SGRQ +25% (converted to SGRQ-c)	0.174	0.309	−2,850	**Dominant**

Abbreviations: 6MWT, 6-minute walk test; CI, confidence interval; FEV_1, forced expiratory volume in 1 second; FF/UMEC/VI, fluticasone furoate, umeclidinium bromide, and vilanterol; Fib, fibrinogen; ICER, incremental cost-effectiveness ratio; LY, life year; MITT, multiple-inhaler triple therapy; mMRC, modified Medical Research Council; QALY, quality-adjusted life year; SGRQ, St. George's Respiratory Questionnaire; SGRQ-c, St. George's Respiratory Questionnaire for COPD patients.

Conversely, the lowest cost savings of €2,629 were noted in the scenario in which the baseline SGRQ score was increased by 25%. These findings highlight the robustness of FF/UMEC/VI as a preferred treatment choice over non-ELLIPTA MITT across various sensitivity analyses, with variations in cost savings depending on the specific scenario parameters.

Probabilistic Analysis

Results of the probabilistic analysis are presented in Table 5. Compared with non-ELLIPTA MITT, FF/UMEC/VI provided an additional 0.177 LYs (95% range: 0.065, 0.322) and 0.261 QALYs (0.186, 0.346), with a cost savings of €2,801 (€3,517, €2,220). Across all simulations, FF/UMEC/VI was associated with lower costs and higher QALYs, as depicted in the CE scatter plot (Figure 1). The net benefit acceptability curve indicated that FF/UMEC/VI had a 100% probability of being cost-

Table 5 Probabilistic Base Case Results: FF/UMEC/VI Vs Non-ELLIPTA MITT Costs (2023 Euros)

Probabilistic (Lifetime)	FF/UMEC/VI	Non-ELLIPTA MITT	Incremental
Cumulative number of exacerbations over timeframe			
Moderate	8.852	8.843	0.009
Severe	2.782	2.851	−0.069
Total	11.634	11.693	0.362
Moderate exacerbations PPPY	0.977	0.996	−0.018
Severe exacerbations PPPY	0.305	0.319	−0.014
Total exacerbations PPPY	1.283	1.315	−0.032
Outcomes at end of timeframe			
Accumulated LYs (undiscounted)	9.059	8.882	0.177 (0.065, 0.322)
Accumulated QALYs	4.491	4.230	0.261 (0.186, 0.346)

(*Continued*)

Table 5 (Continued).

Probabilistic (Lifetime)	FF/UMEC/VI	Non-ELLIPTA MITT	Incremental
Costs at end of timeframe (€)			
Accumulated costs total	24,282	27,083	−2,801 (−3,517, −2,220)
Drug costs	9,448	11,696	−2,248 (−2,688, −1,858)
Total nondrug costs	14,834	15,388	−554 (−994, −197)
Incremental results			
Incremental cost (€)			−2,801 (−3,517, −2,220)
Incremental QALYs			0.261 (0.186, 0.346)
ICER (QALY)			Dominant

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

effective at a willingness-to-pay threshold of €30,000 per QALY (Figure 2). A €30,000 per QALY threshold was selected because FF/UMEC/VI demonstrated a 100% probability of being cost-effective at this willingness-to-pay level.

Discussion

The present analysis used a validated disease progression model to extrapolate outcomes from the 24-week INTREPID trial over a lifetime horizon. Cost data from Germany were applied together with the trial results to assess CE in German patients with COPD. Treatment with FF/UMEC/VI using a single ELLIPTA inhaler showed improved clinical benefits, including reduced exacerbations, increased survival, and gains in QALYs, with associated cost savings. FF/UMEC/VI remained the dominant treatment option across all scenario analyses. Sensitivity analyses of the treatment effects had minimal impact on the model results.

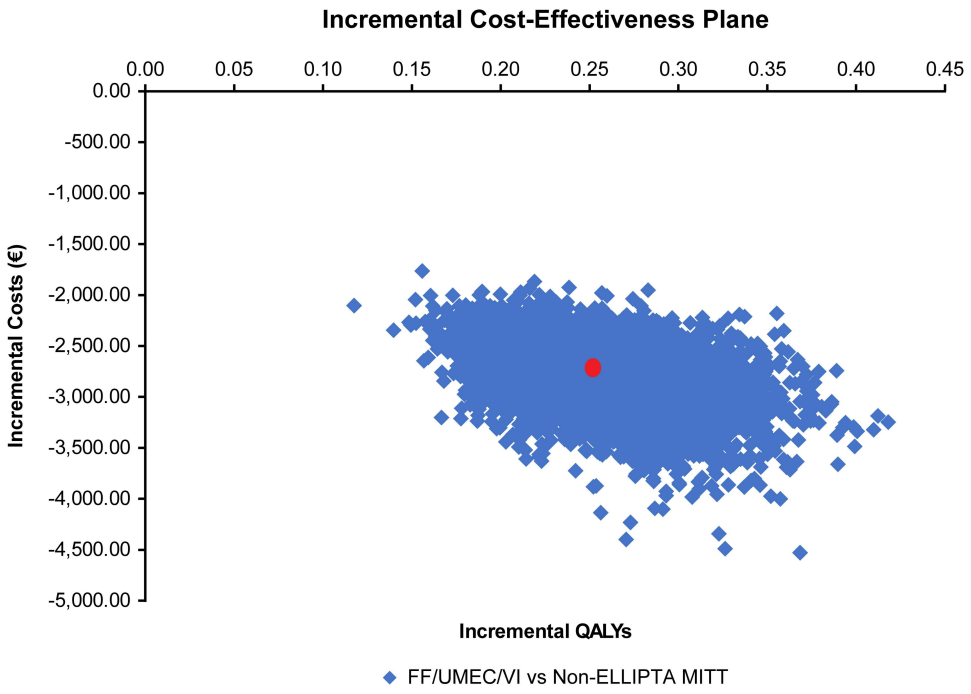

Figure 1 Incremental Cost-Effectiveness Plane: FF/UMEC/VI vs Non-ELLIPTA MITT.
Note: The red dot represents the mean ICER.
Abbreviations: FF/UMEC/VI, fluticasone furoate, umeclidinium bromide, and vilanterol; ICER, incremental cost-effectiveness ratio; MITT, multiple-inhaler triple therapy; QALY, quality-adjusted life year.

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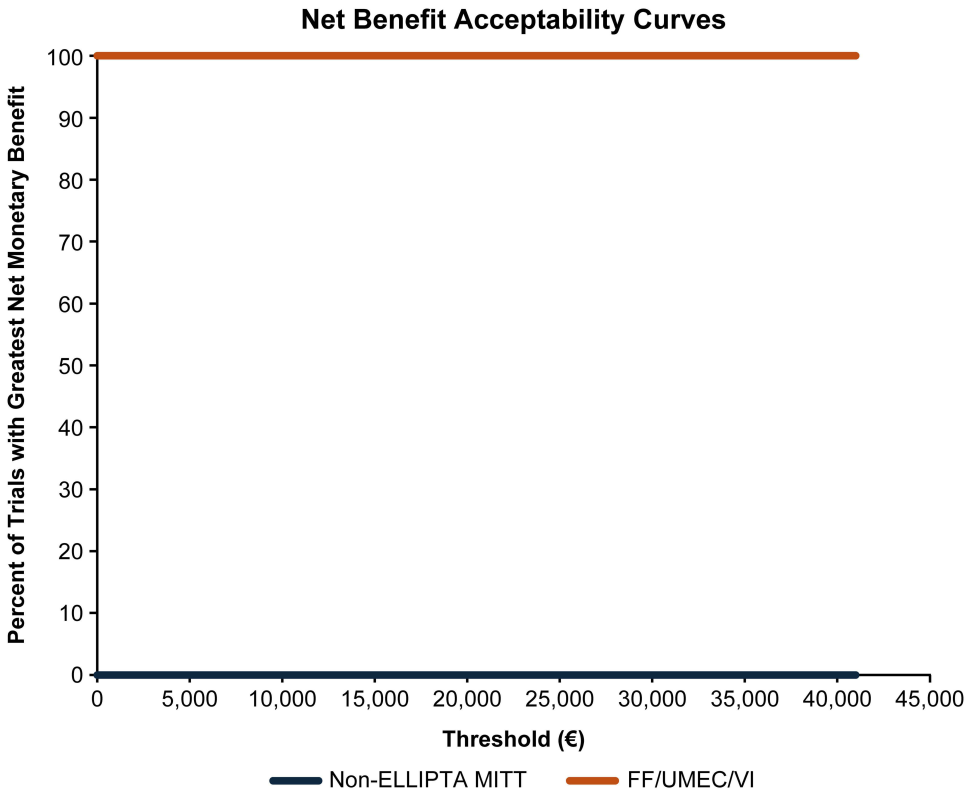

Figure 2 Net Benefit Acceptability Curves: FF/UMEC/VI vs Non-ELLIPTA MITT.
Abbreviations: FF/UMEC/VI, fluticasone furoate, umeclidinium bromide, and vilanterol; MITT, multiple-inhaler triple therapy.

Our findings are consistent with previous reports in the UK population[19] demonstrating the CE of FF/UMEC/VI delivered via a single ELLIPTA inhaler compared with that of MITT in patients with COPD. Further, cost savings associated with FF/UMEC/VI using the single ELLIPTA inhaler were a result of reduced drug unit costs and decreased healthcare resource utilization.[19] In our analysis, cost savings with the single ELLIPTA inhaler were due to lower drug unit costs, maintenance expenses, and exacerbation-related costs. Studies have indicated that patients with COPD receiving MITT exhibit lower adherence[10,11] and higher critical inhaler errors than those receiving single-inhaler treatment,[34] leading to increased exacerbations, hospitalizations, and healthcare costs.[35–38] Thus, streamlining treatment regimens for patients with COPD is anticipated to enhance health outcomes and reduce healthcare costs.

The published and validated GALAXY COPD model uses a wide array of baseline patient characteristics and clinical measures to parameterize the modeled target population characteristics and treatment effects. These characteristics include patient demographics, exacerbation history, COPD symptom severity, lung function, and HRQoL. By incorporating these characteristics, the model maximizes the information used to predict long-term disease progression. Although this is a strength of the GALAXY model, it can become a limitation when the complete set of baseline parameters is unavailable for the patient population being modeled. In the INTREPID trial, data on baseline fibrinogen levels, 6MWT, mMRC dyspnea scale scores, smoking status, and SGRQ scores were not available. Predicted or analogous data were used to derive the baseline values for these parameters. Notably, fibrinogen serves as a significant predictor of annual exacerbations, with a 10% reduction in baseline fibrinogen levels associated with a 5%–6% decrease in predicted exacerbations per year. In a study conducted by Mannino et al (2015),[39] the average baseline fibrinogen level among participants with COPD included in a combined dataset of four publicly funded studies and one industry-sponsored study was 351.7 ± 89.3 mg/dL. Among the individual studies within this dataset, the highest mean fibrinogen level (397.3 mg/dL) was reported in the ECLIPSE study, which measured fibrinogen levels at baseline and longitudinally over 3 years in participants with COPD with GOLD stages II, III, or IV (n=2,118).[39] Consequently, as our study predicted baseline fibrinogen levels using an equation derived from ECLIPSE data, there is a possibility of overestimation, potentially

leading to inflated predicted exacerbation rates. However, sensitivity analyses conducted on all model parameters (including baseline fibrinogen, 6MWT, and mMRC score) revealed that the incremental cost-effectiveness ratio (ICER) remained largely unchanged compared with the base case results.

In the present analysis, healthcare resource utilization associated with COPD health states and exacerbation events was derived from estimates in a published NICE economic model report (2018),[27] with unit costs sourced from German-specific references. While this approach provided a reliable estimate of healthcare costs, it was deemed important to consider healthcare resource utilization from a German healthcare perspective as an alternative. Following an extensive literature review, resource utilization estimates from a German study conducted by Price et al (2011)[30] was incorporated as a scenario analysis, which utilized the same unit costs as those in the base case analysis. The results of this analysis did not alter the overall findings compared with those of the base case scenario, with FF/UMEC/VI maintaining its status as the dominant treatment option.

An additional aspect to be considered in the current analysis was the focus on the 24-week discontinuation rate data collected exclusively from the INTREPID trial. Due to the unavailability of discontinuation data at 52 weeks, the 24-week data were utilized for the first year, with no further data on treatment discontinuation in subsequent years. Consequently, for subsequent years, the discontinuation rates were assumed to be 0% for both treatment arms in the base case scenario. To validate this assumption, two sensitivity analyses were conducted: one assuming discontinuation rates for subsequent years to be consistent with those for the first year and the other assuming zero discontinuations for both the first and subsequent years. The results from these analyses remained consistent with those from the base case, showing no significant alteration in the overall outcomes (FF/UMEC/VI continued to be the dominant treatment option). Thus, it can be inferred that discontinuation rates had a minimal impact on the CE of FF/UMEC/VI.

It is important to highlight the differences in the healthcare reimbursement systems between Germany and countries such as the UK, where organizations such as NICE rely on comprehensive health economic evaluations, including CE analyses.[40] In Germany, the reimbursement process for approved drugs does not mandate CE analyses. Instead, reimbursement decisions are primarily influenced by the outcomes of the early benefit assessment, which focuses exclusively on the clinical efficacy and safety of a drug compared with appropriate comparator therapies.[41] Furthermore, the ultimate price of a drug in Germany is typically negotiated between the manufacturer and the representatives of the statutory health insurance system/payors.[42] Moreover, while CE analyses in countries such as the UK often involve metrics such as QALYs and ICERs to assess the CE of treatments, these metrics are not typically used in Germany's reimbursement decisions. While our study findings remain valid and relevant, it is essential to contextualize them within the framework of the German reimbursement system. Furthermore, in Germany, numerous rebate contracts exist between manufacturers and payors at both national and regional levels. Although the existence of these rebate contracts is public knowledge, the exact negotiated prices of drugs are typically not disclosed. This lack of transparency can impact the accuracy of cost estimations in health economic evaluations because the "true" costs of some inhaled medicines may not be fully known.

Conclusions

Based on the results of this analysis, SITT with FF/UMEC/VI offers clinical benefits and cost savings compared with non-ELLIPTA MITT for adult patients with COPD in Germany. These findings suggest that FF/UMEC/VI has the potential to reduce the economic burden associated with COPD, warranting its consideration by physicians as a preferred treatment option.

Abbreviations

6MWT, 6-minute walk test; CAT, COPD assessment test; CE, cost-effectiveness; CI, confidence interval; COPD, chronic obstructive pulmonary disease; DMP, disease management program; FEV_1, forced expiratory volume in 1 second; FF/UMEC/VI, fluticasone furoate, umeclidinium, and vilanterol; Fib, fibrinogen; GOLD, Global Initiative for Chronic Obstructive Lung Disease; HRQoL, health-related quality of life; ICER, incremental cost-effectiveness ratio; ICS, inhaled corticosteroid; ITT, intent-to-treat; LABA, long-acting β-agonist; LAMA, long-acting muscarinic antagonist; LY, life year; MITT, multiple-inhaler triple therapy; mMRC, modified Medical Research Council; NICE, National Institute for Health and Care Excellence; OR, odds ratio; PPPY, per patient per year; QALY, quality-adjusted life year; SD, standard deviation; SE, standard error; SGRQ, St. George's Respiratory Questionnaire; SGRQ-c, St. George's Respiratory Questionnaire for COPD patients; SITT, single-inhaler triple therapy.

Data Sharing Statement

Anonymized individual participant data and study documents can be requested for further research from https://www.gsk-studyregister.com/en/.

Ethics Approval and Informed Consent

Ethics committee approval and informed consent from patients were not required for this analysis. As the study utilized existing data from a previously published study involving patient characteristics and treatment effects, there was no direct interaction with patients or the requirement of collection of individual patient data.

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Author Contributions

All authors made a significant contribution to the work reported, whether that is 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 article; 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.

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Disclosure

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