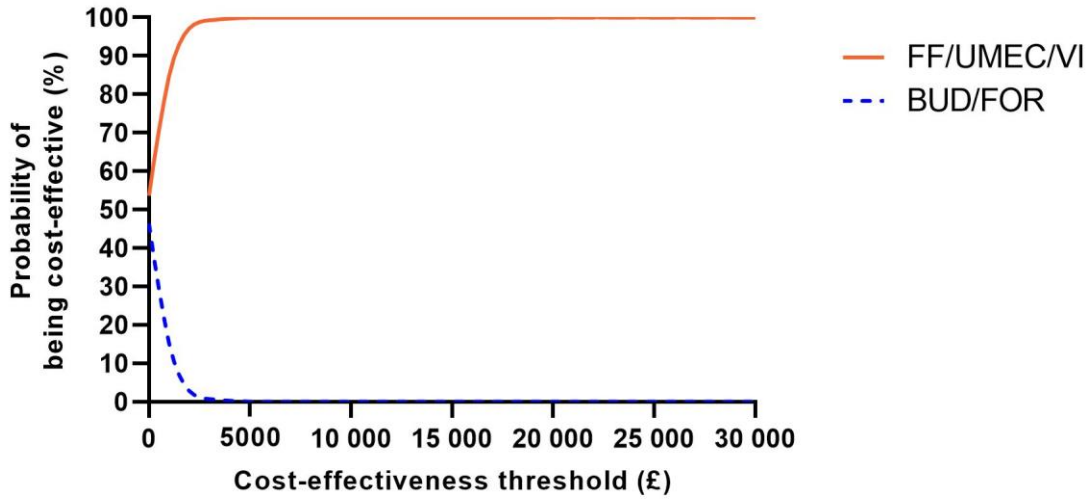
Supplementary Appendix

SUPPLEMENTARY FIGURE S1 QALY cost-effectiveness acceptability curves of FF/UMEC/VI *versus* BUD/FOR (EXT population[#]; PA).



FF: fluticasone furoate; UMEC: umeclidinium; VI: vilanterol; BUD: budesonide; FOR: formoterol; PA: probabilistic analysis; QALY: quality-adjusted life year; EXT: extension. [#]: patients treated for up to 52 weeks.

SUPPLEMENTARY TABLE S1 Coefficients estimated within the FEV_1 (mL) random intercept equation fit using data from TORCH[#]

Variable	Point estimate	Standard error
Intercept	1275.6	35.9
Slope (years)	–40.9	4.5
Recent exacerbation history*	–30.6	5.9
Age, years		
<55	Referent	
55–<65	–203.0	23.6
65–<75	–326.5	23.1
≥75	–402.6	29.5
Sex		
Male	293.9	17.1
Female	Referent	
BMI, kg/m^2		
<20	Referent	
20–<25	153.3	24.5
25–<29	244.5	25.4
≥29	348.7	25.9
Exacerbation history (moderate or severe, in the previous 12 months)		
0	Referent	
1	–0.03	17.7
≥2	–55.0	17.4
Baseline SGRQ total score		
<38	Referent	
38–<50	–93.9	19.4
50–<62	–161.1	20.0
≥62	–185.9	20.7

FEV_1: forced expiratory volume in 1 s; BMI: body mass index; SGRQ: St. George's Respiratory Questionnaire. [#]: source: Calverley *et al.*, 2007 [10] and Vestbo *et al.*, 2004 [11]; *a recent exacerbation history is defined as an exacerbation occurring within the previous year.

SUPPLEMENTARY TABLE S2 Coefficients estimated within the exacerbation random intercept equation fit using data from TORCH[#]

Variable	Point estimate	Standard error
Intercept	–0.96	0.11
Treatment arm[¶]		
ICS/LABA	Referent	
Placebo	0.03	0.07
ICS alone	–0.12	0.07
LABA alone	0.05	0.07
Recent exacerbation history*	0.9	0.06
FEV_1 percent predicted		
<30% (very severe COPD)	Referent	
30–<50% (severe COPD)	–0.14	0.06
50–<80% (moderate COPD)	–0.49	0.08
>80% (non-COPD)	–0.98	0.22
Sex		
Male	–0.16	
Female	Referent	
Exacerbation history (moderate or severe, in the previous 12 months)		
0	Referent	
1	0.26	0.07
≥2	0.43	0.06
Baseline SGRQ total score		
<38	Referent	
38–<50	0.20	0.07
50–<62	0.22	0.07
≥62	0.26	0.07

ICS: inhaled corticosteroid; LABA: long-acting β_2-agonist; FEV_1: forced expiratory volume in 1 s; COPD: chronic obstructive pulmonary disease; SGRQ: St. George's Respiratory Questionnaire. [#]: source: Calverley *et al.*, 2007 [10] and Vestbo *et al.*, 2004 [11]; [¶]: it was assumed that all patients were treated with at least an ICS/LABA; *: a recent exacerbation history is defined as an exacerbation occurring within the previous year.

SUPPLEMENTARY TABLE S3 Annual transition probabilities (based on statistical equations for FEV_1 decline over time)

COPD severity health state transition	Transition probability
Moderate COPD to Severe COPD (no recent exacerbation history)	0.041
Moderate COPD to Severe COPD (recent exacerbation history)	0.088
Severe COPD to Very severe COPD (no recent exacerbation history)	0.070
Severe COPD to Very severe COPD (recent exacerbation history)	0.143

Moderate COPD (FEV_1 percent predicted 50–<80%); Severe COPD (FEV_1 percent predicted 30–<50%); Very severe COPD (FEV_1 percent predicted <30%). A recent exacerbation history is defined as an exacerbation occurring within the previous year

FEV_1: forced expiratory volume in 1 s; COPD: chronic obstructive pulmonary disease.

SUPPLEMENTARY TABLE S4 Treatment effect and patient distribution across the health states defined by FEV_1 and exacerbation status at the end of the FULFIL trial (week 24, ITT population)

	FF/UMEC/VI *versus* BUD/FOR	
FEV_1 increment (mL) (mean score difference)	171 (95% CI: 148, 194)	
SGRQ change (mean score difference)	–2.2 (95% CI: –3.5, –1.0)	
Moderate exacerbation reduction (RR)	0.79 (95% CI: 0.6, 1.04)	
Severe exacerbation reduction (RR)	0.54 (95% CI: 0.27, 1.08)	
	FF/UMEC/VI	**BUD/FOR**
No within-trial exacerbations		
Very severe COPD (FEV_1 percent predicted<30%)	11.0%	16.0%
Severe COPD (FEV_1 percent predicted 30–<50%)	38.9%	45.6%
Moderate COPD (FEV_1 percent predicted 50–<80%)	39.9%	25.4%
With within-trial exacerbations		
Very severe COPD (FEV_1 percent predicted<30%)	1.5%	3.9%
Severe COPD (FEV_1 percent predicted 30–<50%)	5.0%	6.2%
Moderate COPD (FEV_1 percent predicted 50–<80%)	3.2%	2.3%
Deaths	0.4%	0.7%
Mean moderate exacerbations per patient	0.11	0.15
Mean severe exacerbations per patient	0.01	0.03
Mean pneumonia per patient	0.02	0.01

FEV_1: forced expiratory volume in 1 s; ITT: intent to treat; FF: fluticasone furoate; UMEC: umeclidinium; VI: vilanterol; BUD: budesonide; FOR: formoterol; CI: confidence interval; SGRQ: St. George's Respiratory Questionnaire; RR: relative risk.

SUPPLEMENTARY TABLE S5 Summary of analysis assumptions

Detail
The patient population in the FULFIL trial is representative of the target UK COPD population, eligible for treatment with FF/UMEC/VI
Treatment effect for the reduction in exacerbations with FF/UMEC/VI is limited only to the duration of the trial
In the Markov model, exacerbation treatment effect is incorporated indirectly as a result of the shift in FEV_1 percent predicted health-state distribution
Risk of an exacerbation increases with increasing COPD severity (defined by decreasing FEV_1 percent predicted), and is higher for individuals who experienced an exacerbation during the previous year
Of all predicted exacerbations by COPD category, it is assumed that 80% are moderate and 20% are severe
Treatment discontinuation only occurs within the trial period; no further discontinuation was included after the FULFIL trial duration
Mortality rate in the EXT population (follow-up 52 weeks) for FULFIL is unknown, thus it was assumed to occur at the same rate as the ITT population (follow-up 24 weeks)
Pneumonia does not have a direct impact on mortality

UK: United Kingdom; COPD: chronic obstructive pulmonary disease; FF: fluticasone furoate; UMEC: umeclidinium; VI: vilanterol; FEV_1: forced expiratory volume in 1 s; EXT: extension; ITT: intent to treat.

SUPPLEMENTARY TABLE S6 OWSA: pre-specified upper and lower limits for pre-selected parameters, Markov model

Parameter	Base case	Lower limit	Upper limit
Utility - moderate COPD (±20%)	0.787	0.630	0.944
Utility - severe COPD (±20%)	0.750	0.600	0.900
Utility - very severe COPD (±20%)	0.647	0.518	0.776
Pneumonia disutility (±20%)	–0.011	–0.013	–0.009
Exacerbation rates in moderate COPD - no recent exacerbation history (±20%)	0.299	0.239	0.359
Exacerbation rates in moderate COPD - recent exacerbation history (±20%)	0.735	0.588	0.882
Exacerbation rates in very severe COPD - recent exacerbation history (±20%)	1.200	0.960	1.440
Risk of mortality in very severe COPD (±20%)	8.330	6.664	9.996
Discount rates	3.5%	0.0%	5.0%
Cost BUD/FOR (±20%)	£38.00	£30.40	£45.60
Cost FF/UMEC/VI (±20%)	£49.50	£39.60	£59.40
COPD maintenance costs (±20%)			
Moderate COPD	£203	£163	£244
Severe COPD	£677	£541	£812
Very severe COPD	£2090	£1672	£2508

OWSA: one-way sensitivity analysis; COPD: chronic obstructive pulmonary disease; BUD: budesonide; FOR: formoterol; FF: fluticasone furoate; UMEC: umeclidinium; VI: vilanterol.

A recent exacerbation history is defined as an exacerbation occurring within the previous year

SUPPLEMENTARY TABLE S7 Distributions used in the PA

Parameter	Distribution	Justification
Patient characteristics[#]	Normal	Assumed normally distributed in the population
COPD mortality rates	Log normal	
Relative risk[¶]	Log normal	Ratio, additive on log scale
Trial-based model probabilities	Beta/Dirichlet	Constrained on interval of 0 to 1
Regression parameters[+]	Multivariate normal	To capture correlation between normally distributed regression parameters
Other unit costs	Gamma	Constrained on interval of 0 to positive infinity
Resource-use rates	Gamma	Constrained on interval of 0 to positive infinity
Resource-use probabilities	Beta	Constrained on interval of 0 to 1
Health-state utilities	Beta	Constrained on interval 0 and 1
QALY loss	Gamma	Constrained on interval of 0 to positive infinity

PA: probabilistic analysis; COPD: chronic obstructive pulmonary disease; QALY: quality-adjusted life year; FEV_1: forced expiratory volume in 1 s. [#]: age, height; [¶]: COPD mortality, exacerbations; [+]: FEV_1 decline, exacerbations.

SUPPLEMENTARY TABLE S8 Base-case results: EXT (lifetime horizon[#]) population and ITT subgroup populations

	EXT population[#]			Severe COPD or worse[¶]			History of exacerbations[+]		
	FF/UMEC/VI	**BUD/FOR**	**Incremental**	**FF/UMEC/VI**	**BUD/FOR**	**Incremental**	**FF/UMEC/VI**	**BUD/FOR**	**Incremental**
Outcomes									
Predicted cumulative exacerbations									
Moderate exacerbations	5.940	6.007	–0.067	5.751	5.739	0.011	5.797	5.846	–0.049
Severe exacerbations	1.478	1.615	–0.137	1.414	1.421	–0.007	1.435	1.458	–0.022
Any moderate and/or severe exacerbation	7.417	7.622	–0.205	7.165	7.160	0.005	7.232	7.304	–0.072
Total LYs (discounted)	9.643	8.977	0.666	8.409	7.916	0.493	9.725	9.121	0.604
Total QALYs (discounted)	7.054	6.411	0.643	5.982	5.512	0.470	7.242	6.671	0.571
Costs									
Maintenance	£7850	£9190	–£1340	£8871	£9784	–£913	£6296	£7377	–£1081
Moderate exacerbation	£2502	£2544	–£42	£2484	£2492	–£8	£2427	£2475	–£48
Severe exacerbation	£7054	£7552	–£497	£6955	£7008	–£52	£6823	£6989	–£166
Pneumonia	£4285	£3955	£331	£3952	£3637	£315	£4545	£4179	£365
Treatment	£5219	£3545	£1675	£4500	£3075	£1425	£5244	£3568	£1676
Discontinuation	£405	£631	–£227	£370	£587	–£217	£435	£688	–£253
Total costs	£27 316	£27 416	–£101	£27 133	£26 582	£551	£25 769	£25 276	£494
ICER (cost/LY gained)	Dominant	Referent	–	£1118	Referent	–	£817	Referent	–
ICER (cost/QALY gained)	Dominant	Referent	–	£1172	Referent	–	£864	Referent	–

EXT: extension; ITT: intent to treat; COPD: chronic obstructive pulmonary disease; FF: fluticasone furoate; UMEC: umeclidinium; VI: vilanterol; BUD: budesonide; FOR: formoterol; LY: life year; QALY: quality-adjusted life year; ICER: incremental cost-effectiveness ratio; FEV_1: forced expiratory volume in 1 s. [#]: patients treated for up to 52 weeks; [¶]: patients with FEV_1 percent predicted <50% at screening, with 24 weeks' follow-up; [+]: patients with ≥1 severe or ≥2 moderate exacerbations in the 12 months prior to randomisation.