Supplementary Materials

Real-World Comparative Effectiveness Study in Patients with Asthma Initiating Fluticasone Furoate/Vilanterol or Beclometasone Dipropionate/Formoterol Fumarate in General Practice in England

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Supplementary Methods

The data were provided by patients and collected by the National Health Service (NHS) providers as part of their care and support. Secondary care administrative data from Hospital Episode Statistics (HES) were linked to Clinical Practice Research Datalink (CPRD) Aurum. HES contains details on all inpatient admissions (APC), outpatient (OP) appointments and Accident & Emergency (A&E) datasets contain details of all admissions to, or attendances at, English NHS healthcare providers. The 2019 English Index of Multiple Deprivation was used to provide a composite measure of extent of deprivation of each Lower Layer Super Output Area in England (1). Only practices that were eligible for the linkage scheme were included in this study.

Modification to inverse probability of treatment weighting (IPTW) was determined after observing the distribution of the propensity scores (PS) of all the participants. The weights derived from the PS for the IPTW models were used to create a pseudo-population, where the distribution of covariates in the population was independent of treatment assignment. This allowed an unbiased estimation of the average treatment effect in the entire population by accounting for the influence of covariates on the results. Coefficients from each IPTW model were exponentiated to produce more familiar average treatment effect, e.g., rate ratio and hazard ratio. A standardised mean difference (SMD) of less than 10% in the weighted cohort was indicative of adequate balance being achieved between the treatment cohorts, i.e., considered quantitative evidence of relative balance of covariates.

Additional Outcome Analyses

Further secondary outcomes included the time-to-first asthma exacerbation, assessed via Kaplan–Meier (KM) survival analysis and on-treatment analysis. Asthma symptom control was indirectly assessed by capturing the number of short-acting β_2-agonist (SABA) prescriptions prescribed throughout

the follow up period and described as the rate per person per year (PPPY). Rescue medications prescribed at index were not included. Healthcare resource use (HCRU) was reported as the number of events PPPY, including all-cause primary care consultations, all-cause asthma related hospitalisations, all-cause outpatient attendances and all-cause emergency visits. Both intention-to-treat and on-treatment analyses were conducted to compare all-cause HCRU.

Exploratory outcomes included describing a step-up in inhaled corticosteroid long-acting β_2-agonist (ICS/LABA) dosage (considered as a change in category to a higher dosage on the day of the first date of the higher dosage prescription) and seasonal variation in FF/VI prescribing for each month within observation period. These were analysed descriptively using on-treatment analysis and KM survival analysis.

Supplementary Results

Inverse Probability of Treatment Weighting

Perfect predictors (where one category was 0 when split by the index therapy variable i.e., you would predict everyone to be in the other category) were identified within baseline respiratory therapies for the 'short-acting muscarinic antagonist (SAMA)/SABA' category of the primary estimand analysis and in the 'SAMA/SABA' and 'long-acting muscarinic antagonist/LABA' categories for the supplementary estimand 2 analysis, and hence were removed from these IPTW models. Of the remaining covariates, only 'number of all cause outpatient attendances' was not sufficiently balanced for inclusion in the IPTW model, for the primary study outcome (both primary estimand and supplementary estimand 1) as well as the secondary study outcomes of time-to-first exacerbation, rate of severe exacerbations, asthma symptom control and oral corticosteroid (OCS) dose/duration and treatment persistence. The standard mean differences achieved in the weighted cohort showed adequate balance for the majority of

covariates for the primary study outcome supplementary estimand 2, as well as secondary outcomes comparing exacerbations as stratified by index dose and HCRU. An example histogram showing the distribution of propensity scores for both treatment groups for the primary study outcome, primary estimand, is shown in Fig. S1.

Asthma Exacerbations

Time to first overall asthma exacerbation was longer in the fluticasone furoate/vilanterol (FF/VI) cohort relative to the beclomethasone dipropionate/formoterol fumarate (BDP/FOR) cohort for all time points (i.e., 3, 6, 9 and 12 months of follow up) (Table S4). More specifically, patients indexed on FF/VI had a numerically lower hazard of first on-treatment exacerbation than patients indexed on BDP/FOR (hazard ratio [HR], 0.88 [upper 95% confidence interval, 1.13]) although this was not statistically significant (p=0.2046).

The while-on index treatment population indicated a numerically higher annual rate of severe asthma exacerbations in the FF/VI cohort (0.0651) versus the BDP/FOR cohort (0.0243), with a rate ratio of 2.6791 although this was not statistically significant (p=0.9663). The number of events was 49.2 for FF/VI and 192.2 for BDP/FOR, resulting in a rate difference that was magnified by the small number of patients in the FF/VI group (*n* = 2116) versus BDP/FOR group (*n* = 26,881) and use of IPTW methodology.

Patients indexed on FF/VI had a lower rate of asthma exacerbations, when stratified by body mass index <28.5 kg/m^2 or >28.5 kg/m^2 than patients on BDP/FOR (weighted rate ratios <1) (Table S5). For the severe exacerbation comparisons, only the body mass index >28.5 kg/m^2 stratification had a weighted rate ratio <1 (Table S5). None of these comparison results met the prespecified significance threshold.

Among a subgroup of patients indexed to one of two treatment groups: FF/VI or BDP/FOR dry powder inhaler the rate ratio was 0.492 (p<0.013) in patients who continued the treatment un-interrupted for 12 months.

Among a subgroup of patients to have received both an ICS prescription and a SABA prescription in the baseline period the rate ratio for FF/VI versus BDP/FOR was 0.559 ($p<0.031$) in patients who continued the treatment un-interrupted for 12 months (Table S6).

Asthma Symptom Control

Patients indexed on FF/VI were prescribed a higher number SABA cannisters during the follow-up period compared with patients indexed on BDP/FOR (weighted-average treatment effect 2.84 [p=0.9961], upper 95% confidence interval 4.6014).

Total All-cause and Total Asthma-related Healthcare Resource Utilisation

Only average asthma-related length of stay had a coefficient which was indicative of lower healthcare resource use for patients indexed on FF/VI than BDP/FOR; however, it did not meet the prespecified significance threshold (Table S7).

Seasonal Variation in Indexing

The percentage of patients indexed for low-dose treatment of both cohorts was highest in January and February (analysed across the index period from 01 December 2015–28 February 2019). For both the BDP/FOR and FF/VI treatment cohorts, the percentage of patients indexed was high in the winter months and dropped in the spring (Figure S3).

Reference

1. Ministry of Housing CLG. The English Indices of Deprivation 2019 (IoD2019). Available from: https://assets.publishing.service.gov.uk/government/uploads/system/uploads/attachment_data/file/835115/IoD2019_Statistical_Release.pdf.

Supplementary Tables and Figures

Table S1 Estimand overview for analyses of the primary study outcome

Estimand	**Strategies for intercurrent events**		
	While on-index treatment (endpoint measurements considered until time of an ICE)	**On indexed treatment (including data regardless of whether an ICE occurred)**	**Patients who continued index treatment for 12 months without interruption (i.e., only patients not experiencing an ICE)**
Treatment switching from FF/VI to BDP/FOR or vice versa	While on treatment	Treatment policy	Principal stratum
Study treatment discontinuation due to any reason	While on treatment	Treatment policy	Principal stratum
Death by all cause	While alive	While alive	While alive
Loss to follow up due to any reason	While on treatment	While on treatment	Principal stratum
Intake of rescue medication including SABA	Treatment policy	Treatment policy	Treatment policy

BDP/FOR beclometasone dipropionate/formoterol fumarate, *FF/VI* fluticasone furoate/vilanterol, *ICE* intercurrent event, *SABA* short-acting β_2-agonist

Table S2 Estimand overview for analyses of the secondary study outcomes

Variable (study outcome)	Population level summary	ICE	
		Description	Strategy
1. Time-to-first asthma exacerbation 2. Number of severe asthma exacerbation 3. Number of asthma exacerbations stratified by the following dose groups a) Low-medium dose FF/VI and low dose BDP/FOR b) Low-medium dose FF/VI and medium dose BPD/FOR c) Low-medium dose FF/VI and low-medium dose BDP/FOR d) High dose FF/VI and high dose BDP/ FOR 4. Number of SABA canisters during the study period 5. Total HCRU related to asthma and all causes* 6. Dose of oral corticosteroid 7. Indicator variable indicating whether the patient is adherent 8. Time-to-first non-persistence of indexed therapy	1. Hazard ratio of time-to-first asthma exacerbation of FF/VI to BDP/FOR 2. Ratio of severe asthma exacerbation rate of FF/VI to BDP/FOR 3. Ratio of asthma exacerbation rate of FF/VI to BDP/FOR among patients in the following dose groups a) Low-medium dose FF/VI and low dose BDP/FOR b) Low-medium dose FF/VI and medium dose BDP/FOR c) Low-medium dose FF/VI and low-medium dose BDP/FOR d) High dose FF/VI and high dose BDP/ FOR 4. Difference of the frequency of SABA canister per patient year for FF/VI and BDP/FOR 5. Difference of rate of HCRU events (Per Patient Year) for FF/VI and BDP/FOR 6. Difference in cumulative OCS dosage and mean duration of OCS treatment	1) Treatment switching from indexed therapy to any of non-indexed therapy 2) Study treatment discontinuation due to any reason, lost to follow up and death 3) Intake of rescue medication (including SABA)	ICE 1 and 2: while on treatment strategy This strategy has been used since we wanted to estimate the treatment effects when the patients were actively on the indexed treatment, excluding the effects of treatment switch and study treatment discontinuation 3. ICE 3 was addressed using the treatment policy strategy since effect of the rescue medication (including SABA) was considered part of the treatment effect

		between FF/VI and BDP/FOR 7. Proportion of patients showing treatment adherence 8. Hazard ratio of time-to-first non-persistence of FF/VI to BDP/FOR

*A supplementary estimand was constructed for outcome 5 (as mentioned in the above table) using the same estimands attributes above except that the estimand strategy used treatment policy (instead of while on), except for death. The intercurrent event of death was handled using the while alive strategy
BDP/FOR beclometasone dipropionate/formoterol fumarate, *FF/VI* fluticasone furoate/vilanterol, *HCRU* healthcare resource utilisation, *ICE* intercurrent event, *SABA* short-acting β_2-agonist

Table S3 Covariates for potential inclusion in the IPTW model for the while on-index treatment (primary estimand) analysis

	Unweighted			Weighted		
	BDP/FOR	**FF/VI**	**SMD**	**BDP/FOR**	**FF/VI**	**SMD**
Age (in years) at index	48.514	49.503	0.057	48.583	48.475	0.006
Patient sex						
Female	0.626	0.574	0.105	0.622	0.634	0.025
Male	0.374	0.426	0.105	0.378	0.366	0.025
Index year						
2015	0.020	0.024	0.024	0.020	0.019	0.013
2016	0.271	0.254	0.039	0.270	0.251	0.042
2017	0.323	0.293	0.066	0.321	0.329	0.016
2018	0.319	0.354	0.074	0.322	0.334	0.027
2019	0.066	0.075	0.035	0.067	0.067	0.002
Patients' region						
North West	0.241	0.340	0.219	0.249	0.240	0.019
West Midlands	0.203	0.124	0.214	0.197	0.192	0.013
South East Coast	0.180	0.159	0.055	0.178	0.175	0.008
South West	0.127	0.209	0.220	0.133	0.135	0.005
London	0.110	0.077	0.114	0.107	0.109	0.007
Yorkshire and The Humber	0.043	0.050	0.031	0.044	0.042	0.009
East Midlands	0.037	0.005	0.219	0.035	0.037	0.015
North East	0.036	0.012	0.159	0.034	0.046	0.057
East of England	0.023	0.023	0.003	0.023	0.023	0.001
Socioeconomic status						
1st quintile (least deprived)	0.159	0.146	0.036	0.158	0.151	0.020
2nd quintile	0.190	0.173	0.046	0.189	0.180	0.023
3rd quintile	0.186	0.185	0.003	0.186	0.190	0.009
4th quintile	0.205	0.218	0.031	0.206	0.222	0.040
5th quintile (most deprived)	0.259	0.278	0.042	0.261	0.257	0.009
BMI at baseline	29.638	29.712	0.011	29.642	29.572	0.010
Baseline CCI	0.721	0.699	0.031	0.719	0.705	0.020
Comorbidities in 12 months pre-index and at index						
Depression	0.397	0.411	0.030	0.398	0.416	0.036
Anxiety	0.261	0.267	0.014	0.262	0.282	0.046
Obesity	0.207	0.226	0.045	0.209	0.213	0.011
Diabetes	0.107	0.115	0.027	0.108	0.101	0.022
Cataract	0.065	0.063	0.006	0.065	0.065	0.000
Osteoporosis	0.036	0.043	0.034	0.037	0.038	0.005
Chronic rhinosinusitis	0.033	0.039	0.029	0.034	0.033	0.004
IBD	0.014	0.013	0.013	0.014	0.012	0.019
Number of asthma exacerbations at baseline						
0	0.862	0.872	0.030	0.863	0.850	0.037

1	0.111	0.095	0.052	0.110	0.125	0.048
2+	0.027	0.033	0.033	0.027	0.025	0.016
Number of moderate asthma exacerbations at baseline						
0	0.896	0.904	0.028	0.896	0.898	0.005
1	0.084	0.071	0.048	0.083	0.083	0.001
2+	0.020	0.025	0.031	0.020	0.019	0.010
Number of severe asthma exacerbations at baseline						
0	0.962	0.963	0.006	0.962	0.949	0.065
1	0.035	0.034	0.004	0.035	0.049	0.072
2+	0.003	0.003	0.009	0.003	0.002	0.018
Baseline respiratory therapies						
ICS	0.745	0.639	0.231	0.737	0.747	0.023
OCS	0.308	0.303	0.010	0.307	0.305	0.005
LTRA	0.037	0.041	0.018	0.038	0.035	0.013
LAMA	0.001	0.006	0.099	0.001	0.003	0.048
SAMA	0.006	0.007	0.013	0.006	0.006	0.001
Number of all cause consultations at baseline	13.881	14.006	0.009	13.885	13.817	0.005
Number of all cause outpatient attendances in baseline	3.606	3.325	0.036	3.587	7.906	0.157
Number of all cause inpatient attendances in baseline	0.473	0.433	0.027	0.470	0.485	0.010
Number of asthma related inpatient attendances in baseline	0.262	0.257	0.006	0.262	0.283	0.024
Number of all cause A&E visits in baseline	0.473	0.464	0.007	0.472	0.562	0.072
Number of asthma related A&E visits in baseline	0.087	0.073	0.038	0.086	0.105	0.051

A&E Accident & Emergency, *BDP/FOR* beclometasone dipropionate/formoterol fumarate, *CCI* Charlson Comorbidity Index, *FF/VI* fluticasone furoate/vilanterol, *GERD* gastroesophageal reflux disease, *IBD* inflammatory bowel disease, *IPTW* inverse probability of treatment weighting, *SABA* short-acting β_2-agonist, *SMD* standard mean difference

Table S4 Time to first asthma exacerbation (*while on-treatment analysis*)*

	Time (months)	At risk, *n*	Fail, *n*	Survivor function
BDP/FOR	0	28,656	560	1.000
	3	9197	183	0.970
	6	5392	90	0.945
	9	3888	60	0.927
	12	3103	4	0.911
FF/VI	0	2240	36	1.000
	3	970	21	0.980
	6	636	17	0.955
	9	449	3	0.924
	12	366	1	0.917

*Endpoint measurements considered until time of an ICE (ICEs include treatment switching from FF/VI to BDP/FOR or vice versa, loss to follow-up and study treatment discontinuation due to any reason)
BDP/FOR beclometasone dipropionate/formoterol fumarate, *CI* confidence interval, *FF/VI* fluticasone furoate/vilanterol, *ICE* intercurrent event

Table S5 Weighted average treatment effects for the rate of overall and severe asthma exacerbations, stratified by BMI above or below median

		Rate ratio	P>z	Upper 95% CI	Prespecified significance threshold met?
Overall exacerbations	BMI <28.5 kg/m^2	0.8617	0.2600	1.35	N
	BMI >28.5 kg/m^2	0.7807	0.0730	1.03	N
Severe exacerbations	BMI <28.5 kg/m^2	1.2725	0.6616	3.29	N
	BMI >28.5 kg/m^2	0.9802	0.4823	2.05	N

BMI body mass index, *CI* confidence interval, *N* no

Table S6 Comparative effectiveness in subgroup of patients who were on both ICS and SABA at baseline (weighted population)

	BDP/FOR	FF/VI
While on index treatment (Primary Estimand)	N=23197	N=1599
Number of exacerbations during follow-up	1049	79
Rate (PPPD)	0.00039	0.00036
Rate ratio (P value)	0.92 (p=0.35)	
Supplementary Estimand 1	N=21580	N=1469
Number of exacerbations during follow-up	2432	180
Rate (PPPD)	0.0003	0.0003
Rate ratio (P value)	1.08 (p=0.70)	
Supplementary Estimand 2 (uninterrupted index treatment for 12 months)	N=2794	N=257
Number of exacerbations during follow-up	301	15
Rate (PPPD)	0.0003	0.0002
Rate Ratio (P value)	0.559 (p=0.031)	
Time to first exacerbation	N=21492	N=1442
	HR 0.86 [p=0.19]	
Risk of treatment discontinuation	N=19323	N=1283
	HR 0.76 [p<0.0001]	
Mean number of OCS prescription PPPY	N=21643	N=1483
	0.34	0.37
Rate ratio for the cumulative OCS dosage (P value)	N=23197	N=1599
	0.69 (p=0.11)	

BDP/FOR beclometasone dipropionate/formoterol fumarate, *FF/VI* fluticasone furoate/vilanterol, *HR* hazard ratio, *ICS* inhaled corticosteroid, *OCS* oral corticosteroid, *PPPD* per person per day, *PPPY per person per year, SABA* short-acting β_2-agonist

Table S7 Weighted average treatment effect for all-cause and asthma-related HCRU

	Coefficient	P>z	Upper 95% CI	Prespecified significance threshold met?
Number of all-cause consultations	0.68	0.9989	1.02	N
Number of asthma-related consultations	0.04	0.8175	0.12	N
Number of respiratory referrals	0.001	0.6227	0.007	N
Number of all cause outpatient attendances	3.51	0.8688	8.67	N
Number of asthma related outpatient attendances	0.03	0.7201	0.12	N
Number of all cause inpatient attendances	0.03	0.9502	0.06	N
Number of asthma related inpatient attendances	0.02	0.8942	0.04	N
Average all cause length of stay	0.02	0.5295	0.45	N
Average asthma-related length of stay	-0.45	0.0692	0.05	N
Cumulative all cause length of stay	0.15	0.9728	0.28	N
Cumulative asthma related length of stay	0.09	0.9383	0.19	N
Number of all cause A&E visits	0.04	0.9845	0.07	N
Number of asthma related A&E visits	0.01	0.9631	0.02	N

A&E Accident & Emergency, *CI* confidence interval, *HCRU* healthcare resource use, *N* no

Primary Objective (primary estimand)

Univariable regressions

	p-value
Index year (BDP/FOR)	< 0.001
Patient's ethnicity	.2724
Medical Research Council (MRC) dyspnoea scale score	.077
Baseline CCI (BDP/FOR)	.0217
Comorbidities prior to (and incl.) index (BDP/FOR) - Anxiety	< 0.001
Comorbidities prior to (and incl.) index (BDP/FOR) - Atopy	.9053
Comorbidities prior to (and incl.) index (BDP/FOR) - Apnoea	.4502
Comorbidities prior to (and incl.) index (BDP/FOR) - Cataract	.0029
Comorbidities prior to (and incl.) index (BDP/FOR) - Depression	< 0.001
Comorbidities prior to (and incl.) index (BDP/FOR) - Diabetes	.0205
Comorbidities prior to (and incl.) index (BDP/FOR) - GERD	.3318
Comorbidities prior to (and incl.) index (BDP/FOR) - Glaucoma	.9939
Comorbidities prior to (and incl.) index (BDP/FOR) - Osteoporosis	.0016
Comorbidities prior to (and incl.) index (BDP/FOR) - Obesity	< 0.001
Comorbidities prior to (and incl.) index (BDP/FOR) - Chronic rhinosinusitis	< 0.001
Comorbidities prior to (and incl.) index (BDP/FOR) - IBD	.0319
Time (years) since initial diagnosis (BDP/FOR)	.7876
AEC (10^9 cells/L)(BDP/FOR)	.4272
GINA Treatment step in the three months prior to index (BDP/FOR)	.2195
Number of asthma exacerbations in baseline (BDP/FOR)	< 0.001
Number of mod asthma exacerbations in baseline (BDP/FOR)	< 0.001
Number of sev asthma exacerbations in baseline (BDP/FOR)	< 0.001
Baseline respiratory therapies - ICS	.0077
Baseline respiratory therapies - LABA	.625
Baseline respiratory therapies - LAMA	.108
Baseline respiratory therapies - LAMA/LAMA	.0413
Baseline respiratory therapies - LTRA	< 0.001
Baseline respiratory therapies - Other controller medications	.1999
Baseline respiratory therapies - SABA	.1305
Baseline respiratory therapies - SAMA	< 0.001
Baseline respiratory therapies - SAMA/SABA	.0511
Baseline respiratory therapies - OCS	< 0.001
Number of SABA in baseline (BDP/FOR)	.3728
Number of all cause consultations in baseline (BDP/FOR)	< 0.001
Number of all cause outpatient attendances in baseline (BDP/FOR)	< 0.001
Number of all cause inpatient attendances in baseline (BDP/FOR)	< 0.001
Number of asthma related inpatient attendances in baseline (BDP/FOR)	< 0.001
Number of all cause A&E visits in baseline (BDP/FOR)	< 0.001
Number of asthma related A&E visits in baseline (BDP/FOR)	< 0.001

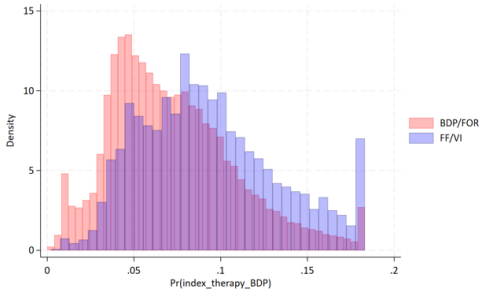
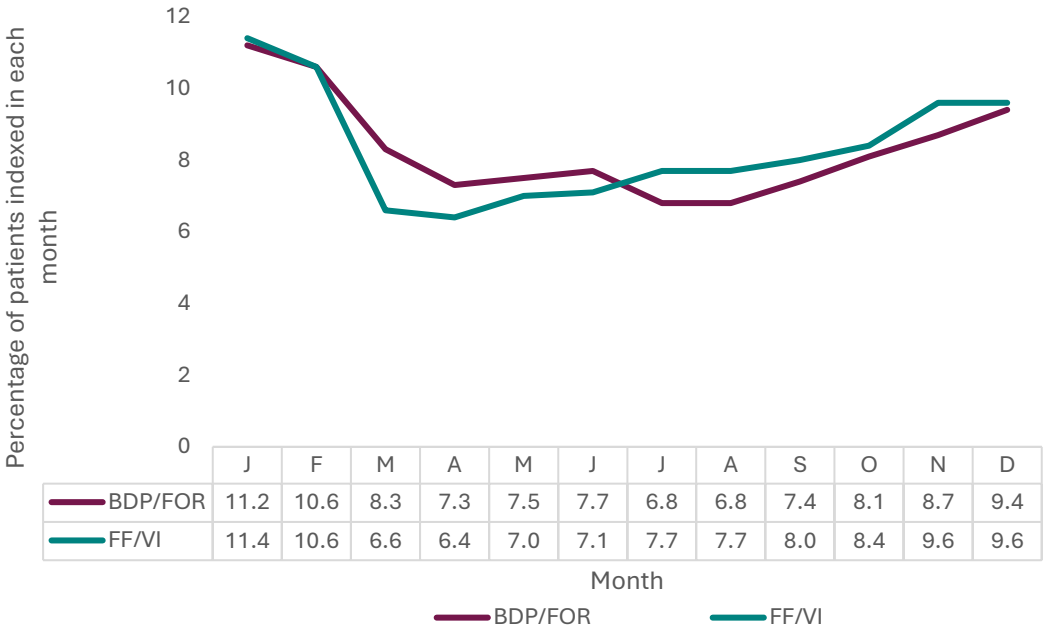


Fig. S1 Distribution of propensity scores for both treatment groups for the primary study outcome, primary estimand. Orange shading indicates SMDs of <0.1, i.e., covariates having sufficient balance between treatment groups. *A&E* Accident and Emergency, *AEC* absolute eosinophil count, *BDP/FOR* beclometasone dipropionate/formoterol fumarate, *CCI* Charlson Comorbidity Index, *GERD* gastroesophageal reflux disease, *GINA* Global Initiative for Asthma, *FF/VI* fluticasone furoate/vilanterol, *IBD* irritable bowel disease, *ICS* inhaled corticosteroid, *LABA* long-acting β_2-agonist, *LAMA* long-acting muscarinic antagonist, *LTRA* leukotriene receptor antagonist, *OCS* oral corticosteroid, *SABA* short-acting β_2-agonist, *SAMA* short-acting muscarinic antagonist, *SMD* standard mean difference

Fig. S2 SMDs for covariates for the potential inclusion in the IPTW model for the comparison of FF/VI versus BDP/FOR. *A&E* Accident & Emergency, *BMI* body mass index, *CCI* Charlson Comorbidity Index,

GERD gastroesophageal reflux disease, *GINA* Global Initiative for Asthma, *ICS* inhaled corticosteroid, *IPTW* inverse probability of treatment weighting, *SMD* standard mean difference, *SABA* short-acting β_2-agonist, *SES* socioeconomic status



	J	F	M	A	M	J	J	A	S	O	N	D
BDP/FOR	11.2	10.6	8.3	7.3	7.5	7.7	6.8	6.8	7.4	8.1	8.7	9.4
FF/VI	11.4	10.6	6.6	6.4	7.0	7.1	7.7	7.7	8.0	8.4	9.6	9.6

Fig. S3 Percentage of patients indexed on low-dose treatment in each calendar month. *BDP/FOR* beclometasone dipropionate/formoterol fumarate, *FF/VI* fluticasone furoate/vilanterol

1. Ministry of Housing CLG. The English Indices of Deprivation 2019 (IoD2019). 2019 [Available from: https://assets.publishing.service.gov.uk/government/uploads/system/uploads/attachment_data/file/835115/IoD2019_Statistical_Release.pdf.