Supplementary Materials

Real-world Comparative Effectiveness in Patients with Asthma Newly Initiating Fluticasone Furoate/Vilanterol or Budesonide/Formoterol: A United Kingdom General Practice Cohort Study

Ashley Woodcock,[1] John Blakey,[2,3] Arnaud Bourdin,[4] Giorgio Walter Canonica, [5,6] Christian Domingo,[7] Alexander Ford,[8] Rosie Hulme,[8] Theo Tritton,[8] Ines Palomares,[9] Sanchayita Sadhu,[10] Arunangshu Biswas,[10] Manish Verma[11]

[1]Division of Infection, Immunity and Respiratory Medicine, Manchester Academic Health Sciences Centre, The University of Manchester and Manchester University NHS Foundation Trust, Greater Manchester, UK; [2]Respiratory Medicine, Sir Charles Gairdner Hospital, Perth, WA, Australia; [3]Medical School, Curtin University, Perth, WA, Australia; [4]Department of Respiratory Diseases, INSERM U1046, University of Montpellier, Montpellier, France; [5]Department of Biomedical Sciences, Humanitas University, Milan, Italy; [6]Personalized Medicine Asthma & Allergy Unit, IRCCS Humanitas Research Hospital, Milan, Italy; [7]Department of Pulmonary Medicine, Parc Taulí Hospital Universitari, Institut d'Investigació i Innovació Parc Taulí (I3PT-CERCA), Universitat Autònoma de Barcelona, Sabadell, Spain; [8]Adelphi Real World, Bollington, Cheshire, UK; [9]VEO-Value Evidence & Outcomes – Europe, Specialty & General Medicines TAs, GSK, Brentford, Middlesex, UK; [10]Biostatistics, GSK, Bangalore, India; [11]Global Medical Affairs, General Medicine, GSK, Mumbai, India

Corresponding author: Manish Verma; GSK House, Dr. Annie Besant Road, Worli, Mumbai 400030, India; Email: manish.8.verma@gsk.com

SUPPLEMENTARY METHODS

Clinical Practice Research Datalink Aurum captures diagnoses, symptoms, prescriptions, referrals, and tests for over 20 million patients as of May 2022 (1), while the Hospital Episode Statistics Admitted Patient Care and Accident & Emergency datasets contain details of all admissions to, or attendances at English National Health Service 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 (2). Only practices that were eligible for the linkage scheme were included in this study.

Additional outcome analyses

In addition to those reported in the main manuscript, the following secondary study outcomes were also assessed:

- Time-to-first asthma exacerbation was measured using Kaplan–Meier (KM) survival analysis and on-treatment analysis.
- Asthma symptom control considered the mean number of short-acting β_2-agonist (SABA) canisters per patient per year (PPPY), excluding rescue medications prescribed at index.
- All-cause healthcare resource utilisation (HCRU) included primary care consultations, asthma-related hospitalisations, outpatient attendances and emergency visits, and was reported as the number of events PPPY. Both intention-to-treat and on-treatment analyses were conducted for HCRU.

Exploratory outcomes were to compare rate of overall and severe asthma exacerbations in patients newly initiating fluticasone furoate/vilanterol (FF/VI) versus budesonide/formoterol (BUD/FOR), stratified by body mass index (BMI) above or below study median; to determine seasonal variation in prescribing trends for low-dose FF/VI and low-dose BUD/FOR and time from index to inhaled corticosteroid (ICS) dose step-up among all low-dose indexed patients.

SUPPLEMENTARY RESULTS

Inverse probability of treatment weighting (IPTW)

The 'short-acting muscarinic antagonist/SABA' category for baseline respiratory therapies was removed due to being a perfect predictor (where one category was 0 when split by the index therapy variable i.e. you would predict everyone to be in the other category). Of the remaining covariates, 'number of all cause outpatient attendances' was not sufficiently balanced at baseline for inclusion in the IPTW model, for the primary study outcome (primary estimand), the secondary study outcome of time-to-first exacerbation, rate of severe exacerbations or cumulative oral corticosteroid (OCS) dose. Similarly, 'number of all-cause Accident and Emergency (A&E) visits' was not adequately balanced for inclusion in the IPTW model for the primary study outcome (primary estimand) or secondary outcome of time-to-first exacerbation. 'Severe asthma exacerbations at baseline' was also not included in the time-to-first exacerbation IPTW model while 'number of all cause inpatient visits' was not included in the IPTW model for the mean number of OCS prescriptions. The standard mean differences achieved in the weighted cohort showed adequate balance for the majority of covariates for the primary study outcome (both supplementary estimands 1 and 2), as well as secondary outcomes comparing exacerbations as stratified by index dose, asthma symptom control, HCRU and treatment persistence. An example histogram showing the distribution of propensity scores for both treatment groups for the primary study outcome, primary estimand, is shown in **Figure S1**.

Asthma exacerbations

Time to first overall asthma exacerbation was longer in the FF/VI cohort relative to the BUD/FOR cohort for all time points (i.e. 3, 6, 9 and 12 months of follow up) (**Table S4**). There was a numerically lower hazard of first on-treatment exacerbation in the FF/VI group than the BUD/FOR group, with a hazard ratio (HR) of 0.800 (upper 95% confidence interval, 1.06), however this was not significant (P = 0.958).

In the while on-treatment population there was a numerically higher annual rate of severe asthma exacerbations in the FF/VI group (0.0955) than in the BUD/FOR group (0.0294), with a rate ratio of 3.25,

however this was not statistically significant (*P* = 0.9807). The number of severe exacerbation events was 72 for the FF/VI group and 46 for the BUD/FOR group, resulting in a rate difference that was magnified by the small number of patients in the FF/VI group (*n* = 2119) versus BUD/FOR group (*n* = 7163) and use of IPTW methodology.

For both body mass index (BMI) strata, the overall asthma exacerbation rate ratio was <1, indicating that patients receiving FF/VI had a lower rate of exacerbations than patients receiving BUD/FOR, however only the result for patients with BMI >28.5 kg/m^2 was significant (upper 95% confidence interval 0.95, *P* = 0.031) (**Table S5**). For severe exacerbations, the BMI >28.5 kg/m^2 stratum had a rate ratio <1, however this did not meet the prespecified significance threshold.

Among a subgroup of patients indexed to one of two treatment groups: FF/VI or BUD/FOR dry powder inhaler (DPI), the rate ratio was 0.35 (*P* < 0.001) 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 BUD/FOR was 0.3 (*P* = 0.0013) in patients who continued the treatment un-interrupted for 12 months (**Table S6**).

Asthma symptom control

The average treatment effect was 3.3526 (*P* = 0.9538), indicating a higher mean number of short-acting β_2-agonist canisters prescribed for patients in the fluticasone furoate/vilanterol (FF/VI) group than the budesonide/formoterol (BUD/FOR) group. This result did not meet the prespecified significance threshold.

Total all-cause and total asthma-related healthcare resource utilisation

Average all-cause and asthma-related length of stay and cumulative asthma-related length of stay had a coefficient indicative of lower healthcare resource use for patients indexed on FF/VI than BUD/FOR;

however, only cumulative all-cause length of stay and asthma-related length of stay met the prespecified significance threshold (**Table S7**).

Seasonal variation in indexing

For both low-dose treatment groups (analysed across the index period from 01 December 2015–28 February 2019), the greatest percentage of patients were indexed in January, with overall indexing peaking in the winter months and decreasing during spring (**Fig. S3**).

REFERENCES

1. Clinical Practice Research Datalink CPRD Aurum. March 2022. Release Notes 2022. Available from: https://www.cprd.com/cprd-aurum-march-2022-dataset .
2. 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 BUD/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

BUD/FOR, budesonide/formoterol; 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 (Endpoint)	Population level summary	ICE	
		Description	Strategy
1. Time-to-first asthma exacerbation 2. Number of severe asthma exacerbations 3. Number of asthma exacerbations stratified by the following dose groups a) Low-to-medium dose FF/VI and low-dose BUD/FOR b) Low-to-medium dose FF/VI and medium-dose BUD/FOR c) Low-to--medium dose FF/VI and low–to–medium dose BUD/FOR d) High-dose FF/VI and high-dose BUD/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 BUD/FOR 2. Ratio of severe asthma exacerbation rate of FF/VI to BUD/FOR 3. Ratio of asthma exacerbation rate of FF/VI to BUDP/FOR among patients in the following dose groups a) Low-to-medium dose FF/VI and low-dose BUD/FOR b) Low-to-medium dose FF/VI and medium-dose BUD/FOR c) Low-to-medium dose FF/VI and low-to-medium dose BUD/FOR d) High-dose FF/VI and high-dose BUD/ FOR 4. Difference of the frequency of SABA canister per patient year for FF/VI and BUD/FOR 5. Difference of rate of HCRU events (Per Patient Year) for FF/VI and BUD/FOR 6. Difference in cumulative OCS dosage and mean duration of OCS treatment between FF/VI and BUD/FOR 7. Proportion of patients showing treatment adherence 8. Hazard ratio of time-to-first non-persistence of FF/VI to BUD/FOR	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

*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. BUD/FOR, budesonide/formoterol; 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		
	BUD/FOR	**FF/VI**	**SMD**	**BUD/FOR**	**FF/VI**	**SMD**
Age (in years) at index	45.112	49.146	0.238	46.007	45.230	0.046
Patient sex						
Male	0.380	0.431	0.105	0.391	0.382	0.019
Female	0.620	0.569	0.105	0.609	0.618	0.019
Patient socioeconomic status (SES)						
1st quintile (least deprived)	0.170	0.149	0.059	0.165	0.157	0.020
2nd quintile	0.185	0.175	0.026	0.182	0.181	0.002
3rd quintile	0.198	0.185	0.033	0.195	0.203	0.019
4th quintile	0.230	0.215	0.037	0.228	0.235	0.015
5th quintile (most deprived)	0.216	0.276	0.139	0.230	0.224	0.014
BMI at baseline	29.053	29.609	0.080	29.190	29.199	0.001
Comorbidities pre-index and at index						
Anxiety	0.220	0.265	0.106	0.230	0.246	0.036
Depression	0.344	0.411	0.139	0.359	0.365	0.011
Osteoporosis	0.028	0.040	0.064	0.031	0.031	0.001
Obesity	0.181	0.217	0.091	0.190	0.201	0.028
Chronic rhinosinusitis	0.026	0.035	0.052	0.028	0.026	0.013
GINA Treatment step in the three months pre-index						
Steps 1 or 2	0.295	0.337	0.091	0.304	0.285	0.043
Step 2	0.024	0.027	0.021	0.025	0.021	0.026
Step 3	0.194	0.255	0.146	0.207	0.209	0.004
Step 4	0.083	0.123	0.132	0.092	0.086	0.021
Step 5	0.001	0.000	0.009	0.001	0.000	0.017
No treatment	0.403	0.257	0.315	0.371	0.399	0.057
Number of asthma exacerbations at baseline						
0						
1	0.077	0.078	0.004	0.077	0.092	0.054
2+	0.021	0.026	0.031	0.022	0.022	0.001
Number of moderate asthma exacerbations at baseline						
0						
1	0.053	0.053	0.002	0.053	0.050	0.014
2+	0.014	0.019	0.036	0.016	0.014	0.014
Number of severe asthma exacerbations at baseline						
0						
1	0.030	0.032	0.014	0.031	0.047	0.087
2+	0.004	0.003	0.023	0.004	0.006	0.028
Baseline respiratory therapies						

LTRA	0.038	0.043	0.029	0.039	0.035	0.020
Other controller medications	0.002	0.002	0.015	0.002	0.002	0.006
SAMA	0.003	0.004	0.015	0.004	0.003	0.014
OCS	0.191	0.246	0.133	0.204	0.203	0.002
Number of all-cause consultations at baseline	11.348	13.678	0.178	11.868	12.095	0.018
Number of all-cause outpatient attendances at baseline	3.445	3.249	0.024	3.427	7.661	0.160
Number of all-cause inpatient attendances at baseline	0.435	0.418	0.009	0.433	0.525	0.048
Number of asthma-related inpatient attendances at baseline	0.252	0.249	0.003	0.253	0.322	0.060
Number of all-cause A&E visits at baseline	0.437	0.447	0.008	0.442	0.572	0.106
Number of asthma-related A&E visits at baseline	0.081	0.069	0.033	0.079	0.111	0.084

A&E, Accident and Emergency; BMI, body mass index; BUD/FOR, budesonide/formoterol; FF/VI, fluticasone furoate/vilanterol; GINA, Global Initiative for Asthma; ICS, inhaled corticosteroid; IPTW, inverse probability of treatment weighting; LTRA, leukotriene receptor antagonist; OCS, oral corticosteroid; SAMA, short-acting muscarinic antagonist; SES, socioeconomic status, SMD, standard mean difference; Q, quartile.

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

	Time (months)	At risk, *n*	Fail, *n*	Survivor function
BUD/FOR	0	7704	134	1.000
	3	1652	30	0.971
	6	911	19	0.949
	9	628	8	0.926
	12	486	1	0.912
FF/VI	0	2283	33	1.000
	3	840	19	0.980
	6	533	9	0.953
	9	368	2	0.934
	12	311	1	0.929

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

Table S5. Average rate of overall and severe asthma exacerbations stratified by BMI group

		Rate ratio	*P* > z	Upper 95% CI
Overall exacerbations	BMI <28.5 kg/m^2	0.6660	0.0734	1.06
	BMI >28.5 kg/m^2	0.6624	0.031	0.95
Severe exacerbations	BMI <28.5 kg/m^2	1.9473	0.8277	6.21
	BMI >28.5 kg/m^2	0.9933	0.4946	2.24

BMI, body mass index; CI, confidence interval.

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

	BUD/FOR	**FF/VI**
While on index treatment (Primary Estimand)	*N* = 3798	*N* = 1474
Number of exacerbations during follow-up	163	70
Rate (PPPD)	0.0005	0.0003
Rate ratio (*P* value)	0.75 (*P* = 0.10)	
Supplementary Estimand 1	*N* = 3497	*N* = 1368
Number of exacerbations during follow-up	443	161
Rate (PPPD)	0.0004	0.0003
Rate ratio (*P* value)	0.93 (*P* = 0.32)	
Supplementary Estimand 2 (uninterrupted index treatment for 12 months)	*N* = 300	*N* = 245
Number of exacerbations during follow-up	68	17
Rate (PPPD)	0.0006	0.0002
Rate ratio (*P* value)	0.3 (*P* = 0.0013)	
Time to first exacerbation	*N* = 4107	*N* = 1570
	HR 0.84 [*P* = 0.17]	
Risk of treatment discontinuation	*N* = 3328	*N* = 1282
	HR 0.69 [P < 0.0001]	
Mean number of OCS prescription PPPY	*N* = 3497	*N* = 1368
	0.49	0.3
Rate ratio for the cumulative OCS dosage (P value)	*N* = 3497	*N* = 1368
	0.507 (*P* = 0.043)	

BUD/FOR, budesonide/formoterol; 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 (average treatment effect)	***P* > z**	**Upper 95% CI**	**Prespecified significance threshold met?**
Number of all-cause consultations	1.09	1.00	1.42	N
Number of asthma-related consultations	0.14	0.9987	0.22	N
Number of respiratory referrals	-0.0009	0.3789	0.004	N
Number of all-cause outpatient attendances	0.52	0.9096	1.15	N
Number of asthma-related outpatient attendances	0.05	0.9915	0.09	N
Number of all-cause inpatient attendances	0.05	0.9964	0.09	N
Number of asthma-related inpatient attendances	0.04	0.9940	0.06	N
Average all-cause length of stay	-0.40	0.0749	0.06	N
Average asthma-related length of stay	-0.38	0.1159	0.14	N
Cumulative all-cause length of stay	-4.94	<0.0001	-4.53	Y
Cumulative asthma-related length of stay	-2.98	<0.0001	-2.75	Y
Number of all-cause A&E visits	0.04	0.9959	0.06	N
Number of asthma-related A&E visits	0.01	0.9497	0.02	N

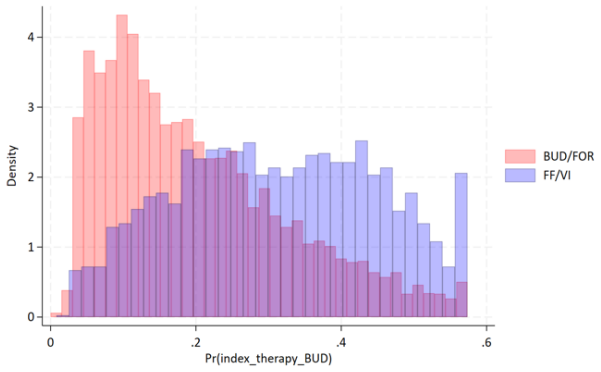
A&E, Accident and Emergency; CI, confidence interval; HCRU, healthcare resource utilisation; N, no; Y, yes.

Fig. S1. Distribution of propensity scores for both treatment groups for the primary study outcome, primary estimand

Primary Objective (primary estimand)

Univariable regressions

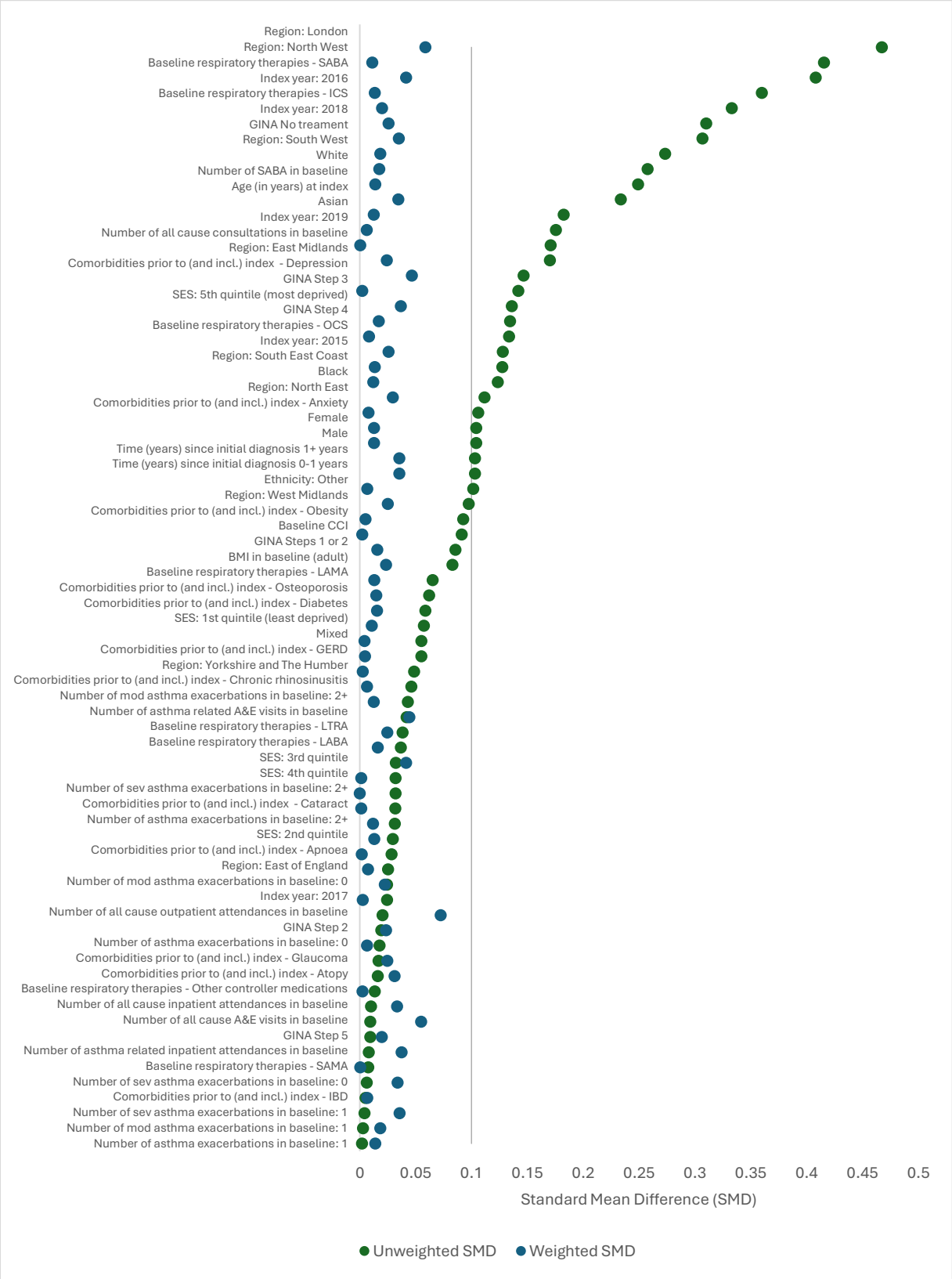
	p-value
Index year (BUD/FOR)	.3942
Patient's ethnicity	.1712
Medical Research Council (MRC) dyspnoea scale score	.8947
Baseline CCI (BUD/FOR)	.2173
Comorbidities prior to (and incl.) index (BUD/FOR) - Anxiety	.0248
Comorbidities prior to (and incl.) index (BUD/FOR) - Atopy	.5405
Comorbidities prior to (and incl.) index (BUD/FOR) - Apnoea	.8112
Comorbidities prior to (and incl.) index (BUD/FOR) - Cataract	.861
Comorbidities prior to (and incl.) index (BUD/FOR) - Depression	< 0.001
Comorbidities prior to (and incl.) index (BUD/FOR) - Diabetes	.6353
Comorbidities prior to (and incl.) index (BUD/FOR) - GERD	.1106
Comorbidities prior to (and incl.) index (BUD/FOR) - Glaucoma	.4203
Comorbidities prior to (and incl.) index (BUD/FOR) - Osteoporosis	.0036
Comorbidities prior to (and incl.) index (BUD/FOR) - Obesity	< 0.001
Comorbidities prior to (and incl.) index (BUD/FOR) - Chronic rhinosinusitis	.0234
Comorbidities prior to (and incl.) index (BUD/FOR) - IBD	.3309
Time (years) since initial diagnosis (BUD/FOR)	.1092
AEC (10^9 cells/L)(BUD/FOR)	.8226
GINA Treatment step in the three months prior to index (BUD/FOR)	< 0.001
Number of asthma exacerbations in baseline (BUD/FOR)	< 0.001
Number of mod asthma exacerbations in baseline (BUD/FOR)	< 0.001
Number of sev asthma exacerbations in baseline (BUD/FOR)	< 0.001
Baseline respiratory therapies - ICS	.4891
Baseline respiratory therapies - LABA	.3794
Baseline respiratory therapies - LAMA	.6476
Baseline respiratory therapies - LAMA/LAMA	.983
Baseline respiratory therapies - LTRA	< 0.001
Baseline respiratory therapies - Other controller medications	.0115
Baseline respiratory therapies - SABA	.3006
Baseline respiratory therapies - SAMA	.0629
Baseline respiratory therapies - SAMA/SABA	< 0.001
Baseline respiratory therapies - OCS	< 0.001
Number of SABA in baseline (BUD/FOR)	.9124
Number of all cause consultations in baseline (BUD/FOR)	< 0.001
Number of all cause outpatient attendances in baseline (BUD/FOR)	< 0.001
Number of all cause inpatient attendances in baseline (BUD/FOR)	< 0.001
Number of asthma related inpatient attendances in baseline (BUD/FOR)	< 0.001
Number of all cause A&E visits in baseline (BUD/FOR)	< 0.001
Number of asthma related A&E visits in baseline (BUD/FOR)	< 0.001



Orange shading indicates SMDs of <0.1, i.e., covariates having sufficient balance between treatment groups.

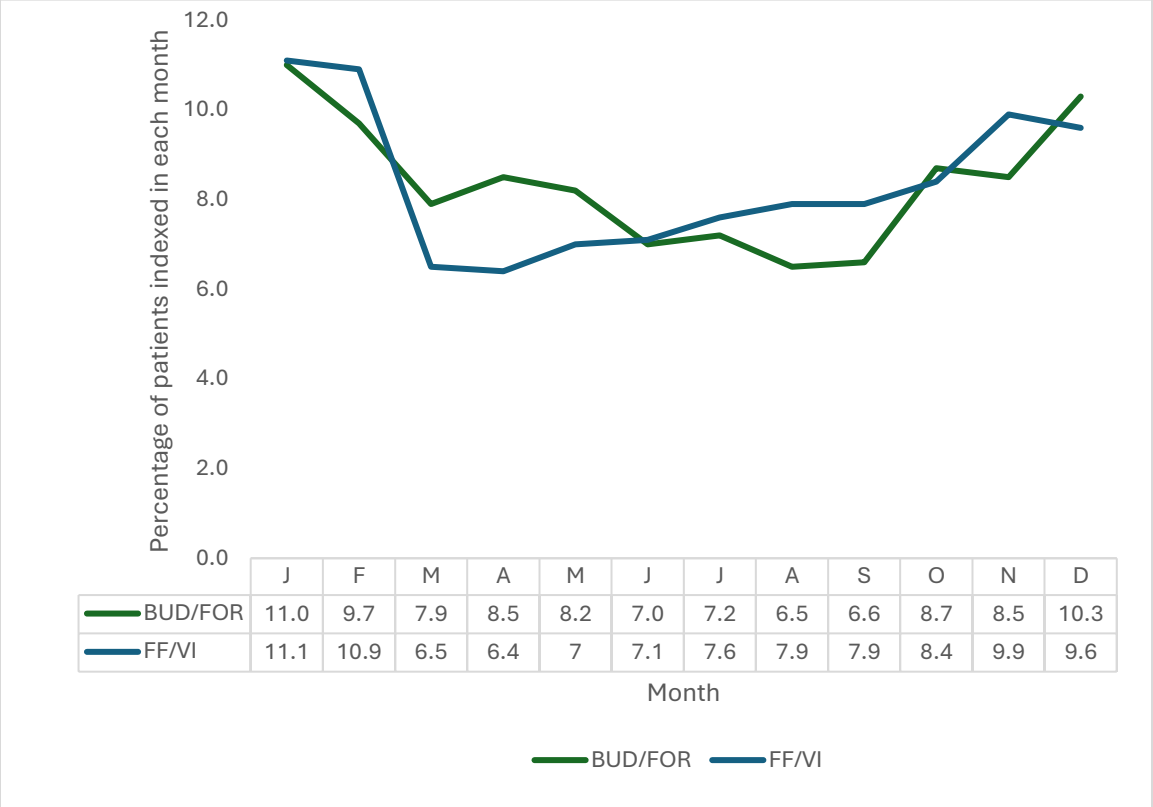
A&E, Accident and Emergency; AEC, absolute eosinophil count; BUD/FOR, budesonide/formoterol; CCI, Charlson Comorbidity Index; GERD, gastroesophageal reflux disease; GINA, Global Initiative for Asthma; FF/VI, fluticasone furoate/vilanterol; IBD, irritable bowel disease; ICS, inhaled corticosteroid; LABA, 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 BUD/FOR



A&E, Accident and Emergency; BMI, body mass index; CCI, Charlson Comorbidity Index; GERD, gastro-esophageal 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.

Fig. S3 Percentage of patients indexed on low-dose treatment in each calendar month



	J	F	M	A	M	J	J	A	S	O	N	D
BUD/FOR	11.0	9.7	7.9	8.5	8.2	7.0	7.2	6.5	6.6	8.7	8.5	10.3
FF/VI	11.1	10.9	6.5	6.4	7	7.1	7.6	7.9	7.9	8.4	9.9	9.6

BUD/FOR, budesonide/formoterol; FF/VI, fluticasone furoate/vilanterol.