SUPPLEMENTARY MATERIAL

Supplemental Methods

The anonymized patient data for this matched cohort study were drawn from two United Kingdom (UK) primary care electronic datasets used extensively for pharmacoepidemiologic research and described in detail in prior publications: the General Practice Research Database (GPRD), now part of the Clinical Practice Research Datalink (CPRD), and the Optimum Patient Care Research Database (OPCRD) [1–5]. All individuals in the UK have their electronic medical records housed at their primary care practice, where information from secondary care and hospitalizations is also aggregated. Several sources cite the reliability of prescribing data in the GPRD (now CPRD), considered one of the leading primary care datasets in the world [3–5]. While we do not have validation of prescribing data in the OPCRD, in the UK, the pharmacist must dispense as predefined by the doctor, which suggests that prescribing data in the OPCRD are similarly reliable.

The study was conducted according to standards recommended for observational research [6, 7], including an *a priori* analysis plan, use of well-maintained databases, study registration with commitment to publish, and an independent steering committee.

We defined the presence of asthma as at least two prescriptions for asthma during a baseline year, no recorded diagnosis of any chronic respiratory disease other than asthma, and the step-up in asthma therapy. While we did not require a coded diagnosis for asthma, 96–98% of patients in each cohort had a database Read code for asthma diagnosis.

Allowed ICS during the baseline year included beclomethasone, budesonide, or fluticasone administered by pressurized metered-dose inhaler (pMDI) or breath-actuated pMDI (BAI); patients prescribed an ICS/LABA combination inhaler were excluded.

Information on asthma-related resource use during the baseline and outcome years was extracted from the databases. We calculated total asthma-related direct costs in 2011 pounds sterling (£) from the UK National Health Service (NHS) perspective using unit costs obtained from UK national data sources [8–10], summarized in Supplementary Table S1, and including the costs of asthma-related drugs and devices (inhaled corticosteroid [ICS], long-acting β_2-agonist [LABA], fixed-dose combination [FDC] ICS/LABA inhalers, short-acting β_2-agonist [SABA], leukotriene receptor antagonist [LTRA], theophylline, and oral corticosteroids), primary care consultations, and hospitalizations. In addition, we included antibiotics dispensed for lower respiratory tract infection, because in practice asthma exacerbations can be confused with respiratory infection and treated with antibiotics, and the capture of antibiotic prescribing has been recommended by expert group consensus for assessing asthma healthcare utilization and costs [11, 12]. Costs of asthma-related primary care consultations and hospital attendance (inpatient, outpatient, and emergency department [ED]) in the database included the costs of all events with a lower respiratory code (all asthma codes and lower respiratory tract infection codes).

Our composite effectiveness measure, risk-domain asthma control, included all of the following: 1) no asthma-related hospital attendance or admission, ED attendance, out-of-hours attendance,

or outpatient hospital attendance; and 2) no prescription for an acute course of oral corticosteroids; and 3) no primary care consultation for lower respiratory tract infection. As reported in previous publications [13–16], this measure therefore captured the absence of asthma exacerbations (items 1 and 2, per expert group consensus [17]) and the absence of consultation for lower respiratory tract infection (considered potentially a marker of an asthma exacerbation [11–12], as noted above).

Details of Matching

We conducted matched cohort analyses, using two-way matching for the three cohorts, to compare outcomes for age- and sex-matched patients with similar asthma severity and baseline asthma control. Patients were matched sequentially on sex, age (±5 years), and the following markers of asthma severity and asthma control during the baseline year: the last ICS daily dose prescribed before the index date (categorized as 1–50, 51–100, 101–200, 201–300, 301–400, and >400 μg/day), risk-domain asthma control status (controlled or not controlled; defined above), the mean daily dose of SABA (categorized as 0, 1–200, 201–400, and >400 μg/day), and the number of primary care consultations for asthma with no oral corticosteroid prescription (0, 1, or ≥2). The latter criterion captured clinical attendance for asthma when patients were not experiencing an exacerbation, while the risk-domain asthma control measure captured clinical attendance with an associated oral corticosteroid prescription.

Statistical Analyses

The costs of treatments were compared via the differences in mean asthma-related healthcare costs per patient per year during the outcome period, both unadjusted and adjusted for potential confounders. We report the arithmetic mean asthma-related healthcare costs as the preferred statistic, even though distributions were skewed (see Results), as this is the most conservative way to account for costs from a health system perspective; moreover, means can be multiplied by a target population to estimate total costs and (sensitivity analyses being performed by making means vary around their confidence intervals) are therefore of most use to policy-makers and providers. Two-way comparisons of summary costs between matched cohorts were carried out using conditional logistic regression. Generalized linear models with a log link and gamma distribution were used to estimate adjusted mean asthma-related healthcare costs per year during the outcome period. Differences in adjusted mean costs are reported with 95% confidence intervals (CIs) found by bootstrapping methods, using 1000 random samples taken, with replacement, from the dataset. The bootstrapping technique is a non-parametric method for constructing CIs and has the advantage that the intervals obtained do not depend on parametric assumptions of the sampling distribution of the costs [18].

The effectiveness of treatments for matched cohorts were compared via the difference in the proportion of patients with asthma control during the outcome year, both unadjusted and adjusted for potential confounders. Differences between treatment cohorts at baseline considered possibly important (p <0.10), and baseline variables predictive (p <0.05) of asthma control in multivariable analyses, were examined for co-linearity and clinical importance to select those used as potential confounders (Table S2). Adjusted proportions were estimated using generalized linear models with a logit link and binomial distribution. Proportions and differences in

proportions of patients with asthma control were reported with 95% CIs found by bootstrapping methods, using the 1000 random samples taken, with replacement, from the dataset.

The two-way differences in total asthma-related costs and proportions of patients with asthma control for the 1000 random samples were displayed graphically on cost-effectiveness planes. When the point estimates for differences in costs and effectiveness indicated a trade-off between treatments (Fig. 1, quadrants I and III), we calculated an incremental cost-effectiveness ratio (ICER) as the ratio of the difference in total asthma-related healthcare costs per patient per year (namely, the incremental cost) to the difference in proportions of patients with asthma control (namely, the incremental gain in effectiveness). Double counting may have occurred in this analysis since the numerator included the difference in costs of asthma-related resource utilization and the risk-domain asthma control effectiveness measure was a function of asthma-related events. Therefore, the ICER does not represent the extra amount of money needed to achieve an additional controlled patient. The cost estimates in the ICERs are interpreted as the willingness-to-pay over and above the cost to achieve an additional controlled patient. In other words, ICERs in this case represent the monetary value of the intangible benefit to patients or society beyond the cost to achieve an additional controlled patient over the outcome period [19]. When all the replicated data were in one quadrant of the cost-effectiveness plane, the ICER was reported with a 95% CI found by bootstrapping methods.

Confidence intervals for ICERs cannot be calculated when the spread of the replicated data covers more than one quadrant of the cost-effectiveness plane because the ICER is interpreted differently across the four quadrants [20]. Therefore, when replicated data covered more than one quadrant, we produced a cost-effectiveness acceptability curve (CEAC) in conjunction with the ICER. The CEAC depicts the proportion of the distribution of cost and effectiveness differences (based on the bootstrap samples) that lie below a given price line as the price line varies from 0 to infinity [21]. This price line is a measure of a decision-maker's willingness to pay for increased effectiveness [22].

Supplemental Results

Comparison 1: Asthma Step-Up Therapy Using an Increased Dose of Extrafine-Particle ICS vs. Add-On LABA by FDC ICS/LABA Inhaler

During the baseline year, asthma-related resource use was similar in the two cohorts (Table S3). However, total baseline asthma-related healthcare costs were slightly but significantly higher in the ICS step-up cohort compared with the FDC ICS/LABA cohort (mean, £126 vs. £118; P <0.001) because of higher ICS inhaler costs: during the baseline year a higher proportion of patients in the ICS step-up cohort, as compared with the FDC ICS/LABA cohort, were prescribed extrafine-particle beclomethasone, a more expensive option, and a lower proportion were prescribed standard fine-particle beclomethasone, a less expensive option (data not shown). When ICS inhalers were excluded, there were no significant differences between cohorts in baseline asthma-related drug costs or total asthma-related healthcare costs (mean, £83 vs. £82; P = 0.85; Table S3).

Comparison 2: Asthma Step-Up Therapy Using an Increased Dose of Extrafine-Particle ICS vs.

Add-On LABA by Separate Inhaler

During the baseline year, the costs of ICS inhalers were higher in the ICS step-up cohort than the separate ICS+LABA cohort (Table S3), again because a higher proportion of patients in the ICS step-up cohort were prescribed extrafine-particle beclomethasone. Instead, the mean cost of primary care asthma consultations was higher in the separate ICS+LABA cohort, and total baseline asthma-related healthcare costs were similar in the two cohorts, both with and without ICS costs (Table S3).

Comparison 3: Asthma Step-Up Therapy Using Add-On LABA by FDC ICS/LABA Inhaler vs. Add-On LABA by Separate Inhaler

After matching, there were 7529 patients in the FDC ICS/LABA cohort and 15,058 patients in the separate ICS+LABA cohort. The percentage of patients meeting the risk-domain asthma control measure increased from 58% at baseline to 72% and 68% in FDC ICS/LABA and separate ICS+LABA cohorts, respectively. The full results for this two-way comparison are reported in Tables S4–S6 and Figure S1. In brief, during the outcome year, patients adding a separate LABA had significantly lower mean baseline-adjusted asthma-related healthcare costs (mean £377; 95% CI, £372–£381) compared with patients adding LABA as a FDC with ICS (mean £395; £388–£402). When combined with the adjusted effectiveness results—using asthma control as the effectiveness measure—there was a 100% probability that prescribing an FDC ICS/LABA inhaler would be more costly but also more effective than adding a separate LABA inhaler (a trade-off). The ICER was £382 (95% CI, £195–£639).

Outcome Year Costs for Patients According to Asthma Control and Treatment Cohort

In all cohorts uncontrolled asthma was associated with increased costs (Table S7). The magnitude of the difference was slightly smaller but still highly significant and economically important when ICS-related costs were included in the calculations.

Supplemental Discussion

The main drivers of asthma-related direct costs are prescription medications and healthcare resource use associated with asthma exacerbations, particularly hospital admissions. The relative proportions of costs attributed to medications versus hospitalizations vary from study to study, as do the proportions of direct and indirect costs making up the total of asthma-related costs [23–26]. In the UK healthcare setting, we found that drug costs varied widely from 29% (for the separate ICS+LABA cohort in comparison 2) to 58% (for the ICS step-up cohorts) to 79% of total direct costs (for the FDC ICS/LABA cohort in comparison 3). Thus, a larger reduction in exacerbations would be needed to offset higher medication costs for the latter two step-up options.

Patients in the ICS step-up cohort were prescribed a mean of 7.1 SABA inhalers during the outcome year as compared with 5.4 and 6.5 inhalers in the FDC ICS/LABA and separate ICS+LABA cohorts, respectively. This was an expected finding because patients receiving LABA will use less SABA. In the companion effectiveness study [13], we found a median

difference between ICS step-up and FDC ICS/LABA cohorts in SABA of 55 μg/day, which represents an additional two-thirds of a puff of β_2-agonist use per day.

There was an imbalance in the numbers of unmatched patients, which we addressed by matching in a 1:2 ratio for comparisons 2 and 3 to maximize both cohort sizes and the number of matched groupings, and thus the power of statistical tests. This approach served to minimize the lack of comparability between cohorts because of size; nonetheless, this could remain a possibility. Treatment cohorts were matched according to several criteria reflecting baseline asthma severity and control, as determined (and limited) by the measures available in the datasets: the last prescribed ICS dose was used as a proxy for severity, while the baseline risk-domain asthma control measure captured the absence of severe exacerbations, and symptom control was captured by matching on SABA dose.

References

1. Clinical Practice Research Datalink. Available at: http://www.cprd.com/home/. Accessed February 16, 2016.
2. Optimum Patient Care Research Database (OPCRD). Available at: http://optimumpatientcare.org/opcrd/. Accessed February 16, 2016.
3. Walley T, Mantgani A. The UK General Practice Research Database. Lancet. 1997;350:1097–9.
4. Jick SS, Kaye JA, Vasilakis-Scaramozza C, et al. Validity of the General Practice Research Database. Pharmacotherapy. 2003;23:686–9.
5. Tannen RL, Weiner MG, Xie D. Use of primary care electronic medical record database in drug efficacy research on cardiovascular outcomes: comparison of database and randomised controlled trial findings. BMJ 2009;338:b81.
6. Berger ML, Mamdani M, Atkins D, et al. Good research practices for comparative effectiveness research: defining, reporting and interpreting nonrandomized studies of treatment effects using secondary data sources: the ISPOR Good Research Practices for Retrospective Database Analysis Task Force Report--Part I. Value Health. 2009;12(8):1044–52.
7. Roche N, Reddel H, Martin R, et al. Quality standards for real-world research. Focus on observational database studies of comparative effectiveness. Ann Am Thorac Soc. 2014;11 Suppl 2:S99–S104.
8. Personal Social Services Research Unit. Unit Costs of Health and Social Care 2007. 2007. Available at: http://www.pssru.ac.uk/project-pages/unit-costs/2007/index.php. Accessed February 16, 2016.
9. Department of Health. NHS reference costs 2010–11. Crown. 2011. Available at: http://www.dh.gov.uk/en/Publicationsandstatistics/Publications/PublicationsPolicyAndGuidance/DH_131140. Accessed February 16, 2016.
10. Prescription Services, National Health Service (NHS) Business Services Authority. Dictionary of Medicines and Devices (dm+d) database. Prescription Services,. 2012. Available at: http://dmd.medicines.org.uk. Accessed February 16, 2016.
11. Akinbami LJ, Sullivan SD, Campbell JD, et al. Asthma outcomes: healthcare utilization and costs. J Allergy Clin Immunol. 2012;129(3 Suppl):S49–64.
12. Vanderweil SG, Tsai CL, Pelletier AJ, et al. Inappropriate use of antibiotics for acute

asthma in United States emergency departments. Acad Emerg Med. 2008;15:736–43.
13. Israel E, Roche N, Martin RJ, et al. Increased dose of inhaled corticosteroid vs. add-on long-acting beta-agonist for step-up therapy in asthma. Ann Am Thorac Soc. 2015;12:798–806.
14. Colice G, Martin RJ, Israel E, et al. Asthma outcomes and costs of therapy with extrafine beclomethasone and fluticasone. J Allergy Clin Immunol. 2013;132:45–54.
15. Barnes N, Price D, Colice G, et al. Asthma control with extrafine-particle hydrofluoroalkane-beclometasone vs. large-particle chlorofluorocarbon-beclometasone: a real-world observational study. Clin Exp Allergy. 2011;41:1521–32.
16. Price D, Martin RJ, Barnes N, et al. Prescribing practices and asthma control with hydrofluoroalkane-beclomethasone and fluticasone: a real-world observational study. J Allergy Clin Immunol. 2010;126:511–8 e1–10.
17. Reddel HK, Taylor DR, Bateman ED, et al. An official American Thoracic Society/European Respiratory Society statement: asthma control and exacerbations: standardizing endpoints for clinical asthma trials and clinical practice. Am J Respir Crit Care Med. 2009;180:59–99.
18. Briggs AH, Wonderling DE, Mooney CZ. Pulling cost-effectiveness analysis up by its bootstraps: a non-parametric approach to confidence interval estimation. Health Econ. 1997;6:327–40.
19. Mullins CD. Double counting and the reporting of cost per event avoided. Clin Ther. 2006;28(4):602–3.
20. O'Brien BJ, Briggs AH. Analysis of uncertainty in health care cost-effectiveness studies: an introduction to statistical issues and methods. Stat Methods Med Res. 2002;11:455–68.
21. van Hout BA, Al MJ, Gordon GS, et al. Costs, effects and C/E-ratios alongside a clinical trial. Health Econ. 1994;3:309–19.
22. Lothgren M, Zethraeus N. Definition, interpretation and calculation of cost-effectiveness acceptability curves. Health Econ. 2000;9:623–30.
23. Bahadori K, Doyle-Waters MM, Marra C, et al. Economic burden of asthma: a systematic review. BMC Pulm Med. 2009;9:24.
24. Cisternas MG, Blanc PD, Yen IH, et al. A comprehensive study of the direct and indirect costs of adult asthma. J Allergy Clin Immunol. 2003;111:1212–8.
25. Barnett SB, Nurmagambetov TA. Costs of asthma in the United States: 2002–2007. J Allergy Clin Immunol. 2011;127:145–52.
26. Sullivan PW, Ghushchyan VH, Slejko JF, et al. The burden of adult asthma in the United States: evidence from the Medical Expenditure Panel Survey. J Allergy Clin Immunol. 2011;127:363–9 e1–3.

Table S1. Unit costs for healthcare resources used in the study (2011 pounds sterling, £).

Health care resource type	Unit costs (2011 £)	Source
Primary care consultation[a]	36.00	Personal Social Services Research Unit (PSSRU) report: Unit costs of Health and Social Care 2011 [8]
Hospital attendance:		
Respiratory outpatient consultation[b]	135.00	
Respiratory inpatient admissions[c]	768.34	National Health Service Reference Costs 2010–11 [9]
Respiratory emergency room visit	139.76	
Drugs[d]	--	Official source of British National Formulary drug prices (http://dmd.medicines.org.uk) [10]

[a] Primary care (general practice) consultation cost was based on an average duration visit (11.7 minutes).

[b] Outpatient department attendance was priced as a "respiratory medicine face-to-face contact."

[c] Inpatient admission was priced as a "non-elective admission" using the weighted average of Healthcare Resource Group (HRG) codes DZ15.

[d] Unit costs for drugs and devices were obtained from the UK National Health Service Business Services Authority (NHSBSA) Prescription service via the dm+d service.

Table S2. Potential confounders considered.

Potential confounders examined at (or closest to) the relevant index date: • Age • Marker of socioeconomic status • Sex • Height • Weight • Lung function, in terms of peak flow readings • Smoking status • ICS dose at the index date
Potential confounders examined regardless of when they occurred relative to the index date: • Date of first asthma, other respiratory, and allergy-related diagnosis (where known) • Other respiratory or other confounding diagnoses, including: rhinitis, smoking history, COPD, GERD, and cardiac disease. Comorbidities were expressed using the Charlson Comorbidity Index (CCI).
Potential confounders examined in the year before the index date: • All asthma, allergy, and other respiratory treatments • The total ICS dose prescribed • Number of primary care consultations for asthma or other respiratory illness • Mean daily SABA dose • Proxy composite measure for asthma control • Number of hospital outpatient department (OPD) attendances where asthma was recorded as the reason for referral • Number of asthma or possibly respiratory-related hospitalizations (a non-specific hospitalization code and an asthma / respiratory code within a 1-week window) • Number of prescriptions for any antibiotic where the reason for the prescription is either a lower or upper respiratory tract infection • Other medications that might interfere with asthma control, e.g., beta blockers, non-steroidal anti-inflammatory drugs, and acetaminophen • Total healthcare and component costs (for cost-effectiveness comparisons).

COPD Chronic obstructive pulmonary disease, *GERD* Gastroesophageal reflux disease, *ICS* Inhaled corticosteroid, *SABA* Short-acting β_2-agonist.

Table S3. Comparisons 1 and 2: Baseline demographic and matching characteristics and asthma-related resource use and costs for the matched cohorts.

Characteristic	ICS step-up vs. FDC ICS/LABA			ICS step-up vs. separate ICS+LABA		
	ICS dose step-up (*N* = 3036)	FDC ICS/LABA (*N* = 3036)	*P* value[a]	ICS dose step-up (*N* = 3232)	Separate ICS+LABA (*N* = 6464)	*P* value[a]
Female sex, n (%)[b]	1811 (59.7)	1811 (59.7)	n/a	1959 (60.6)	3918 (60.6)	n/a
Age at index date, mean (SD)[b]	42.7 (16.4)	42.6 (16.5)	0.013	42.4 (16.4)	42.3 (16.4)	0.072
Non-smokers 61–80 y, n (%)	417 (13.7)	429 (14.1)	0.27	426 (13.2)	826 (12.8)	0.18
Risk-domain asthma control, n (%)[b]	1978 (65.2)	1978 (65.2)	n/a	2094 (64.8)	4188 (64.8)	n/a
Mean daily SABA dose, n (%)[b]						
0 µg/d	145 (4.8)	145 (4.8)	n/a	131 (4.1)	262 (4.1)	n/a
1–200 µg/d	1241 (40.9)	1241 (40.9)		1318 (40.8)	2636 (40.8)	
201–400 µg/d	754 (24.8)	754 (24.8)		814 (25.2)	1628 (25.2)	
>400 µg/d	896 (29.5)	896 (29.5)		969 (30.0)	1938 (30.0)	
Last ICS dose before index date, mean (SD) µg/d[b]	199 (44)	200 (51)	n/a	193 (49)	194 (54)	n/a
Asthma consultation/no severe exacerbation, n (%)[b]						
0	1122 (37.0)	1122 (37.0)	n/a	1157 (35.8)	2314 (35.8)	n/a
1	1063 (35.0)	1063 (35.0)		1136 (35.1)	2272 (35.1)	
≥2	851 (28.0)	851 (28.0)		939 (29.1)	1878 (29.1)	
Smoking status, n (%)[c]						
Current smoker	592 (22.5)	575 (20.6)	<0.001	625 (22.3)	1165 (21.5)	<0.001
Ex-smoker	477 (18.2)	516 (18.4)		503 (18.0)	956 (17.7)	
Non-smoker	1559 (59.3)	1706 (61.0)		1673 (59.7)	3291 (60.8)	
Baseline asthma-related[d] resource use:						
ICS inhalers, mean (SD)	4.1 (3.8)	4.1 (3.7)	0.97	4.1 (3.7)	4.4 (3.8)	<0.001
Median (IQR)	3 (2–6)	3 (2–6)		3 (2–6)	3 (2–6)	
Primary care asthma consultations, mean (SD)	1.2 (1.3)	1.3 (1.3)	0.22	1.3 (1.2)	1.4 (1.3)	<0.001
Median (IQR)	1 (0–2)	1 (0–2)		1 (0–2)	1 (0–2)	
Asthma-related hospitalizations, mean (SD)	0.0 (0.3)	0.1 (0.3)	0.13	0.0 (0.2)	0.0 (0.2)	0.13
Baseline asthma-related[d] costs (£):						
Cost of ICS inhalers, mean (SD)	44 (47)	36 (38)	<0.001	43 (46)	38 (39)	<0.001
Total asthma drug costs including ICS, mean (SD)	72 (76)	63 (61)	<0.001	71 (75)	65 (67)	<0.001
Total asthma drug costs excluding ICS, mean (SD)	28 (46)	27 (39)	0.44	28 (45)	28 (43)	0.33
Cost of primary care asthma consultations, mean (SD)	45 (45)	46 (47)	0.22	46 (45)	49 (48)	<0.001
Cost of asthma-related hospitalizations, mean (SD)	10 (78)	9 (63)	0.78	10 (79)	9 (74)	0.51
Total asthma-related healthcare costs, mean (SD)	126 (124)	118 (105)	<0.001	127 (123)	123 (117)	0.083
Total asthma-related costs excluding ICS, mean (SD)	83 (107)	82 (92)	0.85	84 (108)	85 (103)	0.48

Note: Baseline data and effectiveness results for the ICS step-up vs. FDC ICS/LABA comparison have been published [13]. Mean costs are reported, despite substantially skewed distributions, because mean values can be multiplied by a target population to estimate total costs and thus are of most interest for policy-makers and providers.

[a] Conditional logistic regression.

[b] Matching criterion (matching for age was ±5 years).

[c] Recorded smoking data were available for 2628 (86.6%) and 2797 (92.1%) of patients in extrafine-particle ICS step-up and FDC ICS/LABA combination cohorts and for 2801 (86.7%) and 5412 (83.7%) in extrafine-particle ICS step-up and separate ICS+LABA cohorts, respectively.

[d] *Asthma-related* includes all database events coded for asthma and lower respiratory tract infection.

FDC Fixed-dose combination, *ICS* Inhaled corticosteroid, *IQR* Interquartile range, *LABA* Long-acting β_2-agonist, *SABA* Short-acting β_2-agonist, *SD* Standard deviation.

Table S4. Comparison 3: Baseline demographic and matching characteristics and asthma-related resource use and costs for the matched cohorts.

Characteristic	FDC ICS/LABA vs. separate ICS+LABA		
	FDC ICS/LABA (*N* = 7529)	**Separate ICS+LABA (*N* = 15,058)**	***p* Value[a]**
Female sex, n (%)[b]	4689 (62.3)	9378 (62.3)	n/a
Age at index date, mean (SD)[b]	42.1 (16.1)	42.2 (15.9)	0.031
Non-smokers 61–80 y, n (%)	878 (11.7)	1694 (11.2)	
Risk-domain asthma control, n (%)[b]	4400 (58.4)	8800 (58.4)	n/a
Mean daily SABA dose, n (%)[b]			
0 μg/d	208 (2.8)	416 (2.8)	n/a
1–200 μg/d	2563 (34.0)	5126 (34.0)	
201–400 μg/d	2022 (26.9)	4044 (26.9)	
>400 μg/d	2736 (36.3)	5472 (36.3)	
Last ICS dose before index date, mean (SD) μg/d[b]	295 (187)	293 (185)	n/a
Asthma consultation/no severe exacerbation, n (%)[b]			
0	2351 (31.2)	4702 (31.2)	n/a
1	2542 (33.8)	5084 (33.8)	
≥2			
Smoking status, n (%)[c]			
Current smoker	1564 (22.7)	2,992 (24.0)	<0.001
Ex-smoker	1255 (18.2)	2190 (17.6)	
Non-smoker	4076 (59.1)	7283 (58.4)	
Baseline asthma-related[d] resource use:			
ICS inhalers, mean (SD)	4.7 (4.0)	5.0 (4.3)	<0.001
Median (IQR)	4 (2–6)	4 (2–7)	
Primary care asthma consultations, mean (SD)	1.5 (1.4)	1.6 (1.5)	<0.001
Median (IQR)	1 (0–2)	1 (1–2)	
Asthma-related hospitalizations, mean (SD)	0.1 (0.3)	0.0 (0.2)	<0.001
Baseline asthma-related[§] costs (£)[e]:			
Cost of ICS inhalers, mean (SD)	58 (77)	57 (73)	0.91
Total asthma drug costs including ICS, mean (SD)	91 (102)	89 (97)	0.14
Total asthma drug costs excluding ICS, mean (SD)	33.1 (48)	32 (46)	0.008
Cost of primary care asthma consultations, mean (SD)	54 (50)	58 (55)	<0.001
Cost of asthma-related hospitalizations, mean (SD)	13 (85)	12 (85)	0.19
Total asthma-related healthcare costs, mean (SD)	158 (147)	158 (146)	0.81
Total asthma-related costs excluding ICS, mean (SD)	100 (115)	101 (117)	0.72

[a] Conditional logistic regression.

[b] Matching criterion (matching for age was ±5 years).

[c] Recorded smoking data were available for 6895 (91.6%) and 12,465 (82.8%) in FDC ICS/LABA and separate ICS+LABA cohorts, respectively.

[d] *Asthma-related* includes all database events coded for asthma and lower respiratory tract infection.

[e] Mean costs are reported, despite substantially skewed distributions, because mean values can be multiplied by a target population to estimate total costs and thus are of most interest for policy-

makers and providers.

FDC Fixed-dose combination, *ICS* Inhaled corticosteroid, *IQR* Interquartile range, *LABA* Long-acting β_2-agonist, *SD* Standard deviation.

Table S5. Comparison 3: Mean asthma-related drug prescriptions and unadjusted costs during the outcome year for patients prescribed add-on LABA by FDC ICS/LABA inhaler or separate inhaler. [a]

	Mean (SD) resource use			Mean (SD) resource cost, £		
Asthma-related resource[‡]	**FDC ICS/LABA (*N* = 7529)**	**Separate ICS+LABA (*N* = 15,058)**	***p* Value[b]**	**FDC ICS/LABA (*N* = 7529)**	**Separate ICS+LABA (*N* = 15,058)**	***p* Value[b]**
ICS inhalers	0.8 (2.4)	5.0 (4.4)	<0.001	10 (38)	62 (83)	<0.001
FDC ICS/LABA inhalers	9.8 (7.7)	1.7 (4.8)	<0.001	315 (285)	64 (188)	<0.001
Long-acting β_2-agonist inhalers	0.1 (3.0)	6.2 (22.7)	<0.001	3 (27)	165 (159)	<0.001
Short-acting β_2-agonist inhalers	6.1 (7.3)	7.2 (8.3)	<0.001	24 (49)	27 (58)	<0.001
Leukotriene receptor antagonist prescriptions	0.3 (1.3)	0.2 (1.3)	0.012	9 (45)	7 (41)	0.005
Antibiotic prescriptions	1.1 (1.8)	1.1 (1.7)	0.91	5 (43)	4 (18)	0.016
Oral corticosteroid prescriptions	0.4 (1.1)	0.5 (1.2)	<0.001	2 (7)	2 (8)	<0.001
Total mean medication costs	--	--	--	368 (311)	332 (278)	<0.001
Total mean medication costs, excluding ICS	--	--	--	42 (87)	205 (187)	<0.001
Primary care asthma consultations	1.0 (1.3)	1.3 (1.7)	<0.001	36 (48)	45 (60)	<0.001
Total asthma-related hospitalizations	0.1 (0.3)	0.1 (0.3)	0.18	11 (83)	14 (100)	<0.001
Asthma-related inpatient	0.0 (0.1)	0.0 (0.1)	0.34	5 (71)	8 (88)	0.015
Asthma-related outpatient	0.0 (0.1)	0.0 (0.1)	0.015	5 (37)	6 (37)	0.76
Asthma-related emergency department visit	0.0 (0.3)	0.0 (0.3)	0.76	1 (11)	1 (12)	0.38
Total asthma-related primary and secondary care, including ICS costs	--	--	--	415 (344)	391 (322)	<0.001
Total asthma-related primary and secondary care, excluding ICS costs	--	--	--	89 (141)	265 (229)	<0.001

[a] Mean values are reported, despite substantially skewed distributions, because mean values can be multiplied by a target population to estimate total costs and thus are of most interest for policy-makers and providers.

[b] Conditional logistic regression.

[c] *Asthma-related* includes all database events coded for asthma and lower respiratory tract infection.

FDC Fixed-dose combination, *ICS* Inhaled corticosteroid, *LABA* Long-acting β_2-agonist.

Table S6. Comparison 3: Incremental cost-effectiveness analysis: add-on LABA by FDC ICS/LABA inhaler vs. separate inhaler.

	FDC ICS/LABA (*N* = 7529)	**Separate ICS+LABA (*N* = 15,058)**
Risk-domain asthma control, adjusted[a] OR (95% CI)	1.0	0.94 (0.92–0.95)
Risk-domain asthma control, adjusted[a] proportion (95% CI)[c]	0.72 (0.71–0.73)	0.67 (0.66–0.68)
Difference relative to FDC ICS/LABA (95% CI)[c]	--	-0.05 (-0.04 to -0.06)
Adjusted[b] mean asthma-related healthcare costs per patient per year (95% CI)[c]	£395 (£388–£402)	£377 (£372–£381)
Difference relative to FDC ICS/LABA (95% CI)[c]		-£18 (-£26 to -£10)
Cost-effectiveness ratio (ICER)	Trade Off – separate LABA less costly but less effective £382 (£195–£639)	

[a] Adjusted for: smoking status (current smoker/ ex-smoker/ nonsmoker/ not specified), number of primary care consultations, and ICS medication possession ratio.

[b] Adjusted for baseline asthma-related healthcare costs.

[c] Confidence intervals determined using bootstrapping methods with 1000 random samples.

CI Confidence interval, *FDC* Fixed-dose combination, *ICER* Incremental cost-effectiveness ratio, *ICS* Inhaled corticosteroid, *LABA* Long-acting β_2-agonist, *OR* Odds ratio.

Table S7. Asthma-related healthcare resource costs during the outcome year, according to asthma control and treatment cohort.

	Comparison 1: Mean (SD) cost, £[a]					
	ICS step-up (*N* = 3036)			FDC ICS/LABA (*N* = 3036)		
Asthma-related resource[c]	**Controlled (*n* = 2278)**	**Not controlled (*n* = 758)**	***P* value**[b]	**Controlled (*n* = 2275)**	**Not controlled (*n* = 761)**	***P* value**[b]
Total asthma-related healthcare costs	180 (175)	320 (314)	<0.001	302 (214)	431 (330)	<0.001
Total asthma -related costs excluding ICS	67 (94)	159 (211)	<0.001	60 (87)	144 (179)	<0.001
	Comparison 2: Mean (SD) cost, £[a]					
	ICS step-up (N = 3232)			**Separate ICS+LABA (N = 6464)**		
	Controlled (*n* = 2436)	**Not controlled (*n* = 796)**	***P* value**[b]	**Controlled (*n* = 4573)**	**Not controlled (*n* = 1891)**	***P* value**[b]
Total asthma -related healthcare costs	182 (176)	316 (309)	<0.001	303 (239)	446 (350)	<0.001
Total asthma -related costs excluding ICS	68 (95)	156 (204)	<0.001	216 (174)	317 (262)	<0.001
	Comparison 3: Mean (SD) cost, £[a]					
	FDC ICS/LABA (*N* = 7529)			**Separate ICS+LABA (*N* = 15,058)**		
	Controlled (*N* = 5408)	**Not controlled (*N* = 2121)**	***P* value**[b]	**Controlled (*N* = 10,170)**	**Not controlled (*N* = 4888)**	***P* value**[b]
Total asthma-related healthcare costs	366 (285)	539 (439)	<0.001	337 (267)	503 (392)	<0.001
Total asthma -related costs excluding ICS	64 (85)	153 (217)	<0.001	228 (187)	340 (284)	<0.001

[a] Mean values are reported, despite substantially skewed distributions, because mean values can be multiplied by a target population to estimate total costs and thus are of most interest for policy-makers and providers.

[b] Mann-Whitney test.

[c] *Asthma-related* includes all database events coded for asthma and lower respiratory tract infection.

FDC Fixed-dose combination, *ICS* Inhaled corticosteroid, *LABA* Long-acting β_2-agonist, *SD* Standard deviation.

Fig. S1 Comparison 3: Cost-effectiveness plane showing the spread of the estimated differences in cost and effectiveness, based on 1000 replicated samples, between the FDC ICS/LABA cohort and the separate ICS+LABA cohort. There is a 100% probability that stepping up asthma therapy by adding a separate LABA is less costly but less effective compared with switching to FDC ICS/LABA therapy (a trade-off). *FDC* Fixed-dose combination, *ICS* Inhaled corticosteroid, *LABA* Long-acting β_2-agonist.