Supplementary Methods

Matching

Matching was done using the most relevant confounders of the association between the treatment (BF Spiromax vs. BF Turbuhaler) and the primary outcome (achieving risk domain control [RDC]).

Confounders that are unbalanced between the treatment arms can bias associations of interest between the treatment arms and the outcomes. Potential confounders were identified based on a combination of baseline imbalance, bias potential in relation to the primary outcome, as well as expert judgement. Through this, the most relevant confounders were used for direct matching. As it is necessary to limit the number of variables used for direct matching to avoid overly restricting the patient population, variables that do not relevantly affect the association of interest were excluded.

After matching, this approach was repeated in the matched sample to identify any residual confounding, selecting confounders for direct adjustment in the outcome analyses.

Baseline balance

Together with the baseline characterisation, the difference between the arms was quantified using the standardized mean difference (SMD). This measure is not affected by the number of observations in a sample, gives the size of the difference, and, thus, is a better way to judge imbalance than a P-value of a hypothesis test of difference. The SMD was calculated as described below. A SMD of ≤10% was taken as sufficient balance between the arms.

Formulae for standardised difference

Continuous covariate:

$SDD = \frac{(\overline{x_t} - \overline{x_r})}{\sqrt{\frac{s_t^2 + s_r^2}{2}}}$,

where $\overline{x_t}$, $\overline{x_r}$ denote the sample means and s_t ,s_r the standard deviations

Binary Covariate:

$SDD = \frac{(\widehat{p_t} - \widehat{p_r})}{\sqrt{\frac{\hat{p}_t(1-\hat{p}_t)+\hat{p}_r(1-\hat{p}_r)}{2}}}$,

where $\widehat{p_t}$,$\widehat{p_r}$ denote the proportion of patients in each category

Categorical (>2 categories) Covariate:

$SDD = \sqrt{(T-C)'S^{-1}(T-C)}$

where S is a $(k-1) \times (k-1)$ covariance matrix:

$$S = [S_{kl}] = \begin{cases} \frac{\hat{p}_{1k}\,(1-\hat{p}_{1k}) + \hat{p}_{2k\,(1-\hat{p}_{2k})}}{2} , k = l \\ \frac{\hat{p}_{1k}\,\hat{p}_{1l} + \hat{p}_{2k}\,\hat{p}_{2l}}{2}, \quad k \neq l \end{cases}$$

, $= (\hat{p}_{12}, \dots, \hat{p}_{1k})'$, $C = (\hat{p}_{22}, \dots, \hat{p}_{2k})'$ and $\hat{p}_{jk} = P\,(category\ k | treatment\ arm\ j)$, $j = 1,2$, $k = 2,3, \dots$, k

Bias potential

Bias potential assesses the degree to which the observed association between the exposure of interest and the outcome is affected by conditioning on another variable. It is also called change-in-estimate. In the case of the primary outcome, a binary indicator for achieving RDC, the definition of bias potential was:

$$Bias\ potential = abs(1 - e^{(\beta_{crude} - \beta_{adjusted})})$$

where β_{crude} = ln(OR) (=natural log of the odds ratio) of exposure from the model without the covariate and β_{crude} = ln(OR) of exposure after adding the covariate to the model. It is called *bias potential* since the bias was estimated without other covariates in the model. To what extent a variable introduces bias into a model will depend on the total model.

A bias potential of ≥2% was considered to indicate a relevant change in the association between the outcome and exposure. Often a cut-off of 5% or even 10% is used to select confounders during model building [44], but a more sensitive cut-off was applied for this study.

The baseline variables with the highest bias potential, that were also insufficiently balanced (SMD >10%), were presented to a panel of clinical experts for the final selection of variables to use for matching.

Matching process

Exact matching for categorical variables and matching within a maximum calliper (maximum distance allowed between a case and a control) for continuous variables was used to match patients, using nearest neighbour variable mixed matching with a match maximum of 3:1 without replacement. Patients in the asthma and COPD groups were matched separately with disease-specific matching criteria.

Mixed matching is a process that utilises more of the data by matching varying numbers of control arm patients to a treatment arm patient. In other words, there will be a cohort of unique patients matched 1:1, another cohort of unique patients matched 2:1, and a third cohort of unique patients matched 3:1. The analyses were conducted using all the matched patients even though some patients had 1 matched control while other patients had 3 matched controls. This imbalance in number of controls matched to cases could introduce residual confounding. Therefore, we verified our assumption that this would not affect the study outcomes through a sensitivity analysis, in which the outcome analyses were also undertaken in the subpopulation of patients in the BF Spiromax arm with exactly 3 matched patients in the BF Turbuhaler arm.

Although the patients in the BF Turbuhaler arm could have multiple records per patient to optimise

the matching process, only one record per patient contributed to the matching.

Matching was repeated 20 times with a different random patient sequence to select the run that resulted in the highest number of matched patients.

Missing data were treated as random and were not imputed. If a selected confounder had more than 20% of missing data, it was not considered as a potential matching variable. If the proportion of missing data was below 20%, the variable was encoded into a categorical variable, adding a category for the observations with missing values, enabling this variable to be used for matching.

Post-matching evaluation

The quality of the matching was evaluated using the same methods used to identify the confounders: standardised difference in combination with bias potential.

To minimise the number of covariates used to adjust the outcome model, a forward assessment of bias potential was used. The identified confounders were entered one-by-one, and the relative change in the effect size of exposure was assessed against the effect size before introducing the variable. If the relative change in effect size was ≥0.02, the variables remained in the model, and the next one was evaluated.

Supplementary Table 1. Patient characteristics in unmatched analysis

Variable	Asthma				COPD			
	BF Spiromax (n=265)	BF Turbuhaler (n=32,071)	P-Value	SMD	BF Spiromax (n=155)	BF Turbuhaler (n=17,315)	P-Value	SMD
Mean (SD) age, years	56.3 (15.5)	50.4 (17.4)	<0.0001	12.1	70.2 (9.1)	69.9 (11.0)	0.0109	3.5
Males, n (%)	121 (45.7)	13,520 (42.2)	<0.0001	5.5	77 (49.7)	9,198 (53.1)	0.5883	0.6
Body mass index, n (%)								
<18.5 kg/m^2	4 (1.6)	395 (1.3)			7 (4.6)	725 (4.2)		
≥18.5 to <25 kg/m^2	68 (27.2)	8,604 (27.8)	<0.0001	5.2	48 (31.8)	5,480 (32.0)	0.0001	5.3
≥25 to <30 kg/m^2	89 (35.6)	10,614 (34.3)			50 (33.1)	5,685 (33.2)		
≥30 kg/m^2	89 (35.6)	11,325 (36.6)			46 (30.5)	5,239 (30.6)		
Smoking status, n (%)								
Non-smoker	129 (49.6)	17,291 (54.2)	0.1366	2.0	18 (11.6)	2,518 (14.6)	<0.0001	10.7
Current smoker	47 (18.1)	5,736 (18.0)			42 (27.1)	4,948 (28.7)		
Ex-smoker	84 (32.3)	8,857 (27.8)			95 (61.3)	9,800 (56.8)		
Comorbidities, n (%)								
Ischaemic heart disease	15 (5.7)	1,945 (6.1)	<0.0001	8.5	29 (18.7)	3,771 (21.8)	0.0021	3.4
Heart failure	1 (0.4)	338 (1.1)	<0.0001	5.7	5 (3.2)	1,115 (6.4)	0.0228	2.2
Diabetes	21 (7.9)	2,297 (7.2)	<0.0001	8.5	20 (12.9)	2,533 (14.6)	0.0273	2.6
Probable pneumonia	1 (0.4)	136 (0.4)	0.6341	0.9	2 (1.3)	298 (1.7)	0.0023	3.5
GERD	41 (15.5)	3,896 (12.1)	0.0001	3.8	25 (16.1)	2,709 (15.6)	0.0030	3.5
Rhinitis	63 (23.8)	6,341 (19.8)	0.2007	0.8	17 (11.0)	1,544 (8.9)	<0.0001	7.2
Charlson Comorbidity Index, n (%)								
0	74 (27.9)	10,394 (32.4)	<0.0001	8.1	102 (65.8)	10,018 (57.9)	0.0002	4.3
1–4	164 (61.9)	19,749 (61.6)			37 (23.9)	5,220 (30.1)		
≥5	27 (10.2)	1,928 (6.0)			16 (10.3)	2,077 (12.0)		
Drug therapy, n (%)								
ICS+LABA	225 (84.9)	26,879 (83.8)			38 (24.5)	6,987 (40.4)		
ICS+LABA+LAMA	11 (4.2)	615 (1.9)	<0.0001	13.0	108 (69.7)	9,244 (53.4)	<0.0001	21.7
ICS+LABA+LAMA+LTRA	4 (1.5)	298 (0.9)			8 (5.2)	625 (3.6)		
ICS+LABA+LTRA	25 (9.4)	4,278 (13.3)			1 (0.6)	459 (2.7)		
Other	0 (0.0)	1 (0.0)			0 (0.0)	0 (0.0)		

SABA average daily dose, n (%)								
0	65 (27.2)	9,929 (34.2)	<0.0001	1.4	27 (18.4)	3,927 (25.7)	0.0003	4.8
>0 to ≤200 µg*	74 (31.0)	8,268 (28.4)			23 (15.6)	3,109 (20.4)		
>200 to ≤400 µg*	57 (23.8)	6,576 (22.6)			37 (25.2)	3,487 (22.8)		
>400 to ≤600 µg*	27 (11.3)	2,237 (7.7)			32 (21.8)	2,524 (16.5)		
>600 µg*	16 (6.7)	2,058 (7.1)			28 (19.0)	2,215 (14.5)		
ICS average daily dose, n (%)								
≤400 µg†	113 (42.6)	17,184 (53.6)	<0.0001	77.9	33 (21.3)	5,886 (34.0)	<0.0001	150.1
>400 to ≤800 µg†	103 (38.9)	10,701 (33.4)			77 (49.7)	7,369 (42.6)		
>800 to ≤1600 µg†	44 (16.6)	3,772 (11.8)			41 (26.5)	3,497 (20.2)		
>1600 µg†	5 (1.9)	414 (1.3)			4 (2.6)	563 (3.3)		
No. of exacerbations in baseline year, n (%)								
0	203 (76.6)	23,095 (72.0)	<0.0001	16.4	59 (38.1)	6,477 (37.4)	<0.0001	9.9
1	45 (17.0)	5,503 (17.2)			46 (29.7)	4,381 (25.3)		
2	12 (4.5)	2,108 (6.6)			16 (10.3)	2,772 (16.0)		
≥3	5 (1.9)	1365 (4.3)			34 (21.9)	3,685 (21.3)		
Disease control using RDC, n (%)	184 (69.4)	19,082 (59.5)	<0.0001	8.7	59 (38.1)	6,477 (37.4)	<0.0001	7.6

*Salbutamol equivalents; †Beclomethasone equivalents.

P-value = p-value for the Kruskal-Wallis equality-of-populations rank test, or the Pearson's chi-square test of independent categories, where appropriate

BF, budesonide/formoterol; GERD, gastroesophageal reflux disease; ICS, inhaled corticosteroid; LABA, long-acting β_2-agonist; LAMA, long-acting muscarinic antagonist; LTRA, leukotriene receptor antagonist; RDC, risk domain control; SABA, short-acting β_2-agonist; SD, standard deviation; SMD, standardized mean difference