

SUPPLEMENTARY APPENDIX

Persistence and Adherence to ICS/LABA Drugs in UK Asthma Patients: A New-User Cohort Study

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Glossary

ACT Asthma Control Test, *BDP/FM* beclometasone dipropionate/formoterol, *BUD/FM* budesonide/formoterol, *COPD* chronic obstructive pulmonary disease, *FF/VI* fluticasone furoate/vilanterol, *ICS/LABA* inhaled corticosteroid/long-acting beta₂-agonist, *KM* Kaplan–Meier, *IMRD* IQVIA Medical Research Database, *MART* maintenance and reliever therapy, *PDC* proportion of days covered, *PS* propensity score, *PSM* PS matching

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Methods

Exclusion criteria

Patients were excluded if they

- had at least one recorded diagnosis of COPD at any time in their medical history
- had < 12 months' medical history prior to the index date
- had a prescription of any ICS/LABA combination at any time prior to the index date
- were aged < 12 years (for those initiating FF/VI and BUD/FM treatment) or < 18 years (for those initiating BDP/FM treatment).

Follow-up period information: discontinuation, adherence, and SABD rescue use analyses

There were no restrictions on the minimum follow-up period for the discontinuation analysis, and patient time was censored at the earliest of either: end of the study period, end of enrolment in IMRD, transfer out of practice, switch to another ICS/LABA treatment, occurrence of the outcome, or death. For the adherence and SABD rescue use analyses, follow-up was from the index date until the earliest of either 1 year after the index date or censored date (end of study period, end of enrolment in IMRD, transfer out of practice, switch of treatment, or death).

Data cleaning

Data cleaning was conducted as follows: patients with a single prescription for >365 days, those who switched to another therapy between the first and second prescription of the index therapy, and those whose second prescription was recorded beyond the study end date, after exit from the IQVIA Medical Research Database or after death, were excluded. Rules were set if patients were prescribed multiple prescriptions on the same day: index therapy and ICS/LABA non-index therapy prescribed on the same day was considered a switch to another treatment; the date of switch was considered the end date of the previous prescription; two or more different ICS/LABA index therapies prescribed on the same day was considered as a switch to another treatment; the date of switch was considered the end date of the previous prescription and multiple prescription of the same index therapies on the same day was not considered a switch, and the length of the medications given on the same day were summed up to calculate the total duration of the prescription.

Covariates and confounders

Age, sex, available comorbidities (lung cancer, cystic fibrosis, atopic dermatitis, allergic rhinitis, type I and II diabetes, obesity, cardiovascular disease, acute anxiety disorder, and depression) and asthma medication, exacerbations, and healthcare resource use over the past 12 months were stipulated *a priori* to be included as potential covariates for propensity score matching (PSM). Clinical measures for asthma severity (ICS and SABD prescription history, exacerbations, number of hospital and general practitioner visits, and duration of

hospitalisation in the 12 months prior to index) were included in the matching to adjust for potential confounding effects by disease severity.

Year of index was additionally identified as a potential confounder on the basis of the descriptive analysis and epidemiological review, and was inherently unbalanced due to different launch dates and uptake in the market. As matching was unable to provide balance, the variable was instead included as a confounder in the regression analyses. Daily dose was identified as a potential effect modifier, but due to the inability to balance between groups, daily dose was not incorporated in the PSM. As distributions of the low/medium/high daily dose were markedly different between FF/VI, BUD/FM, and BDP/FM, the decision was made to stratify based on low/medium daily dose versus high daily dose in the final analysis. For patients with missing daily dose information, the daily dose was imputed based on medication strength and prescribed puffs per day, and further classified as low, medium, or high dose according to the Global Initiative for Asthma guidelines [1] (with the exception of FF/VI, which has only low and high doses) based on the ICS component alone. Where puffs per day data were missing, the following medians were used to impute daily dosage: one puff per day for FF/VI, three for BUD/FM, and four for BDP/FM.

Descriptive statistics

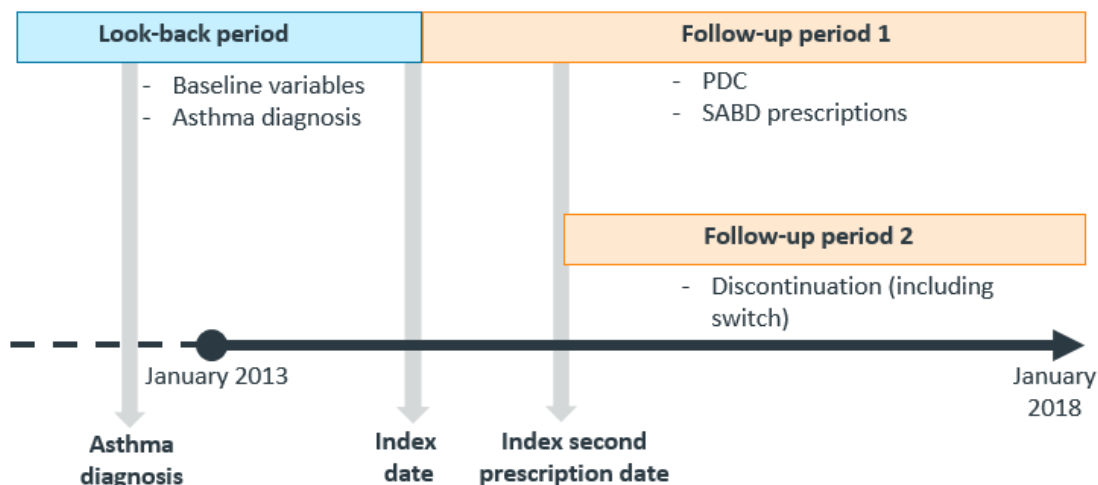
Continuous variables were described by the mean, standard deviation, median, 25th and 75th percentiles, minimum and maximum values, and were compared using Student's t-test (unpaired). Categorical variables were described by the number and percentage of patients in each category, and were compared using the chi-square test (unordered) or the Cochran–Mantel–Haenszel test (ordered).

Reference

1. The Global Initiative for Asthma. Pocket Guide for Asthma Management and Prevention. <https://ginasthma.org/pocket-guide-for-asthma-management-and-prevention/>. Date last updated: 2019. Accessed November 11, 2019.

Supplementary Figures/Tables

Fig. S1 Study schematic for GlaxoSmithKline plc., study number 209967.



Look-back period: A look-back period of 1 year before the index date was required wherein the patient must have been registered in the database. This provided ≥ 1 year of patient medical history to determine prescription history and the variables to be considered for inclusion in the propensity score model.

Index date: Defined as the date of the first recorded prescription of FF/VI or the comparator ICS/LABA (BDP/FM or BUD/FM [of strengths 200/6, 100/6, and 400/12 μg]) within the study time period.

Index second prescription date: Defined as the next prescription of the index treatment following index date. All patients included in the study were required to have had two prescriptions of the index treatment. In an attempt to avoid potential bias in time-to-event analysis when comparing FF/VI versus comparator ICS/LABA (due to differential length of time between the first and second prescriptions when patients were not able to experience the outcome of interest; i.e., discontinuation), the index date for the discontinuation analysis was set as the date of the second prescription.

Switch defined as switch from FF/VI to a comparator ICS/LABA (BUD/FM, BDP/FM) or vice versa, or from comparator ICS/LABA (BUD/FM, BDP/FM) to FF/VI or the other non-index comparator ICS/LABA.

BDP/FM: beclometasone dipropionate/formoterol; BUD/FM: budesonide/formoterol; FF/VI: fluticasone furoate/vilanterol; ICS: inhaled corticosteroids; LABA: long-acting beta₂-agonist; PDC: proportion of days covered; SABD: short-acting bronchodilator.

Table S1 Number of ICS prescriptions pre-index for FF/VI versus BUD/FM

| ICS* | Total (N = 4217) | FF/VI (n = 945) | BUD/FM (n = 3272) |
|------|------------------|-----------------|-------------------|
| 0 | 1010 (24.0) | 200 (21.2) | 810 (24.8) |
| 1 | 648 (15.4) | 162 (17.1) | 486 (14.9) |
| 2 | 587 (13.9) | 145 (15.3) | 442 (13.5) |
| 3 | 459 (10.9) | 107 (11.3) | 352 (10.8) |
| 4 | 363 (8.6) | 84 (8.9) | 279 (8.5) |
| 5 | 304 (7.2) | 60 (6.3) | 244 (7.5) |
| 6+ | 846 (20.1) | 187 (19.8) | 659 (20.1) |

BUD/FM: budesonide/formoterol; FF/VI: fluticasone furoate/vilanterol; ICS: inhaled corticosteroids.

Data are shown as *n* (%).

*Number of ICS prescriptions in 12 months prior to index.

Table S2 Number of ICS prescriptions pre-index for FF/VI versus BDP/FM

| ICS* | Total (N = 4367) | FF/VI (n = 902) | BUD/FM (n = 3465) |
|------|------------------|-----------------|-------------------|
| 0 | 783 (17.9) | 193 (21.4) | 590 (17.0) |
| 1 | 746 (17.1) | 157 (17.4) | 589 (17.0) |
| 2 | 667 (15.3) | 140 (15.5) | 527 (15.2) |
| 3 | 576 (13.2) | 98 (10.9) | 478 (13.8) |
| 4 | 401 (9.2) | 81 (9.0) | 320 (9.2) |
| 5 | 303 (6.9) | 56 (6.2) | 247 (7.1) |
| 6+ | 891 (20.4) | 177 (19.6) | 714 (20.6) |

BDP/FM: beclometasone dipropionate/formoterol; FF/VI: fluticasone furoate/vilanterol; ICS: inhaled corticosteroids.

Data are shown as *n* (%).

*Number of ICS prescriptions in 12 months prior to index.

Table S3 PDC data for FF/VI versus BUD/FM

| a) PDC | | | | | | | |
|---|-------------|----------------------------|---------------------------|-------------------------------|------------------------------|-----------|-----------------|
| | | FF/VI (<i>n</i> = 937) | | | BUD/FM (<i>n</i> = 3232) | | |
| PDC (days) | | | | | | | |
| Mean (SD) | | 77.7 (25.3) | | | 72.4 (26.1) | | |
| Median | | 88.2 | | | 77.7 | | |
| Interquartile range | | 61.4–100.0 | | | 50.7–100.0 | | |
| T-test <i>p</i> -value | | | | < 0.0001 | | | |
| PDC (≥ 50%) | | | | | | | |
| <i>n</i> (%) | | 780 (83.2) | | | 2447 (75.7) | | |
| Chi ² test <i>p</i> -value | | | | < 0.0001 | | | |
| PDC (≥ 80%) | | | | | | | |
| <i>n</i> (%) | | 545 (58.2) | | | 1562 (48.3) | | |
| Chi ² test <i>p</i> -value | | | | < 0.0001 | | | |
| b) PDC with adjustments and stratifications (≥50% PDC) | | | | | | | |
| | Study group | <i>n</i> | Adherent, <i>n</i> (%) | Non-adherent, <i>n</i> (%) | OR | 95% CI | <i>p</i> -value |
| PS-matched | FF/VI | 937 | 780 (83.2) | 157 (16.8) | 1.59 | 1.32–1.93 | < 0.001 |
| | BUD/FM | 3232 | 2447 (75.7) | 785 (24.3) | 1.00 | Ref. | |
| Adjusted for year of initiation | FF/VI | 936 | 779 (83.2) | 157 (16.8) | 1.35 | 1.09–1.67 | 0.006 |
| | BUD/FM | 3232 | 2447 (75.7) | 785 (24.3) | 1.00 | Ref. | |
| Stratified low/medium dose and adjusted for year of initiation | FF/VI | 709 | 606 (85.5) | 103 (14.5) | 1.57 | 1.23–2.02 | < 0.001 |
| | BUD/FM | 3131 | 2373 (75.8) | 758 (24.2) | 1.00 | Ref. | |
| Stratified high dose and | FF/VI | 227 | 173 (76.2) | 54 (23.8) | 1.09 | 0.55–2.09 | 0.808 |

| | | | | | | | |
|---|--------------------|-----------------|-----------------------------------|--|-----------|---------------|-----------------------|
| adjusted for year of initiation | BUD/FM | 101 | 74 (73.3) | 27 (26.7) | 1.00 | Ref. | |
| c) PDC with adjustments and stratifications (≥ 80% PDC) | | | | | | | |
| | Study group | <i>n</i> | Adherent, <i>n</i> (%) | Non- adherent, <i>n</i> (%) | OR | 95% CI | <i>p</i>-value |
| PS-matched | FF/VI | 937 | 545 (58.2) | 392 (41.8) | 1.49 | 1.28–1.72 | < 0.001 |
| | BUD/FM | 3232 | 1562 (48.3) | 1670 (51.7) | 1.00 | Ref. | |
| Adjusted for year of initiation | FF/VI | 936 | 544 (58.1) | 392 (41.9) | 1.28 | 1.08–1.52 | 0.004 |
| | BUD/FM | 3232 | 1562 (48.3) | 1670 (51.7) | 1.00 | Ref. | |
| Stratified low/medium dose and adjusted for year of initiation | FF/VI | 709 | 415 (58.5) | 294 (41.5) | 1.28 | 1.06–1.55 | 0.009 |
| | BUD/FM | 3131 | 1519 (48.5) | 1612 (51.5) | 1.00 | Ref. | |
| Stratified high dose and adjusted for year of initiation | FF/VI | 227 | 129 (56.8) | 98 (43.2) | 1.63 | 0.90–2.96 | 0.106 |
| | BUD/FM | 101 | 43 (42.6) | 58 (57.4) | 1.00 | Ref. | |

BUD/FM: budesonide/formoterol; CI: confidence interval; FF/VI: fluticasone furoate/vilanterol; OR: odds ratio; PDC: proportion of days covered; PS: propensity score; Ref.: Reference; SD: standard deviation.

Table S4 PDC data for FF/VI versus BDP/FM

| a) PDC | | | | | | | |
|---|--------------------|-----------------|-----------------------------------|---------------------------------------|-----------|------------------------------------|-----------------------|
| | | | FF/VI (n = 894) | | | BDP/FM (n = 3433) | |
| PDC (days) | | | | | | | |
| Mean (SD) | | | 78.2 (25.1) | | | 71.0 (26.0) | |
| Median | | | 89.2 | | | 75.9 | |
| Interquartile range | | | 61.6–100.0 | | | 50.5–98.0 | |
| T-test <i>p</i> -value | | | | | < 0.0001 | | |
| PDC (≥ 50%) | | | | | | | |
| <i>n</i> (%) | | | 748 (83.7) | | | 2600 (75.7) | |
| Chi ² test <i>p</i> -value | | | | | < 0.0001 | | |
| PDC (≥ 80%) | | | | | | | |
| <i>n</i> (%) | | | 527 (58.9) | | | 1571 (45.8) | |
| Chi ² test <i>p</i> -value | | | | | < 0.0001 | | |
| b) PDC with adjustments and stratifications (≥ 50% PDC) | | | | | | | |
| | Study group | <i>n</i> | Adherent, <i>n</i> (%) | Non-adherent, <i>n</i> (%) | OR | 95% CI | <i>p</i>-value |
| PS-matched | FF/VI | 894 | 748 (83.7) | 146 (16.3) | 1.64 | 1.36–2.00 | < 0.001 |
| | BDP/FM | 3433 | 2600 (75.7) | 833 (24.3) | 1.00 | Ref. | |
| Adjusted for year of initiation | FF/VI | 893 | 747 (83.7) | 146 (16.3) | 1.50 | 1.23–1.83 | < 0.001 |
| | BDP/FM | 3433 | 2600 (75.7) | 833 (24.3) | 1.00 | Ref. | |
| Stratified low/medium dose and adjusted for year of initiation | FF/VI | 672 | 578 (86.0) | 94 (14.0) | 1.77 | 1.40–2.26 | < 0.001 |
| | BDP/FM | 3301 | 2503 (75.8) | 798 (24.2) | 1.00 | Ref. | |
| Stratified high dose and | FF/VI | 221 | 169 (76.5) | 52 (23.5) | 1.27 | 0.73–2.23 | 0.391 |

| | | | | | | | |
|--|--------------------|----------|----------------------------|--------------------------------|-----------|---------------|----------------|
| adjusted for year of initiation | BDP/FM | 132 | 97 (73.5) | 35 (26.5) | 1.00 | Ref. | |
| c) PDC with adjustments and stratifications (≥ 80% PDC) | | | | | | | |
| | Study group | n | Adherent, n (%) | Non-adherent, n (%) | OR | 95% CI | p-value |
| PS-matched | FF/VI | 894 | 527 (58.9) | 367 (41.1) | 1.70 | 1.47–1.98 | <0.001 |
| | BDP/FM | 3433 | 1571 (45.8) | 1862 (54.2) | 1.00 | Ref. | |
| Adjusted for year of initiation | FF/VI | 893 | 526 (58.9) | 367 (41.1) | 1.57 | 1.35–1.83 | <0.001 |
| | BDP/FM | 3433 | 1571 (45.8) | 1862 (54.2) | 1.00 | Ref. | |
| Stratified low/medium dose and adjusted for year of initiation | FF/VI | 672 | 397 (59.1) | 275 (40.9) | 1.56 | 1.31–1.85 | <0.001 |
| | BDP/FM | 3301 | 1516 (45.9) | 1785 (54.1) | 1.00 | Ref. | |
| Stratified high dose and adjusted for year of initiation | FF/VI | 221 | 129 (58.4) | 92 (41.6) | 2.26 | 1.39–3.68 | 0.001 |
| | BDP/FM | 132 | 55 (41.7) | 77 (58.3) | 1.00 | Ref. | |
| BDP/FM: beclometasone dipropionate/formoterol; CI: confidence interval; FF/VI: fluticasone furoate/vilanterol; OR: odds ratio; PDC: proportion of days covered; PS: propensity score; Ref.: Reference; SD: standard deviation. | | | | | | | |