Final report

Off-label prescribing and adverse events for fluticasone propionate / formoterol

An observational evaluation of prescribing of fixed-dose combination inhaled corticosteroid / long-acting beta2-agonist (ICS/LABA): fluticasone propionate / formoterol (FP/FOR) and adverse events in routine primary care at 36-months post launch

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Contents

Index of tables

Index of figures

List of abbreviations

AE	Adverse Event
A&E	Accident and Emergency
BDP/FOR	Beclometasone/Formoterol
BMI	Body Mass Index
BUD/FOR	Budesonide/Formoterol
CCI	Charlson Comorbidity Index
CI	Confidence Interval
COPD	Chronic Obstructive Pulmonary Disease
CPRD	Clinical Practice Research Datalink
DPI	Dry Powder Inhaler
ENCePP	European Network of Centres for Pharmacoepidemiology and Pharmacovigilance
GERD	Gastroesophageal Reflux Disease
GP	General Practitioner
FDC	Fixed Dose Combination
FP/FOR	Fluticasone/Formoterol
FP/SAL	Fluticasone/Salmeterol
HES	Hospital Episode Statistics
ICS	Inhaled Corticosteroid
IQR	Interquartile Range
LABA	Long-Acting Beta-Agonist
LAMA	Long-Acting Muscarinic Antagonist
LRTI	Lower Respiratory Tract Infection
LTRA	Leukotriene receptor antagonist
MART	Maintenance and reliever therapy
MDI	Metered Dose Inhaler
MHRA	Medicines and Healthcare products Regulatory Agency
ONS	Office of National Statistics
QOF	Quality and Outcomes Framework
RiRL	Research in Real life Limited
SABA	Short-Acting Beta2 Agonist
SAE	Serious Adverse Event
SAMA	Short-Acting Muscarinic Antagonist

1 Abstract

1.1 Title, subtitle, date and author

Title: Off-label prescribing and adverse events for fluticasone propionate / formoterol

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1.2 Keywords

Fluticasone proprionate/formoterol, off-label, adverse events, historical, cohort

1.3 Rationale and background

Observational studies allow the evaluation of patients in a non-interventional setting and provide a means to study and better understand prescribing practices and adherence to guidelines and licence indications in clinical practice. As such, these studies are increasingly recommended to provide post-marketing surveillance and pharmacovigilance data in addition to insight into medicinal product utilisation patterns. Based on this, the Medicines and Healthcare products Regulatory Agency recommended Mundipharma Research Limited carry out a post-launch observational study of FP/FOR using CPRD to evaluate the safety of FP/FOR over a longer period than that in the pre-launch clinical trial in patients for whom the drug is licensed and to evaluate off-label use of the drug.

FP/FOR was given marketing authorization in August 2012 and launched on 25th September 2012 for the regular treatment of asthma in the UK [6]. The proposed study characterised prescribing incidence of licensed and off-label FP/FOR and evaluate the safety in patients prescribed with FP/FOR and the various comparator FDC ICS/LABA in the UK. This study was divided into 2 stages, 18 months and 36 months post FP/FOR launch, to describe the prescribing incidence and adverse events associated to FP/FOR and its comparators at 18-month post FP/FOR launch before a full-matched analysis at 36-month post FP/FOR launch. This report considers Stage 2: 36 months post-launch. The results for Stage 1 (18 month evaluation) have been described in a separate report.

1.4 Research question and objectives

The research question was to quantify the incidence of on and off-label prescribing of FP/FOR and other FDC ICS/LABA therapies in the UK and evaluate adverse events for patients prescribed these therapies. Additionally, it aimed to describe demographics, medication and disease-related characteristics for these patients.

The co-primary objectives were as follows:

- To quantify the incidence of on and off-label prescribing of FP/FOR and other FDC ICS/LABA therapies over 36 months post launch
- To evaluate adverse events in patients prescribed FP/FOR versus other FDC ICS/LABA therapies for both licensed and off-label groups within 36 months post FP/FOR launch

The secondary objectives were as follows:

- To describe demographic, medication and disease-related characteristics for patients prescribed FP/FOR and other FDC ICS/LABA therapies for both licensed and off-label groups within 36 months post FP/FOR launch

1.5 Study design

This study was a descriptive (prescribing prevalence and patient characterisation) and exploratory (evaluation of adverse events), historical cohort database study of patients initiating on FP/FOR and other FDC ICS/LABA therapy on or after 25th September 2015 (launch of FP/FOR) and up until 24th September 2015 (36 months post launch).

1.6 Setting

The extracted cohort consisted of all patients ≥4 years old captured in CPRD during the period from 25th September 2015 until 24th September 2015 (i.e. 36-months post UK launch of FP/FOR, where FP/FOR launch was on 25th September 2012) who initiated on any FDC ICS/LABA [including FP/FOR, fluticasone/salmeterol (FP/SAL), budesonide/formoterol (BUD/FOR), beclomethasone/formoterol (BDP/FOR)].

1.7 Subjects and study size

The analyses considered licensed and off-label subgroups which were patients aged ≥18 years with asthma, patients aged ≥12 and <18 years with asthma, patients aged ≥4 and <12 years with asthma, patients with COPD (and no asthma, aged ≥31 years) and patients prescribed ICS/LABA as the “MART” regimen (aged ≥18 years). The comparison groups for FP/FOR were other FDC ICS/LABA therapies, licensed for that indication in the UK, including

FP/SAL DPI, FP/SAL MDI, BUD/FOR and BDP/FOR.

We intended to use all patients available in CPRD who were eligible for the study. A feasibility count from CPRD identified 239,176 research quality (acceptable) patients with a prescription for an FDC ICS/LABA during the study period, which included 10,589 patients prescribed FP/FOR.

1.8 Variables and data sources

Patient characterisation considered a range of demographic characteristics, disease characteristics, comorbidities, GP consultations and hospitalisations, exacerbations and other prescribed medications at and prior to the index date. Adverse events and serious adverse events (outside of any asthma-related events) were evaluated from a list of pre-specified events including COPD exacerbations, lower respiratory tract infections, pneumonia and cardiac arrhythmias and ischaemia. Serious adverse events were considered as any of the adverse events (from the pre-specified list) which resulted in death or required inpatient hospitalisation.

This study was conducted using the Clinical Practice Research Datalink (CPRD) which is a large computerized primary care database and contains de-identified, longitudinal data from 5 million active medical records from more than 600 subscribing practices throughout the UK. Linked databases to CPRD were used; hospital episode statistics (HES) to qualify hospital-related events and Office of National Statistics (ONS) Mortality Data to provide more specific information around cause of death.

1.9 Results

The prescribing rate was lower for FP/FOR than other FDC ICS/LABAs in all subgroups studied. For patients with asthma aged ≥18 years who were prescribed FP/FOR on-label, the prescribing rate was 13.85 per 1000 person years compared to 20.30, 27.75, 28.13 and 27.72 per 1000 person years for FP/SAL DPI, FP/SAL MDI, BUD/FOR and BDP/FOR respectively. For patients with COPD, the prescribing rate of FP/FOR was 10.18 compared to 100.04, 70.89 and 40.81 for FP/SAL DPI, BUD/FOR and BDP/FOR respectively. The prescribing rate was particularly low for patients with asthma aged ≥4 and <12 years (0.75 per 1000 person years) and patients with asthma aged ≥12 and <18 years who were prescribed FP/FOR on-label and off-label (4.84 per 1000 person years and 0.44 per 1000 person years respectively). Furthermore, of those prescribed FP/FOR, 80.8% were patients with asthma aged ≥18 years, 9.2% did not have a diagnosis of asthma or COPD and 6.2% had a diagnosis of COPD

(definition 1). Less than 5% of patients prescribed FP/FOR were aged <18 years with asthma.

For patients with asthma aged ≥18 years, for the majority of incidence rates of adverse events and rate of occurrence of first adverse event was similar between FP/FOR and the licensed comparators. In the total cohort, where the rates of occurrence of first events differed, this was in favour of FP/FOR versus the comparators (incidence rate of cardiac arrhythmia or ischaemia, hyperglycaemia, cataracts and pneumonia was lower for FP/FOR than DPI FP/SAL; incidence rate of LRTI and "any new adverse event" was lower for FP/FOR than DPI FP/SAL and MDI FP/SAL; rate of occurrence of first record of anxiety/depression and "any new adverse events" was higher for all comparators than FP/FOR; rate of occurrence of first LRTI was higher for FP/SAL DPI and BUD/FOR than FP/FOR; rate of occurrence of first oral candidiasis record was higher for BUD/FOR and BDP/FOR than FP/FOR). The only results where a higher rate of occurrence of first adverse event for FP/FOR was observed was within the sub-analysis (split by initiators and switchers) for two adverse events (higher rate of occurrence of first dysphonia record for FP/FOR than FP/SAL DPI; higher rate of occurrence of first other local oral adverse events for FP/FOR than BUD/FOR); there were no differences between FP/FOR and the other comparators for these adverse events in these subgroups. Considering serious adverse events, FP/FOR was always similar or better than the comparators in all studied. Rate of occurrence of first inpatient hospitalisation associated with an adverse event was higher for FP/SAL MDI and BUD/FOR than FP/FOR. The rate of occurrence of first cardiac arrhythmia and ischemia associated inpatient hospitalisation and anxiety/depression associated inpatient hospitalisation was higher for several of the comparators than for FP/FOR. These results appeared to be driven by those that switched FDC ICS/LABA, particularly for cardiac arrhythmia and ischaemia associated inpatient hospitalisations.

For patients with COPD, the number of patients prescribed FP/FOR was fairly low (n=399) but numbers allowed for some analyses to be conducted. There was no difference in the total cohort for incidence rate or rate of occurrence of first event of those adverse events studied, or numbers were too low to allow analysis. However, the sub-analysis split by initiators and switchers suggested that the rate of occurrence of first COPD exacerbation was higher for FP/FOR than FP/SAL DPI in those that switched FDC ICS/LABA, although this difference was not seen when compared with BUD/FOR or BDP/FOR and the reverse was observed for initiators when compared with BUD/FOR and BDP/FOR. This requires further investigation to compare the characteristics of FP/FOR and FP/SAL DPI switchers. Furthermore, this sub-analysis suggested that rate of occurrence of first cardiac arrhythmia or ischaemia was higher

for FP/FOR than FP/SAL DPI, although again this difference was not observed for the other comparators and was based on a small number of events and patients in the FP/FOR group (n=15 events from 164 patients).

Three of the subgroups studied, for which FP/FOR was off-label in all but two doses for patients with asthma aged ≥12 and <18 years, the number of patients to be studied in the FP/FOR groups was low. For patients with asthma aged ≥12 and <18 years, the number of FP/FOR patients in the on-label and off-label groups were 227 and 21 respectively. No difference was observed in the incidence rate or rate of occurrence of first event for any adverse event studied, or numbers were too low to allow analysis. Similarly, when considering adverse events associated with inpatient hospitalisation, less than five events were observed and there were no deaths associated with adverse events reported for FP/FOR. Unsurprisingly, for patients with asthma aged ≥4 and <12 years, as above, the number of patients in the FP/FOR group was low (n=27), as use in this age group is off-label. For each adverse event studied and for both inpatient hospitalisations and deaths associated with adverse events, the number of events was less than five or zero. For patients prescribed FDC ICS/LABAs as per the MART regimen, the results were similar to those of patients with asthma aged ≥12 and <18 years whereby, no difference was observed in the incidence rate for any adverse event studied, or numbers were too low to allow analysis. There were no inpatient hospitalisations or deaths associated with adverse events in this subgroup.

Patients were broadly similar at baseline between FDC ICS/LABA treatments within each subgroup. However, across all subgroups, FP/FOR patients were more likely to be switchers rather than initiators of their FDC ICS/LABA therapy for all subgroups. The other main differences noted were that in the patients with asthma aged ≥18 years, the FP/SAL DPI group were older, with more severe disease and more comorbid COPD, ischaemic heart disease and hypertension. This group also received higher doses of their FDC ICS/LABA at index data and more LAMA. They experienced more exacerbations, attended more GP consultations and required more inpatient admissions and outpatient attendances. For patients with COPD, those that were prescribed FP/SAL DPI were prescribed a higher dose of FDC ICS/LABA at the index date and were also more likely to be prescribed LAMA. For this subgroup, the FP/FOR group were less likely to have outpatient attendances or inpatient hospitalisations. Lastly, in the MART subgroup, patients prescribed FP/FOR were less likely to have had exacerbations in the year prior. Data availability, in terms of prior records and length of follow-up, was similar in all groups across all subgroups, except for patients with asthma aged ≥12 and <18 years where length of follow-up was shorter for FP/FOR than the other groups.

1.10 Discussion

For all the adverse events considered FP/FOR was similar or better than the licensed comparators studied, when the subgroups were analysed as a whole (i.e. not split by initiators and switchers). Furthermore, there was no increase observed in serious adverse events for FP/FOR versus the licensed comparators in any of the subgroups studied. In fact, there is evidence to support that FP/FOR may be better than some of its licensed comparators in terms of inpatient hospitalisations associated with adverse events, specifically cardiac ischaemia and arrhythmia and anxiety and depression in patients with asthma aged ≥18 years.

The subgroup analyses, where patients were split by initiation status, suggest that there may be an increase in exacerbations and cardiac arrhythmias and ischaemia in patients with COPD for FP/FOR compared to FP/SAL DPI, for switchers and initiators respectively. However, this was not observed when comparing to BUD/FOR or BDP/FOR. There also may be an increase in dysphonia and other local oral adverse events in patients with asthma aged ≥18 years initiating on FP/FOR versus those initiating FP/SAL DPI and BUD/FOR respectively. However, this was only observed when results were split by initiators and switchers so further investigations would need to consider this and should also consider splitting the analysis of cardiac events into ischaemia and arrhythmia.

A substantial proportion of patients who were prescribed an FDC ICS/LABA in this study did not have either a COPD or asthma diagnosis. This may indicate a frequent practice of trial of medication being given to patients without a confirmed diagnosis, which warrants further investigation. It should be noted that this practice was low for FP/FOR with the majority being prescribed FP/SAL or BUD/FOR. In general, the prescribing rate was lower for FP/FOR than other FDC ICS/LABAs in all subgroups studied. In particular, the majority of prescribing for FP/FOR was for patients with asthma aged ≥18 years and prescription of FP/FOR was lowest for patients aged <18 years with asthma.

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2 Rationale and background

The approval of a drug for marketing in Europe requires completion of Phase I–III clinical trials to provide strong evidence on the safety and efficacy of the product. The licence granted is based on the eligible patient population that participated in the clinical trials. Use of a drug in patient groups outside of those for whom the product is specifically indicated in the license is regarded as “off label”.

Pharmaceutical companies often conduct further studies of a drug following its launch to evaluate the effectiveness and safety profile of the drug in the longer term. One way of evaluating outcomes in a wider representative patient population following product launch, is to perform an observational study in the UK using the CPRD [1]. The CPRD is the world's largest computerised database of anonymised longitudinal medical records from primary care, linked with other healthcare data. Observational studies allow the evaluation of patients in a non-interventional setting and provide a means to study and better understand prescribing practices and adherence to guidelines and licence indications in clinical practice [2]. As such, these studies are increasingly recommended to provide post-marketing surveillance and pharmacovigilance data in addition to insight into medicinal product utilisation patterns. Based on this, the Medicines and Healthcare products Regulatory Agency recommended Mundipharma Research Limited carry out a post-launch observational study of FP/FOR using CPRD to evaluate the safety of FP/FOR over a longer period than that in the pre-launch clinical trial in patients for whom the drug is licensed and to evaluate off-label use of the drug.

Global Initiative for Asthma (GINA) guidelines recommend the addition of a LABA as a valid step-up option for patients whose asthma is not adequately controlled by ICS alone [3]. The combination of ICS and LABA provides both anti-inflammatory and bronchodilatory effects. Data suggest that combination ICS/LABA therapy is most effective when delivered as a fixed dose combination (FDC) inhaler, probably due to simplicity of dosing and improved patient adherence [4]. The rapid-onset bronchodilatory effects of formoterol, as used in FP/FOR, may provide more rapid symptom relief than with slower-acting LABA salmeterol [5].

FP/FOR was given marketing authorization in August 2012 and launched on 25th September 2012 for the regular treatment of asthma in the UK [6]. The 50/5 and 125/5 inhalers are licensed for use in adults and adolescents (≥ 12 years) and the 250/10 inhaler is licensed for use in adults only (≥ 18 years). FP/FOR is indicated either as a step up therapy, for those who have inadequately controlled asthma with ICS and “as required” inhaled short-acting beta-

agonist (SABA), or as a maintenance therapy, for those who are controlled on both an ICS and a LABA [7]. The proposed study characterised prescribing incidence of licensed and off-label FP/FOR and evaluate the safety in patients prescribed with FP/FOR and the various comparator FDC ICS/LABA in the UK.

This study was divided into 2 stages, 18 months and 36 months post FP/FOR launch, to describe the prescribing incidence and adverse events associated to FP/FOR and its comparators at 18-month post FP/FOR launch before a full-matched analysis at 36-month post FP/FOR launch. This report considers Stage 2: 36 months post-launch. The results for Stage 1 (18 month evaluation) have been described in a separate report.

3 Research question and objectives

3.1 Research question

The research question was to quantify the incidence of on and off-label prescribing of FP/FOR and other FDC ICS/LABA therapies in the UK and evaluate adverse events for patients prescribed these therapies. Additionally, it aimed to describe demographics, medication and disease-related characteristics for these patients. This aimed to provide information on the real-world use of FP/FOR and other FDC ICS/LABA therapies prescribed in the UK.

3.2 Study objectives

The co-primary objectives were as follows:

- To quantify the incidence of on and off-label prescribing of FP/FOR and other FDC ICS/LABA therapies over 36 months post launch
- To evaluate adverse events in patients prescribed FP/FOR versus other FDC ICS/LABA therapies for both licensed and off-label groups within 36 months post FP/FOR launch

The secondary objectives were as follows:

- To describe demographic, medication and disease-related characteristics for patients prescribed FP/FOR and other FDC ICS/LABA therapies for both licensed and off-label groups within 36 months post FP/FOR launch

4 Amendments and updates to the protocol

A protocol was submitted for this stage of the study to the Independent Scientific Advisory Committee (ISAC) in order to be granted CPRD data. Amendments and clarifications to the protocol were made as follows.

The original definition of COPD exacerbation did not have any requirement for length of outcome period, however, according to EMA/CHMP guidelines at least one year of outcome data is recommended. Specifically, they state that “an evaluation of the frequency of exacerbations should normally be made over a period of at least one year due to seasonal variation in exacerbation rates. The timing of the study treatment may prove important (e.g. capturing the winter cold season in the majority of patients)”. To comply with this recommendation, the analysis of COPD exacerbations required twelve months of follow-up data. Since the same seasonal variation hold for LRTI and pneumonia, the criteria were applied to these adverse events as well. Furthermore, for “any new adverse events” and “any serious adverse event”, a requirement was included for twelve months of follow-up data as COPD exacerbations, LRTI and pneumonia are taken into consideration in the derivation of these.

The intention in the protocol was to attempt to use matched cohorts to evaluate the adverse events. However, we felt that the limitations of having to group all other comparators together, the risk of having to exclude patients which cannot be matched and potential small sample sizes for some of the populations (as seen in stage 1) would mean that following an adjusted analysis approach for all adverse events would be more appropriate. Therefore, a list of a priori confounders, to adjust for in all models, and a list of potential confounders, to consider for adjustment in the models, were pre-selected.

Further exclusions of patients were made when looking at the data received, including patients with an incorrect date of death and those who did not have any follow-up time (end of drug exposure, death or end of records on the index date).

Data were imputed on the dosing instructions given for FP/FOR, FP/SAL MDI and FP/SAL DPI due to the low availability of data, particularly for FP/SAL DPI. It was assumed for the MDIs that the dosing instructions would be two puffs twice a day and for the DPI, one puff per twice a day. No dosing instructions were imputed for BDP/FOR or BUD/FOR as they can be prescribed as part of the MART regimen. This was done in order to be able to adjust for daily

dose of FDC ICS/LABA in the adjusted models without losing a large number of patients for these analyses. Daily dose was presented before and after imputation in the characterisation so the effect of the imputation can be seen.

The intention in the protocol was to use a procedure to adjust for multiple testing. Since the aim of the study was to evaluate adverse events, a more conservative approach was taken to report the p-values unadjusted.

Duration of COPD and asthma is not a measure that can be reliably obtained from databases such as CPRD and so this measure has been removed from the baseline characteristics. The date of the first record of diagnosis, which is an indicator of the length of diagnosis, was reported, although we cannot be certain whether it is the first diagnosis or the first record of diagnosis only, if for example they moved General Practice (GP) after their initial diagnosis.

Due to the large number of analyses, COPD definition 2 and MART definition 2 were selected to be evaluated for the adverse events analysis. For the prescribing prevalence analysis, only COPD definition 1 was considered, as this is the subgroup for which amalgamated data was available. The definition for COPD definitions 2 and 3 were adjusted to include patients in the subgroups if they had missing values of FEV_1 % predicted or eosinophil counts respectively and these could be recorded at any time.

Surprisingly, a high proportion of patients prescribed an FDC ICS/LABA without a diagnosis were identified. Therefore, a brief evaluation of who these patients were and the possible reasons they could be prescribed this therapy without a diagnosis of asthma or COPD was conducted.

As raised by CPRD, the reason for an outpatient visit is not usually well recorded, which was observed in stage 1, with a low number of asthma and COPD outpatient visits recorded. Therefore, for stage 2, outpatient visits with a “Respiratory” treatment specialty, rather than those specific to asthma or COPD, were considered.

Lastly, in addition to presenting the prescribing rate, the number and percentage of patients receiving each FDC ICS/LABA from each subgroup was reported.

5 Research methods

5.1 Study design

This study was a descriptive (prescribing prevalence and patient characterisation) and exploratory (evaluation of adverse events), historical cohort database study of patients initiating on FP/FOR and other FDC ICS/LABA therapy on or after 25th September 2015 (launch of FP/FOR) and 24th September 2015 (36 months post launch).

5.2 Setting

The extracted cohort consisted of all patients ≥4 years old captured in CPRD during the period from 25th September 2015 until 24th September 2015 (i.e. 36-months post UK launch of FP/FOR, where FP/FOR launch was on 25th September 2012) who initiated on any FDC ICS/LABA [including FP/FOR, fluticasone/salmeterol (FP/SAL), budesonide/formoterol (BUD/FOR), beclomethasone/formoterol (BDP/FOR)].

5.3 Subjects

The extracted cohort consisted of all patients captured in CPRD who initiated on any FDC ICS/LABA [including FP/FOR, fluticasone/salmeterol (FP/SAL), budesonide/ formoterol (BUD/FOR) and beclomethasone/formoterol (BDP/FOR) (see section J)] during the period from 25th September 2012 until 24th September 2015 (i.e. 36-months post UK launch of FP/FOR, where FP/FOR launch was on 25th September 2012). To be included in the cohort, patients either initiated on their first FDC ICS/LABA during the study period (having not been prescribed an FDC ICS/LABA previously) or switched FDC ICS/LABA during the study period (i.e. initiate a new FDC ICS/LABA during the study period, having been prescribed an FDC ICS/LABA previously). Each patient only appeared once in the database constructed for analysis, considering their first initiation on or switch to FDC ICS/LABA during the specified study period.

The evaluation of prescribing prevalence considered those patients who initiate on or switch to FDC ICS/LABA during the 36 months post UK launch of FP/FOR (25th September 2012 – 24th September 2015). The patients used for the denominator data (number of patients in CPRD and each of the asthma and COPD subgroups) were provided as aggregate data by CPRD and similarly covers patients within the CPRD during the 36 month period post launch

of FP/FOR (25th September 2012 to 24th September 2015)*.

The evaluation of adverse events and patient characteristics considered those patients who initiated on or switched to FDC ICS/LABA during the period from 25th September 2012 until 24th September 2015. For each patient, the initiation on FDC ICS/LABA or first switch to a different FDC ICS/LABA during the study period was be considered as the index date. These patients required one year of data prior to the index date which formed a baseline period of 12 months (for patient characterisation and confounder definition). Both initiation and first switch are referred to as initiation from here onwards, unless otherwise specified.
The analyses considered licensed and off-label subgroups which are:

- Patients aged ≥18 years with asthma (asthma patients with comorbid COPD were included in this category)
- Patients aged ≥12 years and <18 years with asthma
- Patients aged ≥4 and <12 years with asthma
- Patients with COPD (and no asthma) (aged ≥31 years†)
    - Definition 1) COPD and no asthma (using QOF Read codes)
    - Definition 2) definition 1 plus FEV_1/FVC ratio<0.7 or not recorded (most recent value recorded at any time)‡
    - Definition 3) definition 2 plus blood eosinophil count ≤0.4x10^9/L or not recorded (as a proxy for asthma using most recent value recorded at any time)
- Patients prescribed ICS/LABA as the "MART" (i.e., maintenance and reliever therapy) regimen (aged ≥18 years with diagnosis of asthma)‡
    - Definition 1: Self-management plan prescribing instructions for FDC ICS/LABA at index date (e.g. "as directed") and absence of SABA prescribing at or in the year after the index date (both criteria must be fulfilled)
    - Definition 2: Self-management plan prescribing instructions for FDC ICS/LABA (e.g. "as directed") at index date and absence of SABA prescribing at or in the year after the index date and presence of SABA prescribing in year prior to index date (all criteria must be fulfilled)

The comparison groups for FP/FOR were other FDC ICS/LABA therapies, licensed for that

* Patients identified for the denominator data must be within the CPRD during this period but it is acceptable that they may have had diagnosis of asthma/COPD and/or measurements of FEV1/FVC ratio/blood eosinophil count recorded during or any time prior to this 36 month period (using most recent values for FEV1/FVC ratio/blood eosinophil count if more than one available) to be counted within the licensed and off-label subgroups.
† COPD is very rare under the age of 31 in the UK
‡ Considered for patient characterisation and adverse events analyses only

indication in the UK.

(i) Patients aged ≥18 years with asthma

Flutiform MDI (FP/FOR):

1. Licensed: 50/5, 125/5, 250/10

Licensed comparators

1. Seretide DPI (FP/SAL) 100/50, 250/50, 500/50
2. Seretide MDI (FP/SAL) 50/25, 125/25, 250/25
3. Symbicort Turbohaler (BUD/FOR) 100/6, 200/6, 400/12
4. Fostair MDI or NEXThaler* (BDP/FOR) 100/6, 200/6†

(ii) Patients aged ≥12 years and <18 years with asthma

Flutiform MDI (FP/FOR):

1. Licensed: 50/5, 125/5
2. Off-label: 250/10

Licensed comparators:

1. Seretide DPI (FP/SAL) 100/50, 250/50, 500/50
2. Seretide MDI (FP/SAL) 50/25, 125/25, 250/25
3. Symbicort Turbohaler (BUD/FOR) 100/6, 200/6, 400/12

(iii) Patients aged ≥4 and <12 years with asthma

Flutiform MDI (FP/FOR):

1. Off-label: 50/5, 125/5, 250/10

Licensed comparators:

Aged 4–11 years: Seretide (FP/SAL) DPI: 100/50; MDI 50/25

Aged 6-12 years: Symbicort Turbohaler (BUD/FOR) 100/6

(iv) Patients with COPD (and no asthma)

Flutiform MDI (FP/FOR):

1. Off-label: 50/5, 125/5, 250/10

Licensed comparators:

1. Seretide DPI (FP/SAL) 500/50
2. Symbicort Turbohaler (BUD/FOR) 200/6, 400/12
3. Fostair MDI‡ or NEXThaler§ (BDP/FOR) 100/6

(v) Prescribed FDC ICS/LABA as the "MART" regimen

Flutiform MDI (FP/FOR):

* Licensed use of Fostair NEXThaler 100/6 in patients aged ≥18 years with asthma from October 2014
† Licensed use of Fostair MDI and Fostair NEXThaler 200/6 in patients aged ≥18 years with asthma from December 2015
‡ Licensed use of Fostair MDI 100/6 in COPD from April 2014
§ Licensed use of Fostair NEXThaler 100/6 in COPD from December 2015

1. Off-label: 50/5, 125/5, 250/10

Licensed comparators:

1. Symbicort Turbohaler (BUD/FOR) 100/6, 200/6
2. Fostair MDI* (BDP/FOR) 100/6

5.4 Variables

Patient characterisation was based on the variables listed below.

(i) Variables examined at (or closest to) the index date:

- Age (at index date)
- Gender
- Height (measurement closest to index date)
- Weight (measurement closest to index date)
- Body Mass Index (BMI) (calculated from height and weight data if available, taken from practice recorded BMI value if not (closest to index date))
- Lung function, in terms of percent predicted peak expiratory flow (PEF)† and percent predicted (forced expiratory volume in 1 second) FEV_1 (PEF only for asthma subgroups <18 years; percent predicted FEV_1 for COPD subgroups only) (closest to index date)
- Smoking status (closest to index date)
- Prescribed FDC ICS/LABA inhaler device, strength (labelled dose per puff), dosing instructions (puffs per day) and prescribed dose per day (dose per puff*puffs per day) (at index date)
- Other respiratory medication prescribed (strength (dose per puff) and dosing instructions (puffs per day)) (SABA, SAMA, LABA, LAMA, ICS, Theophylline, LTRA) (yes/no for Theophylline and LTRA) (at index date)

(ii) Variables examined in the year prior to the index date or ever prior to index date (where data available):

- Indication: asthma and/or chronic obstructive pulmonary disease (COPD)
- Date of first asthma/COPD diagnosis
- Duration of asthma/COPD (to index date)
- Presence of comorbid rhinitis (diagnosis in year prior to index date OR diagnosis ever prior to index date and ≥2 prescriptions for therapy in year prior to index date)
- Presence of comorbid eczema (diagnosis in year prior to index date OR diagnosis ever prior to index date and ≥2 prescriptions for therapy in year prior to index date)
- Presence of comorbid GERD (diagnosis in year prior to index date OR diagnosis ever prior to index date and ≥2 prescriptions for therapy in year prior to index date)
- History of ischemic heart disease (diagnosis ever prior to index date)

* Licensed use of Fostair MDI 100/6 in MART from March 2013

† PEF calculated using Roberts' Equations for adults and Rosenthal's Equations for paediatrics (and incorporating Robinson's Equation for paediatrics ≤1.1m tall).

- History of hypertension (diagnosis ever prior to index date)
- History of ischemic heart disease AND hypertension (diagnosis ever prior to index date)
- Other important unrelated co-morbidities expressed using the Charlson Comorbidity Index (CCI) (year prior to index date)
- Number of respiratory GP consultations that did not result in a prescription for an oral corticosteroid (year prior to index date)
- Number of asthma/COPD (as appropriate for the subgroup) GP consultations that did not result in a prescription for an oral corticosteroid (year prior to the index date)
- Number of respiratory hospital outpatient attendances based on patient having outpatient attendance with treatment speciality recorded as "Respiratory" (year prior to the index date)
- Number of lower respiratory inpatient hospitalisations (year prior to the index date)
- Number of asthma/COPD (as appropriate for the subgroup) inpatient hospitalisations (year prior to the index date)
- Number of asthma/COPD exacerbations (as appropriate for the subgroup)[*] (year prior to index date)
- Number of inhalers prescribed (for each class of therapy separately) (year prior to index date) (SABA, SAMA, LABA, LAMA, ICS, FDC ICS/LABA, Theophylline, LTRA) (number of prescriptions for Theophylline and LTRA)
- Prescription of a spacer (year prior to index date)
- Other medications:
    - Number of pain-relief medication prescriptions (year prior to index date)
    - Number of non-steroidal anti-inflammatory drugs (NSAIDs) prescriptions (year prior to index date)
    - Number of beta-blocker prescriptions (year prior to index date)
- Duration of continuous data available prior to the index date

(iii) Variables examined after index date:

- Duration of FDC ICS/LABA prescription exposure (defined as time from index date to the end of exposure to medication; where the end of exposure to medication is the earlier of (i) date of last prescription of FDC ICS/LABA initiated at the index date + 60 days or (ii) date of another ICS/LABA prescription (either separate or fixed dose))
- Length of follow-up (defined as time from index date to end of records or death)

Adverse events evaluated (outside of any asthma-related events) included:

i. COPD exacerbations[†]

[*] Asthma exacerbations: Asthma-related hospital admission/A&E attendance OR an acute course of oral corticosteroids; COPD exacerbations: COPD-related hospital admission/A&E attendance OR an acute course of oral corticosteroids OR antibiotics prescribed with lower respiratory consultation; Events within two weeks of each other are assumed to be the same event, and were classified as such. Hospital admission and emergency room attendance were identified using HES data

[†] For the adverse events analysis, moderate and severe COPD exacerbations were evaluated: COPD-related hospital admission/emergency room attendance OR an acute course of oral corticosteroids OR antibiotics prescribed with lower respiratory consultation; events within two weeks of each other were

ii. Lower respiratory tract infection (including pneumonia)*
iii. Pneumonia†
iv. Pulmonary embolism
v. Tuberculosis
vi. Oral candidiasis
vii. Dysphonia/hoarse voice
viii. Other local oral adverse events
ix. Adrenal failure
x. Cardiac arrhythmias or ischemia
xi. Hyperglycaemia diagnosis or indication for hyperglycaemia, such as raised blood glucose
xii. Diagnosis of type 2 diabetes mellitus
xiii. Anaphylactic reactions
xiv. Cataract diagnosis
xv. Glaucoma diagnosis
xvi. Hypokalaemia diagnosis
xvii. Diagnosis of anxiety or depression
xviii. Growth retardation‡
xix. Reduced bone mineral density (including osteoporosis, osteoporosis-related fracture, osteopenia or DXA scan result osteoporotic/osteopenic)
xx. All new events – i.e. the event occurs for the first time EVER in the patient's record after initiation of FDC ICS/LABA (only for adverse events and not for serious adverse events)

The outcome period for assessment of adverse events was calculated as ending on the earliest of the following:

- End of FDC ICS/LABA prescription exposure
- End of available records

assumed to be the same event, and were classified as such. Hospital admission and emergency room attendance were identified using HES data and so this analysis was only conducted in those with linked HES/ONS data. For the serious adverse events analysis, inpatient hospitalisations and deaths linked to a ICD-10 COPD code were evaluated. COPD as an adverse events and serious adverse event was only assessed for the COPD subgroups.

* Events within six weeks of each other were assumed to be the same event, and were classified as such

† Events within four weeks of each other are assumed to be the same event, and were classified as such

‡ To be assessed for the asthma subgroups <18 years only. Assessment via height records was not possible so this was assessed via Read code diagnoses (amount of height data is described, in terms of proportion of patients with height measurement pre and post index date)

- Death

For analysis of adverse events and serious adverse events, a maximum of one event per patient after the index date was counted for each analysis. For the analysis of COPD exacerbations, LRTI, pneumonia, “any new adverse events” and “any serious adverse event” a requirement was included for twelve months of follow-up data.

“All new events” was defined as any of the events (from the list above) occurring for the first time ever in the patient’s record after initiation of FDC ICS/LABA. When evaluating COPD exacerbations, lower respiratory tract infections, pneumonia, pulmonary embolism and tuberculosis, adverse events after the index date were counted regardless of the number of events before the index date. For all other adverse events (vi-xix), only patients without the occurrence of the adverse event at baseline were considered at risk.

Due to the limitation of historical database studies where data is primarily taken from primary care databases, the definition of “serious adverse events” for this study was made mostly in line with the intent of European Medicines Agency ICH Topic E 2 A publication on *Clinical Safety Data Management: Definitions and Standards for Expedited Reporting*[*]. The following was considered to be “serious adverse events” for this study. Adverse events (as listed above i-xiv) that (at any dose):

(i) Result in death
(ii) Require inpatient hospitalisation

Serious adverse events were identified from primary and secondary cause ICD-10 codes linked to inpatient hospitalisations and deaths occurring in the cohort (see below for methods to develop ICD-10 code lists). All serious adverse events during the outcome period were reported regardless of prior serious adverse events.

As this is a health records based epidemiological study in which no causality information is available directly or through follow-up, there can be no adverse reaction reporting. Safety analyses of adverse events was only presented within the context of this study.

5.5 Data sources and measurement

This study was conducted using the Clinical Practice Research Datalink (CPRD) [1]. The CPRD is a large computerized primary care database and contains de-identified, longitudinal

[*] *Biomedical Coding Schemes Using UMLS (extended abstract)*. Available online at: http://www.ncsu.edu/chass/philo/LACSI.Abstract.pdf

data from 5 million active medical records from more than 600 subscribing practices throughout the UK. A practice-based quality marker, the “up-to-standard date”, is generated by the CPRD for each subscribing practice and data subsequent to the practice up-to-standard date are considered to be acceptable, research quality, prospectively recorded data. The CPRD is well-validated and used frequently for medical and health research.

Linked databases to CPRD were used including, hospital episode statistics (HES) to qualify hospital-associated events and Office of National Statistics (ONS) Mortality Data to provide more specific information around cause of death. HES and ONS data were used, as in general, they provide more complete and reliable detailed information on inpatient hospitalisations, outpatient attendances and deaths than GP records. HES data was used to identify inpatient hospitalisation associated with adverse events and for patient characterisation regarding hospitalisation (including asthma/COPD/lower respiratory outpatient attendances and inpatient hospitalisations and asthma/COPD exacerbations). ONS data was used to identify deaths associated with adverse events. CPRD estimated that 55% of the patients in their database who meet the inclusion and exclusion criteria for this study would be eligible for linkage. The study population was not restricted to those eligible for linkage as not all endpoints of interest related to hospital-associated events or death. However, analyses regarding hospital-associated events and deaths were only conducted in the subgroup of patients eligible for linkage to HES/ONS data, using data from HES/ONS.

The patients to be used for the denominator data (number of patients in CPRD and each of the asthma and COPD subgroups) were provided as aggregate data by CPRD and similarly covered patients within the CPRD during the 36 month period post launch of FP/FOR (25th September 2012 to 24th September 2015). The patients identified for the denominator data were within the CPRD during this period but they may have had diagnosis of asthma/COPD and/or measurements of FEV_1/FVC ratio/blood eosinophil count recorded any time prior to this 36 month period (using most recent values for FEV_1/FVC ratio/blood eosinophil count if more than one available) to be counted within the licensed and off-label subgroups.

The procedure for developing Read, product and ICD-10 code lists is described below. Search terms were selected based on clinical advice and literature research. These search terms were used to look for Read codes in both version 2 and 3 of the NHS Read code browser, product codes in CPRD’s code browser and ICD-10 codes in the WHO ICD-10 browser. Following this, lists of appropriate Read codes were compiled and cross checked with QOF Read code lists where available. The code lists were reviewed by OPRI’s clinical advisers and

codes added and removed as appropriate for the definition of the variable and the sensitivity required. All code lists were finalised and agreed before analysis of the data begins.

5.6 Bias

All the patients selected for this study were obtained from a large primary care database and relatively few inclusion and exclusion criteria were applied so in this way selection bias should be minimised. However, the period of follow-up may have differed between the FP/FOR and comparators groups, so this was reported and incidence rate and rate of occurrence of first adverse events considered, in order to account for any differences. Misclassification may have occurred but as the data used was historical and routinely recorded, differential misclassification between groups was not expected.

5.7 Study size

We intended to use all patients available in CPRD who were eligible for the study. A feasibility count from CPRD identified 239,176 research quality (acceptable) patients with a prescription for an FDC ICS/LABA during the study period. This included 10,589 patients prescribed FP/FOR. From the results from stage 1, we expected the following population size and power to detect a two-fold increase in risk for each population, assuming the smallest comparator group had three times as many patients in it as FP/FOR (Table 1).

Population	Estimated proportion of patients prescribed FP/FOR	Estimated number of patients on FP/FOR in population	Estimated number in smallest comparator group	Power		
				Adverse event with incidence rate of 0.2 per 100 person years	Adverse event with incidence rate of 2 per 100 person years	Adverse event with incidence rate of 30 per 100 person years
On-label Asthma patients	82%	8,683	26,049	78%	99%	99%
Off-label Asthma patients	1%	106	318	<10%	<10%	81%
COPD definition 1	7%	741	2224	<10%	71%	99%
MART Definition 1	2.5%	264	794	<10%	23%	99%

Table 1: Estimated power for potential incidence rates of adverse events

5.8 Data transformation

No transformations were performed on the data. Quantitative data were categorised either based on existing widely used categorisations, such as underweight, normal weight,

overweight and obese for BMI, or into equal frequency groupings.

5.9 Statistical methods

5.9.1 General

All statistical analyses were conducted using STATA version 14 (StataCorp, College Station, TX: StataCorp LP) and SAS version 9.3 (SAS Institute, Cary, NC).

Variables measured on interval or ratio scale were summarised using the following summary statistics: number of non-missing records (n), minimum, maximum, mean and standard deviation (SD) and median, 25th & 75th percentile. Categorical data were summarised as the number and percentage of patients in each category. In accordance with CPRD policy no cells were presented with fewer than five events.

5.9.2 Prescribing incidence

The rate per 1000 person years of patients prescribed FP/FOR and each FDC ICS/LABA was estimated for all subgroups (see section 5.3) using the following:

Rate of prescribing FDC ICS/LABA per 1000 person years =

$$\frac{Number\ of\ patients\ prescribed\ FDC\ ICS/LABA}{Total\ number\ of\ person\ years} * 1000$$

- The “Number of patients prescribed FDC ICS/LABA” was obtained from patient data
- The ‘Total number of person years’ was obtained as aggregate data for each subgroup over the time period of interest from CPRD (25th September 2012 to 24th September 2015)

Additionally, the number and percentage of patients receiving each FDC ICS/LABA from each subgroup was presented.

The prescribing incidence population was used for this analysis.

5.9.3 Adverse events and serious adverse events evaluation

These analyses were reliant on having enough patients and events and the results from stage 1 indicated that some groups would be very small. If there were less than 20 events in the FP/FOR cohort, results were summarised but not analysed. The following analyses were carried out for each subgroup (see section 5.3) and for both adverse events and serious adverse events.

5.9.3.1 Incidence rates and survival plots

- Incidence rates with 95% confidence intervals (CI) were evaluated using a Poisson distribution* for each adverse event for each FDC ICS/LABA
- Kaplan-Meier survival plots were constructed for each adverse event, showing each FDC ICS/LABA

5.9.3.2 Main analysis

- **Estimation of crude hazard ratio.** For each of the adverse events the hazard ratio (95% confidence interval) was estimated for new FP/FOR users compared to each comparator group using Cox Regression models (i.e. FP/FOR was reference group).
- **Estimation of adjusted hazard ratio.** For each of the adverse events, the adjusted hazard ratio (95% confidence interval) was estimated, adjusting for a priori confounders and a selection of other potential confounders. For the other potential confounders, the decision of inclusion was based on comparing the crude HR for FP/FOR to the HR for FP/FOR in a model adjusted for only the potential confounding factor. If the adjusted HR differed more than 5% from the unadjusted estimate, the potential confounder was included in the multivariable model. Assumptions behind the models were examined using log-min-log and -log(survival) plots.

Due to the estimated small number of deaths and inpatient hospitalisations associated with adverse events, serious adverse events were firstly combined into adverse events associated with inpatient hospitalisation and adverse events associated with death (adverse events considered in section 5.4). If >5 events occurred for a specific adverse event associated with inpatient hospitalisation or death then these were presented separately.

To evaluate whether initiation/switch status had an effect on the FP/FOM vs other FDC ICS/LABA comparisons, an interaction between treatment and initiation/switch status was added into the adjusted model. Estimates of the hazard ratios are presented for each comparison.

* It was intended that confidence intervals would be evaluated assuming a negative binomial distribution, however due to non-convergence a Poisson distribution was used instead

The patient characterisation and adverse events population was used for this analysis.

5.9.4 Subject disposition and characterisation

Patients were characterised according to variables listed in section 5.4. Summary statistics were produced in accordance with section 5.9.1.

5.9.5 Confounding

A priori and other potential confounders were identified prior to analysis.

Covariates a priori used as confounders in all adjusted models were:

- Age (continuous)
- Gender
- BMI (continuous)
- %predicted PEF for asthma subgroups / %predicted FEV1 for COPD subgroups (continuous)
- Smoking status (categorised as current, ex and never smoker)
- Initiator /Switch status
- Prescribed (FDC ICS/LABA) ICS dose per day at index date (dose per puff*puffs per day – FP equivalent) (not for pulmonary embolism, tuberculosis, cardiac arrhythmias/ischaemia or hypokalaemia) (continuous)

Potential confounders considered were:

- Respiratory medication prescribed in year prior to and including the index date (yes/no for each of SABA, SAMA, LABA, LAMA, ICS only, LTRA, Theophylline)
- Comorbidities (yes/no for each) and CCI score (continuous)
- Other prescriptions (spacer, pain-relief medications, NSAIDS, beta-blockers) (yes/no for each)
- Comorbid COPD (for ≥18 asthma subgroup and MART subgroup only)
- Baseline lower respiratory/asthma/COPD GP consults without oral corticosteroid (continuous)
- Baseline respiratory outpatient attendances (yes/no)*****
- Baseline lower respiratory, asthma or COPD inpatient hospitalisation (yes/no)*
- Baseline values of outcome of interest (for COPD exacerbations, LRTI, pneumonia, pulmonary embolism and tuberculosis) (continuous)

* Only considered for models where outcome is based on HES data

5.9.6 Handling of missing values

For all variables, only the observed data from the patients was used in the statistical analyses, i.e. there was no plan to estimate (impute) missing data. However, data were imputed on the dosing instructions given for FP/FOR, FP/SAL MDI and FP/SAL DPI due to the low availability of data, particularly for FP/SAL DPI. It was assumed for the MDIs that the dosing instructions would be two puffs twice a day and for the DPI, one puff twice a day. No dosing instructions were imputed for BDP/FOR or BUD/FOR as they can be prescribed as part of the MART regimen. This was done in order to be able to adjust for daily dose of FDC ICS/LABA in the adjusted models without losing a large number of patients for these analyses. Daily dose was presented before and after imputation in the characterisation so the effect of the imputation can be seen.

The percentage of missing data was reported to show the representativeness of the summary statistics. Missing data was not estimated to be a major issue for key patient characteristics, such as age, sex and QOF recorded comorbidities, which are reliably recorded by GPs in primary care databases. Other patient characteristics may be more poorly recorded. However, there was no expectation of any differential misclassification between the groups to be compared.

5.9.7 QC activities related to quality assessment and verification of programs

In accordance with our internal procedures copies of all programmes, logs and output were passed onto a second statistician for review. The analyses of COPD exacerbations, lower respiratory tract infection (including pneumonia), cardiac arrhythmias and ischemia were fully reviewed.

5.10 Quality control

As mentioned in section 5.5, a practice-based quality marker, the “up-to-standard date”, is generated by the CPRD for each subscribing practice. Data subsequent to the practice “up-to-standard date” are considered to be acceptable, research quality, prospectively recorded data. Additionally, as mentioned in section 5.9, data checking and exploratory data analysis were performed for variables in the dataset before any outcomes analysis. This enabled variables to be checked, for example, for validity of data, missing data and outliers (which

were checked and inaccurately coded data labelled as missing). See section 5.9.7 for details on QC activities.

As this was a study based on secondary use of data, for safety monitoring and safety reporting purposes, where there was a safety relevant result, it was provided on an aggregate level only (no reporting on an individual case level is required) and adverse events were not cross tabulated with other identifiable factors. Therefore, as all data was anonymised and presented on an aggregate level only, this ensured confidentiality was preserved for all patients included in the cohort.

6 Results

6.1 Participants

Of 241,007 patients with an FDC ICS/LABA prescription between 25th September 2012 and 24th September 2015, 87,466 patients met the inclusion criteria to be analysed for prescribing incidence (Figure 1). Of these, 57,543 had a diagnosis of asthma (52,970 ≥18 years, 2470 ≥12 and <18 years, 2103 ≥4 and <12 years). 15,742 had a diagnosis of COPD and were aged ≥31 years. 14,177 patients did not have a recorded diagnosis of asthma or COPD.

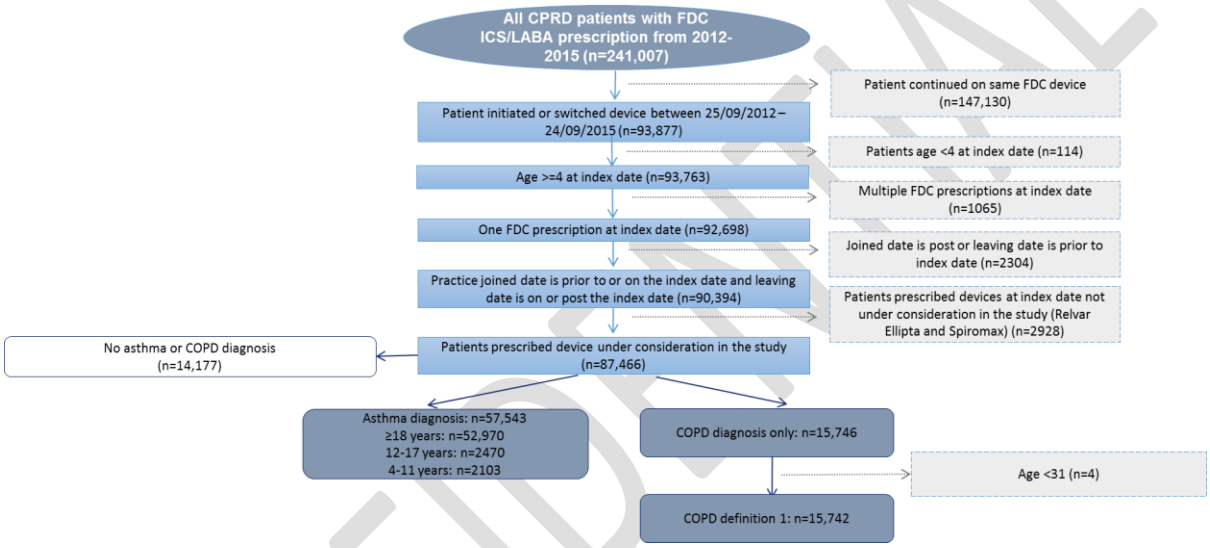

Figure 1: Patient flowchart – Prescribing incidence

For the characterisation and adverse events analysis, of 241,007 patients with an FDC ICS/LABA prescription between 25th September 2012 and 24th September 2015, 44,932 patients had a diagnosis of asthma and were prescribed either FP/FOR or other licensed comparators for that subgroup (41,609 ≥18 years, 1865 ≥12 and <18 years, 1458 ≥4 and <12 years) (Figure 2). Of these, 1437 patients met the criteria for MART definition 1 and 641 patients for MART definition 2. There were 8879 patients identified with a diagnosis of COPD, who were prescribed either FP/FOR or other licensed comparators and were aged ≥31 years (definition 1); 8212 and 7396 patients respectively met the criteria for COPD definitions 2 and 3. 11,187 patients did not have a recorded diagnosis of asthma or COPD.

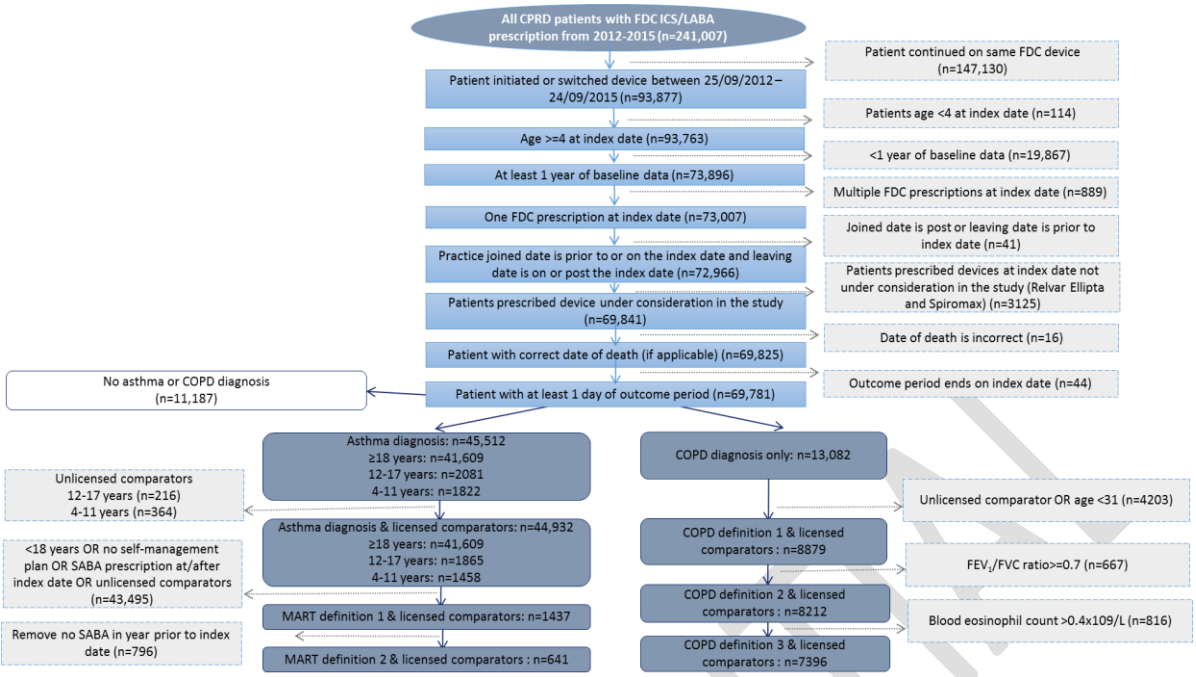

Figure 2: Patient flowchart – Patient characterisation and analysis of adverse events

6.2 Descriptive data

For patient characterisation and adverse events, only patients within the three asthma subgroups (≥18 years, ≥12 and <18 years, ≥4 and <12 years), COPD definition 2 and MART definition 2 were analysed. For the subgroups analysed, between 43% and 67% of patients had HES/ONS linked data available (Table 2). Where outcomes required 12 months follow-up data, between 40% and 57% of patients were eligible. When HES data was also required the percentage of eligible patients dropped to between 17% and 32%.

		Cohort						
		FP/FOR (n=7062)		Comparators (n=62719)				Total (n=69781)
Population		FP/FOR On-label (n=5954)	FP/FOR Off-label (n=1108)	FP/SAL DPI (n=14576)	FP/SAL MDI (n=16444)	BUD/FOR (n=16980)	BDP/FOR (n=14719)	
No recorded diagnosis	Total n(% cohort total)	NA	623 (56%)	2208 (15%)	2656 (16%)	3946 (23%)	1754 (12%)	11187
Asthma patients aged ≥18 years	Total n(% cohort total)	5727 (96%)	NA	6865 (47%)	8948 (54%)	9128 (54%)	10941 (74%)	41609
	Patients with HES n(% population total)	2685 (47%)		4221 (61%)	5187 (58%)	5166 (57%)	6101 (56%)	23360
	Patients with ≥ 1 year of follow-up n(% population total)	2626 (46%)		3060 (45%)	4071 (45%)	4258 (47%)	4966 (45%)	18981
	Patients with HES and ≥ 1 year of follow-up n(% population total)	1169 (20%)		1796 (26%)	2128 (24%)	2245 (25%)	2609 (24%)	9947
Asthma patients aged ≥12 years and <18 years	Total n(% cohort total)	227 (4%)	21 (2%)	288 (2%)	760 (5%)	569 (3%)	NA	1865
	Patients with HES n(% population total)	116 (51%)	13 (62%)	148 (51%)	451 (59%)	300 (53%)		1028
	Patients with ≥ 1 year of follow-up n(% population total)	124 (55%)	10 (48%)	125 (43%)	359 (47%)	265 (47%)		883
	Patients with HES and ≥ 1 year of follow-up n(% population total)	64 (28%)	n<5	48 (17%)	194 (26%)	122 (21%)		431
Asthma patients aged ≥4 and <12 years	Total n(% cohort total)	NA	27 (2%)	149 (1%)	1047 (6%)	235 (1%)	NA	1458
	Patients with HES n(% population total)		14 (52%)	81 (54%)	608 (58%)	131 (56%)		834
	Patients with ≥ 1 year of follow-up n(% population total)		n<5	75 (50%)	602 (57%)	114 (49%)		795
	Patients with HES and ≥ 1 year of follow-up n(% population total)		n<5	33 (22%)	336 (32%)	57 (24%)		427

		Cohort						
		FP/FOR (n=7062)		Comparators (n=62719)				Total (n=69781)
Population		FP/FOR On-label (n=5954)	FP/FOR Off-label (n=1108)	FP/SAL DPI (n=14576)	FP/SAL MDI (n=16444)	BUD/FOR (n=16980)	BDP/FOR (n=14719)	
COPD patients (definition 1)	Total n(% cohort total)	NA	437 (39%)	3923 (27%)	NA	2745 (16%)	1774 (12%)	8879
	Patients with HES n(% population total)		191 (44%)	2346 (60%)		1512 (55%)	927 (52%)	4976
	Patients with ≥ 1 year of follow-up n(% population total)		189 (43%)	2055 (52%)		1392 (51%)	694 (39%)	4330
	Patients with HES and ≥ 1 year of follow-up n(% population total)		76 (17%)	1187 (30%)		708 (26%)	339 (19%)	2310
COPD patients (definition 2)	Total n(% cohort total)	NA	399 (36%)	3678 (25%)	NA	2526 (15%)	1609 (11%)	8212
	Patients with HES n(% population total)		173 (43%)	2201 (60%)		1391 (55%)	844 (52%)	4609
	Patients with ≥ 1 year of follow-up n(% population total)		167 (42%)	1946 (53%)		1299 (51%)	639 (40%)	4051
	Patients with HES and ≥ 1 year of follow-up n(% population total)		67 (17%)	1126 (31%)		657 (26%)	312 (19%)	2162
COPD patients (definition 3)	Total n(% cohort total)	NA	350 (32%)	3333 (23%)	NA	2279 (13%)	1434 (10%)	7396
	Patients with HES n(% population total)		154 (44%)	1984 (60%)		1241 (54%)	754 (53%)	4133
	Patients with ≥ 1 year of follow-up n(% population total)		145 (41%)	1766 (53%)		1171 (51%)	573 (40%)	3655
	Patients with HES and ≥ 1 year of follow-up n(% population total)		61 (17%)	1020 (31%)		586 (26%)	279 (19%)	1946
'MART' regimen (definition 1)	Total n(% cohort total)	NA	249 (22%)	NA	NA	490 (3%)	698 (5%)	1437
	Patients with HES n(% population total)		191 (77%)			294 (60%)	377 (54%)	862
	Patients with ≥ 1 year of follow-up n(% population total)		116 (47%)			208 (42%)	304 (44%)	628
	Patients with HES and ≥ 1 year of follow-up n(% population total)		86 (35%)			125 (26%)	143 (20%)	354
'MART' regimen (definition 2)	Total n(% cohort total)	NA	75 (7%)	NA	NA	246 (1%)	320 (2%)	641
	Patients with HES n(% population total)		50 (67%)			142 (58%)	168 (53%)	360
	Patients with ≥ 1 year of follow-up n(% population total)		35 (47%)			103 (42%)	145 (45%)	283
	Patients with HES and ≥ 1 year of follow-up n(% population total)		24 (32%)			58 (24%)	72 (23%)	154

Table 2: Patients disposition including percentage with HES/ONS linked data available

6.2.1 Patients aged ≥18 years with asthma

Patients aged ≥18 years with asthma were broadly similar across the FDC ICS/LABA groups in terms of demographic characteristics (Table 3). Of note, FP/SAL DPI patients appeared to be older and less likely to be a non-smoker, have slightly more severe disease than other groups (with lower FEV1 % predicted and PEF % predicted than other groups), have a higher proportion of comorbid COPD, ischaemic heart disease and hypertension diagnoses and were prescribed higher doses of FDC ICS/LABA at index date (Table 4, Table 5). A larger proportion of FP/FOR patients were prescribed LTRA and a larger proportion of FP/SAL DPI patients were prescribed LAMA at the index date than the other groups; other prescriptions of respiratory therapy at the index date were similar. Pain relief medication prescriptions and LRTIs in the year prior to index date were higher for FP/SAL DPI. FP/FOR and BDP/FOR patients were more likely to have rhinitis and exacerbations in the year prior were more common in FP/SAL DPI group (Table 8). GP consultations were more common in the FP/SAL DPI group, with outpatient and inpatient hospitalisations more common in FP/SAL DPI and BUD/FOR groups (Table 6). Both FP/FOR and FP/SAL DPI patients were more likely to be switchers rather than initiators of their FDC ICS/LABA treatment; additionally, FP/SAL DPI patients were more likely to have been prescribed LAMA in the year prior (Table 7). CCI score was similar across all groups. Data available prior to index date, duration of FDC ICS/LABA prescription during outcome and length of follow-up was similar between the groups. Occurrence of LRTI, pneumonia and pulmonary embolism during the baseline period was higher for FP/SAL DPI patients but occurrence of tuberculosis was similar between groups (Table 8).

6.2.1.1 Demographic characteristics

		TOTAL COHORT					
	Measure	FP/FOR	FP/SAL DPI	FP/SAL MDI	BUD/FOR	BDP/FOR	p-value
Age at IPD (years)	N (% not missing)	5727 (100.0)	6865 (100.0)	8948 (100.0)	9128 (100.0)	10941 (100.0)	<0.001‡
	Mean (SD)	54.3 (17.4)	59.7 (17.4)	54.4 (18.4)	52.0 (17.9)	53.4 (17.9)	
	Median (IQR)	55 (42, 68)	62 (48, 73)	55 (41, 69)	52 (38, 66)	54 (40, 67)	
	Min, Max	18, 100	18, 100	18, 100	18, 101	18, 99	
Gender	N (% not missing)	5727 (100.0)	6865 (100.0)	8948 (100.0)	9128 (100.0)	10941 (100.0)	<0.001*
	Female, n (%)	3514 (61.4)	4103 (59.8)	5618 (62.8)	5460 (59.8)	6743 (61.6)	
	Male, n (%)	2213 (38.6)	2762 (40.2)	3330 (37.2)	3668 (40.2)	4198 (38.4)	
Height (m) - closest to IPD	N (% not missing)	5615 (98.0)	6757 (98.4)	8705 (97.3)	8847 (96.9)	10718 (98.0)	<0.001‡
	Mean (SD)	1.7 (0.1)	1.7 (0.1)	1.7 (0.1)	1.7 (0.1)	1.7 (0.1)	

		TOTAL COHORT					
	Measure	**FP/FOR**	**FP/SAL DPI**	**FP/SAL MDI**	**BUD/FOR**	**BDP/FOR**	**p-value**
	Median (IQR)	1.6 (1.6, 1.7)	1.6 (1.6, 1.7)	1.6 (1.6, 1.7)	1.7 (1.6, 1.8)	1.7 (1.6, 1.7)	
	Min, Max	(1.2, 2.1)	(1.1, 2.2)	(1.1, 2.1)	(1.2, 2.1)	(1.2, 2.1)	
Weight (kg) - closest to IPD	N (% not missing)	5603 (97.8)	6713 (97.8)	8624 (96.4)	8798 (96.4)	10633 (97.2)	<0.001‡
	Mean (SD)	81.3 (20.2)	79.7 (20.5)	80.4 (20.3)	80.8 (20.1)	81.1 (20.4)	
	Median (IQR)	79 (67, 93)	77 (65, 91)	78 (66, 92)	78.5 (66.2, 92.1)	79 (66, 93)	
	Min, Max	40, 203	40, 220	40, 235	40, 216	40, 214	
BMI (kg/m2)	N (% not missing)	5547 (96.9)	6682 (97.3)	8554 (95.6)	8713 (95.5)	10546 (96.4)	<0.001‡
	Mean (SD)	29.2 (6.6)	28.8 (6.8)	29.0 (6.7)	28.9 (6.7)	29.2 (6.8)	
	Median (IQR)	28.1 (24.6, 32.9)	27.9 (24.0, 32.5)	27.9 (24.3, 32.6)	27.8 (24.2, 32.5)	28.1 (24.5, 32.8)	
	Min, Max	(14.5, 57.8)	(13.4, 59.8)	(13.1, 60.0)	(13.7, 59.8)	14, 60	
BMI (kg/m2) (categorised)	N (% not missing)	5547 (96.9)	6682 (97.3)	8554 (95.6)	8713 (95.5)	10546 (96.4)	<0.001*
	Underweight (BMI<18.5), n (%)	84 (1.5)	184 (2.8)	196 (2.3)	179 (2.1)	200 (1.9)	
	Normal (BMI≥18.5 & BMI<25), n (%)	1463 (26.4)	1877 (28.1)	2354 (27.5)	2512 (28.8)	2810 (26.6)	
	Overweight (BMI≥25 & BMI<30), n (%)	1870 (33.7)	2133 (31.9)	2764 (32.3)	2819 (32.4)	3455 (32.8)	
	Obese (BMI≥30), n (%)	2130 (38.4)	2488 (37.2)	3240 (37.9)	3203 (36.8)	4081 (38.7)	
FEV_1 % predicted	N (% not missing)	2378 (41.5)	4163 (60.6)	4040 (45.1)	4148 (45.4)	4850 (44.3)	<0.001‡
	Mean (SD)	80.2 (23.5)	68.6 (24.3)	76.2 (23.5)	76.2 (23.6)	78.0 (23.6)	
	Median (IQR)	82 (65, 97)	68 (51, 86)	77 (60, 92)	78 (60, 93)	80 (63, 94)	
	Min, Max	6, 169	1, 193	1, 194	1, 171	3, 200	
FEV_1 % predicted (categorised)	N (% not missing)	2378 (41.5)	4163 (60.6)	4040 (45.1)	4148 (45.4)	4850 (44.3)	<0.001*
	<30 (very severe), n (%)	54 (2.3)	189 (4.5)	117 (2.9)	105 (2.5)	134 (2.8)	
	30-49 (severe), n (%)	205 (8.6)	779 (18.7)	434 (10.7)	504 (12.2)	478 (9.9)	
	50-79 (moderate), n (%)	827 (34.8)	1823 (43.8)	1608 (39.8)	1562 (37.7)	1762 (36.3)	
	80+ (mild), n (%)	1292 (54.3)	1372 (33.0)	1881 (46.6)	1977 (47.7)	2476 (51.1)	
PEF % predicted	N (% not missing)	5176 (90.4)	6019 (87.7)	7625 (85.2)	7602 (83.3)	9606 (87.8)	<0.001‡
	Mean (SD)	96.5 (26.2)	85.0 (28.3)	92.4 (26.9)	94.0 (26.9)	94.5 (26.9)	
	Median (IQR)	97.4 (78.2, 115.6)	85.0 (64.2, 105.4)	92.9 (73.5, 113.1)	95.2 (74.8, 114.7)	95.3 (75.0, 115.6)	
	Min, Max	(20.4, 150.0)	(20.0, 150.0)	(20.4, 150.0)	(20.1, 150.0)	(20.1, 150.0)	
Smoking Status	N (% not missing)	5727 (100.0)	6864 (100.0)	8945 (100.0)	9124 (100.0)	10941 (100.0)	<0.001*
	Non-smoker, n (%)	2912 (50.8)	2579 (37.6)	4185 (46.8)	4390 (48.1)	5206 (47.6)	
	Current smoker, n (%)	1014 (17.7)	1650 (24.0)	1837 (20.5)	1841 (20.2)	2223 (20.3)	
	Ex-smoker, n (%)	1801 (31.4)	2635 (38.4)	2923 (32.7)	2893 (31.7)	3512 (32.1)	

Table 3: Demographic characteristics by FDC/ICS LABA (patients aged ≥18 years with asthma)
‡ Kruskal-Wallis test, * Chi-square test, NA – not applicable

6.2.1.2 Medication prescribed at index date

		TOTAL COHORT					
	Measure	FP/FOR	FP/SAL DPI	FP/SAL MDI	BUD/FOR	BDP/FOR	p-value
Continuous data available prior index date (years)	N (% not missing)	5727 (100.0)	6865 (100.0)	8948 (100.0)	9128 (100.0)	10941 (100.0)	<0.001‡
	Mean (SD)	19.5 (13.8)	20.4 (15.6)	18.7 (14.8)	18.0 (14.0)	19.5 (14.8)	
	Median (IQR)	17.8 (8.5, 26.5)	17.7 (8.3, 27.2)	16.4 (6.9, 25.5)	16.0 (6.7, 24.7)	17.2 (7.7, 26.2)	
	Min, Max	(1.0, 85.4)	(1.0, 89.5)	(1.0, 95.2)	(1.0, 94.3)	(1.0, 92.5)	
Length of follow-up period (months)	N (% not missing)	5727 (100.0)	6865 (100.0)	8948 (100.0)	9128 (100.0)	10941 (100.0)	<0.001‡
	Mean (SD)	12.7 (10.4)	13.4 (12.5)	13.5 (11.9)	13.7 (12.0)	13.0 (11.0)	
	Median (IQR)	10.9 (2.7, 19.0)	9.6 (2.0, 22.7)	10.1 (2.1, 21.8)	10.7 (2.0, 22.1)	10.6 (2.9, 19.4)	
	Min, Max	(0.0, 42.5)	(0.0, 43.7)	(0.0, 44.0)	(0.0, 44.0)	(0.0, 44.0)	
Prescribed FDC ICS/LABA inhaler dose (dose per puff)	N (% not missing)	5727 (100.0)	6865 (100.0)	8948 (100.0)	9128 (100.0)	10941 (100.0)	<0.001*
	50/5, n (%)	n≥5	n<5	n<5	n<5	n<5	
	125/5, n (%)	n≥5	n<5	n<5	n<5	n<5	
	250/10, n (%)	n≥5	n<5	n<5	n<5	n<5	
	100/50, n (%)	n<5	n≥5	n<5	n<5	n<5	
	250/50, n (%)	n<5	n≥5	n<5	n<5	n<5	
	500/50, n (%)	n<5	n≥5	n<5	n<5	n<5	
	50/25, n (%)	n<5	n<5	n≥5	n<5	n<5	
	125/25, n (%)	n<5	n<5	n≥5	n<5	n<5	
	250/25, n (%)	n<5	n<5	n≥5	n<5	n<5	
	100/6, n (%)	n<5	n<5	n<5	n≥5	n≥5	
	200/6, n (%)	n<5	n<5	n<5	n≥5	n<5	
	400/12, n (%)	n<5	n<5	n<5	n≥5	n<5	
Prescribed FDC ICS/LABA (FP equivalent dose per day)	N (% not missing)	4928 (86.0)	3186 (46.4)	7557 (84.5)	6525 (71.5)	7827 (71.5)	<0.001‡
	Mean (SD)	652.1 (283.3)	764.8 (349.7)	617.0 (294.8)	301.6 (137.7)	428.6 (112.0)	
	Median (IQR)	500 (500, 1000)	1000 (500, 1000)	500 (500, 1000)	300 (200, 400)	500 (375, 500)	
	Min, Max	100, 2000	150, 2000	50, 2000	50, 1200	125, 1000	
Prescribed FDC ICS/LABA (FP equivalent dose per day) (categorised)	N (% not missing)	4928 (86.0)	3186 (46.4)	7557 (84.5)	6525 (71.5)	7827 (71.5)	<0.001*
	≥50 & <=100, n (%)	10 (0.2)	n<5	22 (0.3)	n≥5	n<5	
	>100 & <=200, n (%)	369 (7.5)	n≥5	1145 (15.2)	n≥5	n≥5	
	>200 & <=400, n (%)	330 (6.7)	n≥5	206 (2.7)	n≥5	n≥5	
	>400 & <600, n (%)	2310 (46.9)	n≥5	3608 (47.7)	n≥5	n≥5	
	≥600 & <1000, n (%)	124 (2.5)	n≥5	29 (0.4)	n≥5	n≥5	
	≥1000, n (%)	1785 (36.2)	n≥5	2547 (33.7)	n<5	n≥5	
Prescribed FDC ICS/LABA using imputed dosing	N (% not missing)	5727 (100.0)	6865 (100.0)	8948 (100.0)	6525 (71.5)	7827 (71.5)	<0.001‡
	Mean (SD)	652.8 (284.4)	737.4 (332.8)	625.0 (296.0)	301.7 (137.7)	428.7 (111.9)	

		TOTAL COHORT					
	Measure	FP/FOR	FP/SAL DPI	FP/SAL MDI	BUD/FOR	BDP/FOR	p-value
instructions (FP equivalent dose per day)	Median (IQR)	500 (500, 1000)	1000 (500, 1000)	500 (500, 1000)	300 (200, 400)	500 (375, 500)	
	Min, Max	100, 2000	200, 2000	50, 2000	50, 1200	125, 1000	
Prescribed FDC ICS/LABA using imputed dosing instructions (FP equivalent dose per day) (categorised)	N (% not missing)	5727 (100.0)	6865 (100.0)	8948 (100.0)	6525 (71.5)	7827 (71.5)	<0.001*
	≥50 & <=100, n (%)	10 (0.2)	n<5	22 (0.2)	n≥5	n<5	
	>100 & <=200, n (%)	471 (8.2)	n≥5	1338 (15.0)	n≥5	n≥5	
	>200 & <=400, n (%)	330 (5.8)	n≥5	206 (2.3)	n≥5	n≥5	
	>400 & <600, n (%)	2695 (47.1)	n≥5	4222 (47.2)	n≥5	n≥5	
	≥600 & <1000, n (%)	124 (2.2)	n≥5	29 (0.3)	n≥5	n≥5	
	≥1000, n (%)	2097 (36.6)	n≥5	3131 (35.0)	n<5	n≥5	
Duration of FDC ICS/LABA prescription (outcome), (months)	N (% not missing)	5727 (100.0)	6865 (100.0)	8948 (100.0)	9128 (100.0)	10941 (100.0)	<0.001‡
	Mean (SD)	13.4 (10.9)	14.1 (13.0)	14.1 (12.3)	14.4 (12.4)	13.7 (11.4)	
	Median (IQR)	11.7 (2.9, 20.2)	10 (2, 24)	10.8 (2.4, 22.6)	11 (2, 23)	11.4 (3.1, 20.5)	
	Min, Max	(0.0, 46.8)	(0.0, 48.3)	(0.0, 48.6)	(0.0, 52.3)	(0.0, 46.5)	
SABA prescriptions	N (% not missing)	5727 (100.0)	6865 (100.0)	8948 (100.0)	9128 (100.0)	10941 (100.0)	0.008*
	No, n (%)	4785 (83.6)	5667 (82.5)	7488 (83.7)	7729 (84.7)	9193 (84.0)	
	Yes, n (%)	942 (16.4)	1198 (17.5)	1460 (16.3)	1399 (15.3)	1748 (16.0)	
SAMA prescriptions	N (% not missing)	5727 (100.0)	6865 (100.0)	8948 (100.0)	9128 (100.0)	10941 (100.0)	<0.001*
	No, n (%)	5674 (99.1)	6780 (98.8)	8887 (99.3)	9081 (99.5)	10879 (99.4)	
	Yes, n (%)	53 (0.9)	85 (1.2)	61 (0.7)	47 (0.5)	62 (0.6)	
LABA prescriptions	N (% not missing)	5727 (100.0)	6865 (100.0)	8948 (100.0)	9128 (100.0)	10941 (100.0)	<0.001*
	No, n (%)	5721 (99.9)	6844 (99.7)	8935 (99.9)	9120 (99.9)	10935 (99.9)	
	Yes, n (%)	6 (0.1)	21 (0.3)	13 (0.1)	8 (0.1)	6 (0.1)	
LAMA prescriptions	N (% not missing)	5727 (100.0)	6865 (100.0)	8948 (100.0)	9128 (100.0)	10941 (100.0)	<0.001*
	No, n (%)	5571 (97.3)	6098 (88.8)	8659 (96.8)	8794 (96.3)	10628 (97.1)	
	Yes, n (%)	156 (2.7)	767 (11.2)	289 (3.2)	334 (3.7)	313 (2.9)	
ICS only prescriptions	N (% not missing)	5727 (100.0)	6865 (100.0)	8948 (100.0)	9128 (100.0)	10941 (100.0)	0.023*
	No, n (%)	5683 (99.2)	6817 (99.3)	8848 (98.9)	9039 (99.0)	10822 (98.9)	
	Yes, n (%)	44 (0.8)	48 (0.7)	100 (1.1)	89 (1.0)	119 (1.1)	
Theophylline prescriptions	N (% not missing)	5727 (100.0)	6865 (100.0)	8948 (100.0)	9128 (100.0)	10941 (100.0)	<0.001*
	No, n (%)	5679 (99.2)	6782 (98.8)	8915 (99.6)	9086 (99.5)	10879 (99.4)	
	Yes, n (%)	48 (0.8)	83 (1.2)	33 (0.4)	42 (0.5)	62 (0.6)	
LTRA prescriptions	N (% not missing)	5727 (100.0)	6865 (100.0)	8948 (100.0)	9128 (100.0)	10941 (100.0)	<0.001*
	No, n (%)	5459 (95.3)	6671 (97.2)	8779 (98.1)	8879 (97.3)	10669 (97.5)	
	Yes, n (%)	268 (4.7)	194 (2.8)	169 (1.9)	249 (2.7)	272 (2.5)	

Table 4: Medication prescribed at index date by FDC/ICS LABA (patients aged ≥18 years with asthma)
‡ Kruskal-Wallis test, * Chi-square test, NA – not applicable

6.2.1.3 Comorbidities

		TOTAL COHORT					
	Measure	FP/FOR	FP/SAL DPI	FP/SAL MDI	BUD/FOR	BDP/FOR	p-value
Presence of asthma and/or COPD	N (% not missing)	5727 (100.0)	6865 (100.0)	8948 (100.0)	9128 (100.0)	10941 (100.0)	<0.001*
	Asthma only, n (%)	5254 (91.7)	4564 (66.5)	7639 (85.4)	7793 (85.4)	9636 (88.1)	
	Asthma & COPD, n (%)	473 (8.3)	2301 (33.5)	1309 (14.6)	1335 (14.6)	1305 (11.9)	
Year of first recorded asthma diagnosis	N (% not missing)	5727 (100.0)	6865 (100.0)	8948 (100.0)	9128 (100.0)	10941 (100.0)	<0.001‡
	Mean (SD)	1996.0 (13.4)	1997.1 (13.6)	1998.3 (12.8)	1998.7 (12.9)	1997.9 (13.1)	
	Median (IQR)	1998 (1990, 2005)	2000 (1991, 2006)	2000 (1992, 2008)	2001 (1992, 2009)	2000 (1991, 2008)	
	Min, Max	1923, 2015	1919, 2015	1931, 2015	1919, 2015	1923, 2015	
Year of first recorded COPD diagnosis	N (% not missing)	474 (8.3)	2304 (33.6)	1313 (14.7)	1337 (14.6)	1309 (12.0)	<0.001‡
	Mean (SD)	2005.9 (7.5)	2005.9 (7.1)	2006.1 (7.6)	2006.7 (7.0)	2006.2 (7.3)	
	Median (IQR)	2007 (2003, 2011)	2007 (2003, 2011)	2008 (2003, 2012)	2008 (2004, 2012)	2007 (2003, 2011)	
	Min, Max	1962, 2015	1933, 2015	1936, 2015	1936, 2015	1947, 2015	
Comorbid rhinitis	N (% not missing)	5727 (100.0)	6865 (100.0)	8948 (100.0)	9128 (100.0)	10941 (100.0)	<0.001*
	No, n (%)	4892 (85.4)	6093 (88.8)	7921 (88.5)	8073 (88.4)	9492 (86.8)	
	Yes, n (%)	835 (14.6)	772 (11.2)	1027 (11.5)	1055 (11.6)	1449 (13.2)	
Comorbid eczema	N (% not missing)	5727 (100.0)	6865 (100.0)	8948 (100.0)	9128 (100.0)	10941 (100.0)	0.022*
	No, n (%)	5272 (92.1)	6327 (92.2)	8235 (92.0)	8493 (93.0)	10049 (91.8)	
	Yes, n (%)	455 (7.9)	538 (7.8)	713 (8.0)	635 (7.0)	892 (8.2)	
Comorbid GERD	N (% not missing)	5727 (100.0)	6865 (100.0)	8948 (100.0)	9128 (100.0)	10941 (100.0)	<0.001*
	No, n (%)	4965 (86.7)	5864 (85.4)	7822 (87.4)	7998 (87.6)	9491 (86.7)	
	Yes, n (%)	762 (13.3)	1001 (14.6)	1126 (12.6)	1130 (12.4)	1450 (13.3)	
History of ischemic heart disease	N (% not missing)	5727 (100.0)	6865 (100.0)	8948 (100.0)	9128 (100.0)	10941 (100.0)	<0.001*
	No, n (%)	5267 (92.0)	5948 (86.6)	8085 (90.4)	8399 (92.0)	10072 (92.1)	
	Yes, n (%)	460 (8.0)	917 (13.4)	863 (9.6)	729 (8.0)	869 (7.9)	
History of hypertension	N (% not missing)	5727 (100.0)	6865 (100.0)	8948 (100.0)	9128 (100.0)	10941 (100.0)	<0.001*
	No, n (%)	4125 (72.0)	4486 (65.3)	6464 (72.2)	6911 (75.7)	7997 (73.1)	
	Yes, n (%)	1602 (28.0)	2379 (34.7)	2484 (27.8)	2217 (24.3)	2944 (26.9)	
History of ischemic heart disease and hypertension	N (% not missing)	5727 (100.0)	6865 (100.0)	8948 (100.0)	9128 (100.0)	10941 (100.0)	<0.001*
	No, n (%)	5434 (94.9)	6315 (92.0)	8426 (94.2)	8708 (95.4)	10442 (95.4)	
	Yes, n (%)	293 (5.1)	550 (8.0)	522 (5.8)	420 (4.6)	499 (4.6)	
Charlson Comorbidity Index (CCI)	N (% not missing)	5727 (100.0)	6865 (100.0)	8947 (100.0)	9127 (100.0)	10940 (100.0)	<0.001‡
	Mean (SD)	3.8 (2.6)	3.7 (3.2)	3.8 (2.7)	3.7 (2.7)	3.9 (2.4)	
	Median (IQR)	4 (4, 4)	4 (3, 4)	4 (4, 4)	4 (4, 4)	4 (4, 4)	
	Min, Max	0, 27	0, 33	0, 31	0, 31	0, 33	
	N (% not missing)	5727 (100.0)	6865 (100.0)	8947 (100.0)	9127 (100.0)	10940 (100.0)	<0.001*
	0, n (%)	974 (17.0)	1654 (24.1)	1594 (17.8)	1706 (18.7)	1475 (13.5)	

		TOTAL COHORT					
	Measure	FP/FOR	FP/SAL DPI	FP/SAL MDI	BUD/FOR	BDP/FOR	p-value
Charlson Comorbidity Index (CCI) (categorised)	1-4, n (%)	4271 (74.6)	4428 (64.5)	6542 (73.1)	6686 (73.3)	8567 (78.3)	
	5+, n (%)	482 (8.4)	783 (11.4)	811 (9.1)	735 (8.1)	898 (8.2)	

Table 5: Comorbidities by FDC/ICS LABA (patients aged ≥18 years with asthma)
‡ Kruskal-Wallis test, * Chi-square test, NA – not applicable

6.2.1.4 Consultations and hospitalisations in year prior to index date

		TOTAL COHORT					
	Measure	FP/FOR	FP/SAL DPI	FP/SAL MDI	BUD/FOR	BDP/FOR	p-value
Respiratory GP consultations without prescription for an oral corticosteroid (categorised)	N (% not missing)	5727 (100.0)	6865 (100.0)	8948 (100.0)	9128 (100.0)	10941 (100.0)	
	0, n (%)	1660 (29.0)	1557 (22.7)	2271 (25.4)	2269 (24.9)	2829 (25.9)	
	1, n (%)	1871 (32.7)	2046 (29.8)	2620 (29.3)	2631 (28.8)	3390 (31.0)	<0.001*
	2, n (%)	1110 (19.4)	1400 (20.4)	1758 (19.6)	1844 (20.2)	2242 (20.5)	
	3+, n (%)	1086 (19.0)	1862 (27.1)	2299 (25.7)	2384 (26.1)	2480 (22.7)	
Asthma GP consultations without prescription for an oral corticosteroid (categorised)	N (% not missing)	5727 (100.0)	6865 (100.0)	8948 (100.0)	9128 (100.0)	10941 (100.0)	
	0, n (%)	2547 (44.5)	3401 (49.5)	4181 (46.7)	4477 (49.0)	4959 (45.3)	
	1, n (%)	2213 (38.6)	2370 (34.5)	3170 (35.4)	3065 (33.6)	3963 (36.2)	<0.001*
	2, n (%)	695 (12.1)	765 (11.1)	1052 (11.8)	1059 (11.6)	1404 (12.8)	
	3+, n (%)	272 (4.7)	329 (4.8)	545 (6.1)	527 (5.8)	615 (5.6)	
COPD GP consultations without prescription for an oral corticosteroid (categorised)	N (% not missing)	5727 (100.0)	6865 (100.0)	8948 (100.0)	9128 (100.0)	10941 (100.0)	
	0, n (%)	5441 (95.0)	5462 (79.6)	8152 (91.1)	8292 (90.8)	10157 (92.8)	
	1, n (%)	211 (3.7)	978 (14.2)	562 (6.3)	600 (6.6)	568 (5.2)	<0.001*
	2, n (%)	57 (1.0)	323 (4.7)	171 (1.9)	177 (1.9)	161 (1.5)	
	3+, n (%)	18 (0.3)	102 (1.5)	63 (0.7)	59 (0.6)	55 (0.5)	
Respiratory hospital outpatient attendances (categorised)	N (% not missing)	2685 (100.0)	4221 (100.0)	5187 (100.0)	5166 (100.0)	6101 (100.0)	
	0, n (%)	2541 (94.6)	3825 (90.6)	4866 (93.8)	4658 (90.2)	5748 (94.2)	<0.001*
	1+, n (%)	144 (5.4)	396 (9.4)	321 (6.2)	508 (9.8)	353 (5.8)	
Lower respiratory inpatient hospitalisations (categorised)	N (% not missing)	2685 (100.0)	4221 (100.0)	5187 (100.0)	5166 (100.0)	6101 (100.0)	
	0, n (%)	2649 (98.7)	3903 (92.5)	4988 (96.2)	4943 (95.7)	5944 (97.4)	<0.001*
	1+, n (%)	36 (1.3)	318 (7.5)	199 (3.8)	223 (4.3)	157 (2.6)	
Asthma inpatient hospitalisations (categorised)	N (% not missing)	2685 (100.0)	4221 (100.0)	5187 (100.0)	5166 (100.0)	6101 (100.0)	
	0, n (%)	2648 (98.6)	4116 (97.5)	5049 (97.3)	4920 (95.2)	5970 (97.9)	<0.001*
	1+, n (%)	37 (1.4)	105 (2.5)	138 (2.7)	246 (4.8)	131 (2.1)	
COPD inpatient hospitalisations (categorised)	N (% not missing)	2685 (100.0)	4221 (100.0)	5187 (100.0)	5166 (100.0)	6101 (100.0)	
	0, n (%)	2679 (99.8)	4031 (95.5)	5089 (98.1)	5047 (97.7)	6033 (98.9)	<0.001*
	1+, n (%)	6 (0.2)	190 (4.5)	98 (1.9)	119 (2.3)	68 (1.1)	
	N (% not missing)	2685 (100.0)	4221 (100.0)	5187 (100.0)	5166 (100.0)	6101 (100.0)	
	0, n (%)	1230 (45.8)	1431 (33.9)	2016 (38.9)	1962 (38.0)	2693 (44.1)	<0.001*

		TOTAL COHORT					
	Measure	FP/FOR	FP/SAL DPI	FP/SAL MDI	BUD/FOR	BDP/FOR	p-value
Asthma or COPD exacerbations (categorised)	1, n (%)	755 (28.1)	1071 (25.4)	1507 (29.1)	1458 (28.2)	1662 (27.2)	
	2+, n (%)	700 (26.1)	1719 (40.7)	1664 (32.1)	1746 (33.8)	1746 (28.6)	

Table 6: Consultations and hospitalisations in year prior to index date by FDC/ICS LABA (patients aged ≥18 years with asthma)
‡ Kruskal-Wallis test, * Chi-square test, NA – not applicable

6.2.1.5 Prescriptions for therapy in year prior to index date

		TOTAL COHORT					
	Measure	FP/FOR	FP/SAL DPI	FP/SAL MDI	BUD/FOR	BDP/FOR	p-value
FDC ICS+LABA inhalers	N (% not missing)	5727 (100.0)	6865 (100.0)	8948 (100.0)	9128 (100.0)	10941 (100.0)	<0.001‡
	Mean (SD)	5.4 (5.4)	5.0 (5.8)	2.6 (5.0)	2.5 (4.7)	3.3 (5.2)	
	Median (IQR)	4 (0, 10)	3 (0, 10)	0 (0, 3)	0 (0, 3)	0 (0, 6)	
	Min, Max	0, 54	0, 52	0, 77	0, 34	0, 92	
FDC ICS+LABA inhalers (categorised)	N (% not missing)	5727 (100.0)	6865 (100.0)	8948 (100.0)	9128 (100.0)	10941 (100.0)	<0.001*
	No, n (%)	1866 (32.6)	2859 (41.6)	6143 (68.7)	6308 (69.1)	6581 (60.1)	
	Yes, n (%)	3861 (67.4)	4006 (58.4)	2805 (31.3)	2820 (30.9)	4360 (39.9)	
SABA inhalers	N (% not missing)	5727 (100.0)	6865 (100.0)	8948 (100.0)	9128 (100.0)	10941 (100.0)	<0.001‡
	Mean (SD)	2.9 (5.8)	4.1 (7.3)	3.4 (6.0)	3.3 (6.0)	3.5 (6.1)	
	Median (IQR)	0 (0, 4)	1 (0, 6)	1 (0, 4)	1 (0, 4)	1 (0, 4)	
	Min, Max	0, 91	0, 84	0, 68	0, 108	0, 76	
SABA inhalers (categorised)	N (% not missing)	5727 (100.0)	6865 (100.0)	8948 (100.0)	9128 (100.0)	10941 (100.0)	<0.001*
	No, n (%)	3205 (56.0)	3349 (48.8)	4382 (49.0)	4381 (48.0)	5263 (48.1)	
	Yes, n (%)	2522 (44.0)	3516 (51.2)	4566 (51.0)	4747 (52.0)	5678 (51.9)	
SAMA inhalers	N (% not missing)	5727 (100.0)	6865 (100.0)	8948 (100.0)	9128 (100.0)	10941 (100.0)	<0.001‡
	Mean (SD)	0.3 (2.8)	0.5 (2.9)	0.2 (1.9)	0.3 (2.4)	0.2 (2.1)	
	Median (IQR)	0 (0, 0)	0 (0, 0)	0 (0, 0)	0 (0, 0)	0 (0, 0)	
	Min, Max	0, 104	0, 52	0, 52	0, 103	0, 68	
SAMA inhalers (categorised)	N (% not missing)	5727 (100.0)	6865 (100.0)	8948 (100.0)	9128 (100.0)	10941 (100.0)	<0.001*
	No, n (%)	5544 (96.8)	6437 (93.8)	8684 (97.0)	8841 (96.9)	10681 (97.6)	
	Yes, n (%)	183 (3.2)	428 (6.2)	264 (3.0)	287 (3.1)	260 (2.4)	
LABA inhalers	N (% not missing)	5727 (100.0)	6865 (100.0)	8948 (100.0)	9128 (100.0)	10941 (100.0)	<0.001‡
	Mean (SD)	0.3 (1.8)	0.6 (2.6)	0.7 (2.5)	0.5 (2.2)	0.5 (2.4)	
	Median (IQR)	0 (0, 0)	0 (0, 0)	0 (0, 0)	0 (0, 0)	0 (0, 0)	
	Min, Max	0, 40	0, 45	0, 52	0, 32	0, 48	
LABA inhalers (categorised)	N (% not missing)	5727 (100.0)	6865 (100.0)	8948 (100.0)	9128 (100.0)	10941 (100.0)	<0.001*
	No, n (%)	5424 (94.7)	6218 (90.6)	7874 (88.0)	8401 (92.0)	10006 (91.5)	

		TOTAL COHORT					
	Measure	FP/FOR	FP/SAL DPI	FP/SAL MDI	BUD/FOR	BDP/FOR	p-value
	Yes, n (%)	303 (5.3)	647 (9.4)	1074 (12.0)	727 (8.0)	935 (8.5)	
LAMA inhalers	N (% not missing)	5727 (100.0)	6865 (100.0)	8948 (100.0)	9128 (100.0)	10941 (100.0)	<0.001‡
	Mean (SD)	1.0 (4.7)	3.7 (8.3)	1.5 (5.5)	1.5 (5.4)	1.4 (5.4)	
	Median (IQR)	0 (0, 0)	0 (0, 0)	0 (0, 0)	0 (0, 0)	0 (0, 0)	
	Min, Max	0, 64	0, 104	0, 60	0, 64	0, 57	
LAMA inhalers (categorised)	N (% not missing)	5727 (100.0)	6865 (100.0)	8948 (100.0)	9128 (100.0)	10941 (100.0)	<0.001*
	No, n (%)	5342 (93.3)	5225 (76.1)	8063 (90.1)	8134 (89.1)	9958 (91.0)	
	Yes, n (%)	385 (6.7)	1640 (23.9)	885 (9.9)	994 (10.9)	983 (9.0)	
ICS only inhalers	N (% not missing)	5727 (100.0)	6865 (100.0)	8948 (100.0)	9128 (100.0)	10941 (100.0)	<0.001‡
	Mean (SD)	1.4 (3.0)	1.7 (3.6)	2.9 (4.0)	2.4 (3.8)	2.6 (3.8)	
	Median (IQR)	0 (0, 1)	0 (0, 2)	1 (0, 4)	1 (0, 3)	1 (0, 4)	
	Min, Max	0, 42	0, 48	0, 44	0, 46	0, 36	
ICS only inhalers (categorised)	N (% not missing)	5727 (100.0)	6865 (100.0)	8948 (100.0)	9128 (100.0)	10941 (100.0)	<0.001*
	No, n (%)	3992 (69.7)	4703 (68.5)	3780 (42.2)	4548 (49.8)	5265 (48.1)	
	Yes, n (%)	1735 (30.3)	2162 (31.5)	5168 (57.8)	4580 (50.2)	5676 (51.9)	
Theophylline prescriptions	N (% not missing)	5727 (100.0)	6865 (100.0)	8948 (100.0)	9128 (100.0)	10941 (100.0)	<0.001‡
	Mean (SD)	0.2 (1.6)	0.3 (2.0)	0.2 (1.7)	0.1 (1.4)	0.2 (1.6)	
	Median (IQR)	0 (0, 0)	0 (0, 0)	0 (0, 0)	0 (0, 0)	0 (0, 0)	
	Min, Max	0, 53	0, 52	0, 54	0, 51	0, 51	
Theophylline prescriptions (categorised)	N (% not missing)	5727 (100.0)	6865 (100.0)	8948 (100.0)	9128 (100.0)	10941 (100.0)	<0.001*
	No, n (%)	5595 (97.7)	6588 (96.0)	8772 (98.0)	8964 (98.2)	10729 (98.1)	
	Yes, n (%)	132 (2.3)	277 (4.0)	176 (2.0)	164 (1.8)	212 (1.9)	
LTRA prescriptions	N (% not missing)	5727 (100.0)	6865 (100.0)	8948 (100.0)	9128 (100.0)	10941 (100.0)	<0.001‡
	Mean (SD)	0.8 (2.7)	0.6 (2.6)	0.4 (2.5)	0.5 (2.1)	0.5 (2.5)	
	Median (IQR)	0 (0, 0)	0 (0, 0)	0 (0, 0)	0 (0, 0)	0 (0, 0)	
	Min, Max	0, 51	0, 52	0, 53	0, 50	0, 53	
LTRA prescriptions (categorised)	N (% not missing)	5727 (100.0)	6865 (100.0)	8948 (100.0)	9128 (100.0)	10941 (100.0)	<0.001*
	No, n (%)	5010 (87.5)	6212 (90.5)	8357 (93.4)	8338 (91.3)	10023 (91.6)	
	Yes, n (%)	717 (12.5)	653 (9.5)	591 (6.6)	790 (8.7)	918 (8.4)	
Spacer prescription	N (% not missing)	5727 (100.0)	6865 (100.0)	8948 (100.0)	9128 (100.0)	10941 (100.0)	<0.001*
	No, n (%)	4509 (78.7)	5729 (83.5)	6218 (69.5)	7958 (87.2)	8417 (76.9)	
	Yes, n (%)	1218 (21.3)	1136 (16.5)	2730 (30.5)	1170 (12.8)	2524 (23.1)	
Pain-relief medication prescriptions (categorised)	N (% not missing)	5727 (100.0)	6865 (100.0)	8948 (100.0)	9128 (100.0)	10941 (100.0)	<0.001*
	No, n (%)	3272 (57.1)	3390 (49.4)	4876 (54.5)	5392 (59.1)	6227 (56.9)	
	Yes, n (%)	2455 (42.9)	3475 (50.6)	4072 (45.5)	3736 (40.9)	4714 (43.1)	
Non-steroidal anti-inflammatory drugs (NSAIDs)	N (% not missing)	5727 (100.0)	6865 (100.0)	8948 (100.0)	9128 (100.0)	10941 (100.0)	0.421*
	No, n (%)	4519 (78.9)	5387 (78.5)	6996 (78.2)	7224 (79.1)	8555 (78.2)	

		TOTAL COHORT					
	Measure	FP/FOR	FP/SAL DPI	FP/SAL MDI	BUD/FOR	BDP/FOR	p-value
prescriptions (categorised)	Yes, n (%)	1208 (21.1)	1478 (21.5)	1952 (21.8)	1904 (20.9)	2386 (21.8)	
Beta-blocker prescriptions (categorised)	N (% not missing)	5727 (100.0)	6865 (100.0)	8948 (100.0)	9128 (100.0)	10941 (100.0)	<0.001*
	No, n (%)	5412 (94.5)	6330 (92.2)	8346 (93.3)	8457 (92.6)	10202 (93.2)	
	Yes, n (%)	315 (5.5)	535 (7.8)	602 (6.7)	671 (7.4)	739 (6.8)	

Table 7: Prescriptions for therapy in year prior to index date by FDC/ICS LABA (patients aged ≥18 years with asthma)

‡ Kruskal-Wallis test, * Chi-square test, NA – not applicable

6.2.1.6 Adverse events during baseline

		TOTAL COHORT					
	Measure	FP/FOR	FP/SAL DPI	FP/SAL MDI	BUD/FOR	BDP/FOR	p-value
Lower Respiratory Tract Infection in baseline	N (% not missing)	5727 (100.0)	6865 (100.0)	8948 (100.0)	9128 (100.0)	10941 (100.0)	<0.001*
	No, n (%)	4562 (79.7)	4640 (67.6)	6643 (74.2)	6802 (74.5)	8465 (77.4)	
	Yes, n (%)	1165 (20.3)	2225 (32.4)	2305 (25.8)	2326 (25.5)	2476 (22.6)	
Pneumonia in baseline	N (% not missing)	5727 (100.0)	6865 (100.0)	8948 (100.0)	9128 (100.0)	10941 (100.0)	<0.001*
	No, n (%)	5707 (99.7)	6765 (98.5)	8860 (99.0)	9026 (98.9)	10851 (99.2)	
	Yes, n (%)	20 (0.3)	100 (1.5)	88 (1.0)	102 (1.1)	90 (0.8)	
Pulmonary Embolism in baseline	N (% not missing)	5727 (100.0)	6865 (100.0)	8948 (100.0)	9128 (100.0)	10941 (100.0)	<0.001*
	No, n (%)	5717 (99.8)	6838 (99.6)	8925 (99.7)	9097 (99.7)	10929 (99.9)	
	Yes, n (%)	10 (0.2)	27 (0.4)	23 (0.3)	31 (0.3)	12 (0.1)	
Tuberculosis in baseline	N (% not missing)	5727 (100.0)	6865 (100.0)	8948 (100.0)	9128 (100.0)	10941 (100.0)	0.773*
	No, n (%)	n≥5	n≥5	n≥5	n≥5	n≥5	
	Yes, n (%)	n<5	n<5	n<5	n<5	n<5	

Table 8: Adverse events occurring in year prior to index date by FDC/ICS LABA (patients aged ≥18 years with asthma)

‡ Kruskal-Wallis test, * Chi-square test, NA – not applicable

6.2.2 Patients aged ≥12 and <18 years with asthma

The FP/FOR groups were small for this subgroup, particularly for the FP/FOR off-label use. Demographics characteristics and disease severity were broadly similar across all treatment groups (Table 9). Dose per day of FDC ICS/LABA and LTRA prescription at the index date was highest for the off-label FP/FOR group, although based on small numbers (Table 10). Prescription of other respiratory treatment at index date was similar across all groups. Off-label FP/FOR patients had a higher proportion of rhinitis and eczema recorded (Table 11). On-label FP/FOR and FP/SAL DPI patients were more likely to be FDC ICS/LABA switchers rather than initiators (Table 13). FP/SAL MDI and off-label FP/FOR patients were more likely to have been prescribed a spacer in the year prior. CCI score, GP consultations, hospitalisations and exacerbations were broadly similar across treatment groups (Table 12). Data available prior to index date, duration of FDC ICS/LABA prescription during outcome and length of follow-up was similar between the groups. Occurrence of LRTI during the baseline period was higher for the off-label FP/FOR group, although based on small numbers (Table 14). There was no significant difference in pneumonia at baseline between the groups and no cases of pulmonary embolism or tuberculosis.

6.2.2.1 Demographic characteristics

		TOTAL COHORT						
	Measure	FP/FOR licensed	FP/FOR off-label	FP/SAL DPI	FP/SAL MDI	BUD/FOR	BDP/FOR	p-value
Age at IPD (years)	N (% not missing)	227 (100.0)	21 (100.0)	288 (100.0)	760 (100.0)	569 (100.0)	NA	<0.001‡
	Mean (SD)	14.8 (1.6)	15.4 (1.4)	14.4 (1.7)	14.2 (1.7)	14.7 (1.7)	NA	
	Median (IQR)	15 (13, 16)	15 (15, 17)	14 (13, 16)	14 (13, 16)	15 (13, 16)	NA	
	Min, Max	12, 17	13, 17	12, 17	12, 17	12, 17	NA	
Gender	N (% not missing)	227 (100.0)	21 (100.0)	288 (100.0)	760 (100.0)	569 (100.0)	NA	0.033*
	Female, n (%)	114 (50.2)	n≥5	142 (49.3)	388 (51.1)	292 (51.3)	NA	
	Male, n (%)	113 (49.8)	n<5	146 (50.7)	372 (48.9)	277 (48.7)	NA	
Height (m) - closest to IPD	N (% not missing)	197 (86.8)	17 (81.0)	217 (75.3)	616 (81.1)	456 (80.1)	NA	.121‡
	Mean (SD)	1.6 (0.1)	1.6 (0.1)	1.6 (0.1)	1.6 (0.1)	1.6 (0.1)	NA	
	Median (IQR)	1.6 (1.6, 1.7)	1.6 (1.6, 1.6)	1.6 (1.5, 1.7)	1.6 (1.5, 1.7)	1.6 (1.5, 1.7)	NA	
	Min, Max	(1.4, 1.9)	(1.4, 1.7)	(1.4, 2.0)	(1.3, 1.9)	(1.3, 1.9)	NA	
Weight (kg) - closest to IPD	N (% not missing)	153 (67.4)	16 (76.2)	176 (61.1)	477 (62.8)	367 (64.5)	NA	.290‡
	Mean (SD)	62.0 (17.1)	70.4 (25.3)	61.4 (19.2)	59.0 (16.0)	60.3 (15.9)	NA	

		TOTAL COHORT						
	Measure	FP/FOR licensed	FP/FOR off-label	FP/SAL DPI	FP/SAL MDI	BUD/FOR	BDP/FOR	p-value
	Median (IQR)	59 (50, 70)	64.5 (54.4, 79.4)	58 (48, 71)	58 (49, 67)	58 (50, 66)	NA	
	Min, Max	(32.8, 120.2)	40, 137	28, 158	26, 125	28, 124	NA	
BMI (kg/m2) (categorised)	N (% not missing)	156 (68.7)	15 (71.4)	170 (59.0)	482 (63.4)	362 (63.6)	NA	0.082*
	Underweight, n (%)	96 (61.5)	n≥5	90 (52.9)	293 (60.8)	241 (66.6)	NA	
	Normal, n (%)	23 (14.7)	n≥5	31 (18.2)	79 (16.4)	55 (15.2)	NA	
	Overweight, n (%)	27 (17.3)	n<5	39 (22.9)	81 (16.8)	53 (14.6)	NA	
	Obese, n (%)	10 (6.4)	n<5	10 (5.9)	29 (6.0)	13 (3.6)	NA	
PEF % predicted	N (% not missing)	164 (72.2)	14 (66.7)	178 (61.8)	504 (66.3)	372 (65.4)	NA	.964‡
	Mean (SD)	96.4 (20.4)	97.5 (17.9)	95.9 (21.9)	97.3 (22.1)	96.7 (20.8)	NA	
	Median (IQR)	97.7 (81.9, 108.8)	105.6 (79.6, 108.8)	97.4 (84.8, 108.8)	97.7 (82.3, 111.8)	97.6 (84.8, 112.2)	NA	
	Min, Max	(44.1, 149.6)	(64.2, 119.4)	(20.4, 149.6)	(25.7, 150.0)	(27.9, 144.1)	NA	
Smoking Status	N (% not missing)	221 (97.4)	21 (100.0)	271 (94.1)	709 (93.3)	547 (96.1)	NA	0.006*
	Non-smoker, n (%)	n≥5	n≥5	n≥5	670 (94.5)	518 (94.7)	NA	
	Current smoker, n (%)	n≥5	n<5	n≥5	32 (4.5)	21 (3.8)	NA	
	Ex-smoker, n (%)	n<5	n<5	n<5	7 (1.0)	8 (1.5)	NA	

Table 9: Demographic characteristics by FDC/ICS LABA (patients aged ≥12 and <18 years with asthma)
‡ Kruskal-Wallis test, * Chi-square test, NA – not applicable

6.2.2.2 Medication prescribed at index date

		TOTAL COHORT						
	Measure	FP/FOR licensed	FP/FOR off-label	FP/SAL DPI	FP/SAL MDI	BUD/FOR	BDP/FOR	p-value
Continuous data available prior index date (years)	N (% not missing)	227 (100.0)	21 (100.0)	288 (100.0)	760 (100.0)	569 (100.0)	NA	<0.001‡
	Mean (SD)	11.4 (4.4)	12.9 (4.8)	10.9 (4.4)	10.6 (4.4)	11.2 (4.7)	NA	
	Median (IQR)	12.6 (8.5, 14.8)	14.5 (10.2, 16.5)	12.3 (7.7, 14.1)	12.0 (7.5, 13.8)	12.6 (7.9, 14.9)	NA	
	Min, Max	(1.2, 17.7)	(1.4, 17.7)	(1.1, 17.5)	(1.0, 17.7)	(1.0, 17.8)	NA	
Length of follow-up period (months)	N (% not missing)	227 (100.0)	21 (100.0)	288 (100.0)	760 (100.0)	569 (100.0)	NA	.077‡
	Mean (SD)	14.0 (10.3)	13.3 (11.1)	12.5 (11.1)	14.0 (11.4)	13.4 (11.8)	NA	
	Median (IQR)	12.8 (4.9, 19.6)	11.1 (4.1, 21.1)	9.2 (2.0, 21.0)	11.3 (3.8, 21.7)	10.4 (2.0, 20.6)	NA	
	Min, Max	(0.1, 41.0)	(1.0, 37.5)	(0.0, 42.2)	(0.0, 43.5)	(0.0, 43.3)	NA	
	N (% not missing)	227 (100.0)	21 (100.0)	288 (100.0)	760 (100.0)	569 (100.0)	NA	<0.001*

		TOTAL COHORT						
	Measure	FP/FOR licensed	FP/FOR off-label	FP/SAL DPI	FP/SAL MDI	BUD/FOR	BDP/FOR	p-value
Prescribed FDC ICS/LABA inhaler dose (dose per puff)	50/5, n (%)	n≥5	n<5	n<5	n<5	n<5	NA	
	125/5, n (%)	n≥5	n<5	n<5	n<5	n<5	NA	
	250/10, n (%)	n<5	n≥5	n<5	n<5	n<5	NA	
	100/50, n (%)	n<5	n<5	n≥5	n<5	n<5	NA	
	250/50, n (%)	n<5	n<5	n≥5	n<5	n<5	NA	
	500/50, n (%)	n<5	n<5	n≥5	n<5	n<5	NA	
	50/25, n (%)	n<5	n<5	n<5	n≥5	n<5	NA	
	125/25, n (%)	n<5	n<5	n<5	n≥5	n<5	NA	
	250/25, n (%)	n<5	n<5	n<5	n≥5	n<5	NA	
	100/6, n (%)	n<5	n<5	n<5	n<5	n≥5	NA	
	200/6, n (%)	n<5	n<5	n<5	n<5	n≥5	NA	
	400/12, n (%)	n<5	n<5	n<5	n<5	n≥5	NA	
Prescribed FDC ICS/LABA (FP equivalent dose per day)	N (% not missing)	200 (88.1)	19 (90.5)	151 (52.4)	647 (85.1)	395 (69.4)	NA	<0.001‡
	Mean (SD)	386.5 (144.1)	1000.0 (0.0)	369.9 (296.0)	363.0 (205.3)	214.7 (113.0)	NA	
	Median (IQR)	500 (200, 500)	1000 (1000, 1000)	200 (200, 500)	250 (200, 500)	200 (100, 200)	NA	
	Min, Max	100, 500	1000, 1000	100, 2000	100, 1000	100, 800	NA	
Prescribed FDC ICS/LABA (FP equivalent dose per day) (categorised)	N (% not missing)	200 (88.1)	19 (90.5)	151 (52.4)	647 (85.1)	395 (69.4)	NA	<0.001*
	≥50 & <=100, n (%)	n<5	n<5	n<5	n≥5	n≥5	NA	
	>100 & <=200, n (%)	n≥5	n<5	n≥5	n≥5	n≥5	NA	
	>200 & <=400, n (%)	n≥5	n<5	n≥5	n≥5	n≥5	NA	
	>400 & <600, n (%)	n≥5	n<5	n≥5	n≥5	n<5	NA	
	≥600 & <1000, n (%)	n<5	n<5	n<5	n<5	n<5	NA	
	≥1000, n (%)	n<5	n≥5	n≥5	n≥5	n<5	NA	
Prescribed FDC ICS/LABA using imputed dosing instructions (FP equivalent dose per day)	N (% not missing)	227 (100.0)	21 (100.0)	288 (100.0)	760 (100.0)	395 (69.4)	NA	<0.001‡
	Mean (SD)	388.1 (143.9)	1000.0 (0.0)	345.0 (257.8)	381.4 (222.4)	214.7 (113.0)	NA	
	Median (IQR)	500 (200, 500)	1000 (1000, 1000)	200 (200, 500)	250 (200, 500)	200 (100, 200)	NA	
	Min, Max	100, 500	1000, 1000	100, 2000	100, 1000	100, 800	NA	
Prescribed FDC ICS/LABA using imputed dosing instructions (FP equivalent dose per day) (categorised)	N (% not missing)	227 (100.0)	21 (100.0)	288 (100.0)	760 (100.0)	395 (69.4)	NA	<0.001*
	≥50 & <=100, n (%)	n<5	n<5	n<5	n≥5	n≥5	NA	
	>100 & <=200, n (%)	n≥5	n<5	n≥5	n≥5	n≥5	NA	
	>200 & <=400, n (%)	n≥5	n<5	n≥5	n≥5	n≥5	NA	

		TOTAL COHORT						
	Measure	FP/FOR licensed	FP/FOR off-label	FP/SAL DPI	FP/SAL MDI	BUD/FOR	BDP/FOR	p-value
	>400 & <600, n (%)	n≥5	n<5	n≥5	n≥5	n<5	NA	
	≥600 & <1000, n (%)	n<5	n<5	n<5	n<5	n<5	NA	
	≥1000, n (%)	n<5	n≥5	n≥5	n≥5	n<5	NA	
Duration of FDC ICS/LABA prescription (outcome), (months)	N (% not missing)	227 (100.0)	21 (100.0)	288 (100.0)	760 (100.0)	569 (100.0)	NA	.070‡
	Mean (SD)	14.7 (10.7)	13.9 (11.5)	13.0 (11.5)	14.6 (11.8)	14.0 (12.1)	NA	
	Median (IQR)	13.3 (4.9, 21.0)	11.3 (4.2, 23.0)	10 (2, 22)	11.7 (4.2, 22.7)	11.1 (2.4, 21.6)	NA	
	Min, Max	(0.1, 43.2)	(1.0, 38.4)	(0.0, 43.4)	(0.0, 45.1)	(0.0, 51.2)	NA	
SABA prescriptions	N (% not missing)	227 (100.0)	21 (100.0)	288 (100.0)	760 (100.0)	569 (100.0)	NA	0.861*
	No, n (%)	178 (78.4)	16 (76.2)	232 (80.6)	590 (77.6)	451 (79.3)	NA	
	Yes, n (%)	49 (21.6)	5 (23.8)	56 (19.4)	170 (22.4)	118 (20.7)	NA	
SAMA prescriptions	N (% not missing)	227 (100.0)	21 (100.0)	288 (100.0)	760 (100.0)	569 (100.0)	NA	NA
	No, n (%)	227 (100.0)	21 (100.0)	288 (100.0)	760 (100.0)	569 (100.0)	NA	
LABA prescriptions	N (% not missing)	227 (100.0)	21 (100.0)	288 (100.0)	760 (100.0)	569 (100.0)	NA	0.835*
	No, n (%)	n≥5	n≥5	n≥5	n≥5	n≥5	NA	
	Yes, n (%)	n<5	n<5	n<5	n<5	n<5	NA	
LAMA prescriptions	N (% not missing)	227 (100.0)	21 (100.0)	288 (100.0)	760 (100.0)	569 (100.0)	NA	<0.001*
	No, n (%)	n≥5	n≥5	n≥5	n≥5	n≥5	NA	
	Yes, n (%)	n<5	n<5	n<5	n<5	n<5	NA	
ICS only prescriptions	N (% not missing)	227 (100.0)	21 (100.0)	288 (100.0)	760 (100.0)	569 (100.0)	NA	0.887*
	No, n (%)	n≥5	n≥5	n≥5	750 (98.7)	559 (98.2)	NA	
	Yes, n (%)	n<5	n<5	n<5	10 (1.3)	10 (1.8)	NA	
Theophylline prescriptions	N (% not missing)	227 (100.0)	21 (100.0)	288 (100.0)	760 (100.0)	569 (100.0)	NA	0.027*
	No, n (%)	n≥5	n≥5	n≥5	n≥5	n≥5	NA	
	Yes, n (%)	n<5	n<5	n<5	n<5	n<5	NA	
LTRA prescriptions	N (% not missing)	227 (100.0)	21 (100.0)	288 (100.0)	760 (100.0)	569 (100.0)	NA	<0.001*
	No, n (%)	197 (86.8)	16 (76.2)	264 (91.7)	720 (94.7)	539 (94.7)	NA	
	Yes, n (%)	30 (13.2)	5 (23.8)	24 (8.3)	40 (5.3)	30 (5.3)	NA	

Table 10: Medication prescribed at index date by FDC/ICS LABA (patients aged ≥12 and <18 years with asthma)

‡ Kruskal-Wallis test, * Chi-square test, NA – not applicable

6.2.2.3 Comorbidities

		TOTAL COHORT						
	Measure	FP/FOR licensed	FP/FOR off-label	FP/SAL DPI	FP/SAL MDI	BUD/FOR	BDP/FOR	p-value
Year of first recorded asthma diagnosis	N (% not missing)	227 (100.0)	21 (100.0)	288 (100.0)	760 (100.0)	569 (100.0)	NA	<0.001‡
	Mean (SD)	2005.7 (4.8)	2003.2 (3.1)	2005.4 (4.7)	2006.5 (4.8)	2005.5 (4.8)	NA	
	Median (IQR)	2005 (2002, 2009)	2003 (2001, 2005)	2005 (2002, 2009)	2006 (2003, 2011)	2004 (2002, 2010)	NA	
	Min, Max	1997, 2015	1999, 2009	1997, 2015	1996, 2015	1996, 2015	NA	
Comorbid rhinitis	N (% not missing)	227 (100.0)	21 (100.0)	288 (100.0)	760 (100.0)	569 (100.0)	NA	<0.001*
	No, n (%)	169 (74.4)	12 (57.1)	214 (74.3)	629 (82.8)	453 (79.6)	NA	
	Yes, n (%)	58 (25.6)	9 (42.9)	74 (25.7)	131 (17.2)	116 (20.4)	NA	
Comorbid eczema	N (% not missing)	227 (100.0)	21 (100.0)	288 (100.0)	760 (100.0)	569 (100.0)	NA	0.088*
	No, n (%)	192 (84.6)	16 (76.2)	254 (88.2)	683 (89.9)	506 (88.9)	NA	
	Yes, n (%)	35 (15.4)	5 (23.8)	34 (11.8)	77 (10.1)	63 (11.1)	NA	
Comorbid GERD	N (% not missing)	227 (100.0)	21 (100.0)	288 (100.0)	760 (100.0)	569 (100.0)	NA	0.043*
	No, n (%)	n≥5	n≥5	n≥5	n≥5	n≥5	NA	
	Yes, n (%)	n<5	n<5	n<5	n<5	n<5	NA	
Charlson Comorbidity Index (CCI)	N (% not missing)	227 (100.0)	21 (100.0)	288 (100.0)	760 (100.0)	569 (100.0)	NA	.030‡
	Mean (SD)	3.6 (1.2)	3.0 (1.7)	3.4 (1.5)	3.6 (1.3)	3.6 (1.2)	NA	
	Median (IQR)	4 (4, 4)	4 (4, 4)	4 (4, 4)	4 (4, 4)	4 (4, 4)	NA	
	Min, Max	0, 4	0, 4	0, 4	0, 7	0, 4	NA	
Charlson Comorbidity Index (CCI) (categorised)	N (% not missing)	227 (100.0)	21 (100.0)	288 (100.0)	760 (100.0)	569 (100.0)	NA	0.094*
	0, n (%)	n≥5	n≥5	n≥5	n≥5	n≥5	NA	
	1-4, n (%)	n≥5	n≥5	n≥5	n≥5	n≥5	NA	
	5+, n (%)	n<5	n<5	n<5	n<5	n<5	NA	

Table 11: Comorbidities by FDC/ICS LABA (patients aged ≥12 and <18 years with asthma)
‡ Kruskal-Wallis test, * Chi-square test, NA – not applicable

6.2.2.4 Consultations and hospitalisations in year prior to index date

		TOTAL COHORT						
	Measure	FP/FOR licensed	FP/FOR off-label	FP/SAL DPI	FP/SAL MDI	BUD/FOR	BDP/FOR	p-value
Respiratory GP consultations without prescription for an oral corticosteroid (categorised)	N (% not missing)	227 (100.0)	21 (100.0)	288 (100.0)	760 (100.0)	569 (100.0)	NA	0.349*
	0, n (%)	69 (30.4)	n≥5	76 (26.4)	198 (26.1)	158 (27.8)	NA	
	1, n (%)	74 (32.6)	n≥5	105 (36.5)	225 (29.6)	187 (32.9)	NA	
	2, n (%)	36 (15.9)	n≥5	59 (20.5)	159 (20.9)	109 (19.2)	NA	

		TOTAL COHORT						
	Measure	FP/FOR licensed	FP/FOR off-label	FP/SAL DPI	FP/SAL MDI	BUD/FOR	BDP/FOR	p-value
	3+, n (%)	48 (21.1)	n<5	48 (16.7)	178 (23.4)	115 (20.2)	NA	
Asthma GP consultations without prescription for an oral corticosteroid (categorised)	N (% not missing)	227 (100.0)	21 (100.0)	288 (100.0)	760 (100.0)	569 (100.0)	NA	0.963*
	0, n (%)	97 (42.7)	n≥5	113 (39.2)	285 (37.5)	224 (39.4)	NA	
	1, n (%)	78 (34.4)	n≥5	104 (36.1)	277 (36.4)	212 (37.3)	NA	
	2, n (%)	33 (14.5)	n<5	50 (17.4)	134 (17.6)	83 (14.6)	NA	
	3+, n (%)	19 (8.4)	n<5	21 (7.3)	64 (8.4)	50 (8.8)	NA	
Respiratory hospital outpatient attendances (categorised)	N (% not missing)	116 (100.0)	13 (100.0)	148 (100.0)	451 (100.0)	300 (100.0)	NA	<0.001*
	0, n (%)	n≥5	n≥5	n≥5	n≥5	291 (97.0)	NA	
	1+, n (%)	n<5	n<5	n<5	n<5	9 (3.0)	NA	
Lower respiratory inpatient hospitalisations (categorised)	N (% not missing)	116 (100.0)	13 (100.0)	148 (100.0)	451 (100.0)	300 (100.0)	NA	<0.001*
	0, n (%)	n≥5	n≥5	n≥5	n≥5	n≥5	NA	
	1+, n (%)	n<5	n<5	n<5	n<5	n<5	NA	
Asthma inpatient hospitalisations (categorised)	N (% not missing)	116 (100.0)	13 (100.0)	148 (100.0)	451 (100.0)	300 (100.0)	NA	0.405*
	0, n (%)	n≥5	n≥5	139 (93.9)	424 (94.0)	286 (95.3)	NA	
	1+, n (%)	n<5	n<5	9 (6.1)	27 (6.0)	14 (4.7)	NA	
Asthma exacerbations (categorised)	N (% not missing)	116 (100.0)	13 (100.0)	148 (100.0)	451 (100.0)	300 (100.0)	NA	0.505*
	0, n (%)	67 (57.8)	n<5	80 (54.1)	236 (52.3)	149 (49.7)	NA	
	1, n (%)	30 (25.9)	n<5	41 (27.7)	114 (25.3)	86 (28.7)	NA	
	2+, n (%)	19 (16.4)	n≥5	27 (18.2)	101 (22.4)	65 (21.7)	NA	

Table 12: Consultations and hospitalisations in year prior to index date by FDC/ICS LABA (patients aged ≥12 and <18 years with asthma)
‡ Kruskal-Wallis test, * Chi-square test, NA – not applicable

6.2.2.5 Prescriptions for therapy in year prior to index date

		TOTAL COHORT						
	Measure	FP/FOR licensed	FP/FOR off-label	FP/SAL DPI	FP/SAL MDI	BUD/FOR	BDP/FOR	p-value
FDC ICS+LABA inhalers	N (% not missing)	227 (100.0)	21 (100.0)	288 (100.0)	760 (100.0)	569 (100.0)	NA	<0.001‡
	Mean (SD)	2.5 (4.5)	5.6 (5.5)	2.6 (4.6)	0.8 (2.5)	1.6 (3.7)	NA	
	Median (IQR)	0 (0, 4)	4 (2, 7)	0 (0, 4)	0 (0, 0)	0 (0, 0)	NA	
	Min, Max	0, 40	0, 20	0, 40	0, 20	0, 24	NA	
FDC ICS+LABA inhalers (categorised)	N (% not missing)	227 (100.0)	21 (100.0)	288 (100.0)	760 (100.0)	569 (100.0)	NA	<0.001*
	No, n (%)	134 (59.0)	n<5	177 (61.5)	664 (87.4)	435 (76.4)	NA	
	Yes, n (%)	93 (41.0)	n≥5	111 (38.5)	96 (12.6)	134 (23.6)	NA	
SABA inhalers	N (% not missing)	227 (100.0)	21 (100.0)	288 (100.0)	760 (100.0)	569 (100.0)	NA	.548‡
	Mean (SD)	3.5 (5.6)	5.0 (8.7)	3.9 (6.0)	3.4 (5.6)	3.9 (6.6)	NA	
	Median (IQR)	1 (0, 5)	0 (0, 6)	2 (0, 6)	1 (0, 5)	1 (0, 6)	NA	
	Min, Max	0, 34	0, 33	0, 32	0, 58	0, 66	NA	

		TOTAL COHORT						
	Measure	FP/FOR licensed	FP/FOR off-label	FP/SAL DPI	FP/SAL MDI	BUD/FOR	BDP/FOR	p-value
SABA inhalers (categorised)	N (% not missing)	227 (100.0)	21 (100.0)	288 (100.0)	760 (100.0)	569 (100.0)	NA	
	No, n (%)	112 (49.3)	11 (52.4)	122 (42.4)	344 (45.3)	232 (40.8)	NA	0.169*
	Yes, n (%)	115 (50.7)	10 (47.6)	166 (57.6)	416 (54.7)	337 (59.2)	NA	
SAMA inhalers	N (% not missing)	227 (100.0)	21 (100.0)	288 (100.0)	760 (100.0)	569 (100.0)	NA	
	Mean (SD)	0.0 (0.1)	0.0 (0.0)	0.0 (0.1)	0.0 (0.4)	0.0 (0.3)	NA	.345‡
	Median (IQR)	0 (0, 0)	0 (0, 0)	0 (0, 0)	0 (0, 0)	0 (0, 0)	NA	
	Min, Max	0, 1	0, 0	0, 2	0, 11	0, 4	NA	
SAMA inhalers (categorised)	N (% not missing)	227 (100.0)	21 (100.0)	288 (100.0)	760 (100.0)	569 (100.0)	NA	
	No, n (%)	n≥5	n≥5	n≥5	n≥5	562 (98.8)	NA	0.345*
	Yes, n (%)	n<5	n<5	n<5	n<5	7 (1.2)	NA	
LABA inhalers	N (% not missing)	227 (100.0)	21 (100.0)	288 (100.0)	760 (100.0)	569 (100.0)	NA	
	Mean (SD)	0.4 (2.2)	0.0 (0.0)	0.3 (1.4)	0.5 (2.1)	0.3 (1.4)	NA	.006‡
	Median (IQR)	0 (0, 0)	0 (0, 0)	0 (0, 0)	0 (0, 0)	0 (0, 0)	NA	
	Min, Max	0, 28	0, 0	0, 13	0, 24	0, 14	NA	
LABA inhalers (categorised)	N (% not missing)	227 (100.0)	21 (100.0)	288 (100.0)	760 (100.0)	569 (100.0)	NA	
	No, n (%)	212 (93.4)	n≥5	265 (92.0)	673 (88.6)	533 (93.7)	NA	0.005*
	Yes, n (%)	15 (6.6)	n<5	23 (8.0)	87 (11.4)	36 (6.3)	NA	
LAMA inhalers	N (% not missing)	227 (100.0)	21 (100.0)	288 (100.0)	760 (100.0)	569 (100.0)	NA	
	Mean (SD)	0.0 (0.0)	0.2 (0.6)	0.0 (0.0)	0.0 (0.0)	0.0 (0.0)	NA	<0.001‡
	Median (IQR)	0 (0, 0)	0 (0, 0)	0 (0, 0)	0 (0, 0)	0 (0, 0)	NA	
	Min, Max	0, 0	0, 2	0, 0	0, 0	0, 0	NA	
LAMA inhalers (categorised)	N (% not missing)	227 (100.0)	21 (100.0)	288 (100.0)	760 (100.0)	569 (100.0)	NA	
	No, n (%)	n≥5	n≥5	n≥5	n≥5	n≥5	NA	<0.001*
	Yes, n (%)	n<5	n<5	n<5	n<5	n<5	NA	
ICS only inhalers	N (% not missing)	227 (100.0)	21 (100.0)	288 (100.0)	760 (100.0)	569 (100.0)	NA	
	Mean (SD)	2.6 (3.4)	1.3 (2.9)	2.4 (3.4)	3.3 (3.4)	2.4 (3.1)	NA	<0.001‡
	Median (IQR)	2 (0, 4)	0 (0, 0)	1 (0, 4)	2 (1, 5)	1 (0, 4)	NA	
	Min, Max	0, 14	0, 12	0, 18	0, 22	0, 22	NA	
ICS only inhalers (categorised)	N (% not missing)	227 (100.0)	21 (100.0)	288 (100.0)	760 (100.0)	569 (100.0)	NA	
	No, n (%)	98 (43.2)	16 (76.2)	122 (42.4)	161 (21.2)	218 (38.3)	NA	<0.001*
	Yes, n (%)	129 (56.8)	5 (23.8)	166 (57.6)	599 (78.8)	351 (61.7)	NA	
Theophylline prescriptions	N (% not missing)	227 (100.0)	21 (100.0)	288 (100.0)	760 (100.0)	569 (100.0)	NA	
	Mean (SD)	0.0 (0.0)	0.5 (1.5)	0.0 (0.4)	0.0 (0.4)	0.0 (0.0)	NA	<0.001‡
	Median (IQR)	0 (0, 0)	0 (0, 0)	0 (0, 0)	0 (0, 0)	0 (0, 0)	NA	
	Min, Max	0, 0	0, 6	0, 6	0, 9	0, 0	NA	
Theophylline prescriptions (categorised)	N (% not missing)	227 (100.0)	21 (100.0)	288 (100.0)	760 (100.0)	569 (100.0)	NA	
	No, n (%)	n≥5	n≥5	n≥5	n≥5	n≥5	NA	<0.001*
	Yes, n (%)	n<5	n<5	n<5	n<5	n<5	NA	

		TOTAL COHORT						
	Measure	FP/FOR licensed	FP/FOR off-label	FP/SAL DPI	FP/SAL MDI	BUD/FOR	BDP/FOR	p-value
LTRA prescriptions	N (% not missing)	227 (100.0)	21 (100.0)	288 (100.0)	760 (100.0)	569 (100.0)	NA	<0.001‡
	Mean (SD)	1.2 (2.6)	2.6 (3.4)	1.0 (2.5)	0.6 (2.0)	0.9 (2.5)	NA	
	Median (IQR)	0 (0, 1)	0 (0, 5)	0 (0, 0)	0 (0, 0)	0 (0, 0)	NA	
	Min, Max	0, 13	0, 10	0, 13	0, 14	0, 16	NA	
LTRA prescriptions (categorised)	N (% not missing)	227 (100.0)	21 (100.0)	288 (100.0)	760 (100.0)	569 (100.0)	NA	<0.001*
	No, n (%)	170 (74.9)	11 (52.4)	232 (80.6)	662 (87.1)	455 (80.0)	NA	
	Yes, n (%)	57 (25.1)	10 (47.6)	56 (19.4)	98 (12.9)	114 (20.0)	NA	
Spacer prescription	N (% not missing)	227 (100.0)	21 (100.0)	288 (100.0)	760 (100.0)	569 (100.0)	NA	<0.001*
	No, n (%)	177 (78.0)	13 (61.9)	229 (79.5)	504 (66.3)	476 (83.7)	NA	
	Yes, n (%)	50 (22.0)	8 (38.1)	59 (20.5)	256 (33.7)	93 (16.3)	NA	
Pain-relief medication prescriptions (categorised)	N (% not missing)	227 (100.0)	21 (100.0)	288 (100.0)	760 (100.0)	569 (100.0)	NA	0.277*
	No, n (%)	203 (89.4)	16 (76.2)	252 (87.5)	678 (89.2)	494 (86.8)	NA	
	Yes, n (%)	24 (10.6)	5 (23.8)	36 (12.5)	82 (10.8)	75 (13.2)	NA	
Non-steroidal anti-inflammatory drugs (NSAIDs) prescriptions (categorised)	N (% not missing)	227 (100.0)	21 (100.0)	288 (100.0)	760 (100.0)	569 (100.0)	NA	0.019*
	No, n (%)	207 (91.2)	15 (71.4)	252 (87.5)	692 (91.1)	516 (90.7)	NA	
	Yes, n (%)	20 (8.8)	6 (28.6)	36 (12.5)	68 (8.9)	53 (9.3)	NA	

Table 13: Prescriptions for therapy in year prior to index date by FDC/ICS LABA (patients aged ≥12 and <18 years with asthma)

‡ Kruskal-Wallis test, * Chi-square test, NA – not applicable

6.2.2.6 Adverse events during baseline

		TOTAL COHORT						
	Measure	FP/FOR licensed	FP/FOR off-label	FP/SAL DPI	FP/SAL MDI	BUD/FOR	BDP/FOR	p-value
Lower Respiratory Tract Infection in baseline	N (% not missing)	227 (100.0)	21 (100.0)	288 (100.0)	760 (100.0)	569 (100.0)	NA	0.002*
	No, n (%)	210 (92.5)	14 (66.7)	256 (88.9)	667 (87.8)	483 (84.9)	NA	
	Yes, n (%)	17 (7.5)	7 (33.3)	32 (11.1)	93 (12.2)	86 (15.1)	NA	
Pneumonia in baseline	N (% not missing)	227 (100.0)	21 (100.0)	288 (100.0)	760 (100.0)	569 (100.0)	NA	0.335*
	No, n (%)	n≥5	n≥5	n≥5	n≥5	n≥5	NA	
	Yes, n (%)	n<5	n<5	n<5	n<5	n<5	NA	
Pulmonary Embolism in baseline	N (% not missing)	227 (100.0)	21 (100.0)	288 (100.0)	760 (100.0)	569 (100.0)	NA	NA
	No, n (%)	227 (100.0)	21 (100.0)	288 (100.0)	760 (100.0)	569 (100.0)	NA	
Tuberculosis in baseline	N (% not missing)	227 (100.0)	21 (100.0)	288 (100.0)	760 (100.0)	569 (100.0)	NA	NA
	No, n (%)	227 (100.0)	21 (100.0)	288 (100.0)	760 (100.0)	569 (100.0)	NA	

Table 14: Adverse events occurring in year prior to index date by FDC/ICS LABA (patients aged ≥12 and <18 years with asthma)

‡ Kruskal-Wallis test, * Chi-square test, NA – not applicable

6.2.3 Patients aged ≥4 and <12 years with asthma

The FP/FOR group was small for this subgroup. For patients with asthma aged ≥4 and <12 years, demographic characteristics were broadly similar across treatment groups (Table 15). Comorbidities (except rhinitis), GP consultations, hospitalisations and exacerbations were similar between groups (Table 17, Table 18). The daily dose prescribed at index date was slightly higher for FP/FOR and FP/FOR patients were most likely to be switchers whereas MDI FP/SAL patients were most likely to be initiators (Table 16, Table 19). FP/FOR patients were less likely to be prescribed SABA and ICS (without LABA in FDC) in the year prior. Data available prior to index date was similar between the treatment groups; although duration of FDC ICS/LABA prescription during outcome and length of follow-up was shorter for FP/FOR than the other groups. There was no significant difference in LRTI or pneumonia at baseline between the groups and no cases of pulmonary embolism or tuberculosis (Table 20).

6.2.3.1 Demographic characteristics

		TOTAL COHORT					
	Measure	FP/FOR	FP/SAL DPI	FP/SAL MDI	BUD/FOR	BDP/FOR	p-value
Age at IPD (years)	N (% not missing)	27 (100.0)	149 (100.0)	1047 (100.0)	235 (100.0)	NA	<0.001‡
	Mean (SD)	8.5 (2.5)	8.7 (2.1)	7.6 (2.1)	9.2 (1.6)	NA	
	Median (IQR)	9 (7, 11)	9 (7, 10)	8 (6, 9)	10 (8, 11)	NA	
	Min, Max	4, 11	4, 11	4, 11	6, 11	NA	
Gender	N (% not missing)	27 (100.0)	149 (100.0)	1047 (100.0)	235 (100.0)	NA	0.416*
	Female, n (%)	13 (48.1)	54 (36.2)	434 (41.5)	89 (37.9)	NA	
	Male, n (%)	14 (51.9)	95 (63.8)	613 (58.5)	146 (62.1)	NA	
Height (m) - closest to IPD	N (% not missing)	21 (77.8)	120 (80.5)	794 (75.8)	190 (80.9)	NA	<0.001‡
	Mean (SD)	1.3 (0.2)	1.3 (0.2)	1.3 (0.1)	1.4 (0.1)	NA	
	Median (IQR)	1.3 (1.2, 1.4)	1.3 (1.2, 1.4)	1.3 (1.1, 1.4)	1.4 (1.3, 1.4)	NA	
	Min, Max	(0.9, 1.6)	(1.0, 1.6)	(0.9, 1.7)	(1.1, 1.6)	NA	
Weight (kg) - closest to IPD	N (% not missing)	19 (70.4)	122 (81.9)	751 (71.7)	164 (69.8)	NA	<0.001‡
	Mean (SD)	30.4 (11.8)	31.5 (10.2)	28.0 (10.6)	34.7 (10.5)	NA	
	Median (IQR)	27 (22, 38)	30 (24, 38)	25 (20, 34)	34 (26, 42)	NA	
	Min, Max	15, 65	14, 64	11, 75	18, 75	NA	
BMI (kg/m2) (categorised)	N (% not missing)	16 (59.3)	107 (71.8)	658 (62.8)	152 (64.7)	NA	0.962*
	Underweight, n (%)	n<5	11 (10.3)	61 (9.3)	10 (6.6)	NA	
	Normal, n (%)	n≥5	64 (59.8)	384 (58.4)	95 (62.5)	NA	
	Overweight, n (%)	n<5	18 (16.8)	100 (15.2)	22 (14.5)	NA	
	Obese, n (%)	n<5	14 (13.1)	113 (17.2)	25 (16.4)	NA	
PEF % predicted	N (% not missing)	8 (29.6)	79 (53.0)	442 (42.2)	139 (59.1)	NA	.454‡

		TOTAL COHORT					
	Measure	FP/FOR	FP/SAL DPI	FP/SAL MDI	BUD/FOR	BDP/FOR	p-value
	Mean (SD)	94.1 (29.7)	91.6 (21.9)	94.3 (22.0)	96.1 (24.0)	NA	
	Median (IQR)	94.3 (75.6, 113.0)	91.6 (79.6, 102.7)	94.5 (78.6, 108.7)	98.6 (80.4, 112.2)	NA	
	Min, Max	(45.7, 141.8)	(28.4, 148.4)	(34.0, 149.3)	(23.9, 146.5)	NA	

Table 15: Demographic characteristics by FDC/ICS LABA (patients aged ≥4 and <12 years with asthma)
‡ Kruskal-Wallis test, * Chi-square test, NA – not applicable

6.2.3.2 Medication prescribed at index date

		TOTAL COHORT					
	Measure	FP/FOR	FP/SAL DPI	FP/SAL MDI	BUD/FOR	BDP/FOR	p-value
Continuous data available prior index date (years)	N (% not missing)	27 (100.0)	149 (100.0)	1047 (100.0)	235 (100.0)	NA	<0.001‡
	Mean (SD)	7.1 (2.8)	6.8 (3.1)	6.4 (2.6)	7.2 (3.0)	NA	
	Median (IQR)	7.4 (4.7, 9.6)	7.3 (4.7, 9.7)	6.1 (4.6, 8.5)	7.5 (5.5, 9.8)	NA	
	Min, Max	(1.6, 11.5)	(1.1, 11.8)	(1.0, 11.8)	(1.0, 11.8)	NA	
Length of follow-up period (months)	N (% not missing)	27 (100.0)	149 (100.0)	1047 (100.0)	235 (100.0)	NA	<0.001‡
	Mean (SD)	6.5 (10.7)	13.2 (10.8)	16.3 (11.6)	14.3 (11.7)	NA	
	Median (IQR)	2.0 (0.9, 5.9)	12.1 (2.9, 19.8)	14.2 (5.7, 24.8)	11.3 (3.1, 22.0)	NA	
	Min, Max	(0.2, 40.2)	(0.1, 43.2)	(0.1, 44.0)	(0.2, 43.5)	NA	
Prescribed FDC ICS/LABA inhaler dose (dose per puff)	N (% not missing)	27 (100.0)	149 (100.0)	1047 (100.0)	235 (100.0)	NA	<0.001*
	50/5, n (%)	n≥5	n<5	n<5	n<5	NA	
	125/5, n (%)	n≥5	n<5	n<5	n<5	NA	
	100/50, n (%)	n<5	n≥5	n<5	n<5	NA	
	50/25, n (%)	n<5	n<5	n≥5	n<5	NA	
	100/6, n (%)	n<5	n<5	n<5	n≥5	NA	
Prescribed FDC ICS/LABA (FP equivalent dose per day)	N (% not missing)	19 (70.4)	77 (51.7)	882 (84.2)	192 (81.7)	NA	<0.001‡
	Mean (SD)	342.1 (150.9)	216.9 (59.4)	192.0 (25.8)	155.1 (45.4)	NA	
	Median (IQR)	375 (200, 500)	200 (200, 200)	200 (200, 200)	150 (100, 200)	NA	
	Min, Max	100, 500	100, 400	100, 200	75, 200	NA	
Prescribed FDC ICS/LABA (FP equivalent dose per day) (categorised)	N (% not missing)	19 (70.4)	77 (51.7)	882 (84.2)	192 (81.7)	NA	<0.001*
	≥50 & <=100, n (%)	n<5	n<5	n≥5	n≥5	NA	
	>100 & <=200, n (%)	n≥5	n≥5	n≥5	n≥5	NA	
	>200 & <=400, n (%)	n<5	n≥5	n<5	n<5	NA	
	>400 & <600, n (%)	n≥5	n<5	n<5	n<5	NA	
Prescribed FDC ICS/LABA using imputed dosing instructions (FP equivalent dose per day)	N (% not missing)	27 (100.0)	149 (100.0)	1047 (100.0)	192 (81.7)	NA	<0.001‡
	Mean (SD)	344.4 (150.7)	208.7 (43.4)	193.3 (23.9)	155.2 (45.2)	NA	
	Median (IQR)	375 (200, 500)	200 (200, 200)	200 (200, 200)	150 (100, 200)	NA	
	Min, Max	100, 500	100, 400	100, 200	100, 200	NA	
Prescribed FDC ICS/LABA using imputed dosing	N (% not missing)	27 (100.0)	149 (100.0)	1047 (100.0)	192 (81.7)	NA	<0.001*
	≥50 & <=100, n (%)	n<5	n<5	n≥5	n≥5	NA	

		TOTAL COHORT					
	Measure	FP/FOR	FP/SAL DPI	FP/SAL MDI	BUD/FOR	BDP/FOR	p-value
instructions (FP equivalent dose per day) (categorised)	>100 & <=200, n (%)	n≥5	n≥5	n≥5	n≥5	NA	
	>200 & <=400, n (%)	n<5	n≥5	n<5	n<5	NA	
	>400 & <600, n (%)	n≥5	n<5	n<5	n<5	NA	
Duration of FDC ICS/LABA prescription (outcome), (months)	N (% not missing)	27 (100.0)	149 (100.0)	1047 (100.0)	235 (100.0)	NA	<0.001‡
	Mean (SD)	6.8 (11.3)	13.8 (11.1)	17.1 (11.9)	15.0 (12.0)	NA	
	Median (IQR)	2 (1, 7)	12.6 (3.2, 20.4)	15.1 (6.2, 26.1)	12.7 (3.2, 22.9)	NA	
	Min, Max	(0.2, 42.8)	(0.1, 43.8)	(0.2, 46.0)	(0.2, 44.7)	NA	
SABA prescriptions	N (% not missing)	27 (100.0)	149 (100.0)	1047 (100.0)	235 (100.0)	NA	0.483*
	No, n (%)	21 (77.8)	123 (82.6)	877 (83.8)	188 (80.0)	NA	
	Yes, n (%)	6 (22.2)	26 (17.4)	170 (16.2)	47 (20.0)	NA	
SAMA prescriptions	N (% not missing)	27 (100.0)	149 (100.0)	1047 (100.0)	235 (100.0)	NA	0.032*
	No, n (%)	n≥5	n≥5	n≥5	n≥5	NA	
	Yes, n (%)	n<5	n<5	n<5	n<5	NA	
LABA prescriptions	N (% not missing)	27 (100.0)	149 (100.0)	1047 (100.0)	235 (100.0)	NA	0.424*
	No, n (%)	n≥5	n≥5	n≥5	n≥5	NA	
	Yes, n (%)	n<5	n<5	n<5	n<5	NA	
LAMA prescriptions	N (% not missing)	27 (100.0)	149 (100.0)	1047 (100.0)	235 (100.0)	NA	NA
	No, n (%)	27 (100.0)	149 (100.0)	1047 (100.0)	235 (100.0)	NA	
ICS only prescriptions	N (% not missing)	27 (100.0)	149 (100.0)	1047 (100.0)	235 (100.0)	NA	0.621*
	No, n (%)	n≥5	n≥5	1029 (98.3)	n≥5	NA	
	Yes, n (%)	n<5	n<5	18 (1.7)	n<5	NA	
Theophylline prescriptions	N (% not missing)	27 (100.0)	149 (100.0)	1047 (100.0)	235 (100.0)	NA	NA
	No, n (%)	27 (100.0)	149 (100.0)	1047 (100.0)	235 (100.0)	NA	
LTRA prescriptions	N (% not missing)	27 (100.0)	149 (100.0)	1047 (100.0)	235 (100.0)	NA	0.562*
	No, n (%)	n≥5	131 (87.9)	919 (87.8)	214 (91.1)	NA	
	Yes, n (%)	n<5	18 (12.1)	128 (12.2)	21 (8.9)	NA	

Table 16: Medication prescribed at index date by FDC/ICS LABA (patients aged ≥4 and <12 years with asthma)

‡ Kruskal-Wallis test, * Chi-square test, NA – not applicable

6.2.3.3 Comorbidities

		TOTAL COHORT					
	Measure	FP/FOR	FP/SAL DPI	FP/SAL MDI	BUD/FOR	BDP/FOR	p-value
Year of first recorded asthma diagnosis	N (% not missing)	27 (100.0)	149 (100.0)	1047 (100.0)	235 (100.0)	NA	<0.001‡
	Mean (SD)	2009.4 (3.2)	2009.4 (2.9)	2010.4 (2.7)	2009.5 (3.0)	NA	
	Median (IQR)	2010 (2007, 2013)	2010 (2007, 2012)	2011 (2009, 2012)	2009 (2007, 2012)	NA	

		TOTAL COHORT					
	Measure	**FP/FOR**	**FP/SAL DPI**	**FP/SAL MDI**	**BUD/FOR**	**BDP/FOR**	**p-value**
	Min, Max	2004, 2015	2003, 2014	2002, 2015	2002, 2015	NA	
Comorbid rhinitis	N (% not missing)	27 (100.0)	149 (100.0)	1047 (100.0)	235 (100.0)	NA	<0.001*
	No, n (%)	n≥5	120 (80.5)	915 (87.4)	182 (77.4)	NA	
	Yes, n (%)	n<5	29 (19.5)	132 (12.6)	53 (22.6)	NA	
Comorbid eczema	N (% not missing)	27 (100.0)	149 (100.0)	1047 (100.0)	235 (100.0)	NA	0.644*
	No, n (%)	n≥5	125 (83.9)	904 (86.3)	201 (85.5)	NA	
	Yes, n (%)	n<5	24 (16.1)	143 (13.7)	34 (14.5)	NA	
Comorbid GERD	N (% not missing)	27 (100.0)	149 (100.0)	1047 (100.0)	235 (100.0)	NA	0.314*
	No, n (%)	n≥5	n≥5	1038 (99.1)	n≥5	NA	
	Yes, n (%)	n<5	n<5	9 (0.9)	n<5	NA	
Charlson Comorbidity Index (CCI)	N (% not missing)	27 (100.0)	149 (100.0)	1047 (100.0)	235 (100.0)	NA	.298‡
	Mean (SD)	3.4 (1.4)	3.4 (1.5)	3.6 (1.2)	3.6 (1.2)	NA	
	Median (IQR)	4 (4, 4)	4 (4, 4)	4 (4, 4)	4 (4, 4)	NA	
	Min, Max	0, 4	0, 7	0, 4	0, 4	NA	
Charlson Comorbidity Index (CCI) (categorised)	N (% not missing)	27 (100.0)	149 (100.0)	1047 (100.0)	235 (100.0)	NA	0.037*
	0, n (%)	n<5	n≥5	n≥5	n≥5	NA	
	1-4, n (%)	n≥5	n≥5	n≥5	n≥5	NA	
	5+, n (%)	n<5	n<5	n<5	n<5	NA	

Table 17: Comorbidities by FDC/ICS LABA (patients aged ≥4 and <12 years with asthma)
‡ Kruskal-Wallis test, * Chi-square test, NA – not applicable

6.2.3.4 Consultations and hospitalisations in year prior to index date

		TOTAL COHORT					
	Measure	**FP/FOR**	**FP/SAL DPI**	**FP/SAL MDI**	**BUD/FOR**	**BDP/FOR**	**p-value**
Respiratory GP consultations without prescription for an oral corticosteroid (categorised)	N (% not missing)	27 (100.0)	149 (100.0)	1047 (100.0)	235 (100.0)	NA	0.176*
	0, n (%)	n≥5	38 (25.5)	194 (18.5)	49 (20.9)	NA	
	1, n (%)	n≥5	45 (30.2)	286 (27.3)	67 (28.5)	NA	
	2, n (%)	n<5	28 (18.8)	220 (21.0)	38 (16.2)	NA	
	3+, n (%)	n≥5	38 (25.5)	347 (33.1)	81 (34.5)	NA	
Asthma GP consultations without prescription for an oral corticosteroid (categorised)	N (% not missing)	27 (100.0)	149 (100.0)	1047 (100.0)	235 (100.0)	NA	0.129*
	0, n (%)	n≥5	67 (45.0)	357 (34.1)	79 (33.6)	NA	
	1, n (%)	n≥5	41 (27.5)	376 (35.9)	85 (36.2)	NA	
	2, n (%)	n<5	28 (18.8)	190 (18.1)	42 (17.9)	NA	
	3+, n (%)	n<5	13 (8.7)	124 (11.8)	29 (12.3)	NA	

		TOTAL COHORT					
	Measure	FP/FOR	FP/SAL DPI	FP/SAL MDI	BUD/FOR	BDP/FOR	p-value
Respiratory hospital outpatient attendances (categorised)	N (% not missing)	14 (100.0)	81 (100.0)	608 (100.0)	131 (100.0)	NA	0.265*
	0, n (%)	n≥5	n≥5	600 (98.7)	n≥5	NA	
	1+, n (%)	n<5	n<5	8 (1.3)	n<5	NA	
Lower respiratory inpatient hospitalisations (categorised)	N (% not missing)	14 (100.0)	81 (100.0)	608 (100.0)	131 (100.0)	NA	0.325*
	0, n (%)	n≥5	n≥5	598 (98.4)	n≥5	NA	
	1+, n (%)	n<5	n<5	10 (1.6)	n<5	NA	
Asthma inpatient hospitalisations (categorised)	N (% not missing)	14 (100.0)	81 (100.0)	608 (100.0)	131 (100.0)	NA	0.170*
	0, n (%)	n≥5	75 (92.6)	532 (87.5)	120 (91.6)	NA	
	1+, n (%)	n<5	6 (7.4)	76 (12.5)	11 (8.4)	NA	
Asthma exacerbations (categorised)	N (% not missing)	14 (100.0)	81 (100.0)	608 (100.0)	131 (100.0)	NA	0.307*
	0, n (%)	n≥5	33 (40.7)	244 (40.1)	61 (46.6)	NA	
	1, n (%)	n<5	24 (29.6)	157 (25.8)	37 (28.2)	NA	
	2+, n (%)	n≥5	24 (29.6)	207 (34.0)	33 (25.2)	NA	

Table 18: Consultations and hospitalisations in year prior to index date by FDC/ICS LABA (patients aged ≥4 and <12 years with asthma)
‡ Kruskal-Wallis test, * Chi-square test, NA – not applicable

6.2.3.5 Prescriptions for therapy in year prior to index date

		TOTAL COHORT					
	Measure	FP/FOR	FP/SAL DPI	FP/SAL MDI	BUD/FOR	BDP/FOR	p-value
FDC ICS+LABA inhalers	N (% not missing)	27 (100.0)	149 (100.0)	1047 (100.0)	235 (100.0)	NA	<0.001‡
	Mean (SD)	2.3 (3.8)	1.2 (3.0)	0.1 (0.7)	1.0 (2.6)	NA	
	Median (IQR)	0 (0, 4)	0 (0, 0)	0 (0, 0)	0 (0, 0)	NA	
	Min, Max	0, 14	0, 16	0, 12	0, 13	NA	
FDC ICS+LABA inhalers (categorised)	N (% not missing)	27 (100.0)	149 (100.0)	1047 (100.0)	235 (100.0)	NA	<0.001*
	No, n (%)	16 (59.3)	117 (78.5)	1030 (98.4)	198 (84.3)	NA	
	Yes, n (%)	11 (40.7)	32 (21.5)	17 (1.6)	37 (15.7)	NA	
SABA inhalers	N (% not missing)	27 (100.0)	149 (100.0)	1047 (100.0)	235 (100.0)	NA	.557‡
	Mean (SD)	2.5 (4.5)	2.7 (3.9)	3.0 (4.7)	2.7 (3.6)	NA	
	Median (IQR)	0 (0, 4)	1 (0, 4)	1 (0, 4)	2 (0, 4)	NA	
	Min, Max	0, 18	0, 20	0, 57	0, 26	NA	
SABA inhalers (categorised)	N (% not missing)	27 (100.0)	149 (100.0)	1047 (100.0)	235 (100.0)	NA	0.117*
	No, n (%)	17 (63.0)	70 (47.0)	497 (47.5)	97 (41.3)	NA	
	Yes, n (%)	10 (37.0)	79 (53.0)	550 (52.5)	138 (58.7)	NA	
SAMA inhalers	N (% not missing)	27 (100.0)	149 (100.0)	1047 (100.0)	235 (100.0)	NA	.553‡
	Mean (SD)	0.0 (0.0)	0.0 (0.1)	0.0 (0.5)	0.0 (0.1)	NA	
	Median (IQR)	0 (0, 0)	0 (0, 0)	0 (0, 0)	0 (0, 0)	NA	
	Min, Max	0, 0	0, 1	0, 12	0, 1	NA	

		TOTAL COHORT					
	Measure	FP/FOR	FP/SAL DPI	FP/SAL MDI	BUD/FOR	BDP/FOR	p-value
SAMA inhalers (categorised)	N (% not missing)	27 (100.0)	149 (100.0)	1047 (100.0)	235 (100.0)	NA	
	No, n (%)	n≥5	n≥5	1033 (98.7)	n≥5	NA	0.556*
	Yes, n (%)	n<5	n<5	14 (1.3)	n<5	NA	
LABA inhalers	N (% not missing)	27 (100.0)	149 (100.0)	1047 (100.0)	235 (100.0)	NA	
	Mean (SD)	0.0 (0.0)	0.4 (1.5)	0.5 (1.9)	0.3 (1.3)	NA	
	Median (IQR)	0 (0, 0)	0 (0, 0)	0 (0, 0)	0 (0, 0)	NA	.067‡
	Min, Max	0, 0	0, 12	0, 18	0, 7	NA	
LABA inhalers (categorised)	N (% not missing)	27 (100.0)	149 (100.0)	1047 (100.0)	235 (100.0)	NA	
	No, n (%)	n≥5	131 (87.9)	920 (87.9)	217 (92.3)	NA	0.060*
	Yes, n (%)	n<5	18 (12.1)	127 (12.1)	18 (7.7)	NA	
LAMA inhalers	N (% not missing)	27 (100.0)	149 (100.0)	1047 (100.0)	235 (100.0)	NA	
	Mean (SD)	0.0 (0.0)	0.0 (0.0)	0.0 (0.0)	0.0 (0.0)	NA	
	Median (IQR)	0 (0, 0)	0 (0, 0)	0 (0, 0)	0 (0, 0)	NA	NA
	Min, Max	0, 0	0, 0	0, 0	0, 0	NA	
LAMA inhalers (categorised)	N (% not missing)	27 (100.0)	149 (100.0)	1047 (100.0)	235 (100.0)	NA	
	No, n (%)	27 (100.0)	149 (100.0)	1047 (100.0)	235 (100.0)	NA	NA
ICS only inhalers	N (% not missing)	27 (100.0)	149 (100.0)	1047 (100.0)	235 (100.0)	NA	
	Mean (SD)	3.0 (3.7)	3.2 (3.0)	4.3 (3.2)	3.1 (2.9)	NA	
	Median (IQR)	1 (0, 5)	3 (0, 5)	4 (2, 6)	2 (1, 5)	NA	<0.001‡
	Min, Max	0, 13	0, 15	0, 24	0, 19	NA	
ICS only inhalers (categorised)	N (% not missing)	27 (100.0)	149 (100.0)	1047 (100.0)	235 (100.0)	NA	
	No, n (%)	11 (40.7)	39 (26.2)	59 (5.6)	47 (20.0)	NA	<0.001*
	Yes, n (%)	16 (59.3)	110 (73.8)	988 (94.4)	188 (80.0)	NA	
Theophylline prescriptions	N (% not missing)	27 (100.0)	149 (100.0)	1047 (100.0)	235 (100.0)	NA	
	Mean (SD)	0.0 (0.0)	0.0 (0.0)	0.0 (0.0)	0.0 (0.0)	NA	
	Median (IQR)	0 (0, 0)	0 (0, 0)	0 (0, 0)	0 (0, 0)	NA	.942‡
	Min, Max	0, 0	0, 0	0, 1	0, 0	NA	
Theophylline prescriptions (categorised)	N (% not missing)	27 (100.0)	149 (100.0)	1047 (100.0)	235 (100.0)	NA	
	No, n (%)	n≥5	n≥5	n≥5	n≥5	NA	0.942*
	Yes, n (%)	n<5	n<5	n<5	n<5	NA	
LTRA prescriptions	N (% not missing)	27 (100.0)	149 (100.0)	1047 (100.0)	235 (100.0)	NA	
	Mean (SD)	2.0 (3.9)	1.6 (3.1)	1.9 (3.4)	1.8 (3.2)	NA	
	Median (IQR)	0 (0, 2)	0 (0, 2)	0 (0, 3)	0 (0, 2)	NA	.857‡
	Min, Max	0, 13	0, 14	0, 16	0, 13	NA	
LTRA prescriptions (categorised)	N (% not missing)	27 (100.0)	149 (100.0)	1047 (100.0)	235 (100.0)	NA	
	No, n (%)	19 (70.4)	99 (66.4)	664 (63.4)	149 (63.4)	NA	0.793*
	Yes, n (%)	8 (29.6)	50 (33.6)	383 (36.6)	86 (36.6)	NA	
Spacer prescription	N (% not missing)	27 (100.0)	149 (100.0)	1047 (100.0)	235 (100.0)	NA	0.001*

		TOTAL COHORT					
	Measure	FP/FOR	FP/SAL DPI	FP/SAL MDI	BUD/FOR	BDP/FOR	p-value
	No, n (%)	14 (51.9)	104 (69.8)	623 (59.5)	167 (71.1)	NA	
	Yes, n (%)	13 (48.1)	45 (30.2)	424 (40.5)	68 (28.9)	NA	
Pain-relief medication prescriptions (categorised)	N (% not missing)	27 (100.0)	149 (100.0)	1047 (100.0)	235 (100.0)	NA	
	No, n (%)	22 (81.5)	122 (81.9)	875 (83.6)	209 (88.9)	NA	0.169*
	Yes, n (%)	5 (18.5)	27 (18.1)	172 (16.4)	26 (11.1)	NA	
Non-steroidal anti-inflammatory drugs (NSAIDs) prescriptions (categorised)	N (% not missing)	27 (100.0)	149 (100.0)	1047 (100.0)	235 (100.0)	NA	
	No, n (%)	n≥5	141 (94.6)	994 (94.9)	214 (91.1)	NA	0.069*
	Yes, n (%)	n<5	8 (5.4)	53 (5.1)	21 (8.9)	NA	

Table 19: Prescriptions for therapy in year prior to index date by FDC/ICS LABA (patients aged ≥4 and <12 years with asthma)
‡ Kruskal-Wallis test, * Chi-square test, NA – not applicable

6.2.3.6 Adverse events during baseline

		TOTAL COHORT					
	Measure	FP/FOR	FP/SAL DPI	FP/SAL MDI	BUD/FOR	BDP/FOR	p-value
Lower Respiratory Tract Infection in baseline	N (% not missing)	27 (100.0)	149 (100.0)	1047 (100.0)	235 (100.0)	NA	
	No, n (%)	22 (81.5)	125 (83.9)	895 (85.5)	203 (86.4)	NA	0.852*
	Yes, n (%)	5 (18.5)	24 (16.1)	152 (14.5)	32 (13.6)	NA	
Pneumonia in baseline	N (% not missing)	27 (100.0)	149 (100.0)	1047 (100.0)	235 (100.0)	NA	
	No, n (%)	n≥5	n≥5	1042 (99.5)	n≥5	NA	0.579*
	Yes, n (%)	n<5	n<5	5 (0.5)	n<5	NA	
Pulmonary Embolism in baseline	N (% not missing)	27 (100.0)	149 (100.0)	1047 (100.0)	235 (100.0)	NA	
	No, n (%)	27 (100.0)	149 (100.0)	1047 (100.0)	235 (100.0)	NA	NA
Tuberculosis in baseline	N (% not missing)	27 (100.0)	149 (100.0)	1047 (100.0)	235 (100.0)	NA	
	No, n (%)	27 (100.0)	149 (100.0)	1047 (100.0)	235 (100.0)	NA	NA

Table 20: Adverse events occurring in year prior to index date by FDC/ICS LABA (patients aged ≥4 and <12 years with asthma)
‡ Kruskal-Wallis test, * Chi-square test, NA – not applicable

6.2.4 Patients with COPD only, definition 2

Patients with COPD (definition 2) had similar demographic characteristics, disease severity, comorbidities, exacerbations and GP consultations across the treatment groups (Table 21, Table 23, Table 24). Dose of ICS/LABA at the index date was higher for FP/SAL DPI and FP/FOR; LAMA prescriptions at the index date were higher for FP/SAL DPI (Table 22). In the year prior to the index date, prescription of SABA was higher for BDP/FOR and prescription of LAMA higher for FP/SAL DPI (Table 25). Respiratory outpatient attendances and inpatient hospitalisations were lower for FP/FOR than other treatment groups. The FP/FOR group were more likely to be FDC ICS/LABA switchers than the other treatment groups. Data available prior to index date, duration of FDC ICS/LABA prescription during outcome and length of follow-up was similar between the treatment groups. There was no significant difference in LRTI, pneumonia, pulmonary embolism or tuberculosis at baseline between the groups (Table 26).

6.2.4.1 Demographic characteristics

		TOTAL COHORT					
	Measure	FP/FOR	FP/SAL DPI	FP/SAL MDI	BUD/FOR	BDP/FOR	p-value
Age at IPD (years)	N (% not missing)	399 (100.0)	3678 (100.0)	NA	2526 (100.0)	1609 (100.0)	<0.001‡
	Mean (SD)	70.5 (10.9)	69.9 (10.2)	NA	69.1 (10.7)	70.4 (10.6)	
	Median (IQR)	71 (63, 78)	70 (63, 77)	NA	69 (62, 77)	70 (64, 78)	
	Min, Max	41, 95	36, 98	NA	32, 97	34, 101	
Gender	N (% not missing)	399 (100.0)	3678 (100.0)	NA	2526 (100.0)	1609 (100.0)	0.004*
	Female, n (%)	170 (42.6)	1570 (42.7)	NA	1113 (44.1)	773 (48.0)	
	Male, n (%)	229 (57.4)	2108 (57.3)	NA	1413 (55.9)	836 (52.0)	
Height (m) - closest to IPD	N (% not missing)	393 (98.5)	3644 (99.1)	NA	2506 (99.2)	1596 (99.2)	.004‡
	Mean (SD)	1.7 (0.1)	1.7 (0.1)	NA	1.7 (0.1)	1.7 (0.1)	
	Median (IQR)	1.7 (1.6, 1.7)	1.7 (1.6, 1.7)	NA	1.7 (1.6, 1.7)	1.7 (1.6, 1.7)	
	Min, Max	(1.4, 1.9)	(1.3, 2.0)	NA	(1.2, 2.0)	(1.3, 2.0)	
Weight (kg) - closest to IPD	N (% not missing)	392 (98.2)	3595 (97.7)	NA	2477 (98.1)	1581 (98.3)	.059‡
	Mean (SD)	77.4 (20.1)	75.9 (19.6)	NA	75.4 (19.1)	74.3 (18.4)	
	Median (IQR)	75 (62, 89)	73.8 (61.5, 87.8)	NA	73 (62, 87)	73 (61, 85)	
	Min, Max	(40.5, 146.2)	40, 179	NA	40, 182	40, 150	
BMI (kg/m2)	N (% not missing)	390 (97.7)	3620 (98.4)	NA	2499 (98.9)	1593 (99.0)	.160‡
	Mean (SD)	27.5 (6.5)	27.0 (6.4)	NA	26.7 (6.1)	26.7 (6.1)	

		TOTAL COHORT					
	Measure	FP/FOR	FP/SAL DPI	FP/SAL MDI	BUD/FOR	BDP/FOR	p-value
	Median (IQR)	26.6 (23.2, 30.8)	26.2 (22.5, 30.5)	NA	26.1 (22.4, 30.3)	26.2 (22.4, 30.3)	
	Min, Max	(13.3, 52.4)	(13.1, 57.1)	NA	(13.1, 56.9)	(13.2, 59.9)	
BMI (kg/m2) (categorised)	N (% not missing)	390 (97.7)	3620 (98.4)	NA	2499 (98.9)	1593 (99.0)	0.508*
	Underweight (BMI<18.5), n (%)	20 (5.1)	251 (6.9)	NA	182 (7.3)	109 (6.8)	
	Normal (BMI≥18.5 & BMI<25), n (%)	122 (31.3)	1264 (34.9)	NA	869 (34.8)	545 (34.2)	
	Overweight (BMI≥25 & BMI<30), n (%)	133 (34.1)	1092 (30.2)	NA	775 (31.0)	515 (32.3)	
	Obese (BMI≥30), n (%)	115 (29.5)	1013 (28.0)	NA	673 (26.9)	424 (26.6)	
FEV_1 % predicted	N (% not missing)	365 (91.5)	3435 (93.4)	NA	2320 (91.8)	1494 (92.9)	<0.001‡
	Mean (SD)	57.7 (19.0)	55.9 (20.0)	NA	57.7 (19.7)	57.4 (20.5)	
	Median (IQR)	56 (44, 70)	54 (42, 68)	NA	56 (44, 70)	57 (43, 71)	
	Min, Max	18, 123	8, 190	NA	1, 163	10, 169	
FEV_1 % predicted (categorised)	N (% not missing)	365 (91.5)	3435 (93.4)	NA	2320 (91.8)	1494 (92.9)	0.014*
	<30 (very severe), n (%)	22 (6.0)	270 (7.9)	NA	150 (6.5)	108 (7.2)	
	30-49 (severe), n (%)	103 (28.2)	1112 (32.4)	NA	684 (29.5)	443 (29.7)	
	50-79 (moderate), n (%)	193 (52.9)	1669 (48.6)	NA	1167 (50.3)	741 (49.6)	
	80+ (mild), n (%)	47 (12.9)	384 (11.2)	NA	319 (13.8)	202 (13.5)	
Smoking Status	N (% not missing)	399 (100.0)	3678 (100.0)	NA	2526 (100.0)	1609 (100.0)	0.002*
	Non-smoker, n (%)	35 (8.8)	202 (5.5)	NA	170 (6.7)	127 (7.9)	
	Current smoker, n (%)	141 (35.3)	1437 (39.1)	NA	983 (38.9)	567 (35.2)	
	Ex-smoker, n (%)	223 (55.9)	2039 (55.4)	NA	1373 (54.4)	915 (56.9)	

Table 21: Demographic characteristics by FDC/ICS LABA (patients with COPD only, definition 2)
‡ Kruskal-Wallis test, * Chi-square test, NA – not applicable

6.2.4.2 Medication prescribed at index date

		TOTAL COHORT					
	Measure	FP/FOR	FP/SAL DPI	FP/SAL MDI	BUD/FOR	BDP/FOR	p-value
Continuous data available prior index date (years)	N (% not missing)	399 (100.0)	3678 (100.0)	NA	2526 (100.0)	1609 (100.0)	<0.001‡
	Mean (SD)	21.8 (14.9)	25.4 (17.9)	NA	23.4 (16.4)	23.8 (17.1)	
	Median (IQR)	19.4 (11.2, 28.3)	22.0 (11.6, 35.9)	NA	20.7 (11.1, 30.8)	21.0 (10.9, 31.6)	
	Min, Max	(1.1, 81.6)	(1.0, 92.5)	NA	(1.0, 87.5)	(1.0, 89.3)	
Length of follow-up period (months)	N (% not missing)	399 (100.0)	3678 (100.0)	NA	2526 (100.0)	1609 (100.0)	<0.001‡
	Mean (SD)	12.8 (11.6)	15.4 (12.2)	NA	14.5 (11.7)	10.9 (8.5)	
	Median (IQR)	9.2 (2.5, 20.8)	13.3 (3.5, 25.0)	NA	12.5 (3.1, 23.0)	9.8 (3.5, 15.6)	
	Min, Max	(0.0, 41.9)	(0.0, 44.0)	NA	(0.0, 44.0)	(0.0, 43.5)	

		TOTAL COHORT					
	Measure	FP/FOR	FP/SAL DPI	FP/SAL MDI	BUD/FOR	BDP/FOR	p-value
Prescribed FDC ICS/LABA inhaler dose (dose per puff)	N (% not missing)	399 (100.0)	3678 (100.0)	NA	2526 (100.0)	1609 (100.0)	<0.001*
	50/5, n (%)	n≥5	n<5	NA	n<5	n<5	
	125/5, n (%)	n≥5	n<5	NA	n<5	n<5	
	250/10, n (%)	n≥5	n<5	NA	n<5	n<5	
	500/50, n (%)	n<5	n≥5	NA	n<5	n<5	
	100/6, n (%)	n<5	n<5	NA	n<5	n≥5	
	200/6, n (%)	n<5	n<5	NA	n≥5	n<5	
	400/12, n (%)	n<5	n<5	NA	n≥5	n<5	
Prescribed FDC ICS/LABA (FP equivalent dose per day)	N (% not missing)	316 (79.2)	1491 (40.5)	NA	2040 (80.8)	1233 (76.6)	<0.001‡
	Mean (SD)	763.1 (274.7)	1017.1 (130.3)	NA	375.0 (99.7)	454.1 (95.7)	
	Median (IQR)	1000 (500, 1000)	1000 (1000, 1000)	NA	400 (400, 400)	500 (500, 500)	
	Min, Max	150, 1000	500, 2000	NA	200, 800	188, 1000	
Prescribed FDC ICS/LABA (FP equivalent dose per day) (categorised)	N (% not missing)	316 (79.2)	1491 (40.5)	NA	2040 (80.8)	1233 (76.6)	<0.001*
	>100 & <=200, n (%)	n≥5	n<5	NA	n≥5	n<5	
	>200 & <=400, n (%)	n≥5	n<5	NA	n≥5	n≥5	
	>400 & <600, n (%)	n≥5	n<5	NA	n<5	n≥5	
	≥600 & <1000, n (%)	n<5	n<5	NA	n≥5	n<5	
	≥1000, n (%)	n≥5	n≥5	NA	n<5	n<5	
Prescribed FDC ICS/LABA using imputed dosing instructions (FP equivalent dose per day)	N (% not missing)	399 (100.0)	3678 (100.0)	NA	2040 (80.8)	1233 (76.6)	<0.001‡
	Mean (SD)	763.5 (275.2)	1006.9 (83.4)	NA	375.0 (99.7)	454.2 (95.6)	
	Median (IQR)	1000 (500, 1000)	1000 (1000, 1000)	NA	400 (400, 400)	500 (500, 500)	
	Min, Max	150, 1000	500, 2000	NA	200, 800	250, 1000	
Prescribed FDC ICS/LABA using imputed dosing instructions (FP equivalent dose per day) (categorised)	N (% not missing)	399 (100.0)	3678 (100.0)	NA	2040 (80.8)	1233 (76.6)	<0.001*
	>100 & <=200, n (%)	n≥5	n<5	NA	n≥5	n<5	
	>200 & <=400, n (%)	n≥5	n<5	NA	n≥5	n≥5	
	>400 & <600, n (%)	n≥5	n<5	NA	n<5	n≥5	
	≥600 & <1000, n (%)	n<5	n<5	NA	n≥5	n<5	
	≥1000, n (%)	n≥5	n≥5	NA	n<5	n<5	
Duration of FDC ICS/LABA prescription (outcome), (months)	N (% not missing)	399 (100.0)	3678 (100.0)	NA	2526 (100.0)	1609 (100.0)	<0.001‡
	Mean (SD)	13.6 (12.1)	16.2 (12.7)	NA	15.3 (12.1)	11.8 (8.9)	
	Median (IQR)	10.0 (2.6, 21.5)	14.2 (4.1, 26.2)	NA	13.5 (3.5, 24.1)	10.9 (4.0, 16.9)	
	Min, Max	(0.0, 44.1)	(0.0, 50.1)	NA	(0.0, 46.1)	(0.0, 45.8)	
SABA prescriptions	N (% not missing)	399 (100.0)	3678 (100.0)	NA	2526 (100.0)	1609 (100.0)	0.355*
	No, n (%)	328 (82.2)	3029 (82.4)	NA	2113 (83.7)	1313 (81.6)	
	Yes, n (%)	71 (17.8)	649 (17.6)	NA	413 (16.3)	296 (18.4)	
SAMA prescriptions	N (% not missing)	399 (100.0)	3678 (100.0)	NA	2526 (100.0)	1609 (100.0)	<0.001*
	No, n (%)	385 (96.5)	3621 (98.5)	NA	2500 (99.0)	1592 (98.9)	

		TOTAL COHORT					
	Measure	FP/FOR	FP/SAL DPI	FP/SAL MDI	BUD/FOR	BDP/FOR	p-value
	Yes, n (%)	14 (3.5)	57 (1.5)	NA	26 (1.0)	17 (1.1)	
LABA prescriptions	N (% not missing)	399 (100.0)	3678 (100.0)	NA	2526 (100.0)	1609 (100.0)	0.458*
	No, n (%)	n≥5	3669 (99.8)	NA	2516 (99.6)	1603 (99.6)	
	Yes, n (%)	n<5	9 (0.2)	NA	10 (0.4)	6 (0.4)	
LAMA prescriptions	N (% not missing)	399 (100.0)	3678 (100.0)	NA	2526 (100.0)	1609 (100.0)	<0.001*
	No, n (%)	326 (81.7)	2613 (71.0)	NA	1985 (78.6)	1291 (80.2)	
	Yes, n (%)	73 (18.3)	1065 (29.0)	NA	541 (21.4)	318 (19.8)	
ICS only prescriptions	N (% not missing)	399 (100.0)	3678 (100.0)	NA	2526 (100.0)	1609 (100.0)	0.241*
	No, n (%)	n≥5	n≥5	NA	2519 (99.7)	1603 (99.6)	
	Yes, n (%)	n<5	n<5	NA	7 (0.3)	6 (0.4)	
Theophylline prescriptions	N (% not missing)	399 (100.0)	3678 (100.0)	NA	2526 (100.0)	1609 (100.0)	0.611*
	No, n (%)	n≥5	3633 (98.8)	NA	2498 (98.9)	1596 (99.2)	
	Yes, n (%)	n<5	45 (1.2)	NA	28 (1.1)	13 (0.8)	
LTRA prescriptions	N (% not missing)	399 (100.0)	3678 (100.0)	NA	2526 (100.0)	1609 (100.0)	0.987*
	No, n (%)	n≥5	3665 (99.6)	NA	2517 (99.6)	1603 (99.6)	
	Yes, n (%)	n<5	13 (0.4)	NA	9 (0.4)	6 (0.4)	

Table 22: Medication prescribed at index date by FDC/ICS LABA (patients with COPD only, definition 2)
‡ Kruskal-Wallis test, * Chi-square test, NA – not applicable

6.2.4.3 Comorbidities

		TOTAL COHORT					
	Measure	FP/FOR	FP/SAL DPI	FP/SAL MDI	BUD/FOR	BDP/FOR	p-value
Year of first recorded COPD diagnosis	N (% not missing)	397 (99.5)	3674 (99.9)	NA	2520 (99.8)	1604 (99.7)	<0.001‡
	Mean (SD)	2007.7 (6.9)	2008.2 (5.7)	NA	2008.9 (6.1)	2008.2 (6.4)	
	Median (IQR)	2009 (2005, 2013)	2010 (2006, 2012)	NA	2011 (2007, 2013)	2010 (2005, 2013)	
	Min, Max	1940, 2015	1963, 2015	NA	1950, 2015	1934, 2015	
Comorbid rhinitis	N (% not missing)	399 (100.0)	3678 (100.0)	NA	2526 (100.0)	1609 (100.0)	0.581*
	No, n (%)	383 (96.0)	3539 (96.2)	NA	2416 (95.6)	1537 (95.5)	
	Yes, n (%)	16 (4.0)	139 (3.8)	NA	110 (4.4)	72 (4.5)	
Comorbid eczema	N (% not missing)	399 (100.0)	3678 (100.0)	NA	2526 (100.0)	1609 (100.0)	0.905*
	No, n (%)	375 (94.0)	3451 (93.8)	NA	2360 (93.4)	1504 (93.5)	
	Yes, n (%)	24 (6.0)	227 (6.2)	NA	166 (6.6)	105 (6.5)	
Comorbid GERD	N (% not missing)	399 (100.0)	3678 (100.0)	NA	2526 (100.0)	1609 (100.0)	0.046*
	No, n (%)	346 (86.7)	3203 (87.1)	NA	2192 (86.8)	1356 (84.3)	

		TOTAL COHORT					
	Measure	**FP/FOR**	**FP/SAL DPI**	**FP/SAL MDI**	**BUD/FOR**	**BDP/FOR**	**p-value**
	Yes, n (%)	53 (13.3)	475 (12.9)	NA	334 (13.2)	253 (15.7)	
History of ischemic heart disease	N (% not missing)	399 (100.0)	3678 (100.0)	NA	2526 (100.0)	1609 (100.0)	0.486*
	No, n (%)	318 (79.7)	2938 (79.9)	NA	2033 (80.5)	1263 (78.5)	
	Yes, n (%)	81 (20.3)	740 (20.1)	NA	493 (19.5)	346 (21.5)	
History of hypertension	N (% not missing)	399 (100.0)	3678 (100.0)	NA	2526 (100.0)	1609 (100.0)	0.091*
	No, n (%)	215 (53.9)	2091 (56.9)	NA	1473 (58.3)	881 (54.8)	
	Yes, n (%)	184 (46.1)	1587 (43.1)	NA	1053 (41.7)	728 (45.2)	
History of ischemic heart disease and hypertension	N (% not missing)	399 (100.0)	3678 (100.0)	NA	2526 (100.0)	1609 (100.0)	0.231*
	No, n (%)	350 (87.7)	3284 (89.3)	NA	2251 (89.1)	1408 (87.5)	
	Yes, n (%)	49 (12.3)	394 (10.7)	NA	275 (10.9)	201 (12.5)	
Charlson Comorbidity Index (CCI)	N (% not missing)	399 (100.0)	3675 (99.9)	NA	2525 (100.0)	1609 (100.0)	.003‡
	Mean (SD)	2.2 (4.1)	2.4 (3.8)	NA	2.4 (3.7)	2.2 (3.7)	
	Median (IQR)	0 (0, 4)	0 (0, 4)	NA	0 (0, 4)	0 (0, 4)	
	Min, Max	0, 34	0, 28	NA	0, 27	0, 34	
Charlson Comorbidity Index (CCI) (categorised)	N (% not missing)	399 (100.0)	3675 (99.9)	NA	2525 (100.0)	1609 (100.0)	0.015*
	0, n (%)	261 (65.4)	2137 (58.1)	NA	1439 (57.0)	980 (60.9)	
	1-4, n (%)	95 (23.8)	1111 (30.2)	NA	764 (30.3)	452 (28.1)	
	5+, n (%)	43 (10.8)	427 (11.6)	NA	322 (12.8)	177 (11.0)	

Table 23: Comorbidities by FDC/ICS LABA (patients with COPD only, definition 2)
‡ Kruskal-Wallis test, * Chi-square test, NA – not applicable

6.2.4.4 Consultations and hospitalisations in year prior to index date

		TOTAL COHORT					
	Measure	**FP/FOR**	**FP/SAL DPI**	**FP/SAL MDI**	**BUD/FOR**	**BDP/FOR**	**p-value**
Respiratory GP consultations without prescription for an oral corticosteroid (categorised)	N (% not missing)	399 (100.0)	3678 (100.0)	NA	2526 (100.0)	1609 (100.0)	0.044*
	0, n (%)	97 (24.3)	793 (21.6)	NA	513 (20.3)	354 (22.0)	
	1, n (%)	120 (30.1)	1101 (29.9)	NA	687 (27.2)	468 (29.1)	
	2, n (%)	86 (21.6)	761 (20.7)	NA	545 (21.6)	346 (21.5)	
	3+, n (%)	96 (24.1)	1023 (27.8)	NA	781 (30.9)	441 (27.4)	
COPD GP consultations without prescription for an oral corticosteroid (categorised)	N (% not missing)	399 (100.0)	3678 (100.0)	NA	2526 (100.0)	1609 (100.0)	0.055*
	0, n (%)	184 (46.1)	1614 (43.9)	NA	1109 (43.9)	656 (40.8)	
	1, n (%)	161 (40.4)	1400 (38.1)	NA	926 (36.7)	650 (40.4)	
	2, n (%)	41 (10.3)	462 (12.6)	NA	347 (13.7)	222 (13.8)	

		TOTAL COHORT					
	Measure	FP/FOR	FP/SAL DPI	FP/SAL MDI	BUD/FOR	BDP/FOR	p-value
	3+, n (%)	13 (3.3)	202 (5.5)	NA	144 (5.7)	81 (5.0)	
Respiratory hospital outpatient attendances (categorised)	N (% not missing)	173 (100.0)	2201 (100.0)	NA	1391 (100.0)	844 (100.0)	0.016*
	0, n (%)	159 (91.9)	1970 (89.5)	NA	1207 (86.8)	732 (86.7)	
	1+, n (%)	14 (8.1)	231 (10.5)	NA	184 (13.2)	112 (13.3)	
Lower respiratory inpatient hospitalisations (categorised)	N (% not missing)	173 (100.0)	2201 (100.0)	NA	1391 (100.0)	844 (100.0)	0.030*
	0, n (%)	157 (90.8)	1856 (84.3)	NA	1192 (85.7)	738 (87.4)	
	1+, n (%)	16 (9.2)	345 (15.7)	NA	199 (14.3)	106 (12.6)	
COPD inpatient hospitalisations (categorised)	N (% not missing)	173 (100.0)	2201 (100.0)	NA	1391 (100.0)	844 (100.0)	<0.001*
	0, n (%)	166 (96.0)	1934 (87.9)	NA	1240 (89.1)	776 (91.9)	
	1+, n (%)	7 (4.0)	267 (12.1)	NA	151 (10.9)	68 (8.1)	
COPD exacerbations (categorised)	N (% not missing)	173 (100.0)	2201 (100.0)	NA	1391 (100.0)	844 (100.0)	0.904*
	0, n (%)	48 (27.7)	666 (30.3)	NA	418 (30.1)	247 (29.3)	
	1, n (%)	47 (27.2)	579 (26.3)	NA	350 (25.2)	232 (27.5)	
	2+, n (%)	78 (45.1)	956 (43.4)	NA	623 (44.8)	365 (43.2)	

Table 24: Consultations and hospitalisations in year prior to index date by FDC/ICS LABA (patients with COPD only, definition 2)
‡ Kruskal-Wallis test, * Chi-square test, NA – not applicable

6.2.4.5 Prescriptions for therapy in year prior to index date

		TOTAL COHORT					
	Measure	FP/FOR	FP/SAL DPI	FP/SAL MDI	BUD/FOR	BDP/FOR	p-value
FDC ICS+LABA inhalers	N (% not missing)	399 (100.0)	3678 (100.0)	NA	2526 (100.0)	1609 (100.0)	<0.001‡
	Mean (SD)	4.9 (5.9)	4.0 (5.6)	NA	2.7 (4.9)	4.4 (5.8)	
	Median (IQR)	2 (0, 10)	0 (0, 8)	NA	0 (0, 4)	0 (0, 9)	
	Min, Max	0, 32	0, 50	NA	0, 41	0, 48	
FDC ICS+LABA inhalers (categorised)	N (% not missing)	399 (100.0)	3678 (100.0)	NA	2526 (100.0)	1609 (100.0)	<0.001*
	No, n (%)	191 (47.9)	2142 (58.2)	NA	1746 (69.1)	865 (53.8)	
	Yes, n (%)	208 (52.1)	1536 (41.8)	NA	780 (30.9)	744 (46.2)	
SABA inhalers	N (% not missing)	399 (100.0)	3678 (100.0)	NA	2526 (100.0)	1609 (100.0)	<0.001‡
	Mean (SD)	3.8 (6.5)	4.0 (7.0)	NA	3.9 (6.4)	5.2 (8.1)	
	Median (IQR)	0 (0, 5)	0 (0, 6)	NA	1 (0, 6)	2 (0, 8)	
	Min, Max	0, 34	0, 68	NA	0, 57	0, 90	
SABA inhalers (categorised)	N (% not missing)	399 (100.0)	3678 (100.0)	NA	2526 (100.0)	1609 (100.0)	<0.001*

		TOTAL COHORT					
	Measure	FP/FOR	FP/SAL DPI	FP/SAL MDI	BUD/FOR	BDP/FOR	p-value
	No, n (%)	208 (52.1)	1850 (50.3)	NA	1239 (49.0)	668 (41.5)	
	Yes, n (%)	191 (47.9)	1828 (49.7)	NA	1287 (51.0)	941 (58.5)	
SAMA inhalers	N (% not missing)	399 (100.0)	3678 (100.0)	NA	2526 (100.0)	1609 (100.0)	.026‡
	Mean (SD)	1.1 (5.9)	0.7 (4.1)	NA	0.5 (2.6)	0.7 (3.8)	
	Median (IQR)	0 (0, 0)	0 (0, 0)	NA	0 (0, 0)	0 (0, 0)	
	Min, Max	0, 80	0, 112	NA	0, 51	0, 68	
SAMA inhalers (categorised)	N (% not missing)	399 (100.0)	3678 (100.0)	NA	2526 (100.0)	1609 (100.0)	0.033*
	No, n (%)	360 (90.2)	3395 (92.3)	NA	2366 (93.7)	1501 (93.3)	
	Yes, n (%)	39 (9.8)	283 (7.7)	NA	160 (6.3)	108 (6.7)	
LABA inhalers	N (% not missing)	399 (100.0)	3678 (100.0)	NA	2526 (100.0)	1609 (100.0)	.491‡
	Mean (SD)	0.6 (2.2)	0.7 (2.7)	NA	0.7 (2.7)	0.9 (3.2)	
	Median (IQR)	0 (0, 0)	0 (0, 0)	NA	0 (0, 0)	0 (0, 0)	
	Min, Max	0, 16	0, 30	NA	0, 28	0, 36	
LABA inhalers (categorised)	N (% not missing)	399 (100.0)	3678 (100.0)	NA	2526 (100.0)	1609 (100.0)	0.494*
	No, n (%)	359 (90.0)	3311 (90.0)	NA	2264 (89.6)	1426 (88.6)	
	Yes, n (%)	40 (10.0)	367 (10.0)	NA	262 (10.4)	183 (11.4)	
LAMA inhalers	N (% not missing)	399 (100.0)	3678 (100.0)	NA	2526 (100.0)	1609 (100.0)	.003‡
	Mean (SD)	8.0 (10.2)	9.0 (10.7)	NA	8.1 (10.0)	9.0 (10.2)	
	Median (IQR)	2 (0, 14)	4 (0, 14)	NA	4 (0, 14)	6 (0, 16)	
	Min, Max	0, 52	0, 108	NA	0, 84	0, 56	
LAMA inhalers (categorised)	N (% not missing)	399 (100.0)	3678 (100.0)	NA	2526 (100.0)	1609 (100.0)	0.001*
	No, n (%)	189 (47.4)	1432 (38.9)	NA	1073 (42.5)	648 (40.3)	
	Yes, n (%)	210 (52.6)	2246 (61.1)	NA	1453 (57.5)	961 (59.7)	
ICS only inhalers	N (% not missing)	399 (100.0)	3678 (100.0)	NA	2526 (100.0)	1609 (100.0)	<0.001‡
	Mean (SD)	0.8 (2.5)	0.5 (2.1)	NA	0.7 (2.4)	0.8 (2.3)	
	Median (IQR)	0 (0, 0)	0 (0, 0)	NA	0 (0, 0)	0 (0, 0)	
	Min, Max	0, 17	0, 21	NA	0, 32	0, 24	
ICS only inhalers (categorised)	N (% not missing)	399 (100.0)	3678 (100.0)	NA	2526 (100.0)	1609 (100.0)	<0.001*
	No, n (%)	344 (86.2)	3276 (89.1)	NA	2170 (85.9)	1369 (85.1)	
	Yes, n (%)	55 (13.8)	402 (10.9)	NA	356 (14.1)	240 (14.9)	
Theophylline prescriptions	N (% not missing)	399 (100.0)	3678 (100.0)	NA	2526 (100.0)	1609 (100.0)	.189‡
	Mean (SD)	0.4 (2.0)	0.4 (2.4)	NA	0.3 (2.1)	0.4 (2.0)	
	Median (IQR)	0 (0, 0)	0 (0, 0)	NA	0 (0, 0)	0 (0, 0)	

		TOTAL COHORT					
	Measure	FP/FOR	FP/SAL DPI	FP/SAL MDI	BUD/FOR	BDP/FOR	p-value
	Min, Max	0, 14	0, 51	NA	0, 52	0, 15	
Theophylline prescriptions (categorised)	N (% not missing)	399 (100.0)	3678 (100.0)	NA	2526 (100.0)	1609 (100.0)	0.188*
	No, n (%)	378 (94.7)	3540 (96.2)	NA	2435 (96.4)	1535 (95.4)	
	Yes, n (%)	21 (5.3)	138 (3.8)	NA	91 (3.6)	74 (4.6)	
LTRA prescriptions	N (% not missing)	399 (100.0)	3678 (100.0)	NA	2526 (100.0)	1609 (100.0)	.139‡
	Mean (SD)	0.2 (2.0)	0.1 (0.9)	NA	0.1 (1.1)	0.1 (0.9)	
	Median (IQR)	0 (0, 0)	0 (0, 0)	NA	0 (0, 0)	0 (0, 0)	
	Min, Max	0, 35	0, 14	NA	0, 35	0, 13	
LTRA prescriptions (categorised)	N (% not missing)	399 (100.0)	3678 (100.0)	NA	2526 (100.0)	1609 (100.0)	0.136*
	No, n (%)	391 (98.0)	3638 (98.9)	NA	2496 (98.8)	1581 (98.3)	
	Yes, n (%)	8 (2.0)	40 (1.1)	NA	30 (1.2)	28 (1.7)	
Spacer prescription	N (% not missing)	399 (100.0)	3678 (100.0)	NA	2526 (100.0)	1609 (100.0)	<0.001*
	No, n (%)	303 (75.9)	3026 (82.3)	NA	2205 (87.3)	1270 (78.9)	
	Yes, n (%)	96 (24.1)	652 (17.7)	NA	321 (12.7)	339 (21.1)	
Pain-relief medication prescriptions (categorised)	N (% not missing)	399 (100.0)	3678 (100.0)	NA	2526 (100.0)	1609 (100.0)	0.134*
	No, n (%)	195 (48.9)	1755 (47.7)	NA	1191 (47.1)	715 (44.4)	
	Yes, n (%)	204 (51.1)	1923 (52.3)	NA	1335 (52.9)	894 (55.6)	
Non-steroidal anti-inflammatory drugs (NSAIDs) prescriptions (categorised)	N (% not missing)	399 (100.0)	3678 (100.0)	NA	2526 (100.0)	1609 (100.0)	0.019*
	No, n (%)	333 (83.5)	3030 (82.4)	NA	2007 (79.5)	1299 (80.7)	
	Yes, n (%)	66 (16.5)	648 (17.6)	NA	519 (20.5)	310 (19.3)	
Beta-blocker prescriptions (categorised)	N (% not missing)	399 (100.0)	3678 (100.0)	NA	2526 (100.0)	1609 (100.0)	0.816*
	No, n (%)	321 (80.5)	2986 (81.2)	NA	2065 (81.7)	1298 (80.7)	
	Yes, n (%)	78 (19.5)	692 (18.8)	NA	461 (18.3)	311 (19.3)	

Table 25: Prescriptions for therapy in year prior to index date by FDC/ICS LABA (patients with COPD only, definition 2)

‡ Kruskal-Wallis test, * Chi-square test, NA – not applicable

6.2.4.6 Adverse events during baseline

		TOTAL COHORT					
	Measure	FP/FOR	FP/SAL DPI	FP/SAL MDI	BUD/FOR	BDP/FOR	p-value
Lower Respiratory Tract Infection in baseline	N (% not missing)	399 (100.0)	3678 (100.0)	NA	2526 (100.0)	1609 (100.0)	0.131*
	No, n (%)	259 (64.9)	2338 (63.6)	NA	1564 (61.9)	975 (60.6)	
	Yes, n (%)	140 (35.1)	1340 (36.4)	NA	962 (38.1)	634 (39.4)	

		TOTAL COHORT					
	Measure	**FP/FOR**	**FP/SAL DPI**	**FP/SAL MDI**	**BUD/FOR**	**BDP/FOR**	**p-value**
Pneumonia in baseline	N (% not missing)	399 (100.0)	3678 (100.0)	NA	2526 (100.0)	1609 (100.0)	0.086*
	No, n (%)	391 (98.0)	3597 (97.8)	NA	2464 (97.5)	1555 (96.6)	
	Yes, n (%)	8 (2.0)	81 (2.2)	NA	62 (2.5)	54 (3.4)	
Pulmonary Embolism in baseline	N (% not missing)	399 (100.0)	3678 (100.0)	NA	2526 (100.0)	1609 (100.0)	0.098*
	No, n (%)	n≥5	3666 (99.7)	NA	2511 (99.4)	n≥5	
	Yes, n (%)	n<5	12 (0.3)	NA	15 (0.6)	n<5	
Tuberculosis in baseline	N (% not missing)	399 (100.0)	3678 (100.0)	NA	2526 (100.0)	1609 (100.0)	0.376*
	No, n (%)	n≥5	n≥5	NA	n≥5	n≥5	
	Yes, n (%)	n<5	n<5	NA	n<5	n<5	

Table 26: Adverse events occurring in year prior to index date by FDC/ICS LABA (patients with COPD only, definition 2)

‡ Kruskal-Wallis test, * Chi-square test, NA – not applicable

6.2.5 "MART" regimen, definition 2

The number of MART patients (definition 2) prescribed FP/FOR was low. Demographic characteristics, disease severity, GP consultations, hospitalisations and prescriptions at the index date were similar across treatment groups (Table 27, Table 28, Table 30). Patients in the BDP/FOR group were more likely to have GERD and a history of hypertension, although CCI score was similar across the groups (Table 29). Exacerbations in the year prior were less likely in the FP/FOR treatment group. The FP/FOR group had a lower prescription of ICS prior to the index date; other prior respiratory prescriptions were similar but FP/FOR patients were more likely to be switchers than the other FDC ICS/LABA groups (Table 31). Data available prior to index date, duration of FDC ICS/LABA prescription during outcome and length of follow-up were similar between the treatment groups. There was no significant difference in LRTI or pneumonia at baseline between the groups and no cases of pulmonary embolism or tuberculosis (Table 32).

6.2.5.1 Demographic characteristics

		TOTAL COHORT					
	Measure	FP/FOR	FP/SAL DPI	FP/SAL MDI	BUD/FOR	BDP/FOR	p-value
Age at IPD (years)	N (% not missing)	75 (100.0)	NA	NA	246 (100.0)	320 (100.0)	.002‡
	Mean (SD)	47.1 (15.3)	NA	NA	49.3 (16.7)	53.2 (17.5)	
	Median (IQR)	47 (35, 57)	NA	NA	49 (36, 62)	55 (41, 66)	
	Min, Max	18, 83	NA	NA	18, 88	18, 90	
Gender	N (% not missing)	75 (100.0)	NA	NA	246 (100.0)	320 (100.0)	0.432*
	Female, n (%)	48 (64.0)	NA	NA	150 (61.0)	212 (66.3)	
	Male, n (%)	27 (36.0)	NA	NA	96 (39.0)	108 (33.8)	
Height (m) - closest to IPD	N (% not missing)	74 (98.7)	NA	NA	243 (98.8)	317 (99.1)	.008‡
	Mean (SD)	1.7 (0.1)	NA	NA	1.7 (0.1)	1.7 (0.1)	
	Median (IQR)	1.7 (1.6, 1.8)	NA	NA	1.7 (1.6, 1.8)	1.6 (1.6, 1.7)	
	Min, Max	(1.5, 2.0)	NA	NA	(1.5, 2.0)	(1.5, 2.0)	
Weight (kg) - closest to IPD	N (% not missing)	75 (100.0)	NA	NA	240 (97.6)	310 (96.9)	.414‡
	Mean (SD)	83.5 (21.8)	NA	NA	79.7 (20.6)	80.8 (21.9)	
	Median (IQR)	80 (67, 99)	NA	NA	75 (65, 92)	78 (65, 90)	
	Min, Max	49, 146	NA	NA	48, 192	42, 185	
BMI (kg/m2)	N (% not missing)	74 (98.7)	NA	NA	239 (97.2)	310 (96.9)	.110‡
	Mean (SD)	29.5 (7.8)	NA	NA	28.2 (6.5)	29.4 (7.3)	
	Median (IQR)	27.3 (24.8, 33.1)	NA	NA	27.0 (23.5, 31.0)	28.1 (24.6, 32.3)	
	Min, Max	(17.9, 52.2)	NA	NA	(16.7, 59.3)	(13.9, 56.6)	
	N (% not missing)	74 (98.7)	NA	NA	239 (97.2)	310 (96.9)	0.122*

		TOTAL COHORT					
	Measure	**FP/FOR**	**FP/SAL DPI**	**FP/SAL MDI**	**BUD/FOR**	**BDP/FOR**	**p-value**
BMI (kg/m2) (categorised)	Underweight (BMI<18.5), n (%)	n<5	NA	NA	n<5	11 (3.5)	
	Normal (BMI≥18.5 & BMI<25), n (%)	n≥5	NA	NA	n≥5	77 (24.8)	
	Overweight (BMI≥25 & BMI<30), n (%)	n≥5	NA	NA	n≥5	107 (34.5)	
	Obese (BMI≥30), n (%)	n≥5	NA	NA	n≥5	115 (37.1)	
FEV_1 % predicted	N (% not missing)	18 (24.0)	NA	NA	95 (38.6)	127 (39.7)	.618‡
	Mean (SD)	85.1 (26.2)	NA	NA	81.1 (22.7)	83.2 (22.8)	
	Median (IQR)	91 (71, 101)	NA	NA	86 (69, 97)	87 (69, 98)	
	Min, Max	30, 119	NA	NA	23, 137	26, 143	
FEV_1 % predicted (categorised)	N (% not missing)	18 (24.0)	NA	NA	95 (38.6)	127 (39.7)	0.699*
	<30 (very severe), n (%)	n<5	NA	NA	n<5	n<5	
	30-49 (severe), n (%)	n<5	NA	NA	n≥5	n≥5	
	50-79 (moderate), n (%)	n<5	NA	NA	n≥5	n≥5	
	80+ (mild), n (%)	n≥5	NA	NA	n≥5	n≥5	
PEF % predicted	N (% not missing)	62 (82.7)	NA	NA	219 (89.0)	277 (86.6)	.365‡
	Mean (SD)	101.8 (28.6)	NA	NA	97.5 (24.4)	97.8 (26.7)	
	Median (IQR)	104.3 (86.1, 120.9)	NA	NA	100.0 (84.6, 115.6)	102.0 (77.1, 117.6)	
	Min, Max	(29.4, 149.0)	NA	NA	(33.4, 149.6)	(20.4, 147.0)	
Smoking Status	N (% not missing)	75 (100.0)	NA	NA	246 (100.0)	320 (100.0)	0.238*
	Non-smoker, n (%)	43 (57.3)	NA	NA	144 (58.5)	160 (50.0)	
	Current smoker, n (%)	13 (17.3)	NA	NA	41 (16.7)	55 (17.2)	
	Ex-smoker, n (%)	19 (25.3)	NA	NA	61 (24.8)	105 (32.8)	

Table 27: Demographic characteristics by FDC/ICS LABA ("MART" regimen definition 2)
‡ Kruskal-Wallis test, * Chi-square test, NA – not applicable

6.2.5.2 Medication prescribed at index date

		TOTAL COHORT					
	Measure	**FP/FOR**	**FP/SAL DPI**	**FP/SAL MDI**	**BUD/FOR**	**BDP/FOR**	**p-value**
Continuous data available prior index date (years)	N (% not missing)	75 (100.0)	NA	NA	246 (100.0)	320 (100.0)	.022‡
	Mean (SD)	18.9 (13.4)	NA	NA	17.3 (13.3)	22.6 (18.5)	
	Median (IQR)	18.9 (6.7, 27.0)	NA	NA	16.2 (7.0, 24.7)	17.7 (7.7, 32.3)	
	Min, Max	(1.1, 65.8)	NA	NA	(1.0, 76.1)	(1.1, 77.7)	
	N (% not missing)	75 (100.0)	NA	NA	246 (100.0)	320 (100.0)	.464‡

		TOTAL COHORT					
	Measure	FP/FOR	FP/SAL DPI	FP/SAL MDI	BUD/FOR	BDP/FOR	p-value
Length of follow-up period (months)	Mean (SD)	11.8 (9.9)	NA	NA	12.2 (11.2)	13.2 (11.4)	
	Median (IQR)	10.4 (2.0, 17.6)	NA	NA	9.1 (2.0, 18.7)	10.8 (2.8, 19.9)	
	Min, Max	(0.5, 37.0)	NA	NA	(0.0, 42.0)	(0.0, 43.0)	
Prescribed FDC ICS/LABA inhaler dose (dose per puff)	N (% not missing)	75 (100.0)	NA	NA	246 (100.0)	320 (100.0)	<0.001*
	50/5, n (%)	n<5	NA	NA	n<5	n<5	
	125/5, n (%)	n≥5	NA	NA	n<5	n<5	
	250/10, n (%)	n≥5	NA	NA	n<5	n<5	
	100/6, n (%)	n<5	NA	NA	n≥5	n≥5	
	200/6, n (%)	n<5	NA	NA	n≥5	n<5	
Duration of FDC ICS/LABA prescription (outcome), (months)	N (% not missing)	75 (100.0)	NA	NA	246 (100.0)	320 (100.0)	.373‡
	Mean (SD)	12.3 (10.4)	NA	NA	12.7 (11.6)	13.9 (11.8)	
	Median (IQR)	11 (2, 18)	NA	NA	9 (2, 20)	11.3 (2.9, 20.9)	
	Min, Max	(0.5, 37.5)	NA	NA	(0.0, 43.9)	(0.0, 44.4)	
SABA prescriptions	N (% not missing)	75 (100.0)	NA	NA	246 (100.0)	320 (100.0)	NA
	No, n (%)	75 (100.0)	NA	NA	246 (100.0)	320 (100.0)	
SAMA prescriptions	N (% not missing)	75 (100.0)	NA	NA	246 (100.0)	320 (100.0)	0.023*
	No, n (%)	n≥5	NA	NA	n≥5	n≥5	
	Yes, n (%)	n<5	NA	NA	n<5	n<5	
LABA prescriptions	N (% not missing)	75 (100.0)	NA	NA	246 (100.0)	320 (100.0)	NA
	No, n (%)	75 (100.0)	NA	NA	246 (100.0)	320 (100.0)	
LAMA prescriptions	N (% not missing)	75 (100.0)	NA	NA	246 (100.0)	320 (100.0)	0.304*
	No, n (%)	n≥5	NA	NA	n≥5	n≥5	
	Yes, n (%)	n<5	NA	NA	n<5	n<5	
ICS only prescriptions	N (% not missing)	75 (100.0)	NA	NA	246 (100.0)	320 (100.0)	0.499*
	No, n (%)	n≥5	NA	NA	n≥5	n≥5	
	Yes, n (%)	n<5	NA	NA	n<5	n<5	
Theophylline prescriptions	N (% not missing)	75 (100.0)	NA	NA	246 (100.0)	320 (100.0)	0.193*
	No, n (%)	n≥5	NA	NA	n≥5	n≥5	
	Yes, n (%)	n<5	NA	NA	n<5	n<5	
LTRA prescriptions	N (% not missing)	75 (100.0)	NA	NA	246 (100.0)	320 (100.0)	0.019*
	No, n (%)	n≥5	NA	NA	n≥5	n≥5	
	Yes, n (%)	n<5	NA	NA	n<5	n<5	

Table 28: Medication prescribed at index date by FDC/ICS LABA ("MART" regimen definition 2)
‡ Kruskal-Wallis test, * Chi-square test, NA – not applicable

6.2.5.3 Comorbidities

		TOTAL COHORT					
	Measure	**FP/FOR**	**FP/SAL DPI**	**FP/SAL MDI**	**BUD/FOR**	**BDP/FOR**	**p-value**
Presence of asthma and/or COPD	N (% not missing)	75 (100.0)	NA	NA	246 (100.0)	320 (100.0)	0.052*
	Asthma only, n (%)	n≥5	NA	NA	234 (95.1)	294 (91.9)	
	Asthma & COPD, n (%)	n<5	NA	NA	12 (4.9)	26 (8.1)	
Year of first recorded asthma diagnosis	N (% not missing)	75 (100.0)	NA	NA	246 (100.0)	320 (100.0)	.002‡
	Mean (SD)	1993.8 (13.4)	NA	NA	1999.4 (13.2)	1998.3 (13.0)	
	Median (IQR)	1995 (1986, 2005)	NA	NA	2002 (1993, 2011)	2000 (1991, 2009)	
	Min, Max	1964, 2014	NA	NA	1945, 2015	1945, 2015	
Year of first recorded COPD diagnosis	N (% not missing)	n<5	NA	NA	13 (5.3)	26 (8.1)	.109‡
	Mean (SD)	n<5	NA	NA	2009.0 (3.1)	2005.0 (6.2)	
	Median (IQR)	n<5	NA	NA	2009 (2007, 2012)	2005 (2001, 2010)	
	Min, Max	n<5	NA	NA	2004, 2013	1992, 2015	
Comorbid rhinitis	N (% not missing)	75 (100.0)	NA	NA	246 (100.0)	320 (100.0)	0.471*
	No, n (%)	61 (81.3)	NA	NA	213 (86.6)	277 (86.6)	
	Yes, n (%)	14 (18.7)	NA	NA	33 (13.4)	43 (13.4)	
Comorbid eczema	N (% not missing)	75 (100.0)	NA	NA	246 (100.0)	320 (100.0)	0.725*
	No, n (%)	70 (93.3)	NA	NA	231 (93.9)	295 (92.2)	
	Yes, n (%)	5 (6.7)	NA	NA	15 (6.1)	25 (7.8)	
Comorbid GERD	N (% not missing)	75 (100.0)	NA	NA	246 (100.0)	320 (100.0)	0.013*
	No, n (%)	69 (92.0)	NA	NA	229 (93.1)	274 (85.6)	
	Yes, n (%)	6 (8.0)	NA	NA	17 (6.9)	46 (14.4)	
History of ischemic heart disease	N (% not missing)	75 (100.0)	NA	NA	246 (100.0)	320 (100.0)	0.072*
	No, n (%)	n≥5	NA	NA	235 (95.5)	300 (93.8)	
	Yes, n (%)	n<5	NA	NA	11 (4.5)	20 (6.3)	
History of hypertension	N (% not missing)	75 (100.0)	NA	NA	246 (100.0)	320 (100.0)	0.009*
	No, n (%)	60 (80.0)	NA	NA	200 (81.3)	226 (70.6)	
	Yes, n (%)	15 (20.0)	NA	NA	46 (18.7)	94 (29.4)	
History of ischemic heart disease and hypertension	N (% not missing)	75 (100.0)	NA	NA	246 (100.0)	320 (100.0)	0.268*
	No, n (%)	n≥5	NA	NA	239 (97.2)	309 (96.6)	
	Yes, n (%)	n<5	NA	NA	7 (2.8)	11 (3.4)	
Charlson Comorbidity Index (CCI)	N (% not missing)	75 (100.0)	NA	NA	246 (100.0)	320 (100.0)	.605‡
	Mean (SD)	3.9 (1.8)	NA	NA	3.7 (1.8)	4.0 (2.2)	
	Median (IQR)	4 (4, 4)	NA	NA	4 (4, 4)	4 (4, 4)	
	Min, Max	0, 12	NA	NA	0, 14	0, 21	
	N (% not missing)	75 (100.0)	NA	NA	246 (100.0)	320 (100.0)	0.688*
	0, n (%)	n≥5	NA	NA	29 (11.8)	29 (9.1)	

		TOTAL COHORT					
	Measure	FP/FOR	FP/SAL DPI	FP/SAL MDI	BUD/FOR	BDP/FOR	p-value
Charlson Comorbidity Index (CCI) (categorised)	1-4, n (%)	n≥5	NA	NA	207 (84.1)	272 (85.0)	
	5+, n (%)	n<5	NA	NA	10 (4.1)	19 (5.9)	

Table 29: Comorbidities by FDC/ICS LABA ("MART" regimen definition 2)
‡ Kruskal-Wallis test, * Chi-square test, NA – not applicable

6.2.5.4 Consultations and hospitalisations in year prior to index date

		TOTAL COHORT					
	Measure	FP/FOR	FP/SAL DPI	FP/SAL MDI	BUD/FOR	BDP/FOR	p-value
Respiratory GP consultations without prescription for an oral corticosteroid (categorised)	N (% not missing)	75 (100.0)	NA	NA	246 (100.0)	320 (100.0)	
	0, n (%)	21 (28.0)	NA	NA	62 (25.2)	94 (29.4)	
	1, n (%)	24 (32.0)	NA	NA	59 (24.0)	82 (25.6)	0.415*
	2, n (%)	18 (24.0)	NA	NA	57 (23.2)	72 (22.5)	
	3+, n (%)	12 (16.0)	NA	NA	68 (27.6)	72 (22.5)	
Asthma GP consultations without prescription for an oral corticosteroid (categorised)	N (% not missing)	75 (100.0)	NA	NA	246 (100.0)	320 (100.0)	
	0, n (%)	n≥5	NA	NA	103 (41.9)	141 (44.1)	
	1, n (%)	n≥5	NA	NA	103 (41.9)	103 (32.2)	0.135*
	2, n (%)	n≥5	NA	NA	27 (11.0)	52 (16.3)	
	3+, n (%)	n<5	NA	NA	13 (5.3)	24 (7.5)	
COPD GP consultations without prescription for an oral corticosteroid (categorised)	N (% not missing)	75 (100.0)	NA	NA	246 (100.0)	320 (100.0)	
	0, n (%)	n≥5	NA	NA	n≥5	n≥5	0.282*
	1, n (%)	n<5	NA	NA	n≥5	n≥5	
	2, n (%)	n<5	NA	NA	n<5	n<5	
Respiratory hospital outpatient attendances (categorised)	N (% not missing)	50 (100.0)	NA	NA	142 (100.0)	168 (100.0)	
	0, n (%)	n≥5	NA	NA	136 (95.8)	155 (92.3)	0.077*
	1+, n (%)	n<5	NA	NA	6 (4.2)	13 (7.7)	
Lower respiratory inpatient hospitalisations (categorised)	N (% not missing)	50 (100.0)	NA	NA	142 (100.0)	168 (100.0)	
	0, n (%)	n≥5	NA	NA	n≥5	n≥5	0.596*
	1+, n (%)	n<5	NA	NA	n<5	n<5	
Asthma inpatient hospitalisations (categorised)	N (% not missing)	50 (100.0)	NA	NA	142 (100.0)	168 (100.0)	
	0, n (%)	n≥5	NA	NA	135 (95.1)	163 (97.0)	0.233*
	1+, n (%)	n<5	NA	NA	7 (4.9)	5 (3.0)	
COPD inpatient hospitalisations (categorised)	N (% not missing)	50 (100.0)	NA	NA	142 (100.0)	168 (100.0)	
	0, n (%)	n≥5	NA	NA	n≥5	n≥5	0.098*
	1+, n (%)	n<5	NA	NA	n<5	n<5	
Asthma or COPD exacerbations (categorised)	N (% not missing)	50 (100.0)	NA	NA	142 (100.0)	168 (100.0)	
	0, n (%)	28 (56.0)	NA	NA	47 (33.1)	76 (45.2)	0.030*
	1, n (%)	10 (20.0)	NA	NA	48 (33.8)	39 (23.2)	
	2+, n (%)	12 (24.0)	NA	NA	47 (33.1)	53 (31.5)	

Table 30: Consultations and hospitalisations in year prior to index date by FDC/ICS LABA ("MART" regimen definition 2)
‡ Kruskal-Wallis test, * Chi-square test, NA – not applicable

6.2.5.5 Prescriptions for therapy in year prior to index date

		TOTAL COHORT					
	Measure	FP/FOR	FP/SAL DPI	FP/SAL MDI	BUD/FOR	BDP/FOR	p-value
FDC ICS+LABA inhalers	N (% not missing)	75 (100.0)	NA	NA	246 (100.0)	320 (100.0)	<0.001‡
	Mean (SD)	2.8 (4.1)	NA	NA	1.8 (4.1)	2.9 (4.6)	
	Median (IQR)	0 (0, 6)	NA	NA	0 (0, 0)	0 (0, 6)	
	Min, Max	0, 14	NA	NA	0, 22	0, 22	
FDC ICS+LABA inhalers (categorised)	N (% not missing)	75 (100.0)	NA	NA	246 (100.0)	320 (100.0)	<0.001*
	No, n (%)	44 (58.7)	NA	NA	191 (77.6)	203 (63.4)	
	Yes, n (%)	31 (41.3)	NA	NA	55 (22.4)	117 (36.6)	
SABA inhalers	N (% not missing)	75 (100.0)	NA	NA	246 (100.0)	320 (100.0)	.012‡
	Mean (SD)	4.8 (3.8)	NA	NA	5.2 (5.9)	6.4 (6.0)	
	Median (IQR)	4 (2, 7)	NA	NA	3 (2, 7)	4 (2, 8)	
	Min, Max	1, 19	NA	NA	1, 51	1, 30	
SABA inhalers (categorised)	N (% not missing)	75 (100.0)	NA	NA	246 (100.0)	320 (100.0)	NA
	Yes, n (%)	75 (100.0)	NA	NA	246 (100.0)	320 (100.0)	
SAMA inhalers	N (% not missing)	75 (100.0)	NA	NA	246 (100.0)	320 (100.0)	.625‡
	Mean (SD)	0.0 (0.0)	NA	NA	0.0 (0.1)	0.1 (1.4)	
	Median (IQR)	0 (0, 0)	NA	NA	0 (0, 0)	0 (0, 0)	
	Min, Max	0, 0	NA	NA	0, 1	0, 24	
SAMA inhalers (categorised)	N (% not missing)	75 (100.0)	NA	NA	246 (100.0)	320 (100.0)	0.625*
	No, n (%)	n≥5	NA	NA	n≥5	n≥5	
	Yes, n (%)	n<5	NA	NA	n<5	n<5	
LABA inhalers	N (% not missing)	75 (100.0)	NA	NA	246 (100.0)	320 (100.0)	.639‡
	Mean (SD)	0.3 (1.4)	NA	NA	0.5 (2.4)	0.7 (2.7)	
	Median (IQR)	0 (0, 0)	NA	NA	0 (0, 0)	0 (0, 0)	
	Min, Max	0, 9	NA	NA	0, 20	0, 26	
LABA inhalers (categorised)	N (% not missing)	75 (100.0)	NA	NA	246 (100.0)	320 (100.0)	0.659*
	No, n (%)	70 (93.3)	NA	NA	230 (93.5)	293 (91.6)	
	Yes, n (%)	5 (6.7)	NA	NA	16 (6.5)	27 (8.4)	
LAMA inhalers	N (% not missing)	75 (100.0)	NA	NA	246 (100.0)	320 (100.0)	.134‡
	Mean (SD)	0.0 (0.0)	NA	NA	0.8 (4.0)	0.7 (3.5)	
	Median (IQR)	0 (0, 0)	NA	NA	0 (0, 0)	0 (0, 0)	
	Min, Max	0, 0	NA	NA	0, 28	0, 26	
LAMA inhalers (categorised)	N (% not missing)	75 (100.0)	NA	NA	246 (100.0)	320 (100.0)	0.134*
	No, n (%)	n≥5	NA	NA	233 (94.7)	306 (95.6)	
	Yes, n (%)	n<5	NA	NA	13 (5.3)	14 (4.4)	

		TOTAL COHORT					
	Measure	FP/FOR	FP/SAL DPI	FP/SAL MDI	BUD/FOR	BDP/FOR	p-value
ICS only inhalers	N (% not missing)	75 (100.0)	NA	NA	246 (100.0)	320 (100.0)	.248‡
	Mean (SD)	2.5 (3.8)	NA	NA	2.9 (4.2)	3.0 (3.9)	
	Median (IQR)	0 (0, 4)	NA	NA	1 (0, 4)	2 (0, 4)	
	Min, Max	0, 16	NA	NA	0, 26	0, 17	
ICS only inhalers (categorised)	N (% not missing)	75 (100.0)	NA	NA	246 (100.0)	320 (100.0)	0.043*
	No, n (%)	38 (50.7)	NA	NA	86 (35.0)	131 (40.9)	
	Yes, n (%)	37 (49.3)	NA	NA	160 (65.0)	189 (59.1)	
Theophylline prescriptions	N (% not missing)	75 (100.0)	NA	NA	246 (100.0)	320 (100.0)	.544‡
	Mean (SD)	0.1 (1.3)	NA	NA	0.0 (0.4)	0.1 (1.1)	
	Median (IQR)	0 (0, 0)	NA	NA	0 (0, 0)	0 (0, 0)	
	Min, Max	0, 11	NA	NA	0, 6	0, 15	
Theophylline prescriptions (categorised)	N (% not missing)	75 (100.0)	NA	NA	246 (100.0)	320 (100.0)	0.546*
	No, n (%)	n≥5	NA	NA	n≥5	n≥5	
	Yes, n (%)	n<5	NA	NA	n<5	n<5	
LTRA prescriptions	N (% not missing)	75 (100.0)	NA	NA	246 (100.0)	320 (100.0)	.529‡
	Mean (SD)	0.6 (2.1)	NA	NA	0.3 (1.6)	0.6 (2.2)	
	Median (IQR)	0 (0, 0)	NA	NA	0 (0, 0)	0 (0, 0)	
	Min, Max	0, 11	NA	NA	0, 13	0, 13	
LTRA prescriptions (categorised)	N (% not missing)	75 (100.0)	NA	NA	246 (100.0)	320 (100.0)	0.572*
	No, n (%)	68 (90.7)	NA	NA	227 (92.3)	287 (89.7)	
	Yes, n (%)	7 (9.3)	NA	NA	19 (7.7)	33 (10.3)	
Spacer prescription	N (% not missing)	75 (100.0)	NA	NA	246 (100.0)	320 (100.0)	0.287*
	No, n (%)	59 (78.7)	NA	NA	211 (85.8)	263 (82.2)	
	Yes, n (%)	16 (21.3)	NA	NA	35 (14.2)	57 (17.8)	
Pain-relief medication prescriptions (categorised)	N (% not missing)	75 (100.0)	NA	NA	246 (100.0)	320 (100.0)	0.037*
	No, n (%)	45 (60.0)	NA	NA	163 (66.3)	178 (55.6)	
	Yes, n (%)	30 (40.0)	NA	NA	83 (33.7)	142 (44.4)	
Non-steroidal anti-inflammatory drugs (NSAIDs) prescriptions (categorised)	N (% not missing)	75 (100.0)	NA	NA	246 (100.0)	320 (100.0)	0.071*
	No, n (%)	49 (65.3)	NA	NA	191 (77.6)	247 (77.2)	
	Yes, n (%)	26 (34.7)	NA	NA	55 (22.4)	73 (22.8)	
Beta-blocker prescriptions (categorised)	N (% not missing)	75 (100.0)	NA	NA	246 (100.0)	320 (100.0)	0.854*
	No, n (%)	70 (93.3)	NA	NA	233 (94.7)	300 (93.8)	
	Yes, n (%)	5 (6.7)	NA	NA	13 (5.3)	20 (6.3)	

Table 31: Prescriptions for therapy in year prior to index date by FDC/ICS LABA ("MART" regimen definition 2)

‡ Kruskal-Wallis test, * Chi-square test, NA – not applicable

6.2.5.6 Adverse events during baseline

		TOTAL COHORT					
	Measure	FP/FOR	FP/SAL DPI	FP/SAL MDI	BUD/FOR	BDP/FOR	p-value
Lower Respiratory Tract Infection in baseline	N (% not missing)	75 (100.0)	NA	NA	246 (100.0)	320 (100.0)	0.933*
	No, n (%)	59 (78.7)	NA	NA	189 (76.8)	249 (77.8)	
	Yes, n (%)	16 (21.3)	NA	NA	57 (23.2)	71 (22.2)	
Pneumonia in baseline	N (% not missing)	75 (100.0)	NA	NA	246 (100.0)	320 (100.0)	0.089*
	No, n (%)	n≥5	NA	NA	n≥5	n≥5	
	Yes, n (%)	n<5	NA	NA	n<5	n<5	
Pulmonary Embolism in baseline	N (% not missing)	75 (100.0)	NA	NA	246 (100.0)	320 (100.0)	NA
	No, n (%)	75 (100.0)	NA	NA	246 (100.0)	320 (100.0)	
Tuberculosis in baseline	N (% not missing)	75 (100.0)	NA	NA	246 (100.0)	320 (100.0)	NA
	No, n (%)	75 (100.0)	NA	NA	246 (100.0)	320 (100.0)	

Table 32: Adverse events occurring in year prior to index date by FDC/ICS LABA ("MART" regimen definition 2)
‡ Kruskal-Wallis test, * Chi-square test, NA – not applicable

6.2.6 Availability of height data for asthma cohorts <18 years

Only 31% and 36% of patients had height data available both pre and post index date in the subgroups of patients with asthma aged 12-17 and 4-11 years, respectively. Therefore, height data was not used for analysis of growth retardation and Read code/ ICD-10 code diagnoses were used instead.

6.2.7 Patients without asthma or COPD diagnosis who were prescribed FDC ICS/LABA

Of the 11,187 patients without a diagnosis of asthma or COPD, 94.1% were initiators and 5.9% were switchers. Of this group, only 5.6% were prescribed FP/FOR. 42.2% of patients had no further prescription FDC ICS/LABA inhalers in the outcome period, 53.0% had one further FDC ICS/LABA prescription in the outcome period and 4.8% two or more prescriptions. The Read codes recorded at the time of diagnosis were reviewed; a limited amount of patients had asthma or COPD annual review, monitoring, follow-up or similar codes recorded. These were not included in the identification of asthma or COPD in this study as Read code lists based on QOF were used, which are based on diagnostic codes for these diseases.

6.3 Outcome data

Please see sections 6.1 and 6.2 for a breakdown of the patients available for analysis.

6.4 Main results

6.4.1 Prescribing incidence

The prescribing incidence rate of FP/FOR was lower than the comparators in the on-label subgroups (patients aged ≥18 years with asthma) (Table 33). The incidence rate was particularly low for the off-label groups with asthma aged <18 years. The prescribing incidence rate for patients with COPD was also comparatively low compared to the prescription of on-label FP/SAL DPI, BUD/FOR and BDP/FOR and off-label FP/SAL MDI. Of those prescribed FP/FOR, 80.8% were in the subgroup aged ≥18 years with asthma (Table 34). The next biggest groups were those without a recorded diagnosis of asthma or COPD and those with a diagnosis of COPD (9.2% and 6.2% respectively). The percentage prescribed FP/FOR in the other subgroups was <5%.

	Cohort				
	FP/FOR (n=7713)	DPI FP/SAL (n=18761)	MDI FP/SAL (n=21966)	BUD/FOR (n=22283)	BDP/FOR (n=16743)
CPRD patients	2.02	4.91	5.75	5.83	4.38
Patients aged ≥18 years with asthma	13.85	20.30	27.75	28.13	27.72
Patients aged ≥12 and <18 years with asthma	4.84 0.44*	7.04	18.73	13.51	4.86*
Patients aged ≥4 and <12 years with asthma	0.75*	3.89 0.35*	28.02 7.62*	6.20 1.28*	0.89*
Patients with COPD only, definition 1	10.18*	100.04 29.85*	73.13*	70.89 7.63*	40.81

Table 33: Prescribing incidence rate (36 months post launch of FP/FOR) by FDC ICS/LABA (per 1000 person years

*** Off-label dosage annualized rate, unlabelled – licensed dosage annualized rate (refer to Section 5.3 for licensed dosages)**

	Cohort				
	FP/FOR (n=7713)	DPI FP/SAL (n=18761)	MDI FP/SAL (n=21966)	BUD/FOR (n=22283)	BDP/FOR (n=16743)
No diagnosis	706 (9.2%)	2948 (15.7%)	3553 (16.2%)	4916 (22.1%)	2058 (12.3%)
Patients aged ≥18 years with asthma	6229 (80.8%)	9130 (48.7%)	12485 (56.8%)	12654 (56.8%)	12472 (74.5%)
Patients aged ≥12 and <18 years with asthma	242 (3.1%) 22 (0.3%)*	352 (1.9%)	936 (4.3%)	675 (3.0%)	243 (1.5%)*
Patients aged ≥4 and <12 years with asthma	32 (0.4%)*	167 (0.9%) 15 (0.1%)*	1203 (5.5%) 327 (1.5%)*	266 (1.2%) 55 (0.2%)*	38 (0.2%)*
Patients with COPD only, definition 1	482 (6.2%)*	4736 (25.2%) 1413 (7.5%)*	3462 (15.8%)*	3356 (15.1%) 361 (1.6%)*	1932 (11.5%)

Table 34: Percentage prescribed FDC ICS/LABA of all prescribed FDC ICS/LABA within subgroup (36 months post launch of FP/FOR)

*** Off-label dosage annualized rate, unlabelled – licensed dosage annualized rate (refer Section 5.3 for licensed dosages)**

6.4.2 Adverse events

6.4.2.1 Patients aged ≥18 years with asthma

There was no evidence of a significant difference in the incidence rate of adverse events in patients aged ≥18 years with asthma between the groups for pulmonary embolism, oral candidiasis, dysphonia, other local oral adverse events, type 2 diabetes, glaucoma, anxiety/depression and reduced bone mineral density (Table 35). The number of events was less than five or zero for tuberculosis, anaphylactic reactions, hypokalaemia and adrenal failure. The incidence rate of cardiac arrhythmias and ischaemia, hyperglycaemia, cataracts, pneumonia, LRTI and "any new adverse events" was lower for FP/FOR then DPI FP/SAL (and lower than MDI FP/SAL for the latter two). When considering the rate of occurrence of the first adverse event, there was no evidence of a significant difference after adjustment between FP/FOR and the comparators for dysphonia, other local oral adverse events, type 2 diabetes, reduced bone mineral density, cardiac arrhythmias and ischaemia, hyperglycaemia, cataracts or pneumonia (Table 36). However, for two adverse events, anxiety/depression and any new adverse events, the rate of occurrence of the first event was lower for FP/FOR than all comparators and for two events, LRTI and oral candidiasis, the rate of occurrence of the first event was lower for FP/FOR than FP/SAL DPI and BUD/FOR; and BUD/FOR and BDP/FOR respectively, after adjustment for confounders. When considering the results split by initiators and switchers, there was no evidence of a significant difference observed in the rate of occurrence of the first event for both subgroups between FP/FOR and the licensed comparators for pneumonia, hyperglycaemia, cardiac arrhythmia and ischemia, cataracts or reduced bone mineral density (Table 37). There was also no evidence of a significant difference for the following adverse events in the initiators subgroup; anxiety/depression, LRTIs, any new adverse events and the following in the switcher subgroup; dysphonia, type 2 diabetes and other local oral adverse events. The events where there were differences for the switcher subgroups were LRTI (higher rate of occurrence of first event for BUD/FOR than FP/FOR), oral candidiasis (higher rate of occurrence of first event for BUD/FOR and BDP/FOR than FP/FOR), anxiety/depression and any new adverse events (both showing higher rate of occurrence of first event for all comparators versus FP/FOR). The events where there were differences for the initiator subgroups were dysphonia (higher rate of occurrence of first event for FP/FOR versus FP/SAL DPI), oral candidiasis (higher rate of occurrence of the first event for BDP/FOR than FP/FOR), other local oral adverse events (higher rate of occurrence of the first event for FP/FOR versus BUD/FOR) and type 2 diabetes (higher rate of occurrence of the first event for FP/SAL/ MDI and FP/SAL DPI than FP/FOR).

		Cohort				
		FP/FOR n=5727	DPI FP/SAL n=6865	MDI FP/SAL n=8948	BUD/FOR n=9128	BDP/FOR n=10941
Lower respiratory tract infection	Number of patients at risk (% in cohort)	2626 (46%)	3060 (45%)	4071 (45%)	4258 (47%)	4966 (45%)
	Median (IQR) Exposure time (months)	17.58 (13.54 ,25.03)	18.04 (11.81 ,26.66)	19.06 (13.14 ,27.53)	18.79 (13.40 ,27.63)	17.91 (13.44 ,25.72)
	Number who experienced event (%)	629 (24%)	1221 (40%)	1205 (30%)	1194 (28%)	1174 (24%)
	Total Exposure Time (years)	4101	4838	6802	7179	8090
	Incidence Rate (95% CI) (100 person years)	15.34 (14.18 ,16.58)	25.24 (23.86 ,26.69)	17.72 (16.74 ,18.74)	16.63 (15.72 ,17.60)	14.51 (13.70 ,15.37)
Pneumonia	Number of patients at risk (% in cohort)	2626 (46%)	3060 (45%)	4071 (45%)	4258 (47%)	4966 (45%)
	Median (IQR) Exposure time (months)	19.94 (15.67 ,27.53)	24.15 (17.64 ,32.38)	23.00 (16.62 ,30.95)	22.93 (16.69 ,31.11)	20.42 (15.51 ,28.39)
	Number who experienced event (%)	27 (1%)	86 (3%)	68 (2%)	58 (1%)	59 (1%)
	Total Exposure Time (years)	4823	6427	8248	8657	9380
	Incidence Rate (95% CI) (100 person years)	0.56 (0.38 ,0.82)	1.34 (1.08 ,1.65)	0.82 (0.65 ,1.05)	0.67 (0.52 ,0.87)	0.63 (0.49 ,0.81)
Pulmonary Embolism	Number of patients at risk (% in cohort)	5727 (100%)	6865 (100%)	8948 (100%)	9128 (100%)	10941 (100%)
	Median (IQR) Exposure time (months)	10.87 (2.69 ,18.99)	9.46 (1.97 ,22.64)	10.05 (2.04 ,21.72)	10.64 (1.97 ,22.08)	10.64 (2.83 ,19.29)
	Number who experienced event (%)	8 (0%)	24 (0%)	28 (0%)	30 (0%)	23 (0%)
	Total Exposure Time (years)	6048	7658	10034	10408	11796
	Incidence Rate (95% CI) (100 person years)	0.13 (0.07 ,0.26)	0.31 (0.21 ,0.47)	0.28 (0.19 ,0.40)	0.29 (0.20 ,0.41)	0.19 (0.13 ,0.29)
Tuberculosis	Number of patients at risk (% in cohort)	5727 (100%)	6865 (100%)	8948 (100%)	9128 (100%)	10941 (100%)
	Median (IQR) Exposure time (months)	10.91 (2.69 ,18.99)	9.53 (1.97 ,22.74)	10.12 (2.07 ,21.77)	10.71 (1.97 ,22.11)	10.64 (2.86 ,19.35)
	Number who experienced event (%)	n<5	5 (0%)	0	n<5	n<5
	Total Exposure Time (years)	n<5	7676	NA	n<5	n<5
	Incidence Rate (95% CI) (100 person years)	NA	NA	NA	NA	NA

		Cohort				
		FP/FOR n=5727	DPI FP/SAL n=6865	MDI FP/SAL n=8948	BUD/FOR n=9128	BDP/FOR n=10941
Oral candidiasis	Number of patients at risk (% in cohort)	5657 (99%)	6751 (98%)	8796 (98%)	9003 (99%)	10801 (99%)
	Median (IQR) Exposure time (months)	10.81 (2.66 ,18.76)	9.36 (1.97 ,22.41)	9.95 (2.00 ,21.52)	10.48 (1.97 ,21.88)	10.55 (2.79 ,19.15)
	Number who experienced event (%)	57 (1%)	110 (2%)	120 (1%)	117 (1%)	156 (1%)
	Total Exposure Time (years)	5929	7465	9781	10172	11556
	Incidence Rate (95% CI) (100 person years)	0.96 (0.74 ,1.25)	1.47 (1.22 ,1.78)	1.23 (1.03 ,1.47)	1.15 (0.96 ,1.38)	1.35 (1.15 ,1.58)
Dysphonia/hoarse voice	Number of patients at risk (% in cohort)	5662 (99%)	6796 (99%)	8819 (99%)	9024 (99%)	10836 (99%)
	Median (IQR) Exposure time (months)	10.78 (2.69 ,18.83)	9.36 (1.97 ,22.49)	9.92 (2.04 ,21.49)	10.51 (1.97 ,21.88)	10.58 (2.83 ,19.22)
	Number who experienced event (%)	67 (1%)	62 (1%)	141 (2%)	83 (1%)	89 (1%)
	Total Exposure Time (years)	5937	7538	9787	10206	11634
	Incidence Rate (95% CI) (100 person years)	1.13 (0.89 ,1.43)	0.82 (0.64 ,1.05)	1.44 (1.22 ,1.70)	0.81 (0.66 ,1.01)	0.77 (0.62 ,0.94)
Other local oral adverse events	Number of patients at risk (% in cohort)	5630 (98%)	6742 (98%)	8778 (98%)	8955 (98%)	10739 (98%)
	Median (IQR) Exposure time (months)	10.78 (2.66 ,18.83)	9.26 (1.97 ,22.24)	9.82 (1.97 ,21.32)	10.45 (1.97 ,21.78)	10.51 (2.83 ,19.12)
	Number who experienced event (%)	86 (2%)	109 (2%)	149 (2%)	132 (1%)	162 (2%)
	Total Exposure Time (years)	5893	7418	9707	10098	11468
	Incidence Rate (95% CI) (100 person years)	1.46 (1.18 ,1.80)	1.47 (1.22 ,1.77)	1.53 (1.31 ,1.80)	1.31 (1.10 ,1.55)	1.41 (1.21 ,1.65)
Adrenal failure	Number of patients at risk (% in cohort)	5727 (100%)	6865 (100%)	8948 (100%)	9128 (100%)	10941 (100%)
	Median (IQR) Exposure time (months)	10.91 (2.69 ,18.99)	9.56 (1.97 ,22.74)	10.12 (2.07 ,21.77)	10.71 (1.97 ,22.11)	10.64 (2.86 ,19.35)
	Number who experienced event (%)	0	n<5	0	n<5	0
	Total Exposure Time (years)	NA	n<5	NA	n<5	NA
	Incidence Rate (95% CI) (100 person years)	NA	NA	NA	NA	NA
Cardiac arrhythmias and ischemia	Number of patients at risk (% in cohort)	5557 (97%)	6547 (95%)	8639 (97%)	8823 (97%)	10599 (97%)
	Median (IQR) Exposure time (months)	10.71 (2.63 ,18.76)	8.77 (1.97 ,21.72)	9.72 (1.97 ,21.26)	10.35 (1.97 ,21.72)	10.38 (2.73 ,19.15)
	Number who experienced event (%)	105 (2%)	235 (4%)	228 (3%)	192 (2%)	211 (2%)
	Total Exposure Time (years)	5804	7036	9516	9926	11288
	Incidence Rate (95% CI) (100 person years)	1.81 (1.49 ,2.19)	3.34 (2.94 ,3.80)	2.40 (2.10 ,2.73)	1.93 (1.68 ,2.23)	1.87 (1.63 ,2.14)

		Cohort				
		FP/FOR n=5727	DPI FP/SAL n=6865	MDI FP/SAL n=8948	BUD/FOR n=9128	BDP/FOR n=10941
Hyperglycaemia	Number of patients at risk (% in cohort)	5315 (93%)	6210 (90%)	8251 (92%)	8505 (93%)	10112 (92%)
	Median (IQR) Exposure time (months)	10.71 (2.56 ,18.66)	8.80 (1.97 ,21.85)	9.63 (1.97 ,21.09)	10.32 (1.97 ,21.78)	10.41 (2.73 ,19.12)
	Number who experienced event (%)	111 (2%)	192 (3%)	200 (2%)	168 (2%)	211 (2%)
	Total Exposure Time (years)	5518	6704	9034	9566	10767
	Incidence Rate (95% CI) (100 person years)	2.01 (1.67 ,2.42)	2.86 (2.49 ,3.30)	2.21 (1.93 ,2.54)	1.76 (1.51 ,2.04)	1.96 (1.71 ,2.24)
Diagnosis of type 2 diabetes mellitus	Number of patients at risk (% in cohort)	5655 (99%)	6738 (98%)	8810 (98%)	9014 (99%)	10805 (99%)
	Median (IQR) Exposure time (months)	10.78 (2.69 ,18.76)	9.23 (1.97 ,22.08)	9.87 (2.00 ,21.39)	10.45 (1.97 ,21.78)	10.48 (2.76 ,19.12)
	Number who experienced event (%)	67 (1%)	116 (2%)	120 (1%)	105 (1%)	129 (1%)
	Total Exposure Time (years)	5918	7386	9757	10172	11526
	Incidence Rate (95% CI) (100 person years)	1.13 (0.89 ,1.44)	1.57 (1.31 ,1.88)	1.23 (1.03 ,1.47)	1.03 (0.85 ,1.25)	1.12 (0.94 ,1.33)
Anaphylactic reactions	Number of patients at risk (% in cohort)	5724 (100%)	6864 (100%)	8947 (100%)	9126 (100%)	10936 (100%)
	Median (IQR) Exposure time (months)	10.89 (2.69 ,18.99)	9.56 (1.97 ,22.75)	10.12 (2.07 ,21.75)	10.68 (1.97 ,22.11)	10.64 (2.86 ,19.32)
	Number who experienced event (%)	n<5	0	n<5	n<5	n<5
	Total Exposure Time (years)	n<5	NA	n<5	n<5	n<5
	Incidence Rate (95% CI) (100 person years)	NA	NA	NA	NA	NA
Cataract	Number of patients at risk (% in cohort)	5652 (99%)	6742 (98%)	8844 (99%)	9030 (99%)	10796 (99%)
	Median (IQR) Exposure time (months)	10.81 (2.66 ,18.76)	9.36 (1.97 ,22.24)	9.87 (2.00 ,21.44)	10.55 (1.97 ,21.95)	10.56 (2.83 ,19.22)
	Number who experienced event (%)	63 (1%)	124 (2%)	112 (1%)	73 (1%)	106 (1%)
	Total Exposure Time (years)	5916	7442	9802	10243	11593
	Incidence Rate (95% CI) (100 person years)	1.06 (0.83 ,1.36)	1.67 (1.40 ,1.99)	1.14 (0.95 ,1.38)	0.71 (0.57 ,0.90)	0.91 (0.76 ,1.11)
Glaucoma	Number of patients at risk (% in cohort)	5710 (100%)	6849 (100%)	8928 (100%)	9108 (100%)	10921 (100%)
	Median (IQR) Exposure time (months)	10.87 (2.69 ,18.96)	9.49 (1.97 ,22.60)	10.09 (2.05 ,21.67)	10.64 (1.97 ,22.08)	10.64 (2.86 ,19.32)
	Number who experienced event (%)	8 (0%)	25 (0%)	20 (0%)	12 (0%)	25 (0%)
	Total Exposure Time (years)	6028	7639	10006	10391	11773
	Incidence Rate (95% CI) (100 person years)	0.13 (0.07 ,0.27)	0.33 (0.22 ,0.48)	0.20 (0.13 ,0.31)	0.12 (0.07 ,0.20)	0.21 (0.14 ,0.31)

		Cohort				
		FP/FOR n=5727	DPI FP/SAL n=6865	MDI FP/SAL n=8948	BUD/FOR n=9128	BDP/FOR n=10941
Hypokalaemia	Number of patients at risk (% in cohort)	5724 (100%)	6858 (100%)	8943 (100%)	9121 (100%)	10932 (100%)
	Median (IQR) Exposure time (months)	10.91 (2.71 ,18.99)	9.51 (1.97 ,22.64)	10.12 (2.07 ,21.72)	10.68 (1.97 ,22.08)	10.64 (2.86 ,19.33)
	Number who experienced event (%)	n<5	12 (0%)	14 (0%)	10 (0%)	7 (0%)
	Total Exposure Time (years)	n<5	7657	10045	10406	11795
	Incidence Rate (95% CI) (100 person years)	NA	NA	NA	NA	NA
Anxiety/Depression	Number of patients at risk (% in cohort)	5135 (90%)	6130 (89%)	8023 (90%)	8195 (90%)	9799 (90%)
	Median (IQR) Exposure time (months)	10.15 (2.46 ,18.20)	8.51 (1.97 ,21.16)	9.10 (1.97 ,19.88)	9.69 (1.97 ,20.76)	9.79 (2.53 ,17.97)
	Number who experienced event (%)	296 (6%)	444 (7%)	578 (7%)	580 (7%)	688 (7%)
	Total Exposure Time (years)	5172	6459	8419	8863	9954
	Incidence Rate (95% CI) (100 person years)	5.72 (5.11 ,6.41)	6.87 (6.26 ,7.54)	6.87 (6.33 ,7.45)	6.54 (6.03 ,7.10)	6.91 (6.41 ,7.45)
Reduced bone mineral density	Number of patients at risk (% in cohort)	5687 (99%)	6768 (99%)	8865 (99%)	9044 (99%)	10829 (99%)
	Median (IQR) Exposure time (months)	10.84 (2.69 ,18.86)	9.40 (1.97 ,22.41)	9.99 (2.04 ,21.59)	10.55 (1.97 ,21.95)	10.58 (2.83 ,19.19)
	Number who experienced event (%)	51 (1%)	85 (1%)	78 (1%)	85 (1%)	89 (1%)
	Total Exposure Time (years)	5981	7490	9880	10255	11622
	Incidence Rate (95% CI) (100 person years)	0.85 (0.65 ,1.12)	1.13 (0.92 ,1.40)	0.79 (0.63 ,0.99)	0.83 (0.67 ,1.03)	0.77 (0.62 ,0.94)
Any new adverse events	Number of patients at risk (% in cohort)	2626 (46%)	3060 (45%)	4071 (45%)	4258 (47%)	4966 (45%)
	Median (IQR) Exposure time (months)	16.69 (12.65 ,23.46)	17.63 (11.35 ,25.63)	17.22 (11.47 ,25.59)	17.71 (12.42 ,26.48)	16.53 (12.32 ,23.59)
	Number who experienced event (%)	950 (36%)	1475 (48%)	1796 (44%)	1700 (40%)	1880 (38%)
	Total Exposure Time (years)	3839	4730	6223	6756	7381
	Incidence Rate (95% CI) (100 person years)	24.75 (23.22 ,26.37)	31.19 (29.64 ,32.82)	28.86 (27.56 ,30.23)	25.16 (24.00 ,26.39)	25.47 (24.35 ,26.65)

Table 35: Adverse events evaluation by FDC ICS/LABA for patients aged ≥18 years with asthma

			Comparison (Hazard ratio, 95% CI)			
	Model	Number of observations in model	FP/SAL DPI vs FP/FOR	FP/SAL MDI vs FP/FOR	BUD/FOR vs FP/FOR	BDP/FOR vs FP/FOR
Lower respiratory tract infection	Unadjusted	18981	1.68 (1.53 ,1.85)	1.18 (1.08 ,1.30)	1.11 (1.01 ,1.22)	0.96 (0.87 ,1.06)
	Adjusted for a priori confounders	14165	1.37 (1.23 ,1.51)	1.26 (1.14 ,1.40)	1.53 (1.36 ,1.73)	1.22 (1.09 ,1.36)
	Adjusted for a priori and selected potential confounders*	14165	1.13 (1.02 ,1.26)	1.11 (1.00 ,1.23)	1.23 (1.09 ,1.39)	1.07 (0.95 ,1.20)
Pneumonia	Unadjusted	18981	2.34 (1.51 ,3.60)	1.45 (0.93 ,2.26)	1.18 (0.75 ,1.86)	1.12 (0.71 ,1.76)
	Adjusted for a priori confounders	14165	1.31 (0.83 ,2.06)	1.30 (0.82 ,2.07)	1.94 (1.14 ,3.32)	1.45 (0.86 ,2.44)
	Adjusted for a priori and selected potential confounders†	14165	1.08 (0.68 ,1.72)	1.07 (0.67 ,1.72)	1.52 (0.88 ,2.62)	1.26 (0.75 ,2.13)
Oral candidiasis	Unadjusted	41008	1.60 (1.16 ,2.20)	1.31 (0.96 ,1.80)	1.23 (0.90 ,1.69)	1.42 (1.05 ,1.92)
	Adjusted for a priori confounders	30256	1.64 (1.15 ,2.34)	1.54 (1.08 ,2.19)	1.94 (1.29 ,2.92)	2.26 (1.57 ,3.25)
	Adjusted for a priori and selected potential confounders‡	30256	1.41 (0.98 ,2.02)	1.38 (0.97 ,1.97)	1.62 (1.07 ,2.46)	2.04 (1.42 ,2.95)
Dysphonia/hoarse voice	Unadjusted	41137	0.74 (0.52 ,1.05)	1.29 (0.96 ,1.73)	0.73 (0.53 ,1.01)	0.68 (0.49 ,0.93)
	Adjusted for a priori confounders	30353	0.69 (0.48 ,1.00)	1.27 (0.93 ,1.74)	0.84 (0.57 ,1.26)	0.74 (0.51 ,1.07)
	Adjusted for a priori and selected potential confounders§	30353	0.71 (0.49 ,1.03)	1.23 (0.90 ,1.68)	0.83 (0.55 ,1.24)	0.72 (0.50 ,1.05)
Other local oral adverse events	Unadjusted	40844	1.03 (0.78 ,1.37)	1.07 (0.82 ,1.40)	0.91 (0.70 ,1.20)	0.97 (0.75 ,1.27)
	Adjusted for a priori confounders	30129	1.14 (0.84 ,1.53)	1.10 (0.82 ,1.47)	0.87 (0.61 ,1.22)	1.02 (0.75 ,1.38)
	Adjusted for a priori and selected potential confounders**	30129	1.07 (0.79 ,1.45)	1.04 (0.78 ,1.40)	0.80 (0.57 ,1.14)	0.97 (0.72 ,1.32)

* Selected potential confounders adjusted for: LAMA prescriptions in baseline period or index date, ICS only prescriptions in baseline period or index date, COPD diagnosis, Respiratory GP consultations without prescription for an oral corticosteroid, LRTI adverse event during baseline
† Selected potential confounders adjusted for: LAMA prescriptions in baseline period or index date, ICS only prescriptions in baseline period or index date, History of ischemic heart disease, History of hypertension, COPD diagnosis, Pain-relief medication prescriptions (categorised), Respiratory GP consultations without prescription for an oral corticosteroid, Pneumonia adverse event during baseline
‡ Selected potential confounders adjusted for: LAMA prescriptions in baseline period or index date, COPD diagnosis, Pain-relief medication prescriptions (categorised), Respiratory GP consultations without prescription for an oral corticosteroid
§ Selected potential confounders adjusted for: ICS only prescriptions in baseline period or index date, COPD diagnosis, Respiratory GP consultations without prescription for an oral corticosteroid
** Selected potential confounders adjusted for: Respiratory GP consultations without prescription for an oral corticosteroid

			Comparison (Hazard ratio, 95% CI)			
	Model	Number of observations in model	FP/SAL DPI vs FP/FOR	FP/SAL MDI vs FP/FOR	BUD/FOR vs FP/FOR	BDP/FOR vs FP/FOR
Cardiac arrhythmias and ischemia	Unadjusted	40165	1.88 (1.49 ,2.37)	1.34 (1.06 ,1.69)	1.09 (0.86 ,1.38)	1.03 (0.82 ,1.31)
	Adjusted for a priori confounders	34238	1.30 (1.02 ,1.65)	1.25 (0.97 ,1.59)	1.15 (0.89 ,1.48)	1.05 (0.83 ,1.34)
	Adjusted for a priori and selected potential confounders*	34238	1.14 (0.89 ,1.46)	1.10 (0.86 ,1.41)	1.07 (0.83 ,1.39)	1.01 (0.79 ,1.29)
Hyperglycaemia	Unadjusted	38393	1.48 (1.17 ,1.87)	1.13 (0.90 ,1.43)	0.90 (0.71 ,1.15)	0.99 (0.78 ,1.24)
	Adjusted for a priori confounders	28208	1.20 (0.93 ,1.54)	1.09 (0.85 ,1.40)	1.16 (0.86 ,1.55)	1.17 (0.90 ,1.52)
	Adjusted for a priori and selected potential confounders†	28208	1.15 (0.89 ,1.48)	1.06 (0.82 ,1.37)	1.10 (0.82 ,1.48)	1.14 (0.87 ,1.49)
Diagnosis of type 2 diabetes mellitus	Unadjusted	41022	1.42 (1.05 ,1.92)	1.10 (0.82 ,1.49)	0.93 (0.68 ,1.26)	1.00 (0.74 ,1.34)
	Adjusted for a priori confounders	30266	1.31 (0.94 ,1.81)	1.16 (0.84 ,1.61)	1.11 (0.76 ,1.62)	1.10 (0.78 ,1.56)
	Adjusted for a priori and selected potential confounders‡	30266	1.26 (0.90 ,1.76)	1.14 (0.82 ,1.58)	1.07 (0.73 ,1.57)	1.08 (0.76 ,1.52)
Cataract	Unadjusted	41064	1.57 (1.16 ,2.12)	1.07 (0.79 ,1.46)	0.67 (0.48 ,0.94)	0.86 (0.63 ,1.17)
	Adjusted for a priori confounders	30282	1.07 (0.78 ,1.49)	0.94 (0.68 ,1.32)	0.79 (0.52 ,1.18)	0.97 (0.67 ,1.39)
	Adjusted for a priori and selected potential confounders§	30282	1.02 (0.73 ,1.43)	0.90 (0.65 ,1.26)	0.74 (0.49 ,1.12)	0.93 (0.64 ,1.33)
Anxiety/Depression	Unadjusted	37282	1.23 (1.06 ,1.43)	1.22 (1.06 ,1.40)	1.17 (1.01 ,1.34)	1.21 (1.06 ,1.39)
	Adjusted for a priori confounders	27491	1.28 (1.09 ,1.51)	1.27 (1.09 ,1.49)	1.26 (1.05 ,1.50)	1.30 (1.10 ,1.52)
	Adjusted for a priori and selected potential confounders**	27491	1.28 (1.09 ,1.51)	1.27 (1.09 ,1.49)	1.26 (1.05 ,1.50)	1.30 (1.10 ,1.52)

* Selected potential confounders adjusted for: LAMA prescriptions in baseline period or index date, ICS only prescriptions in baseline period or index date, History of ischemic heart disease, History of hypertension, COPD diagnosis, Pain-relief medication prescriptions (categorised)
† Selected potential confounders adjusted for: LAMA prescriptions in baseline period or index date, ICS only prescriptions in baseline period or index date, History of ischemic heart disease, History of hypertension, COPD diagnosis, Pain-relief medication prescriptions (categorised)
‡ Selected potential confounders adjusted for: LAMA prescriptions in baseline period or index date, History of ischemic heart disease, History of hypertension, COPD diagnosis, Pain-relief medication prescriptions (categorised)
§ Selected potential confounders adjusted for: LAMA prescriptions in baseline period or index date, ICS only prescriptions in baseline period or index date, History of ischemic heart disease, History of hypertension, COPD diagnosis, Pain-relief medication prescriptions (categorised)
** No further confounders selected in addition to a priori confounders

			Comparison (Hazard ratio, 95% CI)			
	Model	Number of observations in model	FP/SAL DPI vs FP/FOR	FP/SAL MDI vs FP/FOR	BUD/FOR vs FP/FOR	BDP/FOR vs FP/FOR
Reduced bone mineral density	Unadjusted	41193	1.34 (0.94 ,1.89)	0.93 (0.65 ,1.32)	0.98 (0.69 ,1.38)	0.90 (0.64 ,1.28)
	Adjusted for a priori confounders	30378	1.13 (0.78 ,1.64)	0.95 (0.65 ,1.39)	1.40 (0.92 ,2.15)	1.26 (0.84 ,1.87)
	Adjusted for a priori and selected potential confounders*	30378	1.06 (0.73 ,1.55)	0.91 (0.62 ,1.33)	1.21 (0.79 ,1.87)	1.17 (0.78 ,1.75)
Any new adverse events	Unadjusted	18981	1.26 (1.16 ,1.37)	1.17 (1.08 ,1.26)	1.02 (0.94 ,1.10)	1.03 (0.95 ,1.11)
	Adjusted for a priori confounders	14165	1.17 (1.07 ,1.28)	1.19 (1.09 ,1.30)	1.16 (1.05 ,1.28)	1.15 (1.05 ,1.26)
	Adjusted for a priori and selected potential confounders†	14165	1.14 (1.04 ,1.25)	1.18 (1.08 ,1.29)	1.13 (1.03 ,1.25)	1.14 (1.04 ,1.25)

Table 36: Rate of occurrence of first adverse event by FDC ICS/LABA for patients aged ≥18 years with asthma

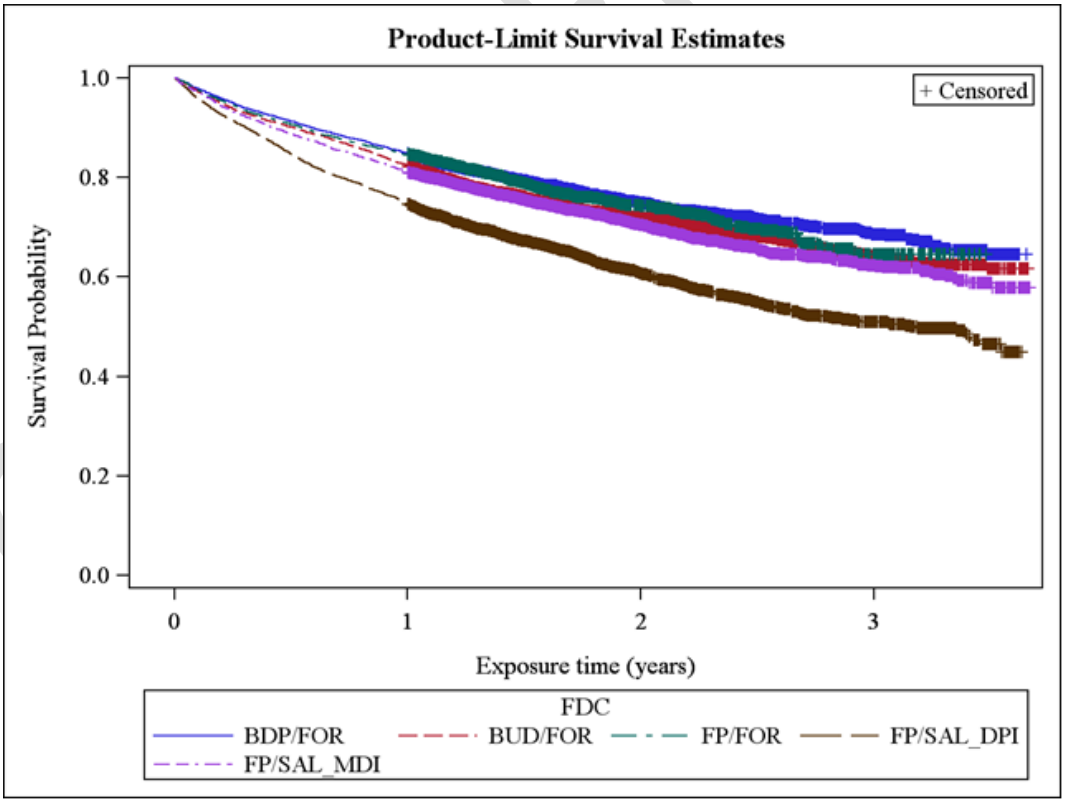

Figure 3: Lower respiratory tract infection evaluation by FDC ICS/LABA (asthma patients ≥18 years old)

* Selected potential confounders adjusted for: LTRA prescriptions in baseline period or index date, LAMA prescriptions in baseline period or index date, ICS only prescriptions in baseline period or index date, History of hypertension, COPD diagnosis, Pain-relief medication prescriptions (categorised), Respiratory GP consultations without prescription for an oral corticosteroid

† Selected potential confounders adjusted for: LAMA prescriptions in baseline period or index date, COPD diagnosis

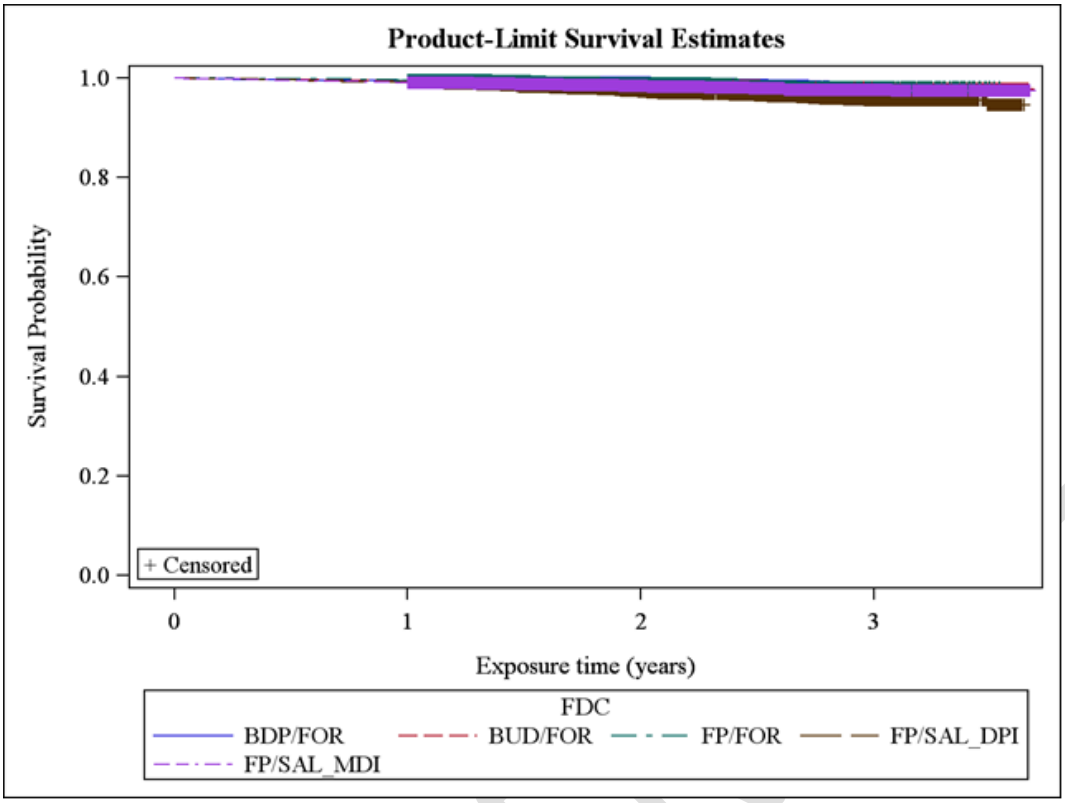

Figure 4: Pneumonia evaluation by FDC ICS/LABA (asthma patients ≥18 years old)

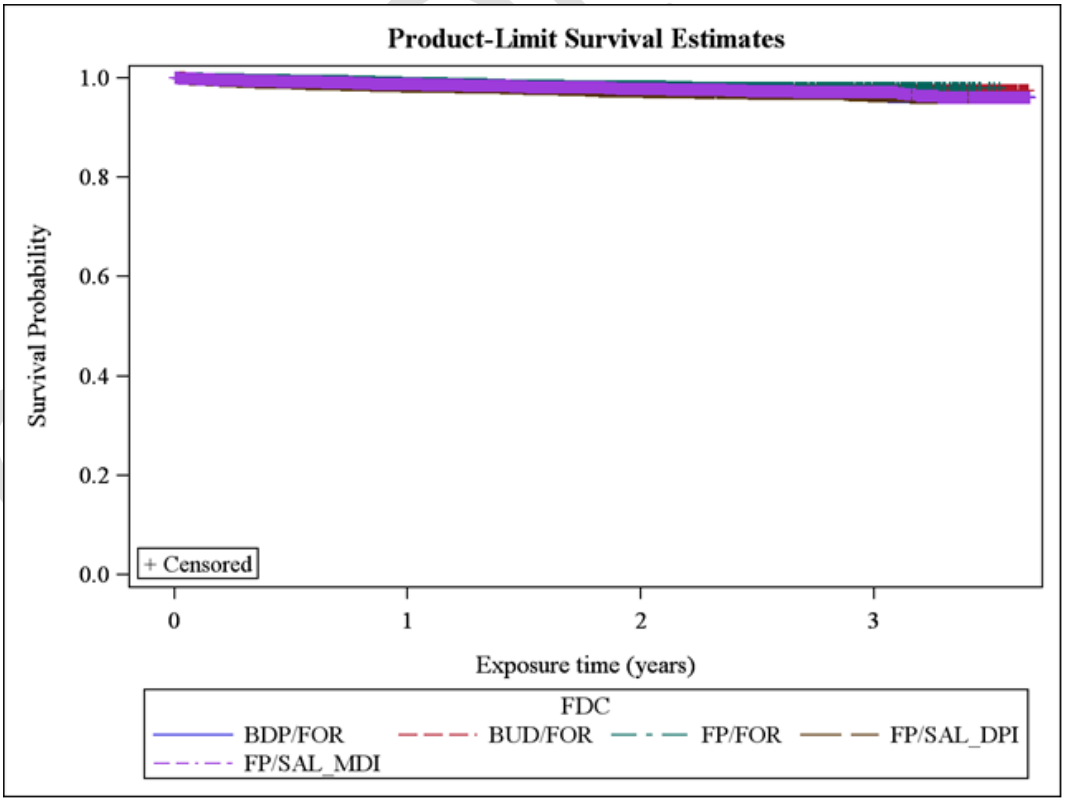

Figure 5: Oral candidiasis evaluation by FDC ICS/LABA (asthma patients ≥18 years old)

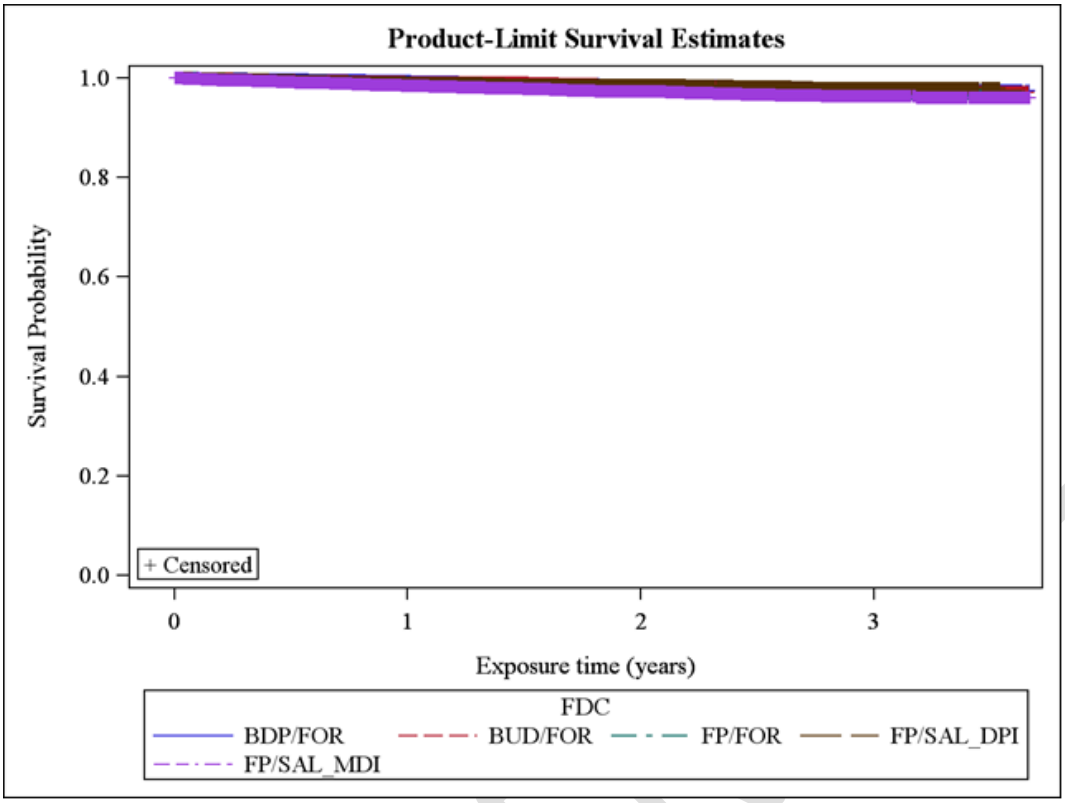

Figure 6: Dysphonia/hoarse voice evaluation by FDC ICS/LABA (asthma patients ≥18 years old)

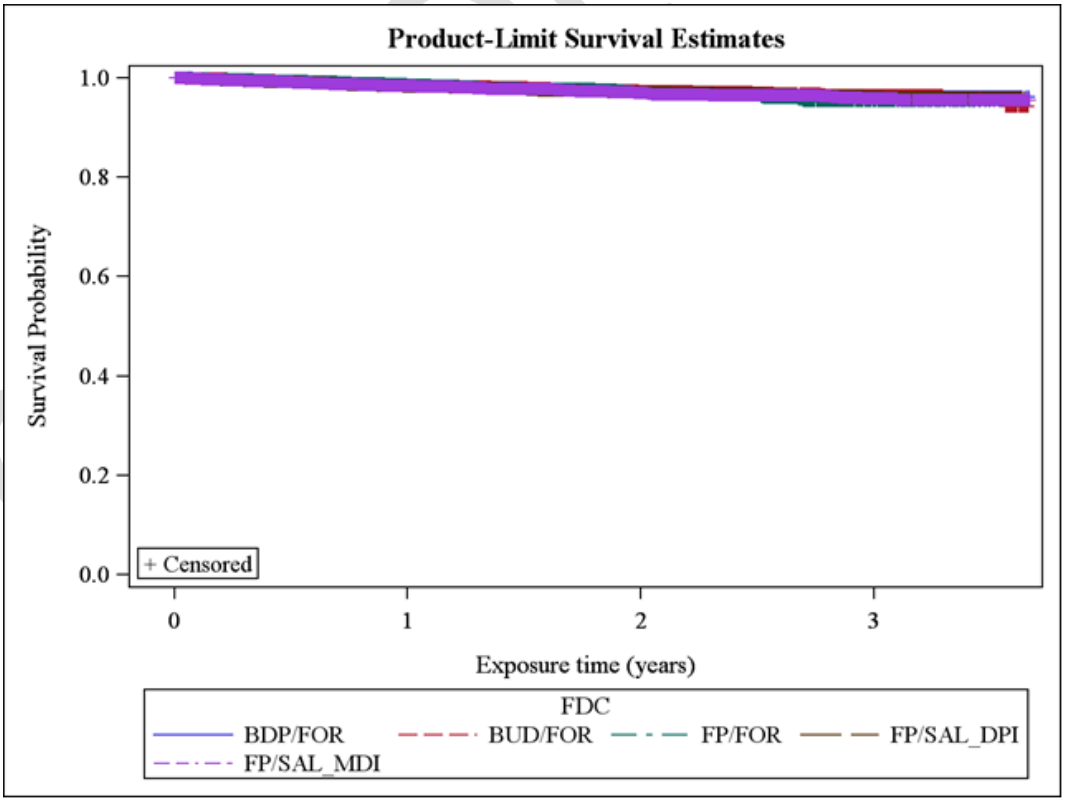

Figure 7: Other local oral event evaluation by FDC ICS/LABA (asthma patients ≥18 years old)

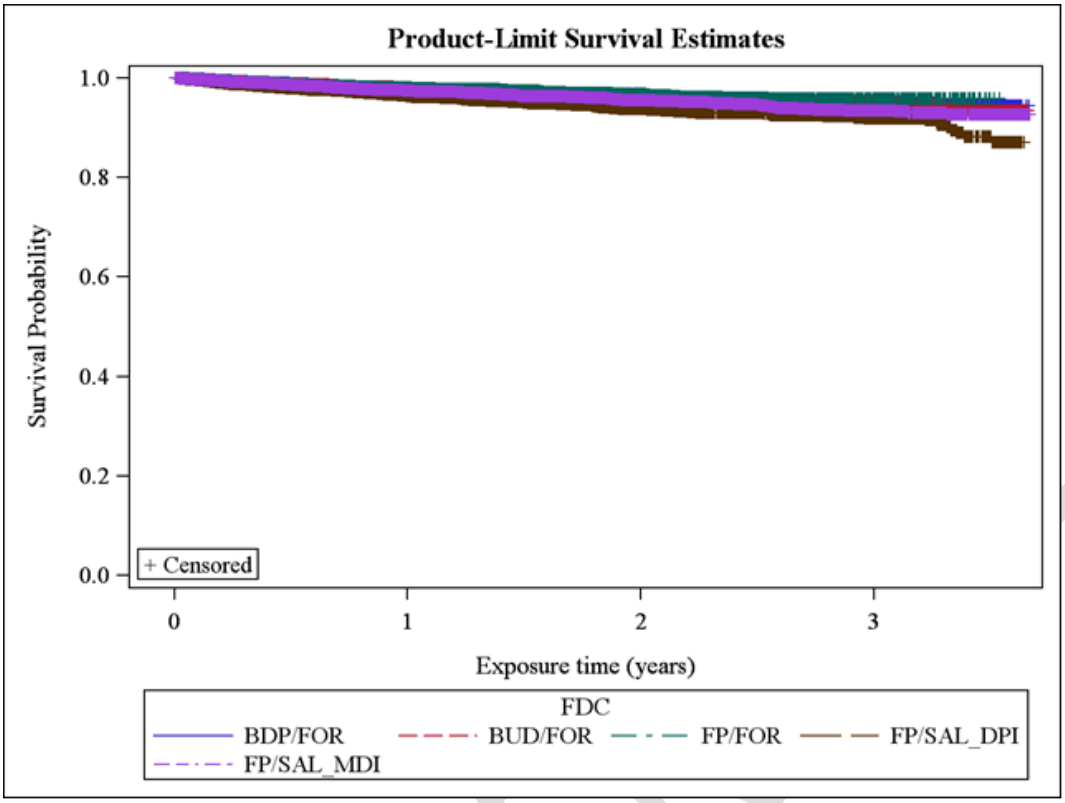

Figure 8: Cardiac arrhythmias and ischaemia evaluation by FDC ICS/LABA (asthma patients ≥18 years old)

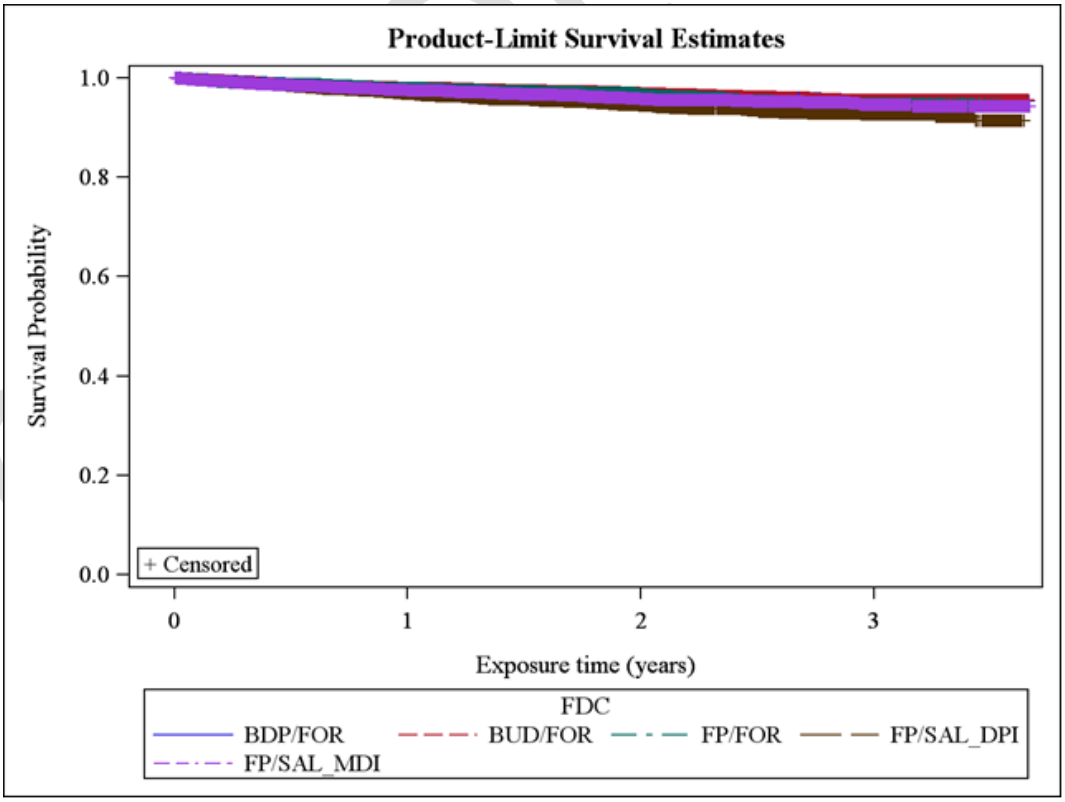

Figure 9: Hyperglycaemia evaluation by FDC ICS/LABA (asthma patients ≥18 years old)

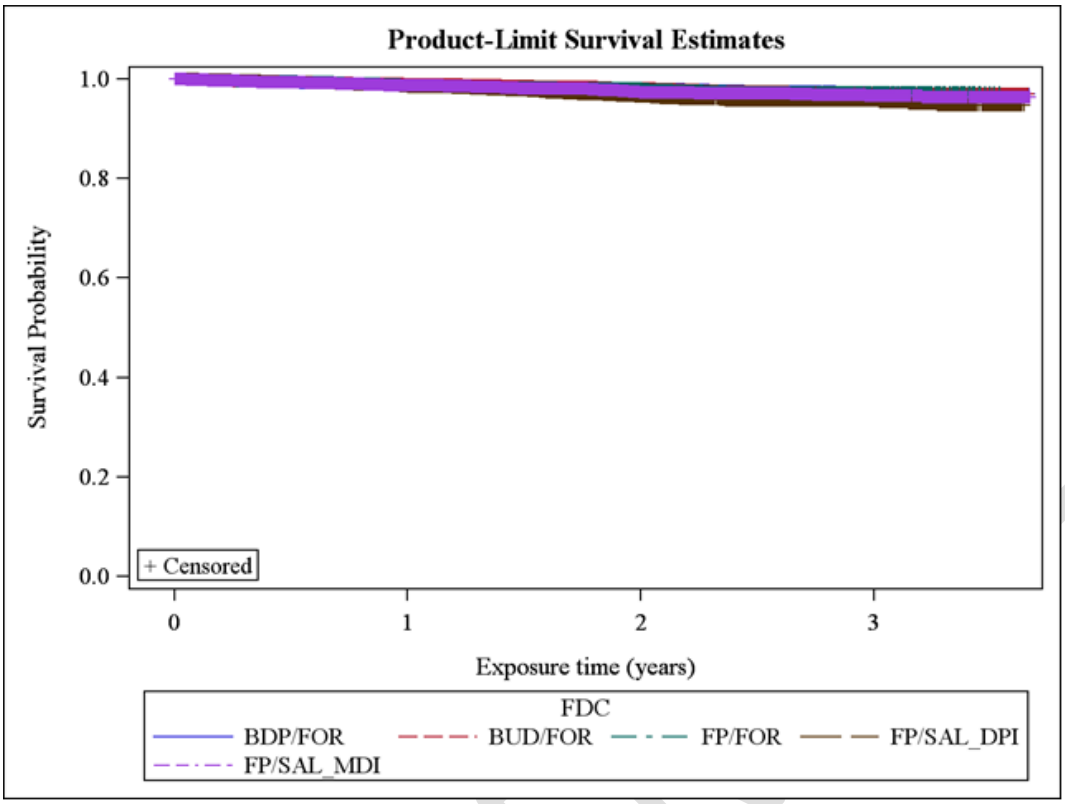

Figure 10: Type 2 diabetes mellitus evaluation by FDC ICS/LABA (asthma patients ≥18 years old)

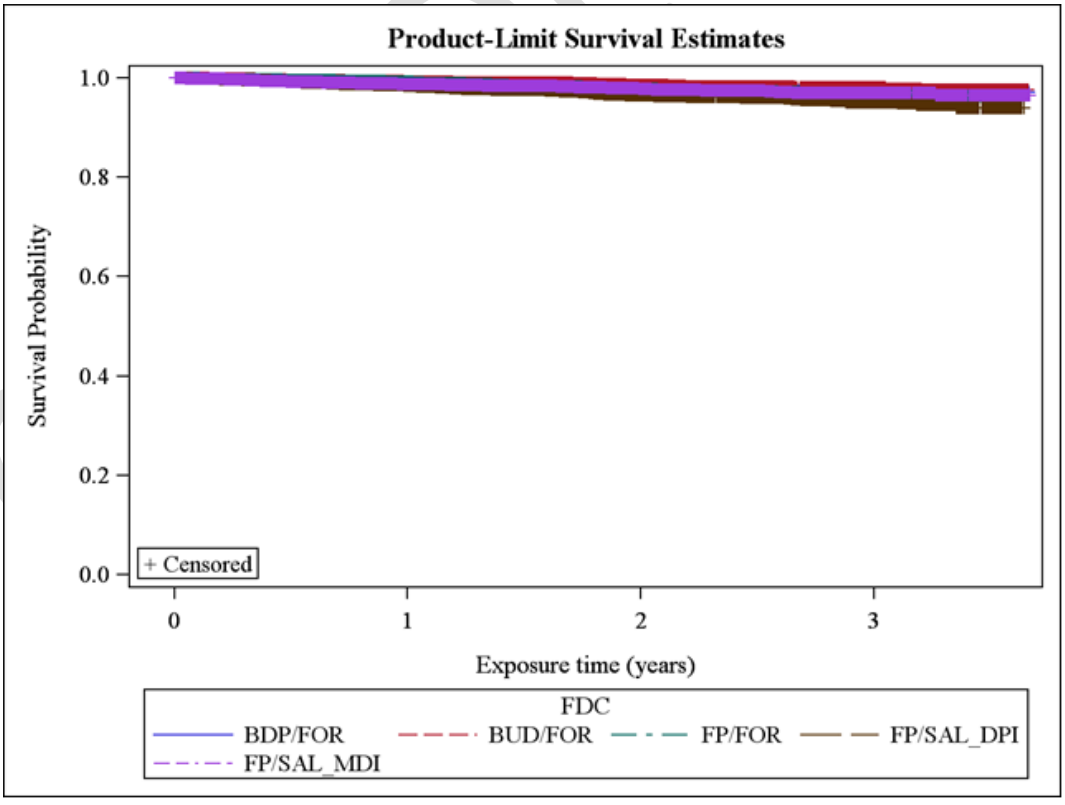

Figure 11: Cataract evaluation by FDC ICS/LABA (asthma patients ≥18 years old)

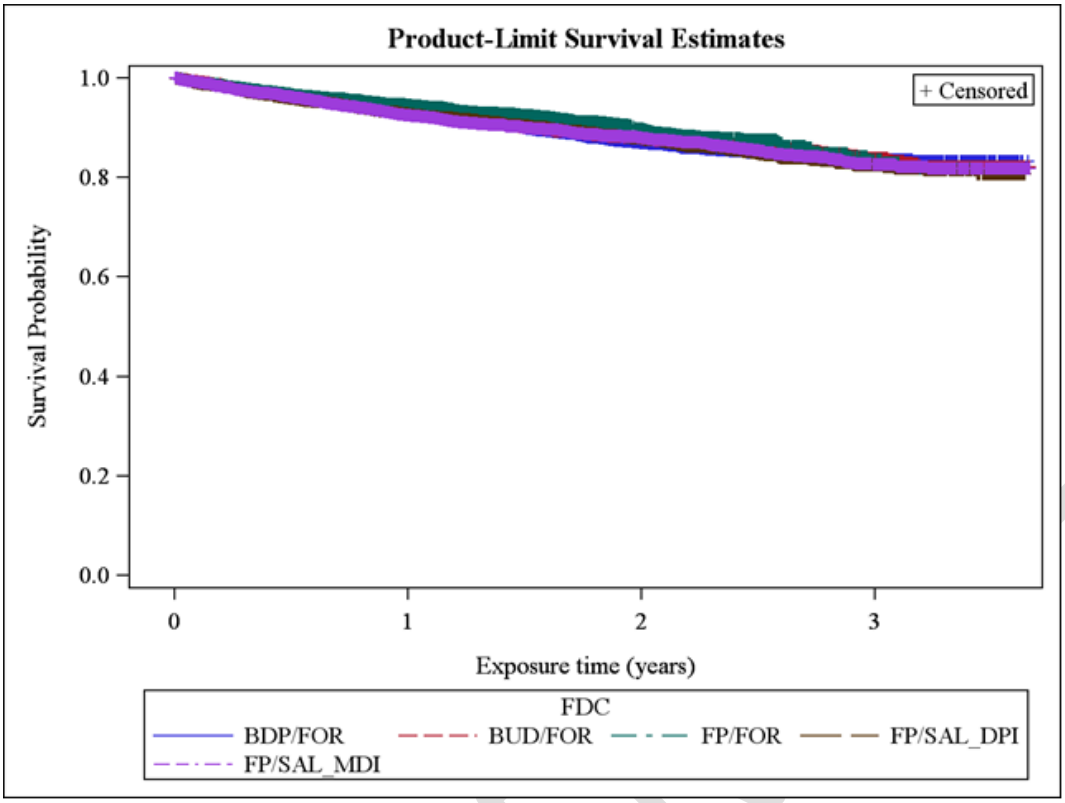

Figure 12: Anxiety/depression evaluation by FDC ICS/LABA (asthma patients ≥18 years old)

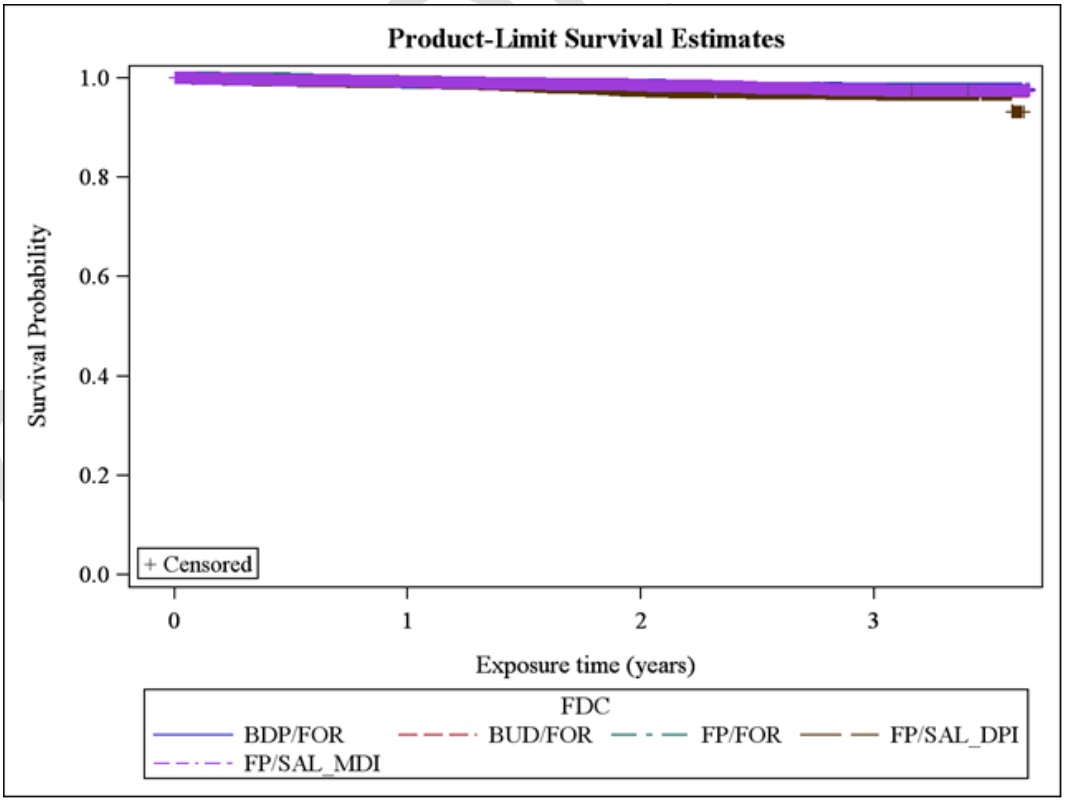

Figure 13: Reduced bone mineral density evaluation by FDC ICS/LABA (asthma patients ≥18 years old)

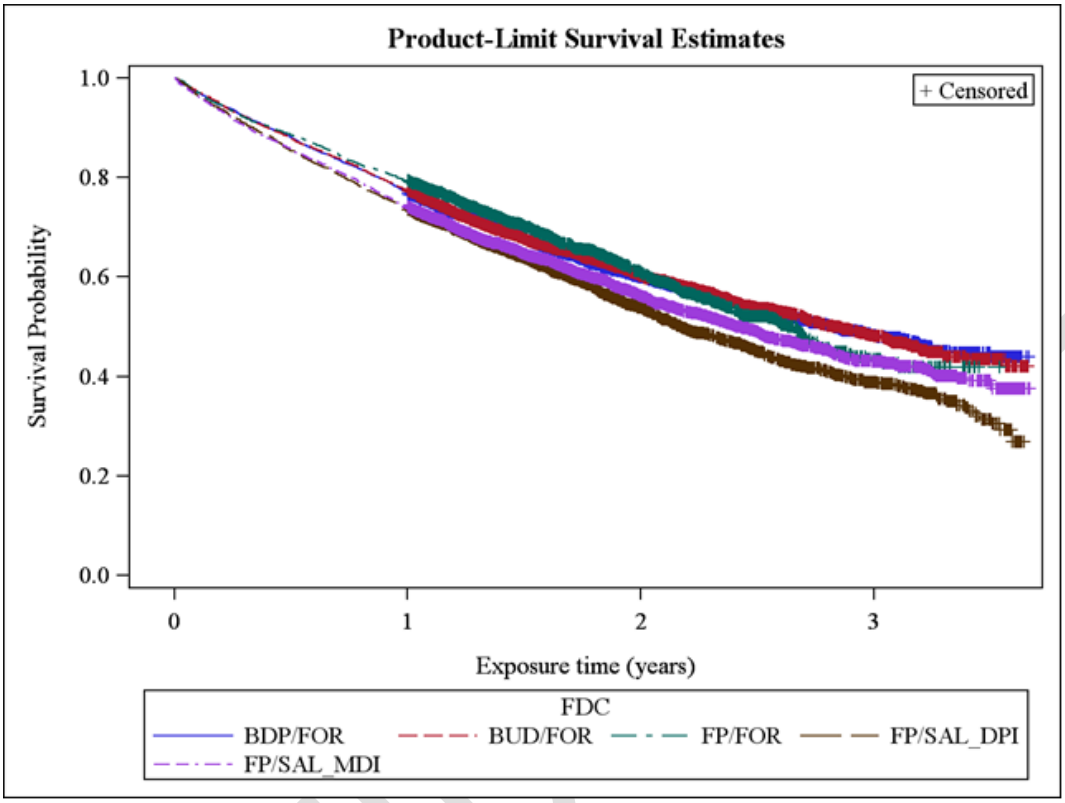

Figure 14: Any new adverse events evaluation by FDC ICS/LABA (asthma patients ≥18 years old)

			Comparison (Hazard ratio, 95% CI)			
	Number of observations in model	Initiator or Switcher	FP/SAL DPI vs FP/FOR	FP/SAL MDI vs FP/FOR	BUD/FOR vs FP/FOR	BDP/FOR vs FP/FOR
Lower respiratory tract infection*	14165	Initiator	1.20 (0.99 ,1.45)	1.16 (0.97 ,1.39)	1.18 (0.97 ,1.43)	1.10 (0.91 ,1.32)
		Switcher	1.11 (0.98 ,1.25)	1.07 (0.93 ,1.22)	1.34 (1.15 ,1.57)	1.06 (0.91 ,1.22)
Pneumonia†	14165	Initiator	0.81 (0.35 ,1.84)	0.63 (0.28 ,1.40)	1.26 (0.56 ,2.85)	1.05 (0.46 ,2.38)
		Switcher	1.21 (0.70 ,2.08)	1.49 (0.85 ,2.63)	1.37 (0.67 ,2.83)	1.20 (0.61 ,2.39)
Oral candidiasis‡	30256	Initiator	1.75 (0.92 ,3.35)	1.40 (0.75 ,2.60)	1.59 (0.82 ,3.08)	2.03 (1.09 ,3.79)
		Switcher	1.24 (0.81 ,1.92)	1.42 (0.90 ,2.23)	1.80 (1.05 ,3.06)	2.16 (1.37 ,3.41)

* Selected potential confounders adjusted for: LAMA prescriptions in baseline period or index date, ICS only prescriptions in baseline period or index date, COPD diagnosis, Respiratory GP consultations without prescription for an oral corticosteroid, LRTI adverse event during baseline
† Selected potential confounders adjusted for: LAMA prescriptions in baseline period or index date, ICS only prescriptions in baseline period or index date, History of ischemic heart disease, History of hypertension, COPD diagnosis, Pain-relief medication prescriptions (categorised), Respiratory GP consultations without prescription for an oral corticosteroid, Pneumonia adverse event during baseline
‡ Selected potential confounders adjusted for: LAMA prescriptions in baseline period or index date, COPD diagnosis, Pain-relief medication prescriptions (categorised), Respiratory GP consultations without prescription for an oral corticosteroid

			Comparison (Hazard ratio, 95% CI)			
	Number of observations in model	Initiator or Switcher	FP/SAL DPI vs FP/FOR	FP/SAL MDI vs FP/FOR	BUD/FOR vs FP/FOR	BDP/FOR vs FP/FOR
Dysphonia/hoarse voice*	30353	Initiator	0.51 (0.27 ,0.95)	1.01 (0.64 ,1.61)	0.68 (0.39 ,1.17)	0.61 (0.36 ,1.04)
		Switcher	0.85 (0.54 ,1.34)	1.38 (0.90 ,2.13)	0.94 (0.52 ,1.68)	0.76 (0.45 ,1.29)
Other local oral adverse events†	30129	Initiator	0.68 (0.42 ,1.11)	0.73 (0.48 ,1.09)	0.59 (0.37 ,0.94)	0.77 (0.50 ,1.18)
		Switcher	1.39 (0.95 ,2.03)	1.40 (0.94 ,2.09)	0.94 (0.56 ,1.55)	1.03 (0.67 ,1.59)
Cardiac arrhythmias and ischemia‡	34238	Initiator	1.26 (0.78 ,2.04)	1.16 (0.74 ,1.81)	1.24 (0.79 ,1.96)	1.30 (0.83 ,2.03)
		Switcher	1.10 (0.83 ,1.47)	1.18 (0.87 ,1.60)	1.01 (0.72 ,1.41)	0.83 (0.61 ,1.14)
Hyperglycaemia§	28208	Initiator	1.48 (0.90 ,2.44)	1.48 (0.93 ,2.36)	1.38 (0.84 ,2.27)	1.41 (0.87 ,2.28)
		Switcher	1.05 (0.78 ,1.42)	0.84 (0.60 ,1.18)	1.07 (0.72 ,1.59)	1.11 (0.79 ,1.55)
Diagnosis of type 2 diabetes mellitus**	30266	Initiator	2.10 (1.01 ,4.35)	2.11 (1.05 ,4.22)	1.93 (0.94 ,3.98)	1.76 (0.86 ,3.61)
		Switcher	1.11 (0.76 ,1.63)	0.85 (0.55 ,1.31)	0.83 (0.49 ,1.39)	0.98 (0.64 ,1.50)
Cataract††	30282	Initiator	1.08 (0.58 ,2.01)	1.08 (0.60 ,1.92)	0.86 (0.45 ,1.62)	0.96 (0.51 ,1.78)
		Switcher	1.01 (0.68 ,1.48)	0.77 (0.49 ,1.20)	0.67 (0.38 ,1.20)	0.97 (0.61 ,1.53)
Anxiety/Depression‡‡	27491	Initiator	1.21 (0.92 ,1.60)	1.17 (0.91 ,1.49)	1.06 (0.81 ,1.38)	1.25 (0.97 ,1.60)
		Switcher	1.31 (1.08 ,1.59)	1.33 (1.08 ,1.65)	1.52 (1.20 ,1.93)	1.26 (1.02 ,1.57)
Reduced bone mineral density§§	30378	Initiator	1.30 (0.66 ,2.54)	0.69 (0.36 ,1.35)	1.23 (0.63 ,2.40)	0.87 (0.44 ,1.73)
		Switcher	0.94 (0.59 ,1.48)	1.13 (0.70 ,1.82)	1.10 (0.61 ,1.96)	1.45 (0.89 ,2.36)
Any new adverse events***	14165	Initiator	1.08 (0.92 ,1.26)	1.11 (0.96 ,1.27)	1.02 (0.88 ,1.19)	1.05 (0.91 ,1.22)
		Switcher	1.16 (1.04 ,1.30)	1.20 (1.07 ,1.35)	1.25 (1.09 ,1.43)	1.19 (1.06 ,1.35)

Table 37: Rate of occurrence of first adverse event by FDC ICS/LABA for patients aged ≥18 years with asthma, split by initiators and switchers

* Selected potential confounders adjusted for: ICS only prescriptions in baseline period or index date, COPD diagnosis, Respiratory GP consultations without prescription for an oral corticosteroid
† Selected potential confounders adjusted for: Respiratory GP consultations without prescription for an oral corticosteroid
‡ Selected potential confounders adjusted for: LAMA prescriptions in baseline period or index date, ICS only prescriptions in baseline period or index date, History of ischemic heart disease, History of hypertension, COPD diagnosis, Pain-relief medication prescriptions (categorised)
§ Selected potential confounders adjusted for: LAMA prescriptions in baseline period or index date, ICS only prescriptions in baseline period or index date, History of ischemic heart disease, History of hypertension, COPD diagnosis, Pain-relief medication prescriptions (categorised)
** Selected potential confounders adjusted for: LAMA prescriptions in baseline period or index date, History of ischemic heart disease, History of hypertension, COPD diagnosis, Pain-relief medication prescriptions (categorised)
†† Selected potential confounders adjusted for: LAMA prescriptions in baseline period or index date, ICS only prescriptions in baseline period or index date, History of ischemic heart disease, History of hypertension, COPD diagnosis, Pain-relief medication prescriptions (categorised)
‡‡ No further confounders selected in addition to a priori confounders
§§ Selected potential confounders adjusted for: LTRA prescriptions in baseline period or index date, LAMA prescriptions in baseline period or index date, ICS only prescriptions in baseline period or index date, History of hypertension, COPD diagnosis, Pain-relief medication prescriptions (categorised), Respiratory GP consultations without prescription for an oral corticosteroid
*** Selected potential confounders adjusted for: LAMA prescriptions in baseline period or index date, COPD diagnosis

6.4.2.2 Patients aged ≥12 and <18 years with asthma

For patients aged ≥12 and <18 with asthma, there was no evidence of a significant difference in the incidence rate of all studied adverse events or the number of events was zero or too low to be reported for on-label FP/FOR versus comparators (Table 38). For off-label FP/FOR, the number of adverse events was zero or less than five in all cases. Only "any new adverse events" had more than 20 events allowing the rate of occurrence of first adverse event to be considered and this showed no evidence of a significant difference in the rate of occurrence of the first event between FP/FOR and the licensed comparators (Table 39). It was observed that the numbers in this model halve when adjusting for confounders, which is due to limited data on BMI and percent predicted PEF for this subgroup. However, as these models were specified a priori, they are presented as originally proposed. There was also no evidence of a significant difference between FP/FOR and the licensed comparators when considering the rate of occurrence of the first event in the initiator and switcher subgroups separately (Table 40).

		Cohort				
		FP/FOR n=227	FP/FOR Off-label n=21	DPI FP/SAL n=288	MDI FP/SAL n=760	BUD/FOR n=569
Lower respiratory tract infection	Number of patients at risk (% in cohort)	124 (55%)	10 (48%)	125 (43%)	359 (47%)	265 (47%)
	Median (IQR) Exposure time (months)	17.68 (13.86 ,23.56)	21.85 (17.58 ,29.01)	21.75 (15.84 ,27.27)	20.86 (14.72 ,28.16)	20.11 (15.44 ,29.44)
	Number who experienced event (%)	14 (11%)	0	14 (11%)	39 (11%)	29 (11%)
	Total Exposure Time (years)	197	NA	229	664	496
	Incidence Rate (95% CI) (100 person years)	7.12 (4.22 ,12.02)	NA	6.12 (3.63 ,10.34)	5.88 (4.29 ,8.04)	5.85 (4.06 ,8.42)
Pneumonia	Number of patients at risk (% in cohort)	124 (55%)	10 (48%)	125 (43%)	359 (47%)	265 (47%)
	Median (IQR) Exposure time (months)	18.63 (14.88 ,25.72)	21.85 (17.58 ,29.01)	22.31 (16.10 ,27.76)	22.37 (16.26 ,30.26)	21.45 (16.82 ,30.32)
	Number who experienced event (%)	0	0	0	0	n<5
	Total Exposure Time (years)	NA	NA	NA	NA	n<5
	Incidence Rate (95% CI) (100 person years)	NA	NA	NA	NA	NA

		Cohort				
		FP/FOR n=227	FP/FOR Off-label n=21	DPI FP/SAL n=288	MDI FP/SAL n=760	BUD/FOR n=569
Pulmonary Embolism	Number of patients at risk (% in cohort)	227 (100%)	21 (100%)	288 (100%)	760 (100%)	569 (100%)
	Median (IQR) Exposure time (months)	12.81 (4.86 ,19.61)	11.10 (4.11 ,21.06)	9.23 (1.97 ,21.03)	11.25 (3.83 ,21.65)	10.41 (1.97 ,20.63)
	Number who experienced event (%)	0	0	0	0	0
	Total Exposure Time (years)	NA	NA	NA	NA	NA
	Incidence Rate (95% CI) (100 person years)	NA	NA	NA	NA	NA
Tuberculosis	Number of patients at risk (% in cohort)	227 (100%)	21 (100%)	288 (100%)	760 (100%)	569 (100%)
	Median (IQR) Exposure time (months)	12.81 (4.86 ,19.61)	11.10 (4.11 ,21.06)	9.23 (1.97 ,21.03)	11.15 (3.83 ,21.60)	10.41 (1.97 ,20.63)
	Number who experienced event (%)	0	0	0	n<5	0
	Total Exposure Time (years)	NA	NA	NA	n<5	NA
	Incidence Rate (95% CI) (100 person years)	NA	NA	NA	NA	NA
Oral candidiasis	Number of patients at risk (% in cohort)	227 (100%)	21 (100%)	286 (99%)	757 (100%)	569 (100%)
	Median (IQR) Exposure time (months)	12.81 (4.83 ,19.61)	11.10 (4.11 ,21.06)	9.23 (1.97 ,20.63)	11.27 (3.84 ,21.62)	10.41 (1.97 ,20.63)
	Number who experienced event (%)	n<5	0	n<5	n<5	n<5
	Total Exposure Time (years)	n<5	NA	n<5	n<5	n<5
	Incidence Rate (95% CI) (100 person years)	NA	NA	NA	NA	NA
Dysphonia/hoarse voice	Number of patients at risk (% in cohort)	227 (100%)	21 (100%)	288 (100%)	758 (100%)	568 (100%)
	Median (IQR) Exposure time (months)	12.81 (4.86 ,19.61)	11.10 (4.11 ,21.06)	9.23 (1.97 ,21.03)	11.29 (3.81 ,21.68)	10.43 (1.97 ,20.70)
	Number who experienced event (%)	0	0	n<5	0	n<5
	Total Exposure Time (years)	NA	NA	n<5	NA	n<5
	Incidence Rate (95% CI) (100 person years)	NA	NA	NA	NA	NA

		Cohort				
		FP/FOR n=227	FP/FOR Off-label n=21	DPI FP/SAL n=288	MDI FP/SAL n=760	BUD/FOR n=569
Other local oral adverse events	Number of patients at risk (% in cohort)	219 (96%)	21 (100%)	284 (99%)	741 (98%)	561 (99%)
	Median (IQR) Exposure time (months)	12.25 (4.57 ,18.99)	11.10 (4.11 ,21.06)	8.94 (1.97 ,20.11)	10.94 (3.81 ,21.03)	10.41 (1.97 ,20.14)
	Number who experienced event (%)	6 (3%)	n<5	10 (4%)	12 (2%)	8 (1%)
	Total Exposure Time (years)	244	n<5	288	846	622
	Incidence Rate (95% CI) (100 person years)	2.45 (1.10 ,5.46)	n<5	3.47 (1.87 ,6.45)	1.42 (0.81 ,2.50)	1.29 (0.64 ,2.57)
Adrenal failure	Number of patients at risk (% in cohort)	227 (100%)	21 (100%)	288 (100%)	760 (100%)	569 (100%)
	Median (IQR) Exposure time (months)	12.81 (4.86 ,19.61)	11.10 (4.11 ,21.06)	9.23 (1.97 ,21.03)	11.25 (3.83 ,21.65)	10.41 (1.97 ,20.63)
	Number who experienced event (%)	0	0	0	0	0
	Total Exposure Time (years)	NA	NA	NA	NA	NA
	Incidence Rate (95% CI) (100 person years)	NA	NA	NA	NA	NA
Cardiac arrhythmias and ischemia	Number of patients at risk (% in cohort)	227 (100%)	21 (100%)	288 (100%)	760 (100%)	569 (100%)
	Median (IQR) Exposure time (months)	12.78 (4.86 ,19.61)	11.10 (4.11 ,17.74)	9.23 (1.97 ,21.03)	11.25 (3.83 ,21.65)	10.41 (1.97 ,20.63)
	Number who experienced event (%)	n<5	n<5	0	0	n<5
	Total Exposure Time (years)	n<5	n<5	NA	NA	n<5
	Incidence Rate (95% CI) (100 person years)	NA	NA	NA	NA	NA
Hyperglycaemia	Number of patients at risk (% in cohort)	227 (100%)	21 (100%)	288 (100%)	758 (100%)	568 (100%)
	Median (IQR) Exposure time (months)	12.81 (4.86 ,19.61)	11.10 (4.11 ,21.06)	9.23 (1.97 ,21.03)	11.15 (3.81 ,21.62)	10.41 (1.97 ,20.70)
	Number who experienced event (%)	0	0	0	n<5	0
	Total Exposure Time (years)	NA	NA	NA	n<5	NA
	Incidence Rate (95% CI) (100 person years)	NA	NA	NA	NA	NA

		Cohort				
		FP/FOR n=227	FP/FOR Off-label n=21	DPI FP/SAL n=288	MDI FP/SAL n=760	BUD/FOR n=569
Diagnosis of type 2 diabetes mellitus	Number of patients at risk (% in cohort)	227 (100%)	21 (100%)	288 (100%)	760 (100%)	569 (100%)
	Median (IQR) Exposure time (months)	12.81 (4.86 ,19.61)	11.10 (4.11 ,21.06)	9.23 (1.97 ,21.03)	11.25 (3.83 ,21.65)	10.41 (1.97 ,20.63)
	Number who experienced event (%)	0	0	0	0	0
	Total Exposure Time (years)	NA	NA	NA	NA	NA
	Incidence Rate (95% CI) (100 person years)	NA	NA	NA	NA	NA
Anaphylactic reactions	Number of patients at risk (% in cohort)	227 (100%)	21 (100%)	288 (100%)	759 (100%)	569 (100%)
	Median (IQR) Exposure time (months)	12.81 (4.86 ,19.61)	11.10 (4.11 ,21.06)	9.23 (1.97 ,21.03)	11.24 (3.81 ,21.65)	10.41 (1.97 ,20.50)
	Number who experienced event (%)	n<5	0	n<5	n<5	n<5
	Total Exposure Time (years)	n<5	NA	n<5	n<5	n<5
	Incidence Rate (95% CI) (100 person years)	NA	NA	NA	NA	NA
Cataract	Number of patients at risk (% in cohort)	227 (100%)	21 (100%)	288 (100%)	760 (100%)	569 (100%)
	Median (IQR) Exposure time (months)	12.81 (4.86 ,19.61)	11.10 (4.11 ,21.06)	9.23 (1.97 ,21.03)	11.25 (3.83 ,21.65)	10.41 (1.97 ,20.63)
	Number who experienced event (%)	0	0	0	0	0
	Total Exposure Time (years)	NA	NA	NA	NA	NA
	Incidence Rate (95% CI) (100 person years)	NA	NA	NA	NA	NA
Glaucoma	Number of patients at risk (% in cohort)	227 (100%)	21 (100%)	288 (100%)	760 (100%)	569 (100%)
	Median (IQR) Exposure time (months)	12.81 (4.86 ,19.61)	11.10 (4.11 ,21.06)	9.23 (1.97 ,21.03)	11.25 (3.83 ,21.65)	10.41 (1.97 ,20.63)
	Number who experienced event (%)	0	0	0	0	0
	Total Exposure Time (years)	NA	NA	NA	NA	NA
	Incidence Rate (95% CI) (100 person years)	NA	NA	NA	NA	NA

		Cohort				
		FP/FOR n=227	FP/FOR Off-label n=21	DPI FP/SAL n=288	MDI FP/SAL n=760	BUD/FOR n=569
Hypokalaemia	Number of patients at risk (% in cohort)	227 (100%)	21 (100%)	288 (100%)	760 (100%)	569 (100%)
	Median (IQR) Exposure time (months)	12.81 (4.86 ,19.61)	11.10 (4.11 ,21.06)	9.23 (1.97 ,21.03)	11.25 (3.83 ,21.65)	10.41 (1.97 ,20.63)
	Number who experienced event (%)	0	0	0	0	0
	Total Exposure Time (years)	NA	NA	NA	NA	NA
	Incidence Rate (95% CI) (100 person years)	NA	NA	NA	NA	NA
Anxiety/Depression	Number of patients at risk (% in cohort)	216 (95%)	20 (95%)	277 (96%)	744 (98%)	549 (96%)
	Median (IQR) Exposure time (months)	12.78 (4.63 ,19.09)	7.59 (1.97 ,19.40)	8.97 (1.97 ,19.91)	10.74 (3.81 ,21.29)	10.25 (1.97 ,20.01)
	Number who experienced event (%)	13 (6%)	n<5	8 (3%)	22 (3%)	29 (5%)
	Total Exposure Time (years)	247	n<5	281	850	595
	Incidence Rate (95% CI) (100 person years)	5.26 (3.05 ,9.05)	n<5	2.85 (1.42 ,5.69)	2.59 (1.70 ,3.93)	4.88 (3.39 ,7.02)
Growth retardation	Number of patients at risk (% in cohort)	227 (100%)	21 (100%)	288 (100%)	760 (100%)	568 (100%)
	Median (IQR) Exposure time (months)	12.81 (4.86 ,19.61)	11.10 (4.11 ,21.06)	9.23 (1.97 ,21.03)	11.25 (3.83 ,21.60)	10.41 (1.97 ,20.57)
	Number who experienced event (%)	0	0	0	n<5	n<5
	Total Exposure Time (years)	NA	NA	NA	n<5	n<5
	Incidence Rate (95% CI) (100 person years)	NA	NA	NA	NA	NA
Reduced bone mineral density	Number of patients at risk (% in cohort)	227 (100%)	21 (100%)	288 (100%)	760 (100%)	569 (100%)
	Median (IQR) Exposure time (months)	12.81 (4.86 ,19.61)	11.10 (4.11 ,21.06)	9.23 (1.97 ,21.03)	11.25 (3.83 ,21.65)	10.41 (1.97 ,20.63)
	Number who experienced event (%)	0	0	0	0	0
	Total Exposure Time (years)	NA	NA	NA	NA	NA
	Incidence Rate (95% CI) (100 person years)	NA	NA	NA	NA	NA

		Cohort				
		FP/FOR n=227	FP/FOR Off-label n=21	DPI FP/SAL n=288	MDI FP/SAL n=760	BUD/FOR n=569
Any new adverse events	Number of patients at risk (% in cohort)	124 (55%)	10 (48%)	125 (43%)	359 (47%)	265 (47%)
	Median (IQR) Exposure time (months)	16.38 (12.78 ,22.87)	19.40 (14.75 ,26.09)	19.25 (14.55 ,25.89)	19.78 (14.09 ,27.04)	19.42 (14.39 ,27.01)
	Number who experienced event (%)	34 (27%)	n<5	27 (22%)	78 (22%)	55 (21%)
	Total Exposure Time (years)	183	n<5	209	625	467
	Incidence Rate (95% CI) (100 person years)	18.63 (13.31 ,26.07)	n<5	12.92 (8.86 ,18.85)	12.48 (9.99 ,15.58)	11.79 (9.05 ,15.35)

Table 38: Adverse events evaluation by FDC ICS/LABA for patients aged ≥12 and <18 years with asthma

			Comparison (Hazard ratio, 95% CI)		
	Model	Number of observations in model	FP/SAL DPI vs FP/FOR	FP/SAL MDI vs FP/FOR	BUD/FOR vs FP/FOR
Any new adverse events	Unadjusted	873	0.69 (0.42 ,1.15)	0.67 (0.45 ,1.01)	0.64 (0.42 ,0.98)
	Adjusted for a priori confounders	422	0.79 (0.41 ,1.53)	0.65 (0.37 ,1.13)	0.69 (0.37 ,1.28)
	Adjusted for a priori and selected potential confounders*	422	0.79 (0.41 ,1.53)	0.65 (0.37 ,1.13)	0.69 (0.37 ,1.28)

Table 39: Rate of occurrence of first adverse event by FDC ICS/LABA for patients ≥12 and <18 years with asthma (FP/FOR on-label)

* No further confounders selected in addition to a priori confounders

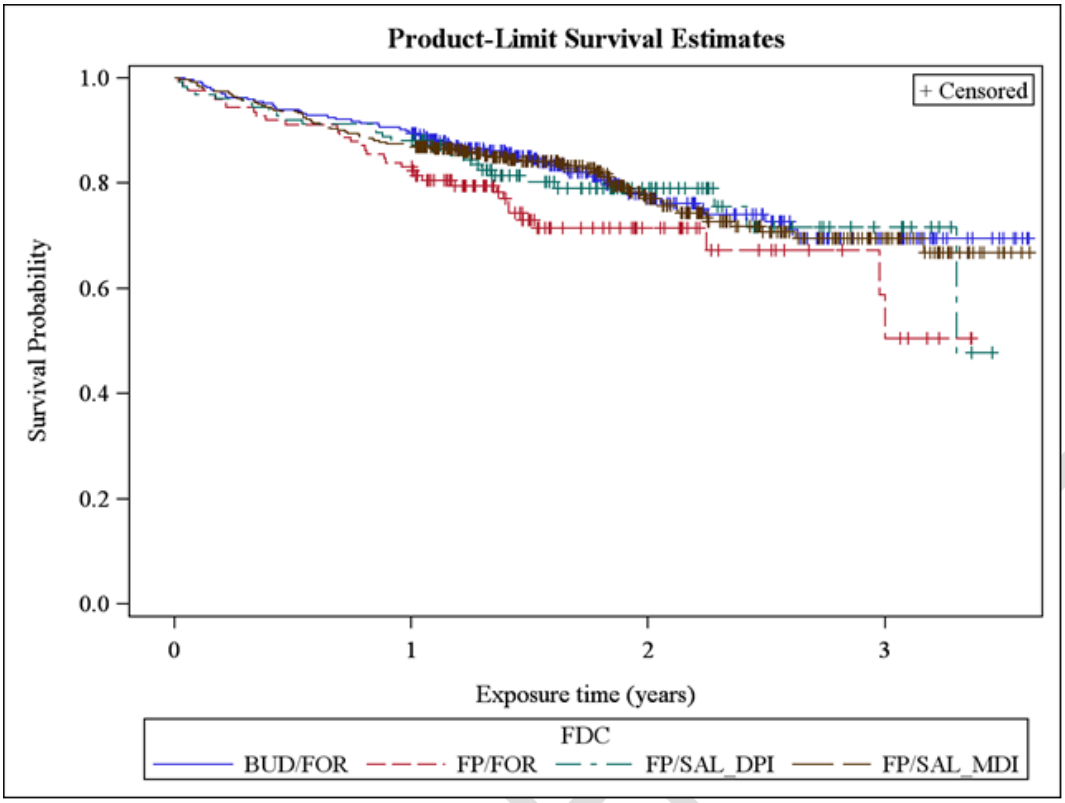

Figure 15: Any new adverse events evaluation by FDC ICS/LABA (asthma patients aged ≥12 and <18 years)

			Comparison (Hazard ratio, 95% CI)		
	Number of observations in model	Initiator or Switcher	FP/SAL DPI vs FP/FOR	FP/SAL MDI vs FP/FOR	BUD/FOR vs FP/FOR
Any new adverse events*	422	Initiator	0.66 (0.28 ,1.56)	0.55 (0.29 ,1.03)	0.58 (0.29 ,1.19)
		Switcher	1.00 (0.36 ,2.75)	0.98 (0.32 ,2.97)	0.94 (0.32 ,2.72)

Table 40: Rate of occurrence of first adverse event by FDC ICS/LABA for patients ≥12 and <18 years with asthma (FP/FOR on-label), split by initiators and switchers

* No further confounders selected in addition to a priori confounders

6.4.2.3 Patients aged ≥4 and <12 years with asthma

For patients aged ≥4 and <12 with asthma, the incidence of rate of all studied adverse events was zero or too low to be reported for FP/FOR versus on label comparators (Table 41). Therefore, no models could be run to assess the rate of occurrence of the first event.

		Cohort			
		FP/FOR n=27	DPI FP/SAL n=149	MDI FP/SAL n=1047	BUD/FOR n=235
Lower respiratory tract infection	Number of patients at risk (% in cohort)	n<5	75 (50%)	602 (57%)	114 (49%)
	Median (IQR) Exposure time (months)	n<5	18.43 (14.82 ,25.79)	20.45 (14.32 ,28.94)	21.22 (14.92 ,28.52)
	Number who experienced event (%)	n<5	8 (11%)	107 (18%)	14 (12%)
	Total Exposure Time (years)	n<5	127	1076	215
	Incidence Rate (95% CI) (100 person years)	NA	NA	NA	NA
Pneumonia	Number of patients at risk (% in cohort)	n<5	75 (50%)	602 (57%)	114 (49%)
	Median (IQR) Exposure time (months)	n<5	19.78 (15.70 ,26.97)	23.49 (16.95 ,30.62)	22.14 (16.07 ,31.11)
	Number who experienced event (%)	n<5	0	n<5	0
	Total Exposure Time (years)	n<5	NA	n<5	NA
	Incidence Rate (95% CI) (100 person years)	NA	NA	NA	NA
Pulmonary Embolism	Number of patients at risk (% in cohort)	27 (100%)	149 (100%)	1047 (100%)	235 (100%)
	Median (IQR) Exposure time (months)	1.97 (0.92 ,5.88)	12.06 (2.89 ,19.78)	14.19 (5.72 ,24.80)	11.33 (3.12 ,22.05)
	Number who experienced event (%)	0	0	0	0
	Total Exposure Time (years)	NA	NA	NA	NA
	Incidence Rate (95% CI) (100 person years)	NA	NA	NA	NA
Tuberculosis	Number of patients at risk (% in cohort)	27 (100%)	149 (100%)	1047 (100%)	235 (100%)
	Median (IQR) Exposure time (months)	1.97 (0.92 ,5.88)	12.06 (2.89 ,19.78)	14.19 (5.72 ,24.80)	11.33 (3.12 ,22.05)
	Number who experienced event (%)	0	0	0	0
	Total Exposure Time (years)	NA	NA	NA	NA
	Incidence Rate (95% CI) (100 person years)	NA	NA	NA	NA
Oral candidiasis	Number of patients at risk (% in cohort)	27 (100%)	148 (99%)	1042 (100%)	235 (100%)
	Median (IQR) Exposure time (months)	1.97 (0.92 ,5.88)	11.88 (2.89 ,19.35)	14.18 (5.72 ,24.80)	11.33 (3.12 ,22.05)
	Number who experienced event (%)	0	0	n<5	0
	Total Exposure Time (years)	NA	NA	n<5	NA
	Incidence Rate (95% CI) (100 person years)	NA	NA	NA	NA

		Cohort			
		FP/FOR n=27	DPI FP/SAL n=149	MDI FP/SAL n=1047	BUD/FOR n=235
Dysphonia/hoarse voice	Number of patients at risk (% in cohort)	27 (100%)	149 (100%)	1046 (100%)	235 (100%)
	Median (IQR) Exposure time (months)	1.97 (0.92 ,5.88)	12.06 (2.89 ,19.78)	14.19 (5.72 ,24.80)	11.33 (3.12 ,22.05)
	Number who experienced event (%)	0	n<5	n<5	n<5
	Total Exposure Time (years)	NA	n<5	n<5	n<5
	Incidence Rate (95% CI) (100 person years)	NA	NA	NA	NA
Other local oral adverse events	Number of patients at risk (% in cohort)	27 (100%)	143 (96%)	1027 (98%)	226 (96%)
	Median (IQR) Exposure time (months)	1.97 (0.92 ,5.88)	12.06 (2.89 ,19.78)	14.00 (5.49 ,24.41)	10.89 (3.06 ,20.14)
	Number who experienced event (%)	0	n<5	30 (3%)	9 (4%)
	Total Exposure Time (years)	NA	n<5	1359	255
	Incidence Rate (95% CI) (100 person years)	NA	NA	NA	NA
Adrenal failure	Number of patients at risk (% in cohort)	27 (100%)	149 (100%)	1047 (100%)	235 (100%)
	Median (IQR) Exposure time (months)	1.97 (0.92 ,5.88)	12.06 (2.89 ,19.78)	14.19 (5.72 ,24.80)	11.33 (3.12 ,22.05)
	Number who experienced event (%)	0	0	0	0
	Total Exposure Time (years)	NA	NA	NA	NA
	Incidence Rate (95% CI) (100 person years)	NA	NA	NA	NA
Cardiac arrhythmias and ischemia	Number of patients at risk (% in cohort)	27 (100%)	149 (100%)	1047 (100%)	234 (100%)
	Median (IQR) Exposure time (months)	1.97 (0.92 ,5.88)	12.06 (2.89 ,19.78)	14.19 (5.72 ,24.80)	11.33 (3.12 ,22.05)
	Number who experienced event (%)	0	0	n<5	0
	Total Exposure Time (years)	NA	NA	n<5	NA
	Incidence Rate (95% CI) (100 person years)	NA	NA	NA	NA
Hyperglycaemia	Number of patients at risk (% in cohort)	27 (100%)	149 (100%)	1046 (100%)	234 (100%)
	Median (IQR) Exposure time (months)	1.97 (0.92 ,5.88)	12.06 (2.89 ,19.78)	14.18 (5.72 ,24.74)	11.35 (3.12 ,22.05)
	Number who experienced event (%)	0	0	0	n<5
	Total Exposure Time (years)	NA	NA	NA	n<5
	Incidence Rate (95% CI) (100 person years)	NA	NA	NA	NA
Diagnosis of type 2 diabetes mellitus	Number of patients at risk (% in cohort)	27 (100%)	149 (100%)	1047 (100%)	235 (100%)
	Median (IQR) Exposure time (months)	1.97 (0.92 ,5.88)	12.06 (2.89 ,19.78)	14.19 (5.72 ,24.80)	11.33 (3.12 ,22.05)
	Number who experienced event (%)	0	0	0	0
	Total Exposure Time (years)	NA	NA	NA	NA
	Incidence Rate (95% CI) (100 person years)	NA	NA	NA	NA

		Cohort			
		FP/FOR n=27	DPI FP/SAL n=149	MDI FP/SAL n=1047	BUD/FOR n=235
Anaphylactic reactions	Number of patients at risk (% in cohort)	27 (100%)	149 (100%)	1044 (100%)	235 (100%)
	Median (IQR) Exposure time (months)	1.97 (0.92 ,5.88)	12.06 (2.89 ,19.78)	14.16 (5.72 ,24.77)	11.33 (3.12 ,22.05)
	Number who experienced event (%)	0	0	n<5	0
	Total Exposure Time (years)	NA	NA	n<5	NA
	Incidence Rate (95% CI) (100 person years)	NA	NA	NA	NA
Cataract	Number of patients at risk (% in cohort)	27 (100%)	149 (100%)	1047 (100%)	235 (100%)
	Median (IQR) Exposure time (months)	1.97 (0.92 ,5.88)	12.06 (2.89 ,19.78)	14.19 (5.72 ,24.80)	11.33 (3.12 ,22.05)
	Number who experienced event (%)	0	0	0	0
	Total Exposure Time (years)	NA	NA	NA	NA
	Incidence Rate (95% CI) (100 person years)	NA	NA	NA	NA
Glaucoma	Number of patients at risk (% in cohort)	27 (100%)	149 (100%)	1047 (100%)	235 (100%)
	Median (IQR) Exposure time (months)	1.97 (0.92 ,5.88)	12.06 (2.89 ,19.78)	14.19 (5.72 ,24.80)	11.33 (3.12 ,22.05)
	Number who experienced event (%)	0	0	0	0
	Total Exposure Time (years)	NA	NA	NA	NA
	Incidence Rate (95% CI) (100 person years)	NA	NA	NA	NA
Hypokalaemia	Number of patients at risk (% in cohort)	27 (100%)	149 (100%)	1047 (100%)	235 (100%)
	Median (IQR) Exposure time (months)	1.97 (0.92 ,5.88)	12.06 (2.89 ,19.78)	14.19 (5.72 ,24.80)	11.33 (3.12 ,22.05)
	Number who experienced event (%)	0	0	0	0
	Total Exposure Time (years)	NA	NA	NA	NA
	Incidence Rate (95% CI) (100 person years)	NA	NA	NA	NA
Anxiety/Depression	Number of patients at risk (% in cohort)	27 (100%)	148 (99%)	1044 (100%)	234 (100%)
	Median (IQR) Exposure time (months)	1.97 (0.92 ,5.88)	11.88 (2.89 ,19.84)	14.14 (5.72 ,24.62)	11.35 (3.12 ,22.05)
	Number who experienced event (%)	0	n<5	6 (1%)	n<5
	Total Exposure Time (years)	NA	n<5	1410	n<5
	Incidence Rate (95% CI) (100 person years)	NA	NA	NA	NA
Growth retardation	Number of patients at risk (% in cohort)	27 (100%)	149 (100%)	1046 (100%)	235 (100%)
	Median (IQR) Exposure time (months)	1.97 (0.92 ,5.88)	12.06 (2.89 ,19.78)	14.18 (5.72 ,24.80)	11.33 (3.12 ,22.05)
	Number who experienced event (%)	0	0	n<5	0
	Total Exposure Time (years)	NA	NA	n<5	NA
	Incidence Rate (95% CI) (100 person years)	NA	NA	NA	NA

		Cohort			
		FP/FOR n=27	DPI FP/SAL n=149	MDI FP/SAL n=1047	BUD/FOR n=235
Reduced bone mineral density	Number of patients at risk (% in cohort)	27 (100%)	149 (100%)	1047 (100%)	235 (100%)
	Median (IQR) Exposure time (months)	1.97 (0.92 ,5.88)	12.06 (2.89 ,19.78)	14.19 (5.72 ,24.80)	11.33 (3.12 ,22.05)
	Number who experienced event (%)	0	0	0	0
	Total Exposure Time (years)	NA	NA	NA	NA
	Incidence Rate (95% CI) (100 person years)	NA	NA	NA	NA
Any new adverse events	Number of patients at risk (% in cohort)	n<5	75 (50%)	602 (57%)	114 (49%)
	Median (IQR) Exposure time (months)	n<5	18.43 (14.62 ,25.79)	20.04 (13.96 ,28.25)	19.12 (14.00 ,27.76)
	Number who experienced event (%)	n<5	10 (13%)	145 (24%)	23 (20%)
	Total Exposure Time (years)	n<5	126	1046	202
	Incidence Rate (95% CI) (100 person years)	NA	NA	NA	NA

Table 41: Adverse events evaluation by FDC ICS/LABA for patients aged ≥4 and <12 years with asthma

6.4.2.4 Patients with COPD only, definition 2

For patients with COPD, there was no evidence of a significant difference incidence in the rate of all studied adverse events or the number of events was zero or too low to be reported for on-label FP/FOR versus comparators (Table 42). For the adverse events where the rate of occurrence of the first event could be analysed (COPD exacerbations, LRTI, cardiac arrhythmia and ischaemia and "any new adverse events"), there was no evidence of a significant difference in the rate of occurrence of the first event for FP/FOR versus the licensed comparators (Table 43). However, when splitting by initiators and switchers, the rate of occurrence of the first event was higher for BUD/FOR and BDP/FOR than FP/FOR initiators and higher for FP/FOR than FP/SAL DPI switchers (Table 44). Furthermore, the rate of occurrence of the first cardiac arrhythmia and ischaemia was higher for FP/FOR compared to FP/SAL DPI for initiators. There was no evidence of a significant difference for LRTIs or "any new adverse events" between FP/FOR and licensed comparators when splitting by initiators and switchers.

		Cohort			
		FP/FOR n=399	DPI FP/SAL n=3678	BUD/FOR n=2526	BDP/FOR n=1609
COPD exacerbation	Number of patients at risk (% in cohort)	67 (39%)	1126 (51%)	657 (47%)	312 (37%)
	Median (IQR) Exposure time (months)	7.16 (2.76 ,17.12)	7.62 (2.60 ,15.67)	9.63 (2.92 ,16.49)	8.64 (3.06 ,14.11)
	Number who experienced event (%)	50 (75%)	880 (78%)	487 (74%)	222 (71%)
	Total Exposure Time (years)	57	980	619	255
	Incidence Rate (95% CI) (100 person years)	87.25 (66.13 ,115.12)	89.80 (84.06 ,95.93)	78.65 (71.97 ,85.96)	87.10 (76.37 ,99.35)
Lower respiratory tract infection	Number of patients at risk (% in cohort)	167 (42%)	1946 (53%)	1299 (51%)	639 (40%)
	Median (IQR) Exposure time (months)	16.07 (7.72 ,26.64)	17.18 (9.66 ,25.69)	16.53 (10.18 ,23.72)	14.49 (8.97 ,18.40)
	Number who experienced event (%)	68 (41%)	851 (44%)	567 (44%)	252 (39%)
	Total Exposure Time (years)	242	2912	1877	753
	Incidence Rate (95% CI) (100 person years)	28.09 (22.14 ,35.62)	29.23 (27.33 ,31.26)	30.21 (27.83 ,32.81)	33.46 (29.57 ,37.85)
Pneumonia	Number of patients at risk (% in cohort)	167 (42%)	1946 (53%)	1299 (51%)	639 (40%)
	Median (IQR) Exposure time (months)	23.46 (16.66 ,30.06)	23.97 (17.71 ,30.78)	22.34 (16.49 ,29.40)	17.02 (14.36 ,21.19)
	Number who experienced event (%)	6 (4%)	73 (4%)	45 (3%)	16 (3%)
	Total Exposure Time (years)	332	4027	2555	1010
	Incidence Rate (95% CI) (100 person years)	1.81 (0.81 ,4.02)	1.81 (1.44 ,2.28)	1.76 (1.32 ,2.36)	1.58 (0.97 ,2.59)

		Cohort			
		FP/FOR n=399	DPI FP/SAL n=3678	BUD/FOR n=2526	BDP/FOR n=1609
Pulmonary Embolism	Number of patients at risk (% in cohort)	399 (100%)	3678 (100%)	2526 (100%)	1609 (100%)
	Median (IQR) Exposure time (months)	9.10 (2.50 ,20.76)	13.21 (3.52 ,24.94)	12.45 (3.06 ,23.00)	9.76 (3.45 ,15.61)
	Number who experienced event (%)	n<5	16 (0%)	10 (0%)	7 (0%)
	Total Exposure Time (years)	n<5	4715	3040	1458
	Incidence Rate (95% CI) (100 person years)	NA	NA	NA	NA
Tuberculosis	Number of patients at risk (% in cohort)	399 (100%)	3678 (100%)	2526 (100%)	1609 (100%)
	Median (IQR) Exposure time (months)	9.23 (2.50 ,20.76)	13.21 (3.52 ,24.97)	12.50 (3.12 ,23.00)	9.76 (3.48 ,15.61)
	Number who experienced event (%)	0	n<5	n<5	n<5
	Total Exposure Time (years)	NA	n<5	n<5	n<5
	Incidence Rate (95% CI) (100 person years)	NA	NA	NA	NA
Oral candidiasis	Number of patients at risk (% in cohort)	395 (99%)	3630 (99%)	2495 (99%)	1583 (98%)
	Median (IQR) Exposure time (months)	9.23 (2.50 ,20.53)	12.94 (3.42 ,24.64)	12.25 (2.92 ,22.87)	9.76 (3.45 ,15.61)
	Number who experienced event (%)	6 (2%)	85 (2%)	45 (2%)	17 (1%)
	Total Exposure Time (years)	418	4601	2975	1434
	Incidence Rate (95% CI) (100 person years)	1.44 (0.64 ,3.20)	1.85 (1.49 ,2.28)	1.51 (1.13 ,2.03)	1.19 (0.74 ,1.91)
Dysphonia/hoarse voice	Number of patients at risk (% in cohort)	397 (99%)	3653 (99%)	2504 (99%)	1595 (99%)
	Median (IQR) Exposure time (months)	9.10 (2.50 ,20.70)	13.04 (3.48 ,24.84)	12.37 (3.04 ,22.74)	9.72 (3.35 ,15.51)
	Number who experienced event (%)	n<5	46 (1%)	30 (1%)	15 (1%)
	Total Exposure Time (years)	n<5	4658	2992	1435
	Incidence Rate (95% CI) (100 person years)	NA	NA	NA	NA
Other local oral adverse events	Number of patients at risk (% in cohort)	395 (99%)	3626 (99%)	2485 (98%)	1591 (99%)
	Median (IQR) Exposure time (months)	9.10 (2.10 ,20.53)	12.93 (3.45 ,24.77)	12.39 (3.12 ,22.77)	9.72 (3.45 ,15.51)
	Number who experienced event (%)	n<5	47 (1%)	31 (1%)	18 (1%)
	Total Exposure Time (years)	n<5	4609	2974	1430
	Incidence Rate (95% CI) (100 person years)	NA	NA	NA	NA

		Cohort			
		FP/FOR n=399	DPI FP/SAL n=3678	BUD/FOR n=2526	BDP/FOR n=1609
Adrenal failure	Number of patients at risk (% in cohort)	399 (100%)	3678 (100%)	2526 (100%)	1609 (100%)
	Median (IQR) Exposure time (months)	9.23 (2.50 ,20.76)	13.27 (3.55 ,24.97)	12.50 (3.12 ,23.00)	9.76 (3.48 ,15.61)
	Number who experienced event (%)	0	0	0	0
	Total Exposure Time (years)	NA	NA	NA	NA
	Incidence Rate (95% CI) (100 person years)	NA	NA	NA	NA
Cardiac arrhythmias and ischemia	Number of patients at risk (% in cohort)	377 (94%)	3392 (92%)	2321 (92%)	1493 (93%)
	Median (IQR) Exposure time (months)	8.02 (1.97 ,19.65)	12.53 (3.35 ,24.18)	11.89 (2.69 ,22.01)	9.43 (3.06 ,15.24)
	Number who experienced event (%)	20 (5%)	197 (6%)	136 (6%)	65 (4%)
	Total Exposure Time (years)	383	4205	2688	1313
	Incidence Rate (95% CI) (100 person years)	5.23 (3.37 ,8.10)	4.68 (4.07 ,5.39)	5.06 (4.28 ,5.99)	4.95 (3.88 ,6.31)
Hyperglycaemia	Number of patients at risk (% in cohort)	357 (89%)	3308 (90%)	2254 (89%)	1444 (90%)
	Median (IQR) Exposure time (months)	8.51 (2.10 ,20.76)	12.60 (3.38 ,24.30)	12.01 (3.02 ,22.64)	9.68 (3.14 ,15.31)
	Number who experienced event (%)	14 (4%)	139 (4%)	81 (4%)	45 (3%)
	Total Exposure Time (years)	376	4125	2663	1273
	Incidence Rate (95% CI) (100 person years)	3.72 (2.20 ,6.28)	3.37 (2.85 ,3.98)	3.04 (2.45 ,3.78)	3.53 (2.64 ,4.73)
Diagnosis of type 2 diabetes mellitus	Number of patients at risk (% in cohort)	391 (98%)	3621 (98%)	2489 (99%)	1576 (98%)
	Median (IQR) Exposure time (months)	8.90 (2.50 ,20.99)	12.91 (3.45 ,24.54)	12.25 (2.99 ,22.67)	9.72 (3.50 ,15.51)
	Number who experienced event (%)	7 (2%)	81 (2%)	45 (2%)	18 (1%)
	Total Exposure Time (years)	418	4577	2965	1417
	Incidence Rate (95% CI) (100 person years)	1.68 (0.80 ,3.51)	1.77 (1.42 ,2.20)	1.52 (1.13 ,2.03)	1.27 (0.80 ,2.02)
Anaphylactic reactions	Number of patients at risk (% in cohort)	399 (100%)	3678 (100%)	2526 (100%)	1609 (100%)
	Median (IQR) Exposure time (months)	9.23 (2.50 ,20.76)	13.27 (3.55 ,24.97)	12.50 (3.12 ,23.00)	9.76 (3.48 ,15.61)
	Number who experienced event (%)	0	0	0	n<5
	Total Exposure Time (years)	NA	NA	NA	n<5
	Incidence Rate (95% CI) (100 person years)	NA	NA	NA	NA

		Cohort			
		FP/FOR n=399	DPI FP/SAL n=3678	BUD/FOR n=2526	BDP/FOR n=1609
Cataract	Number of patients at risk (% in cohort)	384 (96%)	3591 (98%)	2471 (98%)	1558 (97%)
	Median (IQR) Exposure time (months)	8.94 (2.48 ,20.39)	12.78 (3.42 ,24.48)	12.16 (2.92 ,22.64)	9.76 (3.52 ,15.51)
	Number who experienced event (%)	8 (2%)	91 (3%)	54 (2%)	24 (2%)
	Total Exposure Time (years)	401	4518	2927	1399
	Incidence Rate (95% CI) (100 person years)	1.99 (1.00 ,3.99)	2.01 (1.64 ,2.47)	1.85 (1.41 ,2.41)	1.72 (1.15 ,2.56)
Glaucoma	Number of patients at risk (% in cohort)	393 (98%)	3662 (100%)	2508 (99%)	1602 (100%)
	Median (IQR) Exposure time (months)	9.26 (2.50 ,20.70)	13.21 (3.52 ,24.94)	12.44 (3.10 ,23.00)	9.76 (3.48 ,15.57)
	Number who experienced event (%)	n<5	15 (0%)	8 (0%)	7 (0%)
	Total Exposure Time (years)	n<5	4695	3019	1448
	Incidence Rate (95% CI) (100 person years)	NA	NA	NA	NA
Hypokalaemia	Number of patients at risk (% in cohort)	399 (100%)	3673 (100%)	2520 (100%)	1608 (100%)
	Median (IQR) Exposure time (months)	8.97 (2.50 ,20.53)	13.24 (3.55 ,24.94)	12.47 (3.10 ,23.00)	9.77 (3.48 ,15.62)
	Number who experienced event (%)	n<5	7 (0%)	7 (0%)	n<5
	Total Exposure Time (years)	n<5	4716	3034	n<5
	Incidence Rate (95% CI) (100 person years)	NA	NA	NA	NA
Anxiety/Depression	Number of patients at risk (% in cohort)	365 (91%)	3387 (92%)	2313 (92%)	1458 (91%)
	Median (IQR) Exposure time (months)	8.90 (2.50 ,19.78)	12.19 (3.29 ,23.85)	11.37 (2.66 ,21.82)	9.30 (3.15 ,15.05)
	Number who experienced event (%)	16 (4%)	201 (6%)	146 (6%)	68 (5%)
	Total Exposure Time (years)	377	4144	2644	1264
	Incidence Rate (95% CI) (100 person years)	4.24 (2.60 ,6.93)	4.85 (4.22 ,5.57)	5.52 (4.69 ,6.49)	5.38 (4.24 ,6.82)
Reduced bone mineral density	Number of patients at risk (% in cohort)	396 (99%)	3625 (99%)	2481 (98%)	1577 (98%)
	Median (IQR) Exposure time (months)	9.03 (2.45 ,20.47)	12.78 (3.42 ,24.57)	12.29 (3.12 ,22.80)	9.63 (3.35 ,15.44)
	Number who experienced event (%)	5 (1%)	87 (2%)	43 (2%)	22 (1%)
	Total Exposure Time (years)	415	4572	2967	1418
	Incidence Rate (95% CI) (100 person years)	1.20 (0.50 ,2.89)	1.90 (1.54 ,2.35)	1.45 (1.07 ,1.95)	1.55 (1.02 ,2.36)

		Cohort			
		FP/FOR n=399	DPI FP/SAL n=3678	BUD/FOR n=2526	BDP/FOR n=1609
Any new adverse events	Number of patients at risk (% in cohort)	167 (42%)	1946 (53%)	1299 (51%)	639 (40%)
	Median (IQR) Exposure time (months)	16.00 (10.41 ,24.41)	17.12 (10.25 ,25.07)	17.28 (11.33 ,24.25)	14.52 (10.87 ,18.40)
	Number who experienced event (%)	76 (46%)	1002 (51%)	604 (46%)	264 (41%)
	Total Exposure Time (years)	245	2905	1928	772
	Incidence Rate (95% CI) (100 person years)	31.02 (24.78 ,38.84)	34.50 (32.43 ,36.70)	31.33 (28.93 ,33.93)	34.18 (30.29 ,38.56)

Table 42: Adverse events evaluation by FDC ICS/LABA for patients with COPD only, definition 2

			Comparison (Hazard ratio, 95% CI)		
	Model	Number of observations in model	FP/SAL DPI vs FP/FOR	BUD/FOR vs FP/FOR	BDP/FOR vs FP/FOR
COPD exacerbation	Unadjusted	2162	1.04 (0.78 ,1.39)	0.93 (0.69 ,1.24)	0.96 (0.71 ,1.31)
	Adjusted for a priori confounders	1829	0.89 (0.64 ,1.23)	1.21 (0.85 ,1.72)	1.20 (0.84 ,1.71)
	Adjusted for a priori and selected potential confounders*	1829	0.87 (0.63 ,1.20)	1.18 (0.83 ,1.68)	1.18 (0.82 ,1.68)
Lower respiratory tract infection	Unadjusted	4051	1.04 (0.81 ,1.33)	1.06 (0.83 ,1.36)	1.12 (0.85 ,1.46)
	Adjusted for a priori confounders	3417	1.00 (0.76 ,1.32)	1.26 (0.90 ,1.75)	1.23 (0.88 ,1.71)
	Adjusted for a priori and selected potential confounders†	3417	0.98 (0.74 ,1.29)	1.11 (0.80 ,1.54)	1.10 (0.79 ,1.53)
Cardiac arrhythmias and ischemia	Unadjusted	7583	0.91 (0.58 ,1.44)	0.98 (0.61 ,1.57)	0.93 (0.56 ,1.54)
	Adjusted for a priori confounders	6991	0.85 (0.53 ,1.36)	0.93 (0.57 ,1.51)	0.92 (0.55 ,1.54)
	Adjusted for a priori and selected potential confounders‡	6991	0.85 (0.53 ,1.36)	0.93 (0.57 ,1.51)	0.92 (0.55 ,1.54)
Any new adverse events	Unadjusted	4051	1.11 (0.88 ,1.40)	1.01 (0.80 ,1.29)	1.13 (0.87 ,1.46)
	Adjusted for a priori confounders	3417	1.08 (0.83 ,1.41)	1.05 (0.77 ,1.44)	1.22 (0.90 ,1.67)
	Adjusted for a priori and selected potential confounders§	3417	1.08 (0.83 ,1.41)	1.05 (0.77 ,1.44)	1.22 (0.90 ,1.67)

Table 43: Rate of occurrence of first adverse event by FDC ICS/LABA for patients COPD only, definition 2

* Selected potential confounders adjusted for: LAMA prescriptions in baseline period or at index date
† Selected potential confounders adjusted for: Baseline LRTI adverse event
‡ No further confounders selected in addition to a priori confounders
§ No further confounders selected in addition to a priori confounders

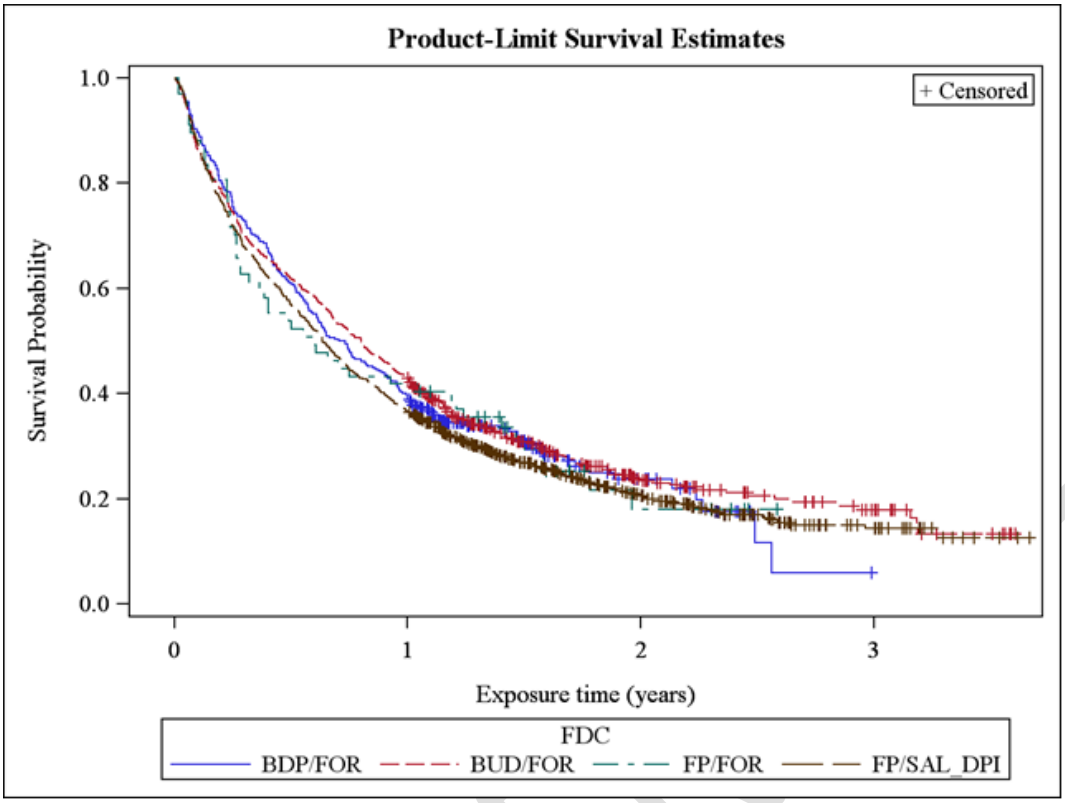

Figure 16: COPD exacerbation evaluation by FDC ICS/LABA (COPD definition 2)

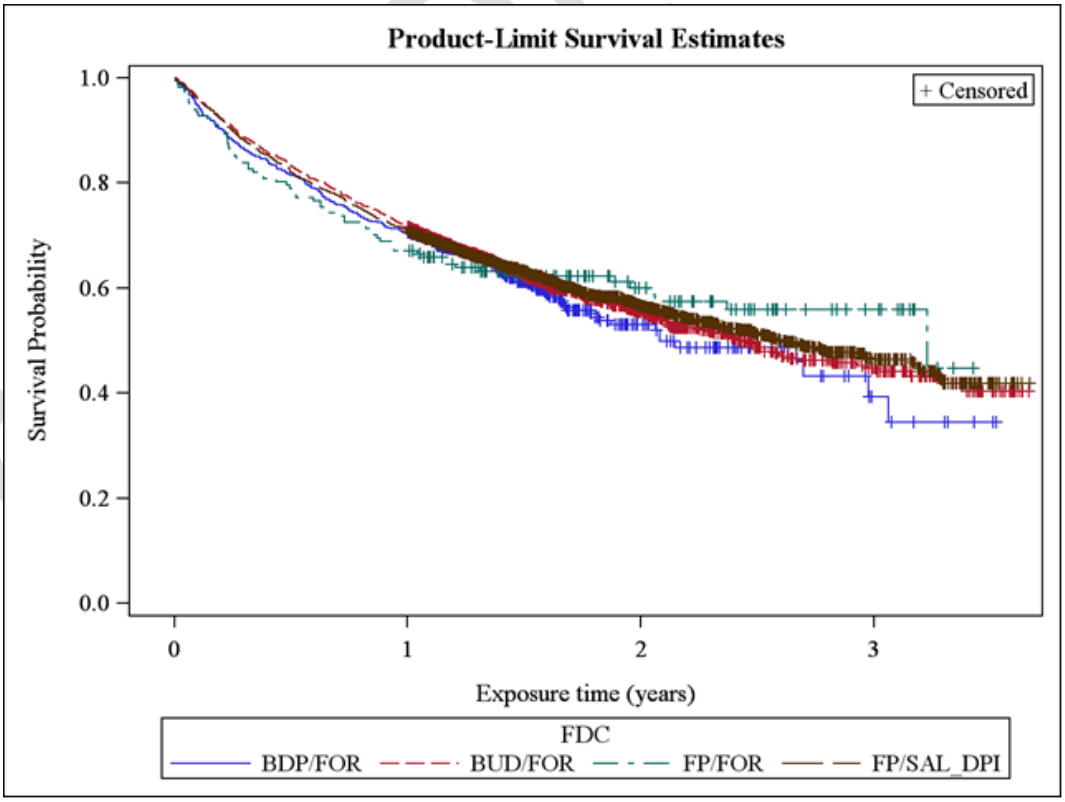

Figure 17: LRTI evaluation by FDC ICS/LABA (COPD definition 2)

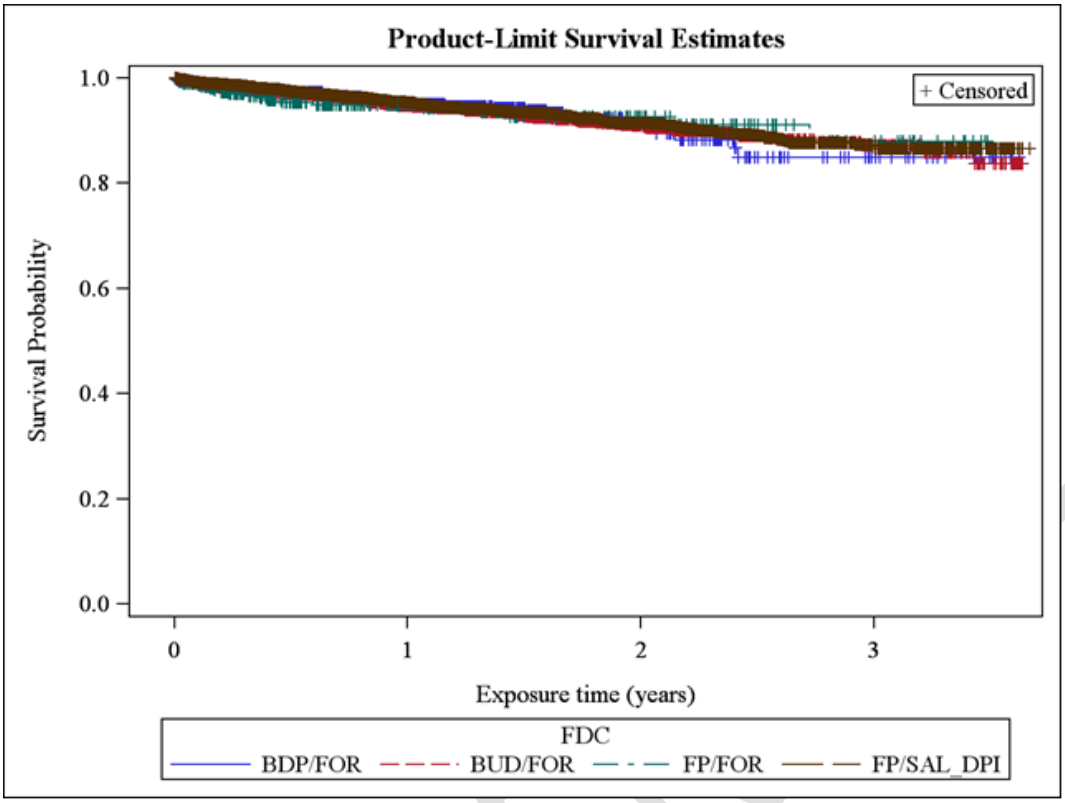

Figure 18: Cardiac arrhythmias and ischaemia evaluation by FDC ICS/LABA (COPD definition 2)

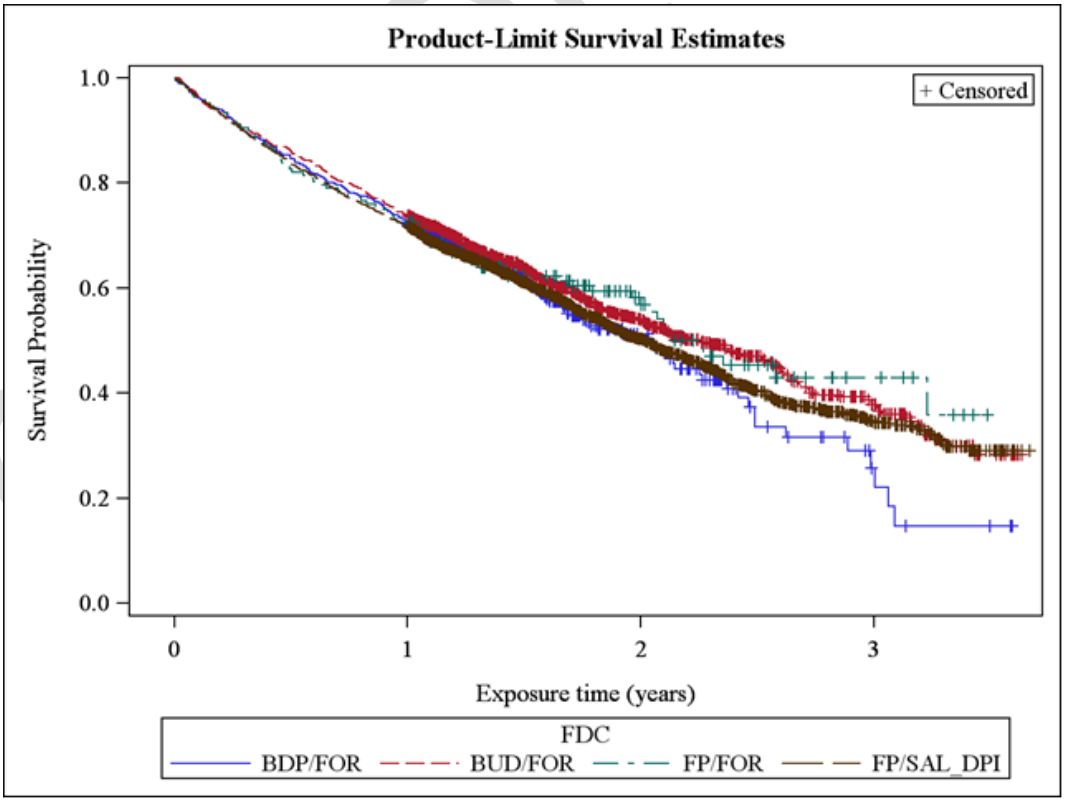

Figure 19: Any new adverse events evaluation by FDC ICS/LABA (COPD definition 2)

			Comparison (Hazard ratio, 95% CI)		
	Number of observations in model	Initiator or Switcher	FP/SAL DPI vs FP/FOR	BUD/FOR vs FP/FOR	BDP/FOR vs FP/FOR
COPD exacerbation*	1829	Initiator	1.52 (0.88 ,2.64)	1.81 (1.05 ,3.10)	1.88 (1.08 ,3.27)
		Switcher	0.60 (0.42 ,0.88)	0.83 (0.52 ,1.32)	0.78 (0.50 ,1.24)
Lower respiratory tract infection†	3417	Initiator	1.25 (0.80 ,1.95)	1.37 (0.86 ,2.18)	1.42 (0.87 ,2.31)
		Switcher	0.84 (0.60 ,1.17)	0.96 (0.64 ,1.45)	0.91 (0.60 ,1.37)
Cardiac arrhythmias and ischemia‡	6991	Initiator	0.48 (0.28 ,0.85)	0.58 (0.33 ,1.02)	0.56 (0.30 ,1.05)
		Switcher	1.94 (0.79 ,4.78)	1.83 (0.71 ,4.70)	1.92 (0.74 ,4.98)
Any new adverse events§	3417	Initiator	1.29 (0.86 ,1.94)	1.23 (0.81 ,1.87)	1.46 (0.95 ,2.26)
		Switcher	0.95 (0.69 ,1.32)	0.91 (0.60 ,1.36)	1.03 (0.69 ,1.56)

Table 44: Rate of occurrence of first adverse event by FDC ICS/LABA for patients with COPD only (definition 2), split by initiators and switchers

* Selected potential confounders adjusted for: LAMA prescriptions in baseline period or at index date
† Selected potential confounders adjusted for: Baseline LRTI adverse event
‡ No further confounders selected in addition to a priori confounders
§ No further confounders selected in addition to a priori confounders

6.4.2.5 "MART" regimen, definition 2

For patients in the MART regimen subgroup, the incidence rate of adverse events was zero or less than five for all except two of the adverse events studied (Table 45). However, in these two adverse events (LRTI and "any new adverse events"), there was no evidence of a significant difference in rates between FP/FOR and the licensed comparators. Due to less than 20 events occurring in each adverse event studied, no models could be run to assess the rate of occurrence of first event.

		Cohort		
		FP/FOR n=75	BUD/FOR n=246	BDP/FOR n=320
Lower respiratory tract infection	Number of patients at risk (% in cohort)	35 (47%)	103 (42%)	145 (45%)
	Median (IQR) Exposure time (months)	15.74 (13.44 ,21.42)	18.33 (13.40 ,27.04)	19.45 (14.59 ,26.84)
	Number who experienced event (%)	6 (17%)	26 (25%)	29 (20%)
	Total Exposure Time (years)	50	173	253
	Incidence Rate (95% CI) (100 person years)	12.09 (5.43 ,26.91)	15.01 (10.22 ,22.04)	11.44 (7.95 ,16.47)
Pneumonia	Number of patients at risk (% in cohort)	35 (47%)	103 (42%)	145 (45%)
	Median (IQR) Exposure time (months)	18.46 (14.82 ,25.23)	22.05 (15.41 ,29.57)	21.68 (16.46 ,29.44)
	Number who experienced event (%)	0	n<5	0
	Total Exposure Time (years)	NA	n<5	NA
	Incidence Rate (95% CI) (100 person years)	NA	NA	NA
Pulmonary Embolism	Number of patients at risk (% in cohort)	75 (100%)	246 (100%)	320 (100%)
	Median (IQR) Exposure time (months)	10.38 (1.97 ,17.58)	9.08 (1.97 ,18.73)	10.84 (2.79 ,19.89)
	Number who experienced event (%)	0	0	0
	Total Exposure Time (years)	NA	NA	NA
	Incidence Rate (95% CI) (100 person years)	NA	NA	NA
Tuberculosis	Number of patients at risk (% in cohort)	75 (100%)	246 (100%)	320 (100%)
	Median (IQR) Exposure time (months)	10.38 (1.97 ,17.58)	9.08 (1.97 ,18.73)	10.84 (2.79 ,19.89)
	Number who experienced event (%)	0	0	0
	Total Exposure Time (years)	NA	NA	NA
	Incidence Rate (95% CI) (100 person years)	NA	NA	NA
Oral candidiasis	Number of patients at risk (% in cohort)	75 (100%)	244 (99%)	313 (98%)
	Median (IQR) Exposure time (months)	10.38 (1.97 ,17.58)	9.08 (1.97 ,18.79)	10.81 (2.63 ,19.91)
	Number who experienced event (%)	0	n<5	n<5
	Total Exposure Time (years)	NA	n<5	n<5
	Incidence Rate (95% CI) (100 person years)	NA	NA	NA

		Cohort		
		FP/FOR n=75	BUD/FOR n=246	BDP/FOR n=320
Dysphonia/hoarse voice	Number of patients at risk (% in cohort)	74 (99%)	245 (100%)	317 (99%)
	Median (IQR) Exposure time (months)	10.09 (1.97 ,16.43)	8.74 (1.97 ,18.56)	10.55 (2.63 ,19.48)
	Number who experienced event (%)	n<5	n<5	n<5
	Total Exposure Time (years)	n<5	n<5	n<5
	Incidence Rate (95% CI) (100 person years)	NA	NA	NA
Other local oral adverse events	Number of patients at risk (% in cohort)	74 (99%)	240 (98%)	316 (99%)
	Median (IQR) Exposure time (months)	10.25 (1.97 ,16.43)	9.12 (1.97 ,18.87)	10.63 (2.69 ,19.71)
	Number who experienced event (%)	0	n<5	7 (2%)
	Total Exposure Time (years)	NA	n<5	342
	Incidence Rate (95% CI) (100 person years)	NA	NA	NA
Adrenal failure	Number of patients at risk (% in cohort)	75 (100%)	246 (100%)	320 (100%)
	Median (IQR) Exposure time (months)	10.38 (1.97 ,17.58)	9.08 (1.97 ,18.73)	10.84 (2.79 ,19.89)
	Number who experienced event (%)	0	0	0
	Total Exposure Time (years)	NA	NA	NA
	Incidence Rate (95% CI) (100 person years)	NA	NA	NA
Cardiac arrhythmias and ischemia	Number of patients at risk (% in cohort)	75 (100%)	241 (98%)	310 (97%)
	Median (IQR) Exposure time (months)	10.38 (1.97 ,17.58)	8.38 (1.97 ,18.73)	10.48 (2.63 ,19.88)
	Number who experienced event (%)	0	n<5	6 (2%)
	Total Exposure Time (years)	NA	n<5	337
	Incidence Rate (95% CI) (100 person years)	NA	NA	NA
Hyperglycaemia	Number of patients at risk (% in cohort)	75 (100%)	235 (96%)	295 (92%)
	Median (IQR) Exposure time (months)	10.12 (1.97 ,16.43)	9.10 (1.97 ,18.73)	10.91 (2.63 ,20.14)
	Number who experienced event (%)	n<5	0	5 (2%)
	Total Exposure Time (years)	n<5	NA	328
	Incidence Rate (95% CI) (100 person years)	NA	NA	NA
Diagnosis of type 2 diabetes mellitus	Number of patients at risk (% in cohort)	75 (100%)	245 (100%)	318 (99%)
	Median (IQR) Exposure time (months)	10.38 (1.97 ,17.58)	9.07 (1.97 ,18.56)	10.63 (2.63 ,19.88)
	Number who experienced event (%)	n<5	n<5	6 (2%)
	Total Exposure Time (years)	n<5	n<5	346
	Incidence Rate (95% CI) (100 person years)	NA	NA	NA

		Cohort		
		FP/FOR n=75	BUD/FOR n=246	BDP/FOR n=320
Anaphylactic reactions	Number of patients at risk (% in cohort)	75 (100%)	246 (100%)	320 (100%)
	Median (IQR) Exposure time (months)	10.38 (1.97 ,17.58)	9.08 (1.97 ,18.73)	10.84 (2.79 ,19.89)
	Number who experienced event (%)	0	0	0
	Total Exposure Time (years)	NA	NA	NA
	Incidence Rate (95% CI) (100 person years)	NA	NA	NA
Cataract	Number of patients at risk (% in cohort)	75 (100%)	245 (100%)	313 (98%)
	Median (IQR) Exposure time (months)	10.38 (1.97 ,17.58)	9.10 (1.97 ,18.73)	10.91 (2.76 ,19.88)
	Number who experienced event (%)	0	0	n<5
	Total Exposure Time (years)	NA	NA	n<5
	Incidence Rate (95% CI) (100 person years)	NA	NA	NA
Glaucoma	Number of patients at risk (% in cohort)	75 (100%)	246 (100%)	319 (100%)
	Median (IQR) Exposure time (months)	10.38 (1.97 ,17.58)	9.08 (1.97 ,18.73)	10.87 (2.76 ,19.91)
	Number who experienced event (%)	0	0	n<5
	Total Exposure Time (years)	NA	NA	n<5
	Incidence Rate (95% CI) (100 person years)	NA	NA	NA
Hypokalaemia	Number of patients at risk (% in cohort)	75 (100%)	246 (100%)	320 (100%)
	Median (IQR) Exposure time (months)	10.38 (1.97 ,17.58)	9.08 (1.97 ,18.73)	10.84 (2.79 ,19.89)
	Number who experienced event (%)	0	0	0
	Total Exposure Time (years)	NA	NA	NA
	Incidence Rate (95% CI) (100 person years)	NA	NA	NA
Anxiety/Depression	Number of patients at risk (% in cohort)	61 (81%)	220 (89%)	290 (91%)
	Median (IQR) Exposure time (months)	8.84 (1.97 ,15.41)	8.23 (1.97 ,18.50)	10.02 (1.97 ,18.33)
	Number who experienced event (%)	n<5	11 (5%)	19 (7%)
	Total Exposure Time (years)	n<5	217	295
	Incidence Rate (95% CI) (100 person years)	NA	NA	NA
Reduced bone mineral density	Number of patients at risk (% in cohort)	73 (97%)	246 (100%)	317 (99%)
	Median (IQR) Exposure time (months)	10.38 (1.97 ,17.58)	9.08 (1.97 ,18.73)	10.81 (2.83 ,19.55)
	Number who experienced event (%)	0	n<5	n<5
	Total Exposure Time (years)	NA	n<5	n<5
	Incidence Rate (95% CI) (100 person years)	NA	NA	NA

		Cohort		
		FP/FOR n=75	BUD/FOR n=246	BDP/FOR n=320
Any new adverse events	Number of patients at risk (% in cohort)	35 (47%)	103 (42%)	145 (45%)
	Median (IQR) Exposure time (months)	16.23 (13.90 ,23.92)	18.43 (13.60 ,26.97)	16.85 (12.45 ,22.34)
	Number who experienced event (%)	9 (26%)	30 (29%)	58 (40%)
	Total Exposure Time (years)	53	171	212
	Incidence Rate (95% CI) (100 person years)	16.89 (8.79 ,32.46)	17.51 (12.24 ,25.05)	27.36 (21.15 ,35.39)

Table 45: Adverse events evaluation by FDC ICS/LABA for "MART" regimen, definition 2

6.4.3 Serious adverse events

6.4.3.1 Patients aged ≥18 years with asthma

For patients aged ≥18 years with asthma, the incidence rate of inpatient hospitalisations associated with adverse events was lower for FP/FOR than FP/SAL MDI or DPI (Table 46). The incidence rate of deaths associated with adverse events was too low for reporting. When considering specific adverse events associated with inpatient hospitalisations, the incidence rate of LRTI, pneumonia, cardiac arrhythmias and ischaemia, type 2 diabetes mellitus and anxiety/depression associated inpatient hospitalisations was lower for FP/FOR than for DPI FP/SAL (for cardiac arrhythmias and ischaemia associated inpatient hospitalisations it was also lower for FP/FOR than FP/SAL MDI and BUD/FOR) (Table 47). For reduced bone mineral density associated inpatient hospitalisations, there was no evidence of a significant difference in incidence rates between comparators. There was also no evidence of a significant difference in the incidence rate of deaths associated with cardiac arrhythmias and ischaemia between FP/FOR and licensed comparators (Table 48). Considering the rate of occurrence of the first inpatient hospitalisation associated with adverse events, the rate was higher for FP/SAL MDI and BUD/FOR compared to FP/FOR after adjustment for confounders (Table 49). For cardiac arrhythmia and ischaemia associated inpatient hospitalisations, the rate of occurrence of the first event was higher for FP/SAL MDI, FP/SAL DPI and BUD/FOR compared to FP/FOR after adjustment for confounders. For anxiety/depression associated inpatient hospitalisations, the rate of occurrence of the first event was higher for FP/SAL MDI, BUD/FOR and BDP/FOR compared to FP/FOR after adjustment for confounders. For LRTI and type 2 diabetes mellitus associated inpatient hospitalisations, there was no evidence of a significant difference in the rate of occurrence of the first event after adjustment for confounders. The split by initiators and switchers revealed no evidence of a significant difference between FP/FOR and the licensed comparators for any of the adverse events studied in the initiators group or in the switchers group for LRTI and type 2 diabetes mellitus (Table 50). However, in the switchers group the rate of occurrence of the first inpatient hospitalisation and anxiety depression associated inpatient hospitalisation was higher for BUD/FOR than FP/FOR and the rate of occurrence of the first cardiac arrhythmias and ischaemia associated inpatient hospitalisation was higher for FP/SAL MDI, FP/SAL DPI and BUD/FOR than FP/FOR switchers.

		Cohort				
		FP/FOR n=5727	DPI FP/SAL n=6865	MDI FP/SAL n=8948	BUD/FOR n=9128	BDP/FOR n=10941
Inpatient hospitalisation associated with adverse events	Number of patients at risk (% in cohort)	1169 (44%)	1796 (43%)	2128 (41%)	2245 (43%)	2609 (43%)
	Median (IQR) Exposure time (months)	19.25 (14.92 ,26.74)	20.63 (14.28 ,29.17)	20.01 (14.85 ,28.27)	20.70 (15.08 ,28.81)	19.02 (14.26 ,27.10)
	Number who experienced event (%)	134 (11%)	434 (24%)	349 (16%)	307 (14%)	294 (11%)
	Total Exposure Time (years)	2033	3219	3819	4107	4578
	Incidence Rate (95% CI) (100 person years)	6.59 (5.56 ,7.81)	13.48 (12.27 ,14.81)	9.14 (8.23 ,10.15)	7.48 (6.68 ,8.36)	6.42 (5.73 ,7.20)
Death associated with adverse events	Number of patients at risk (% in cohort)	1169 (44%)	1796 (43%)	2128 (41%)	2245 (43%)	2609 (43%)
	Median (IQR) Exposure time (months)	21.42 (16.46 ,27.76)	24.03 (17.63 ,31.84)	21.93 (16.28 ,29.85)	22.34 (16.43 ,30.46)	20.50 (15.34 ,28.16)
	Number who experienced event (%)	n<5	32 (2%)	19 (1%)	15 (1%)	5 (0%)
	Total Exposure Time (years)	n<5	3749	4190	4485	4924
	Incidence Rate (95% CI) (100 person years)	NA	NA	NA	NA	NA

Table 46: Total serious adverse events associated with inpatient hospitalisation or death by FDC ICS/LABA (asthma patients ≥18 years old)

		Cohort				
		FP/FOR n=5727	DPI FP/SAL n=6865	MDI FP/SAL n=8948	BUD/FOR n=9128	BDP/FOR n=10941
Inpatient hospitalisation associated with lower respiratory tract infection	Number of patients at risk (% in cohort)	1169 (44%)	1796 (43%)	2128 (41%)	2245 (43%)	2609 (43%)
	Median (IQR) Exposure time (months)	20.70 (16.07 ,27.33)	22.95 (16.07 ,30.98)	21.17 (15.80 ,29.32)	21.75 (15.90 ,29.96)	20.11 (15.01 ,27.89)
	Number who experienced event (%)	50 (4%)	189 (11%)	137 (6%)	127 (6%)	95 (4%)
	Total Exposure Time (years)	2137	3535	4053	4335	4819
	Incidence Rate (95% CI) (100 person years)	2.34 (1.77 ,3.09)	5.35 (4.64 ,6.17)	3.38 (2.86 ,4.00)	2.93 (2.46 ,3.49)	1.97 (1.61 ,2.41)
Inpatient hospitalisation associated with pneumonia	Number of patients at risk (% in cohort)	1169 (44%)	1796 (43%)	2128 (41%)	2245 (43%)	2609 (43%)
	Median (IQR) Exposure time (months)	21.19 (16.39 ,27.53)	23.67 (16.87 ,31.64)	21.59 (16.03 ,29.63)	22.08 (16.23 ,30.29)	20.30 (15.15 ,28.09)
	Number who experienced event (%)	19 (2%)	79 (4%)	69 (3%)	57 (3%)	44 (2%)
	Total Exposure Time (years)	2174	3667	4127	4426	4883
	Incidence Rate (95% CI) (100 person years)	0.87 (0.56 ,1.37)	2.15 (1.73 ,2.69)	1.67 (1.32 ,2.12)	1.29 (0.99 ,1.67)	0.90 (0.67 ,1.21)

		Cohort				
		FP/FOR n=5727	DPI FP/SAL n=6865	MDI FP/SAL n=8948	BUD/FOR n=9128	BDP/FOR n=10941
Inpatient hospitalisation associated with cardiac arrhythmias or ischemia	Number of patients at risk (% in cohort)	2685 (100%)	4221 (100%)	5187 (100%)	5166 (100%)	6101 (100%)
	Median (IQR) Exposure time (months)	9.53 (1.97 ,18.53)	7.75 (1.97 ,20.01)	8.25 (1.97 ,18.50)	8.80 (1.97 ,19.78)	9.30 (2.14 ,17.84)
	Number who experienced event (%)	76 (3%)	313 (7%)	267 (5%)	221 (4%)	200 (3%)
	Total Exposure Time (years)	2672	4215	5087	5310	6084
	Incidence Rate (95% CI) (100 person years)	2.84 (2.27 ,3.56)	7.43 (6.65 ,8.30)	5.25 (4.66 ,5.92)	4.16 (3.65 ,4.75)	3.29 (2.86 ,3.78)
Inpatient hospitalisation associated with type 2 diabetes mellitus	Number of patients at risk (% in cohort)	2685 (100%)	4221 (100%)	5187 (100%)	5166 (100%)	6101 (100%)
	Median (IQR) Exposure time (months)	9.59 (1.97 ,18.69)	8.08 (1.97 ,20.76)	8.38 (1.97 ,18.96)	9.13 (1.97 ,20.07)	9.56 (2.20 ,18.10)
	Number who experienced event (%)	44 (2%)	154 (4%)	118 (2%)	100 (2%)	110 (2%)
	Total Exposure Time (years)	2693	4338	5173	5413	6161
	Incidence Rate (95% CI) (100 person years)	1.63 (1.22 ,2.20)	3.55 (3.03 ,4.16)	2.28 (1.90 ,2.73)	1.85 (1.52 ,2.25)	1.79 (1.48 ,2.15)
Inpatient hospitalisation associated with anxiety/depression	Number of patients at risk (% in cohort)	2685 (100%)	4221 (100%)	5187 (100%)	5166 (100%)	6101 (100%)
	Median (IQR) Exposure time (months)	9.59 (2.04 ,18.99)	8.25 (1.97 ,21.06)	8.41 (1.97 ,19.06)	9.20 (1.97 ,20.11)	9.56 (2.20 ,18.00)
	Number who experienced event (%)	35 (1%)	118 (3%)	107 (2%)	95 (2%)	118 (2%)
	Total Exposure Time (years)	2703	4378	5208	5407	6144
	Incidence Rate (95% CI) (100 person years)	1.29 (0.93 ,1.80)	2.70 (2.25 ,3.23)	2.05 (1.70 ,2.48)	1.76 (1.44 ,2.15)	1.92 (1.60 ,2.30)
Inpatient hospitalisation associated with reduced bone mineral density	Number of patients at risk (% in cohort)	2685 (100%)	4221 (100%)	5187 (100%)	5166 (100%)	6101 (100%)
	Median (IQR) Exposure time (months)	9.76 (2.04 ,19.15)	8.48 (1.97 ,21.49)	8.54 (1.97 ,19.22)	9.35 (1.97 ,20.47)	9.76 (2.33 ,18.37)
	Number who experienced event (%)	12 (0%)	44 (1%)	43 (1%)	26 (1%)	18 (0%)
	Total Exposure Time (years)	2733	4459	5253	5472	6242
	Incidence Rate (95% CI) (100 person years)	0.44 (0.25 ,0.77)	0.99 (0.73 ,1.33)	0.82 (0.61 ,1.10)	0.48 (0.32 ,0.70)	0.29 (0.18 ,0.46)

Table 47: Individual serious adverse events associated with inpatient hospitalisation by FDC ICS/LABA (asthma patients ≥18 years old)

		Cohort				
		FP/FOR n=5727	DPI FP/SAL n=6865	MDI FP/SAL n=8948	BUD/FOR n=9128	BDP/FOR n=10941
Death associated with cardiac arrhythmias or ischemia	Number of patients at risk (% in cohort)	2685 (100%)	4221 (100%)	5187 (100%)	5166 (100%)	6101 (100%)
	Median (IQR) Exposure time (months)	9.79 (2.07 ,19.22)	8.64 (1.97 ,21.75)	8.71 (1.97 ,19.35)	9.43 (1.97 ,20.57)	9.79 (2.37 ,18.43)
	Number who experienced event (%)	9 (0%)	30 (1%)	33 (1%)	19 (0%)	11 (0%)
	Total Exposure Time (years)	2741	4496	5291	5499	6264
	Incidence Rate (95% CI) (100 person years)	0.33 (0.17 ,0.63)	0.67 (0.47 ,0.95)	0.62 (0.44 ,0.88)	0.35 (0.22 ,0.54)	0.18 (0.10 ,0.32)

Table 48: Individual serious adverse events associated with death by FDC ICS/LABA (asthma patients ≥18 years old)

			Comparison (Hazard ratio, 95% CI)			
	Model	Number of observations in model	FP/SAL DPI vs FP/FOR	FP/SAL MDI vs FP/FOR	BUD/FOR vs FP/FOR	BDP/FOR vs FP/FOR
Inpatient hospitalisation associated with adverse events	Unadjusted	9947	2.10 (1.73 ,2.55)	1.42 (1.16 ,1.73)	1.16 (0.95 ,1.43)	0.99 (0.81 ,1.22)
	Adjusted for a priori confounders	7489	1.38 (1.12 ,1.71)	1.52 (1.22 ,1.88)	1.84 (1.44 ,2.36)	1.29 (1.01 ,1.64)
	Adjusted for a priori and selected potential confounders*	7489	1.15 (0.92 ,1.42)	1.29 (1.04 ,1.61)	1.43 (1.12 ,1.84)	1.14 (0.89 ,1.45)
Inpatient hospitalisation associated with lower respiratory tract infection	Unadjusted	9947	2.37 (1.74 ,3.24)	1.48 (1.07 ,2.05)	1.29 (0.93 ,1.79)	0.86 (0.61 ,1.21)
	Adjusted for a priori confounders	7489	1.22 (0.88 ,1.71)	1.45 (1.03 ,2.05)	2.13 (1.44 ,3.17)	1.06 (0.70 ,1.61)
	Adjusted for a priori and selected potential confounders†	7489	0.82 (0.58 ,1.16)	1.08 (0.76 ,1.53)	1.22 (0.81 ,1.82)	0.84 (0.56 ,1.28)
Inpatient hospitalisation associated with cardiac arrhythmias or ischemia	Unadjusted	23360	2.72 (2.12 ,3.50)	1.87 (1.45 ,2.41)	1.51 (1.16 ,1.96)	1.17 (0.90 ,1.52)
	Adjusted for a priori confounders	20122	1.84 (1.41 ,2.39)	1.94 (1.48 ,2.54)	1.84 (1.39 ,2.42)	1.22 (0.92 ,1.61)
	Adjusted for a priori and selected potential confounders‡	20122	1.53 (1.17 ,2.01)	1.56 (1.18 ,2.05)	1.62 (1.22 ,2.14)	1.10 (0.83 ,1.46)

* Selected potential confounders adjusted for: LAMA prescriptions in baseline period or index date, ICS only prescriptions in baseline period or index date, History of ischemic heart disease, History of hypertension, COPD diagnosis, Pain-relief medication prescriptions (categorised), Spacer prescription, Any baseline respiratory inpatient admissions, Baseline LRTI adverse events, Baseline COPD exacerbations

† Selected potential confounders adjusted for: LAMA prescriptions in baseline period or index date, ICS only prescriptions in baseline period or index date, History of ischemic heart disease, COPD diagnosis, Pain-relief medication prescriptions (categorised), Spacer prescription, Any baseline respiratory inpatient admissions, Baseline LRTI adverse events, SAMA prescriptions in baseline period or index date

‡ Selected potential confounders adjusted for: LAMA prescriptions in baseline period or index date, ICS only prescriptions in baseline period or index date, History of ischemic heart disease, History of hypertension, COPD diagnosis, Pain-relief medication prescriptions (categorised), Spacer

			Comparison (Hazard ratio, 95% CI)			
	Model	Number of observations in model	FP/SAL DPI vs FP/FOR	FP/SAL MDI vs FP/FOR	BUD/FOR vs FP/FOR	BDP/FOR vs FP/FOR
Inpatient hospitalisation associated with type 2 diabetes mellitus	Unadjusted	23360	2.29 (1.64 ,3.20)	1.42 (1.00 ,2.01)	1.17 (0.82 ,1.67)	1.10 (0.78 ,1.56)
	Adjusted for a priori confounders	17324	1.58 (1.10 ,2.26)	1.50 (1.04 ,2.17)	1.82 (1.20 ,2.76)	1.37 (0.91 ,2.05)
	Adjusted for a priori and selected potential confounders*	17323	1.39 (0.96 ,2.00)	1.26 (0.87 ,1.83)	1.51 (0.99 ,2.31)	1.23 (0.82 ,1.85)
Inpatient hospitalisation associated with anxiety/depression	Unadjusted	23360	2.16 (1.48 ,3.16)	1.61 (1.10 ,2.36)	1.39 (0.95 ,2.05)	1.50 (1.03 ,2.18)
	Adjusted for a priori confounders	17324	1.74 (1.16 ,2.63)	1.83 (1.21 ,2.77)	2.28 (1.42 ,3.67)	2.08 (1.34 ,3.23)
	Adjusted for a priori and selected potential confounders†	17324	1.46 (0.96 ,2.22)	1.56 (1.03 ,2.37)	1.72 (1.07 ,2.78)	1.80 (1.16 ,2.81)

Table 49: Rate of occurrence of first serious adverse events associated with inpatient hospitalisation by FDC ICS/LABA (asthma patients ≥18 years old)

prescription, Any baseline respiratory inpatient admissions, SAMA prescriptions in baseline period or index date, Beta-blocker prescriptions (categorised)

* Selected potential confounders adjusted for: LAMA prescriptions in baseline period or index date, ICS only prescriptions in baseline period or index date, History of ischemic heart disease, History of hypertension, COPD diagnosis, Pain-relief medication prescriptions (categorised), Spacer prescription, Any baseline respiratory inpatient admissions, SAMA prescriptions in baseline period or index date, Beta-blocker prescriptions (categorised), Charlson Comorbidity Index (CCI)

† Selected potential confounders adjusted for: LAMA prescriptions in baseline period or index date, COPD diagnosis, Pain-relief medication prescriptions (categorised), Any baseline respiratory inpatient admissions

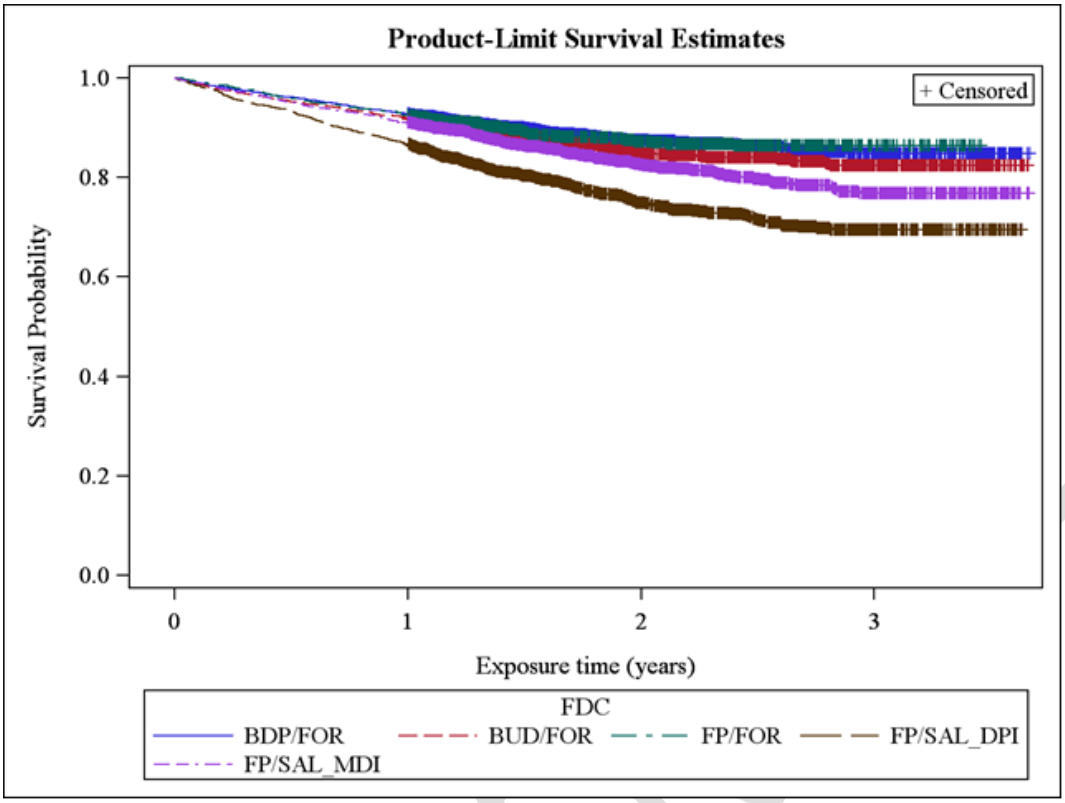

Figure 20: Inpatient hospitalisation evaluation by FDC ICS/LABA (asthma patients ≥18 years old)

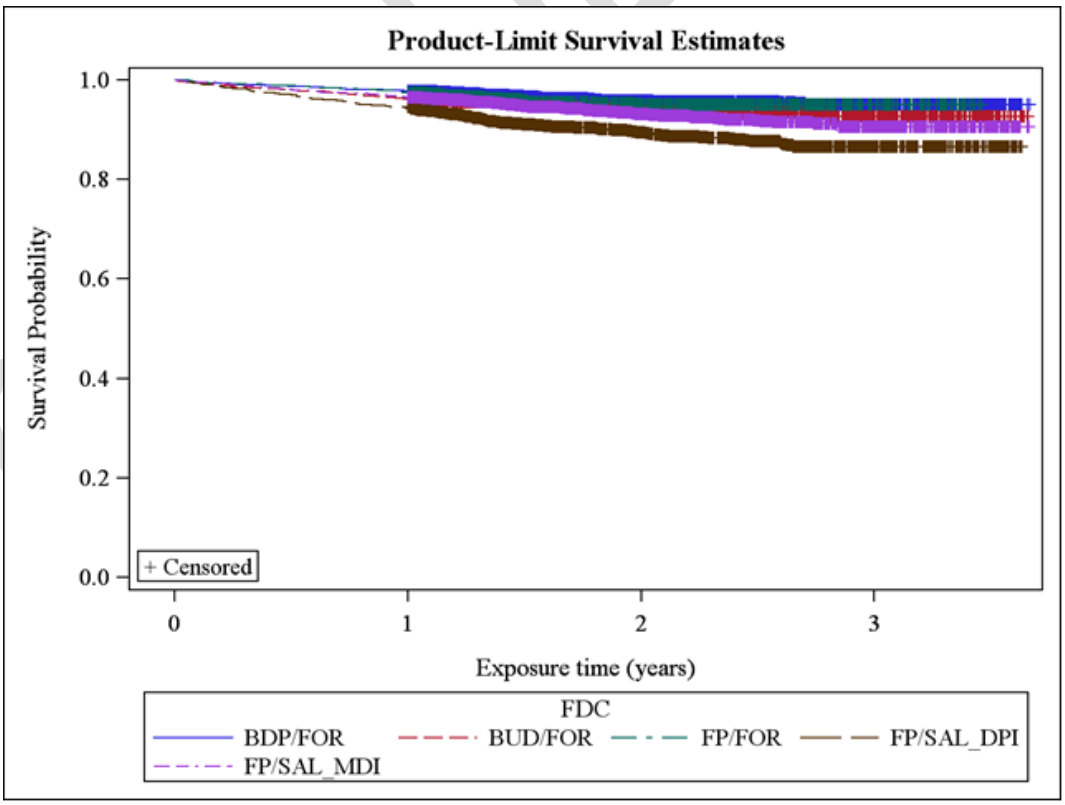

Figure 21: LRTI associated inpatient hospitalisation evaluation by FDC ICS/LABA (asthma patients ≥18 years old)

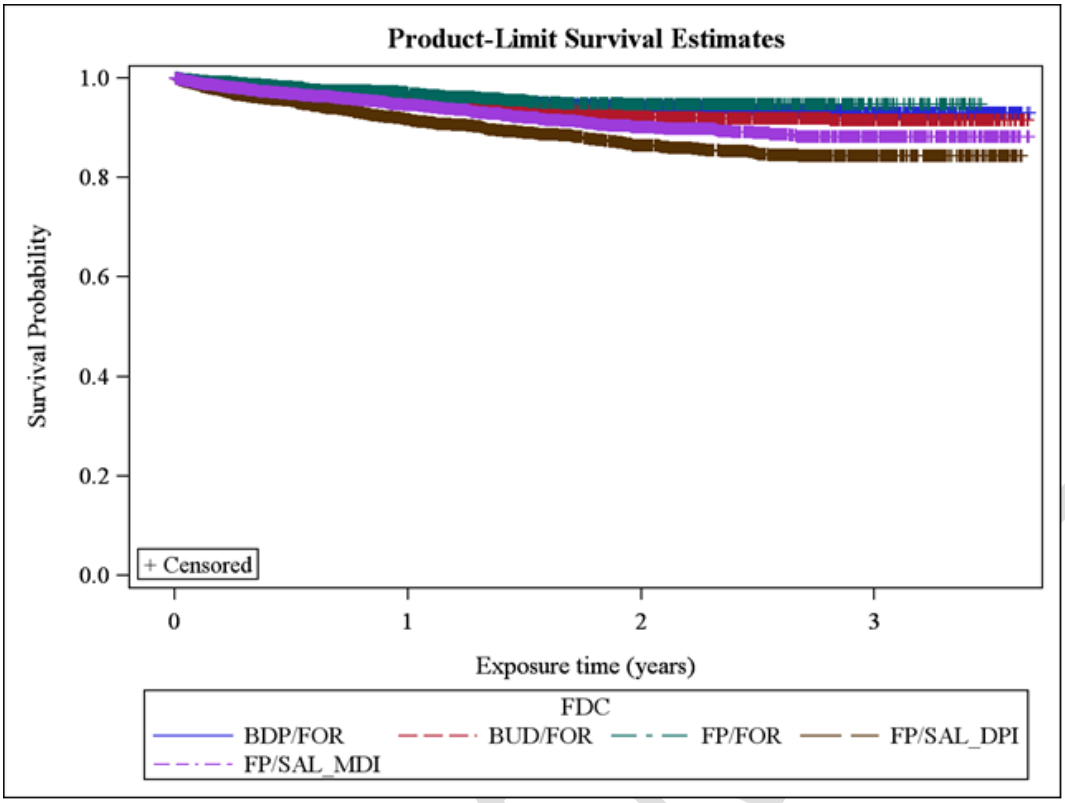

Figure 22: Cardiac ischaemia and arrhythmia associated inpatient hospitalisation evaluation by FDC ICS/LABA (asthma patients ≥18 years old)

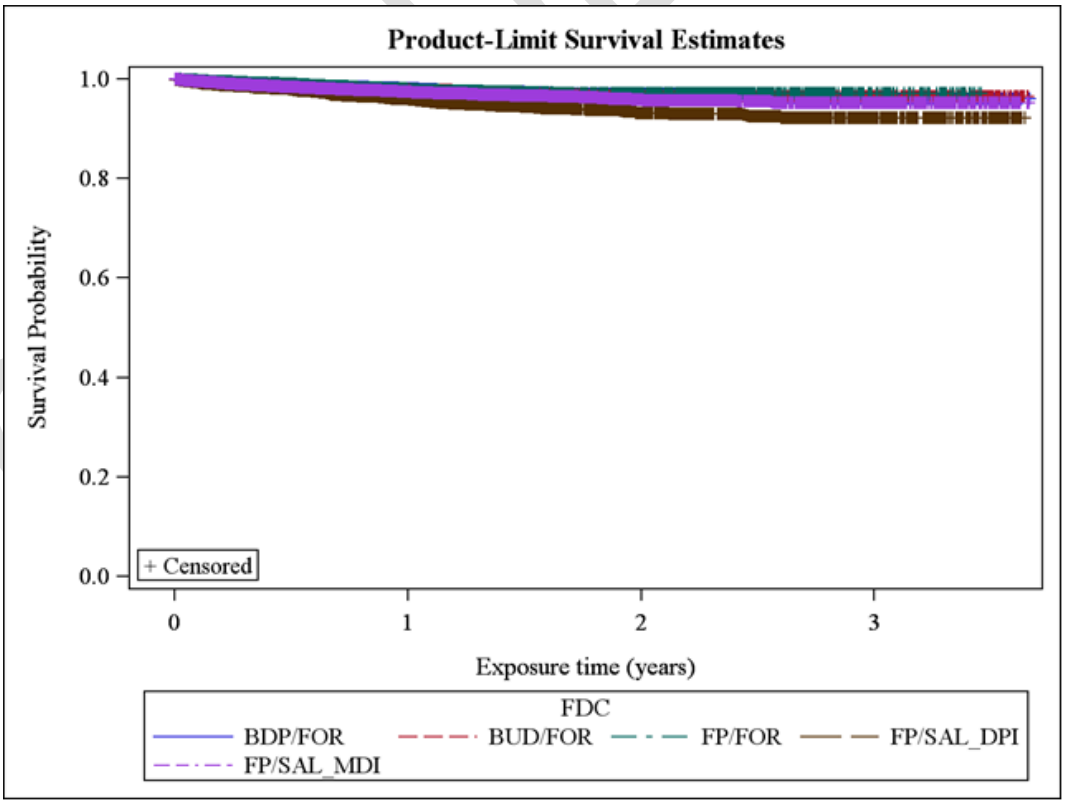

Figure 23: Type 2 diabetes mellitus associated inpatient hospitalisation evaluation by FDC ICS/LABA (asthma patients ≥18 years old)

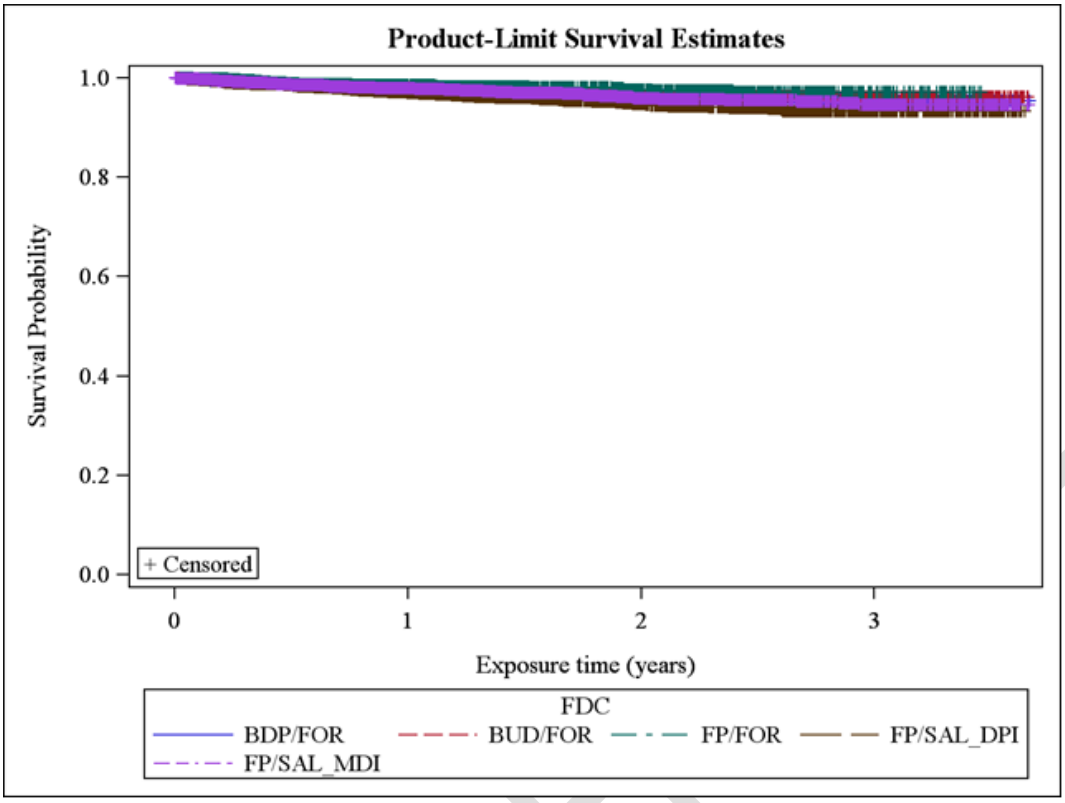

Figure 24: Anxiety/depression associated inpatient hospitalisation evaluation by FDC ICS/LABA (asthma patients ≥18 years old)

			Comparison (Hazard ratio, 95% CI)			
	Number of observations in model	Initiator or Switcher	FP/SAL DPI vs FP/FOR	FP/SAL MDI vs FP/FOR	BUD/FOR vs FP/FOR	BDP/FOR vs FP/FOR
Inpatient hospitalisation associated with adverse events*	7489	Initiator	1.30 (0.85 ,1.99)	1.41 (0.94 ,2.11)	1.51 (0.99 ,2.31)	1.27 (0.83 ,1.94)
		Switcher	1.10 (0.86 ,1.41)	1.27 (0.96 ,1.66)	1.46 (1.07 ,1.99)	1.08 (0.79 ,1.46)
Inpatient hospitalisation associated with lower respiratory tract infection†	7489	Initiator	0.98 (0.49 ,1.95)	1.07 (0.55 ,2.09)	1.06 (0.53 ,2.14)	0.84 (0.40 ,1.75)
		Switcher	0.76 (0.51 ,1.12)	1.10 (0.72 ,1.68)	1.44 (0.89 ,2.33)	0.86 (0.51 ,1.44)
Inpatient hospitalisation associated with cardiac arrhythmias or ischemia‡	20122	Initiator	1.45 (0.85 ,2.48)	1.43 (0.85 ,2.41)	1.58 (0.94 ,2.67)	0.95 (0.56 ,1.63)
		Switcher	1.56 (1.14 ,2.12)	1.61 (1.16 ,2.24)	1.55 (1.09 ,2.20)	1.20 (0.86 ,1.67)
Inpatient hospitalisation associated with type 2 diabetes mellitus§	17323	Initiator	1.76 (0.79 ,3.92)	1.68 (0.77 ,3.67)	1.97 (0.88 ,4.42)	1.25 (0.55 ,2.84)
		Switcher	1.29 (0.85 ,1.94)	1.07 (0.67 ,1.69)	1.36 (0.80 ,2.31)	1.40 (0.87 ,2.25)
Inpatient hospitalisation associated with anxiety/depression**	17324	Initiator	1.26 (0.57 ,2.79)	1.47 (0.70 ,3.08)	1.44 (0.66 ,3.18)	1.82 (0.86 ,3.89)
		Switcher	1.55 (0.96 ,2.52)	1.56 (0.92 ,2.65)	1.97 (1.09 ,3.54)	1.64 (0.93 ,2.89)

Table 50: Rate of occurrence of first serious adverse events associated with inpatient hospitalisation by FDC ICS/LABA (asthma patients ≥18 years old), split by initiators and switchers

* Selected potential confounders adjusted for: LAMA prescriptions in baseline period or index date, ICS only prescriptions in baseline period or index date, History of ischemic heart disease, History of hypertension, COPD diagnosis, Pain-relief medication prescriptions (categorised), Spacer prescription, Any baseline respiratory inpatient admissions, Baseline LRTI adverse events, Baseline COPD exacerbations

† Selected potential confounders adjusted for: LAMA prescriptions in baseline period or index date, ICS only prescriptions in baseline period or index date, History of ischemic heart disease, COPD diagnosis, Pain-relief medication prescriptions (categorised), Spacer prescription, Any baseline respiratory inpatient admissions, Baseline LRTI adverse events, SAMA prescriptions in baseline period or index date

‡ Selected potential confounders adjusted for: LAMA prescriptions in baseline period or index date, ICS only prescriptions in baseline period or index date, History of ischemic heart disease, History of hypertension, COPD diagnosis, Pain-relief medication prescriptions (categorised), Spacer prescription, Any baseline respiratory inpatient admissions, SAMA prescriptions in baseline period or index date, Beta-blocker prescriptions (categorised)

§ Selected potential confounders adjusted for: LAMA prescriptions in baseline period or index date, ICS only prescriptions in baseline period or index date, History of ischemic heart disease, History of hypertension, COPD diagnosis, Pain-relief medication prescriptions (categorised), Spacer prescription, Any baseline respiratory inpatient admissions, SAMA prescriptions in baseline period or index date, Beta-blocker prescriptions (categorised), Charlson Comorbidity Index (CCI)

** Selected potential confounders adjusted for: LAMA prescriptions in baseline period or index date, COPD diagnosis, Pain-relief medication prescriptions (categorised), Any baseline respiratory inpatient admissions

6.4.3.2 Patients aged ≥12 and <18 years with asthma

For patients aged ≥12 and <18 years with asthma, the incidence rate of inpatient hospitalisations associated with adverse events was too low for reporting for FP/FOR (Table 51). The incidence of deaths associated with adverse events was zero for FP/FOR. Therefore, no further analysis of inpatient hospitalisations or deaths associated with adverse events could be carried out for this subgroup.

		Cohort				
		FP/FOR n=227	FP/FOR Off-label n=21	DPI FP/SAL n=288	MDI FP/SAL n=760	BUD/FOR n=569
Inpatient hospitalisation associated with adverse events	Number of patients at risk (% in cohort)	64 (55%)	n<5	48 (32%)	194 (43%)	122 (41%)
	Median (IQR) Exposure time (months)	19.09 (15.26 ,25.82)	n<5	21.04 (14.83 ,25.56)	20.62 (15.74 ,27.50)	20.81 (16.76 ,29.70)
	Number who experienced event (%)	n<5	n<5	n<5	n<5	5 (4%)
	Total Exposure Time (years)	n<5	n<5	n<5	n<5	235
	Incidence Rate (95% CI) (100 person years)	NA	NA	NA	NA	NA
Death associated with adverse events	Number of patients at risk (% in cohort)	64 (55%)	n<5	48 (32%)	194 (43%)	122 (41%)
	Median (IQR) Exposure time (months)	19.35 (15.39 ,25.82)	n<5	21.04 (14.83 ,26.20)	20.70 (15.77 ,27.66)	20.81 (17.05 ,30.19)
	Number who experienced event (%)	0	n<5	0	0	0
	Total Exposure Time (years)	NA	n<5	NA	NA	NA
	Incidence Rate (95% CI) (100 person years)	NA	NA	NA	NA	NA

Table 51: Total serious adverse events associated with inpatient hospitalisation or death by FDC ICS/LABA (asthma patients aged ≥12 and <18 years)

6.4.3.3 Patients aged ≥4 and <12 years with asthma

For patients aged ≥4 and <12 years with asthma, the incidence rate of inpatient hospitalisations and deaths associated with adverse events was too low for reporting for FP/FOR (Table 52). Therefore, no further analysis of inpatient hospitalisations or deaths associated with adverse events could be carried out for this subgroup.

		Cohort			
		FP/FOR n=27	DPI FP/SAL n=149	MDI FP/SAL n=1047	BUD/FOR n=235
Inpatient hospitalisation associated with adverse events	Number of patients at risk (% in cohort)	n<5	33 (41%)	336 (55%)	57 (44%)
	Median (IQR) Exposure time (months)	n<5	19.78 (15.24 ,25.89)	22.21 (15.95 ,30.13)	22.05 (16.43 ,28.39)
	Number who experienced event (%)	n<5	0	13 (4%)	0
	Total Exposure Time (years)	n<5	NA	652	NA
	Incidence Rate (95% CI) (100 person years)	NA	NA	NA	NA
Death associated with adverse events	Number of patients at risk (% in cohort)	n<5	33 (41%)	336 (55%)	57 (44%)
	Median (IQR) Exposure time (months)	n<5	19.78 (15.24 ,25.89)	22.46 (16.34 ,30.55)	22.05 (16.43 ,28.39)
	Number who experienced event (%)	n<5	0	0	0
	Total Exposure Time (years)	n<5	NA	NA	NA
	Incidence Rate (95% CI) (100 person years)	NA	NA	NA	NA

Table 52: Total inpatient hospitalisations and deaths associated with adverse events by FDC ICS/LABA (asthma patients aged ≥4 and <12 years)

6.4.3.4 Patients with COPD only, definition 2

For patients with COPD, there was no evidence of a significant difference in incidence rate of inpatient hospitalisations associated with adverse events for FP/FOR versus licensed comparators (Table 53). The incidence rate of deaths associated with adverse events was too low for reporting. When considering specific adverse events associated with inpatient hospitalisations, there was no evidence of a significant difference in the incidence rate of COPD, LRTI, cardiac arrhythmias and ischaemia, type 2 diabetes mellitus and anxiety/depression associated inpatient hospitalisations for FP/FOR versus other licensed comparators (Table 54). Considering the rate of occurrence of the first inpatient hospitalisations associated with adverse events, there was no evidence of a significant difference between FP/FOR and the comparators before or after adjustment for confounders (Table 55). This remained the case after splitting by initiators and switchers (Table 56).

		Cohort			
		FP/FOR n=399	DPI FP/SAL n=3678	BUD/FOR n=2526	BDP/FOR n=1609
Inpatient hospitalisation associated with adverse events	Number of patients at risk (% in cohort)	67 (39%)	1126 (51%)	657 (47%)	312 (37%)
	Median (IQR) Exposure time (months)	19.25 (13.11 ,26.87)	18.91 (13.01 ,26.97)	18.20 (13.14 ,25.53)	15.62 (12.83 ,19.66)
	Number who experienced event (%)	22 (33%)	415 (37%)	205 (31%)	70 (22%)
	Total Exposure Time (years)	107	1839	1054	424
	Incidence Rate (95% CI) (100 person years)	20.49 (13.49 ,31.11)	22.57 (20.50 ,24.85)	19.44 (16.96 ,22.30)	16.50 (13.05 ,20.85)
Death associated with adverse event	Number of patients at risk (% in cohort)	67 (39%)	1126 (51%)	657 (47%)	312 (37%)
	Median (IQR) Exposure time (months)	23.26 (17.54 ,29.37)	23.82 (17.58 ,30.62)	22.41 (16.56 ,29.44)	18.17 (14.70 ,22.13)
	Number who experienced event (%)	n<5	44 (4%)	12 (2%)	n<5
	Total Exposure Time (years)	n<5	2321	1298	n<5
	Incidence Rate (95% CI) (100 person years)	NA	NA	NA	NA

Table 53: Total inpatient hospitalisations and deaths associated with adverse events by FDC ICS/LABA COPD definition 2)

		Cohort			
		FP/FOR n=399	DPI FP/SAL n=3678	BUD/FOR n=2526	BDP/FOR n=1609
Inpatient hospitalisation associated with COPD	Number of patients at risk (% in cohort)	67 (39%)	1126 (51%)	657 (47%)	312 (37%)
	Median (IQR) Exposure time (months)	19.25 (12.62 ,27.40)	18.60 (12.68 ,27.04)	18.33 (13.24 ,25.89)	15.77 (12.93 ,19.70)
	Number who experienced event (%)	19 (28%)	397 (35%)	182 (28%)	66 (21%)
	Total Exposure Time (years)	108	1817	1061	429
	Incidence Rate (95% CI) (100 person years)	17.63 (11.25 ,27.65)	21.85 (19.80 ,24.11)	17.15 (14.83 ,19.83)	15.39 (12.09 ,19.59)
Inpatient hospitalisation associated with lower respiratory tract infection	Number of patients at risk (% in cohort)	67 (39%)	1126 (51%)	657 (47%)	312 (37%)
	Median (IQR) Exposure time (months)	22.18 (16.72 ,29.37)	20.91 (15.05 ,28.98)	20.96 (15.11 ,28.12)	17.46 (13.98 ,21.32)
	Number who experienced event (%)	8 (12%)	232 (21%)	98 (15%)	29 (9%)
	Total Exposure Time (years)	127	2040	1199	475
	Incidence Rate (95% CI) (100 person years)	6.32 (3.16 ,12.64)	11.37 (10.00 ,12.93)	8.17 (6.70 ,9.96)	6.11 (4.25 ,8.79)
Inpatient hospitalisation associated with cardiac arrhythmias and ischemia	Number of patients at risk (% in cohort)	173 (100%)	2201 (100%)	1391 (100%)	844 (100%)
	Median (IQR) Exposure time (months)	7.39 (2.04 ,19.25)	10.35 (2.63 ,21.95)	9.49 (1.97 ,20.44)	8.57 (2.55 ,14.64)
	Number who experienced event (%)	14 (8%)	268 (12%)	148 (11%)	62 (7%)
	Total Exposure Time (years)	158	2460	1452	692
	Incidence Rate (95% CI) (100 person years)	8.84 (5.23 ,14.92)	10.89 (9.67 ,12.28)	10.19 (8.67 ,11.97)	8.96 (6.98 ,11.49)
Inpatient hospitalisation associated with type 2 diabetes mellitus	Number of patients at risk (% in cohort)	173 (100%)	2201 (100%)	1391 (100%)	844 (100%)
	Median (IQR) Exposure time (months)	7.85 (2.10 ,19.12)	11.47 (2.96 ,23.10)	10.15 (2.04 ,21.16)	8.84 (2.68 ,15.06)
	Number who experienced event (%)	11 (6%)	109 (5%)	67 (5%)	31 (4%)
	Total Exposure Time (years)	162	2596	1514	715
	Incidence Rate (95% CI) (100 person years)	6.81 (3.77 ,12.29)	4.20 (3.48 ,5.07)	4.43 (3.48 ,5.62)	4.33 (3.05 ,6.16)
Inpatient hospitalisation associated with anxiety/depression	Number of patients at risk (% in cohort)	173 (100%)	2201 (100%)	1391 (100%)	844 (100%)
	Median (IQR) Exposure time (months)	8.15 (1.97 ,19.68)	11.76 (3.09 ,23.52)	10.41 (2.14 ,21.22)	8.97 (2.74 ,15.34)
	Number who experienced event (%)	9 (5%)	87 (4%)	44 (3%)	18 (2%)
	Total Exposure Time (years)	165	2636	1530	727
	Incidence Rate (95% CI) (100 person years)	5.45 (2.83 ,10.47)	3.30 (2.67 ,4.07)	2.88 (2.14 ,3.86)	2.48 (1.56 ,3.93)

Table 54: Individual serious adverse events associated with inpatient hospitalisation by FDC ICS/LABA (COPD definition 2)

			Comparison (Hazard ratio, 95% CI)		
	Model	Number of observations in model	FP/SAL DPI vs FP/FOR	BUD/FOR vs FP/FOR	BDP/FOR vs FP/FOR
Inpatient hospitalisation associated with adverse events	Unadjusted	2162	1.12 (0.73 ,1.72)	0.97 (0.62 ,1.50)	0.80 (0.50 ,1.29)
	Adjusted for a priori confounders	1829	1.06 (0.66 ,1.72)	1.18 (0.67 ,2.06)	0.95 (0.54 ,1.68)
	Adjusted for a priori and selected potential confounders*	1829	0.98 (0.61 ,1.59)	1.13 (0.65 ,1.98)	0.93 (0.52 ,1.64)

Table 55: Rate of occurrence of first serious adverse events associated with inpatient hospitalisation by FDC ICS/LABA (COPD definition 2)

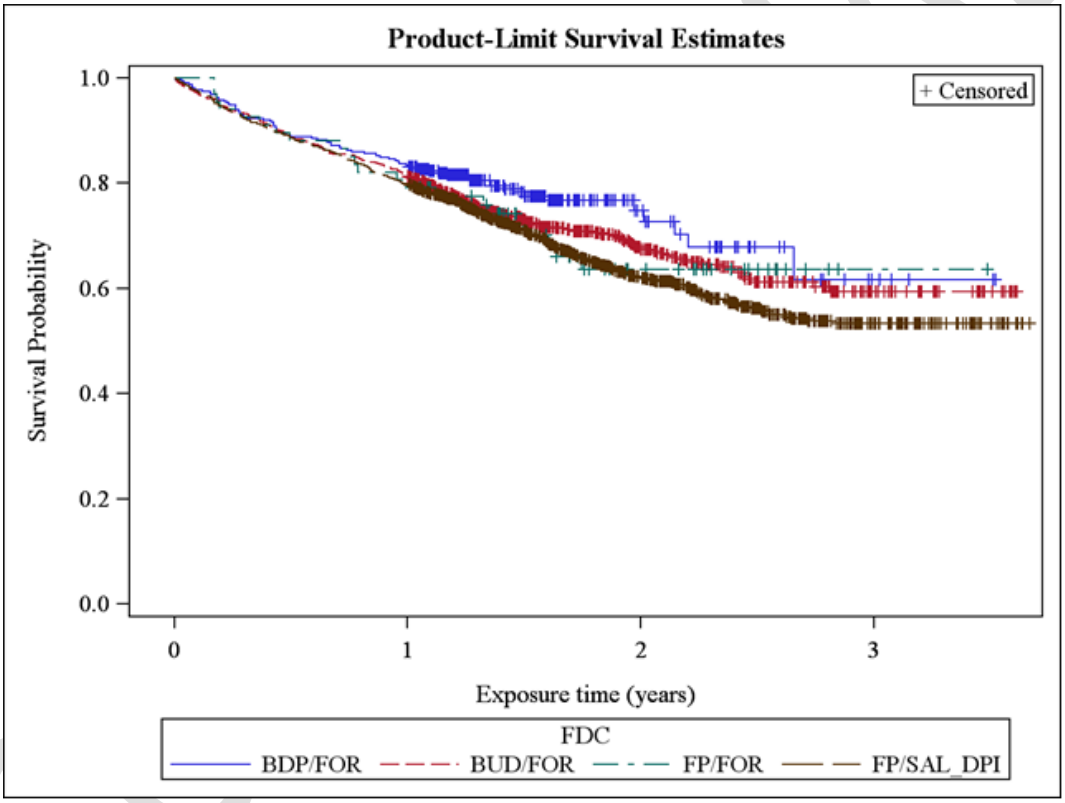

Figure 25: Adverse event associated inpatient hospitalisation evaluation by FDC ICS/LABA (COPD definition 2)

			Comparison (Hazard ratio, 95% CI)		
	Number of observations in model	Initiator or Switcher	FP/SAL DPI vs FP/FOR	BUD/FOR vs FP/FOR	BDP/FOR vs FP/FOR
Inpatient hospitalisation associated with adverse events†	1829	Initiator	1.09 (0.49 ,2.42)	1.30 (0.58 ,2.90)	1.09 (0.47 ,2.55)
		Switcher	0.94 (0.53 ,1.67)	1.00 (0.49 ,2.02)	0.82 (0.39 ,1.70)

Table 56: Rate of occurrence of first serious adverse events associated with inpatient hospitalisation by FDC ICS/LABA (COPD definition 2), split by initiators and switchers

* Selected potential confounders adjusted for: LAMA prescriptions in baseline period or index date, Any baseline respiratory inpatient admissions
† Selected potential confounders adjusted for: LAMA prescriptions in baseline period or index date, Any baseline respiratory inpatient admissions

6.4.3.5 "MART" regimen, definition 2

For patients on the "MART" regimen, the incidence of inpatient hospitalisations and deaths associated with adverse events was zero for FP/FOR (Table 57). Therefore, no further analysis of inpatient hospitalisations or deaths associated with adverse events could be carried out for this subgroup.

		Cohort		
		FP/FOR n=75	BUD/FOR n=246	BDP/FOR n=320
Inpatient hospitalisation associated with adverse events	Number of patients at risk (% in cohort)	24 (48%)	58 (41%)	72 (43%)
	Median (IQR) Exposure time (months)	18.02 (14.39 ,23.98)	20.53 (15.47 ,26.97)	19.50 (15.05 ,32.11)
	Number who experienced event (%)	0	5 (9%)	6 (8%)
	Total Exposure Time (years)	NA	106	134
	Incidence Rate (95% CI) (100 person years)	NA	NA	NA
Death associated with adverse events	Number of patients at risk (% in cohort)	24 (48%)	58 (41%)	72 (43%)
	Median (IQR) Exposure time (months)	18.02 (14.39 ,23.98)	21.59 (16.66 ,27.99)	20.88 (15.74 ,32.11)
	Number who experienced event (%)	0	n<5	0
	Total Exposure Time (years)	NA	n<5	NA
	Incidence Rate (95% CI) (100 person years)	NA	NA	NA

Table 57: Total inpatient hospitalisations and deaths associated with adverse events by FDC ICS/LABA (MART definition 2)

6.5 Other analyses

Not applicable

6.6 Adverse events and adverse reactions

As this was a health records based epidemiological study in which no causality information was available directly or through follow-up, there was no adverse reaction reporting. Safety analyses of adverse events and serious adverse events were only conducted and presented within the context of this study.

7 Discussion

7.1 Key results

The CPRD database contained a large number of patients aged ≥18 years with asthma prescribed FP/FOR (n=5727) and other licensed comparators (between 6865 and 10,941 for all licensed comparators). However, all other asthma subgroups revealed very low numbers of patients prescribed FP/FOR. For patients with asthma aged ≥12 and <18 years, 227 were prescribed FP/FOR on-label and only 21 off-label, compared to at least 288 patients in the licensed comparator groups. Similarly, for patients with asthma aged ≥4 and <12 years, only 27 patients were prescribed FP/FOR, compared to between 149 and 1047 patients in the licensed comparator groups. For patients with COPD only, there were 437, 399 and 350 patients prescribed FP/FOR for definitions 1, 2 and 3 respectively with comparator groups FP/SAL DPI and BUD/FOR containing at least 1434 patients each. Lastly for "MART" regimen subgroups, 249 and 75 patients were prescribed FP/FOR for definitions 1 and 2 respectively compared to between 246 and 698 patients for the licensed comparators. Overall, 5954 patients were prescribed FP/FOR on-label and 485 patients prescribed FP/FOR off-label (when considering patients with asthma aged ≥12 and <18 years, patients with asthma aged ≥4 and <12 years, definition 1 of COPD and definition 1 of MART regimen). There were also 623 patients prescribed FP/FOR who did not have a diagnosis of asthma or COPD recorded and therefore were not considered in the analyses.

The first co-primary objective of this study was to quantify the incidence of on and off-label prescribing for FP/FOR and other FDC ICS/LABA therapies within 36 months post FP/FOR launch. The prescribing rate was lower for FP/FOR than other FDC ICS/LABAs in all subgroups studied. For patients with asthma aged ≥18 years who were prescribed FP/FOR on-label, the prescribing rate was 13.85 per 1000 person years compared to 20.30, 27.75, 28.13 and 27.72 per 1000 person years for FP/SAL DPI, FP/SAL MDI, BUD/FOR and BDP/FOR respectively. For patients with COPD, the prescribing rate of FP/FOR was 10.18 compared to 100.04, 70.89 and 40.81 for FP/SAL DPI, BUD/FOR and BDP/FOR respectively. The prescribing rate was particularly low for patients with asthma aged ≥4 and <12 years (0.75 per 1000 person years) and patients with asthma aged ≥12 and <18 years who were prescribed FP/FOR on-label and off-label (4.84 per 1000 person years and 0.44 per 1000 person years respectively). Furthermore, of those prescribed FP/FOR, 80.8% were patients with asthma aged ≥18 years, 9.2% did not have a diagnosis of asthma or COPD and 6.2% had a diagnosis of COPD (definition 1). Less than 5% of patients prescribed FP/FOR were aged <18 years with asthma.

The second co-primary objective of this study was to evaluate adverse events in patients initiating or switching to FP/FOR and other FDC ICS/LABA therapies for both licensed and off-label groups within 36 months post FP/FOR launch.

For patients with asthma aged ≥18 years, for the majority of incidence rates of adverse events and rate of occurrence of first adverse event was similar between FP/FOR and the licensed comparators. In the total cohort, where the rates of occurrence of first events differed, this was in favour of FP/FOR versus the comparators (incidence rate of cardiac arrhythmia or ischaemia, hyperglycaemia, cataracts and pneumonia was lower for FP/FOR than DPI FP/SAL; incidence rate of LRTI and "any new adverse event" was lower for FP/FOR than DPI FP/SAL and MDI FP/SAL; rate of occurrence of first record of anxiety/depression and "any new adverse events" was higher for all comparators than FP/FOR; rate of occurrence of first LRTI was higher for FP/SAL DPI and BUD/FOR than FP/FOR; rate of occurrence of first oral candidiasis record was higher for BUD/FOR and BDP/FOR than FP/FOR). The only results where a higher rate of occurrence of first adverse event for FP/FOR was observed was within the sub-analysis (split by initiators and switchers) for two adverse events in the switching group (higher rate of occurrence of first dysphonia record for FP/FOR than FP/SAL DPI; higher rate of occurrence of first other local oral adverse events for FP/FOR than BUD/FOR); there were no differences between FP/FOR and the other comparators for these adverse events in these subgroups. Considering serious adverse events, FP/FOR was always similar or better than the comparators in all studied. Rate of occurrence of first inpatient hospitalisation associated with an adverse event was higher for FP/SAL MDI and BUD/FOR than FP/FOR. The rate of occurrence of first cardiac arrhythmia and ischemia associated inpatient hospitalisation and anxiety/depression associated inpatient hospitalisation was higher for several of the comparators than for FP/FOR. These results appeared to be driven by the switchers, particularly for cardiac arrhythmia and ischaemia associated inpatient hospitalisations. However, the particularly high proportion of comorbid COPD in the FP/SAL DPI group should be considered alongside these results, although adjustment for this confounder was included in the models assessing rate of occurrence of first event.

For patients with COPD, the number of patients prescribed FP/FOR was fairly low (n=399) but numbers allowed for some analyses to be conducted. There was no difference in the total cohort for incidence rate or rate of occurrence of first event of those adverse events studied, or numbers were too low to allow analysis. However, the sub-analysis split by initiators and switchers suggests that the rate of occurrence of first COPD exacerbation was higher for

FP/FOR than FP/SAL DPI in those that switched FDC ICS/LABA, although this difference was not seen when compared with BUD/FOR or BDP/FOR and the reverse was observed for initiators when compared with BUD/FOR and BDP/FOR. This requires further investigation to compare the characteristics of FP/FOR and FP/SAL DPI switchers. It may be that as FP/FOR is a new product, patients who switch to this are those that have failed on or had trouble with all the other existing inhalers on the market and this may explain the increased COPD exacerbations in this group compared to FP/SAL DPI. Furthermore, this sub-analysis suggests that rate of occurrence of first cardiac arrhythmia or ischaemia was higher for FP/FOR than FP/SAL DPI, although again this difference was not observed for the other comparators and was based on a small number of events and patients in the FP/FOR group (n=15 events from 164 patients). As this is a combined endpoint, it would be worth further analysis to ascertain if this result is driven by the arrhythmias or ischaemia.

Three of the subgroups studied, for which FP/FOR was off-label, in all but two doses for patients with asthma aged ≥12 and <18 years, the number of patients to be studied in the FP/FOR groups was low. For patients with asthma aged ≥12 and <18 years, the number of FP/FOR patients in the on-label and off-label groups were 227 and 21 respectively. No difference was observed in the incidence rate or rate of occurrence of first event for any adverse event studied, or numbers were too low to allow analysis. Similarly, when considering adverse events associated with inpatient hospitalisation less than five events were observed and there were no deaths associated with adverse events reported for FP/FOR. Unsurprisingly, for patients with asthma aged ≥4 and <12 years, as above, the number of patients in the FP/FOR group was low (n=27), as use in this age group is off-label. For each adverse event studied and for both inpatient hospitalisations and deaths associated with adverse events, the number of events was less than five or zero. For patients prescribed FDC ICS/LABAs as per the MART regimen, the results were similar to those of patients with asthma aged ≥12 and <18 years whereby, no difference was observed in the incidence rate for any adverse event studied, or numbers were too low to allow analysis. There were no inpatient hospitalisations or deaths associated with adverse events in this subgroup.

The secondary objective was to describe demographic, medication and disease-related characteristics for patients prescribed FP/FOR and other FDC ICS/LABA therapies for both licensed and off-label groups. Patients were broadly similar between FDC ICS/LABA treatments within each subgroup. However, across all subgroups, FP/FOR patients were more likely to be switchers rather than initiators of their FDC ICS/LABA therapy for all subgroups. For example, patients with asthma aged ≥18 years, 67% of FP/FOR patients had prescription

of an FDC ICS/LABA prior to the index date compared to 31-58% of comparators and for patients with COPD, 52% of FP/FOR patients had prescription of an FDC ICS/LABA prior to the index date compared to 31-46% of comparators. The other main differences noted were that in the patients with asthma aged ≥18 years, the FP/SAL DPI group were older, with more severe disease and more comorbid COPD, ischaemic heart disease and hypertension. This group also received higher doses of their FDC ICS/LABA at index data and more LAMA. They experienced more exacerbations and attended more GP consultations and required more inpatient admissions and outpatient attendances. For the patients with COPD, those that were prescribed FP/SAL DPI were prescribed a higher dose of FDC ICS/LABA at the index date and were also more likely to be prescribed LAMA. For this subgroup, the FP/FOR group were less likely to have outpatient attendances or inpatient hospitalisations. Lastly, in the MART subgroup, patients prescribed FP/FOR were less likely to have had exacerbations in the year prior. Data availability, in terms of prior records and length of follow-up, was similar in all groups across all subgroups, except for patients with asthma aged ≥12 and <18 years where length of follow-up was shorter for FP/FOR than the other groups.

A substantial proportion of patients (n=11,187, 16%) did not have either a COPD or asthma diagnosis recorded by the time of their initiation or switch to FDC ICS/LABA (index date). The majority were initiators (94%) and had no further or only one further prescription of the FDC ICS/LABA in the outcome period (95%). A limited amount of patients had codes referring to monitoring or management of asthma or COPD which were not included in our code lists as the diagnostic Read code lists were based on QOF to identify asthma and COPD diagnosis. QOF is part of the UK national quality improvement initiative and pay-for-performance scheme, ensuring good reporting of these diseases. Furthermore, a very small proportion of these patients without a diagnosis were prescribed FP/FOR (6%), with the majority being prescribed FP/SAL (43%) or BUD/FOR (35%). We assume that this was a trial of treatment for patients where GPs were unsure of their diagnosis or wanted to see if treatment could improve outcomes, despite a given diagnosis.

In terms of existing studies, FP/FOR has been found to be safe at the recommended doses in all the major clinical trials conducted so far with any adverse events observed being mild [9]. In a 12 month study of FP/FOR in mild to moderate asthmatics aged ≥12 years treated with FP/FOR, the most common adverse events reported were nasopharyngitis, dyspnoea, pharyngitis and headache and the majority were mild to moderate events [10]. Only 3% of adverse events were considered study drug-related and none of the serious adverse events were considered study drug related. It also suggested that when used at recommended doses,

the risk of osteoporosis, growth retardation, cataracts or hypothalamic-pituitary axis suppression is minimal [11]. These findings broadly agree with this study as adverse events were not increased for FP/FOR compared to other FDC ICS/LABA treatments for patients with asthma, with the exception of dysphonia and other local oral adverse events for initiating patients ≥18 years.

A recent RCT comparing FP/FOR versus FP/SAL in children with asthma aged 4-12 years for 12 weeks found no notable differences in safety between the two treatments and no safety concerns were identified with long term FP/FOR therapy [12]. Similarly, no safety concerns were observed for this subgroup, although a very small group of FP/FOR patients were being studied in this subgroup (n=27).

A phase III RCT (the EFFECT trial) is planned to investigate the safety of FP/FOR in patients with COPD over a 52 week period so currently we cannot compare our results for this subgroup [13]. No studies of the use of FP/FOR in the MART regimen were identified, so again, we could not assess our results in the context of other studies for these subgroups of patients.

7.2 Limitations

The analyses were limited by low numbers of patients prescribed FP/FOR, particularly in certain subgroups such as children with asthma aged ≥4 and <18 years and patients on the MART regimen. Furthermore, due to this study being conducted with use of retrospective data from a database we are unable to assess the relatedness of adverse events to the FDC ICS/LABAs.

We acknowledge that mild adverse events are unlikely to be reported by a patient to their GP (e.g. headache) so this study focuses on adverse events which were more severe and likely to be recorded within electronic health records either at the GP or in secondary care. However, some of the adverse events covered here may also not be reported by the patient to their GP but we did not think there would be differential recording between treatment groups.

Although acceptable for the majority of models, there was some evidence that the proportional hazard assumption was not upheld, in particular for “any new adverse events” for the ≥12 and <18 year old asthma patients. For this comparison, the incidence rate was slightly higher in the FP/FOR cohort, though not significantly so.

Finally, as the data source selected for this study is a primary care database there was some missing data, where certain variables were not recorded in the course of routine care. The percentage of missing data was reported to show the representativeness of the summary statistics. Imputation of FDC ICS/LABA dosing instructions may have introduced bias but this data was reported before and after imputation for comparison and this variable was only used as a confounder in the adjusted models.

7.3 Interpretation

For all the adverse events considered FP/FOR was similar or better than the licensed comparators studied, when the subgroups were analysed as a whole (i.e. not split by initiators and switchers). Furthermore, there was no increase observed in serious adverse events for FP/FOR versus the licensed comparators in any of the subgroups studied. In fact, there is evidence to support that FP/FOR may be better than some of its licensed comparators in terms of inpatient hospitalisations associated with adverse events, specifically cardiac ischaemia and arrhythmia and anxiety and depression in patients with asthma aged ≥18 years.

The subgroup analyses, where patients were split by initiation status, suggest that there may be an increase in exacerbations and cardiac arrhythmias and ischaemia in patients with COPD for FP/FOR compared to FP/SAL DPI, for switchers and initiators respectively. However, this was not observed when comparing to BUD/FOR or BDP/FOR. There also may be an increase in dysphonia and other local oral adverse events in patients with asthma aged ≥18 years initiating on FP/FOR versus those initiating FP/SAL DPI and BUD/FOR respectively. However, this was only observed when results were split by initiators and switchers so further investigations would need to consider this and should also consider splitting the analysis of cardiac events into ischaemia and arrhythmia.

A substantial proportion of patients who were prescribed an FDC ICS/LABA in this study did not have either a COPD or asthma diagnosis. This may indicate a frequent practice of trial of medication being given to patients without a confirmed diagnosis, which warrants further investigation. It should be noted that this practice was low for FP/FOR with the majority being prescribed FP/SAL or BUD/FOR. In general, the prescribing rate was lower for FP/FOR than other FDC ICS/LABAs in all subgroups studied. In particular, the majority of prescribing for FP/FOR was for patients with asthma aged ≥18 years and prescription of FP/FOR was lowest for patients aged <18 years with asthma.

7.4 Generalisability

We propose that the results are widely generalizable to the UK as the data was taken from a UK database (CPRD) which has previously been shown to be generally representative of the UK population [14]. However, although CPRD coverage is around 6.9% of the UK population, this research should be validated in other databases [15].

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9 Other information

Not applicable