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 18-months post launch

Date: 14th July 2016

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EU PAS Register No: ENCEPP/SDPP/12330

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Title	Off-label prescribing and adverse events for fluticasone propionate / formoterol
Subtitle	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 18-months post launch
Protocol version number	1.0
EU PAS registration number	ENCEPP/SDPP/12330
Medicinal product	Flutiform ® (fluticasone propionate / formoterol)
Marketing authorisation number	PL 16950/0167 - 0169
Marketing authorisation holder	Napp Pharmaceuticals Limited Cambridge Science Park Milton Road Cambridge United Kingdom CB4 0GW
Country of study	United Kingdom
Milestones	EU PAS registration: 08/02/2016 Dataset received from CPRD: 08/04/2016 Interim report (stage 1): 08/06/2016 Final report (stage 1): 08/07/2016
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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
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

Subtitle: 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 18-months post launch

Date: 30/06/2016

Author: Research in Real Life

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 will characterise 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 1: 18 months post-launch. The results for Stage 2 (36 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 18 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 18 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 18 months post FP/FOR launch

1.5 Study design

This study was a descriptive, historical cohort database study of patients initiating on FP/FOR and other FDC ICS/LABA therapy on or after 1st January 2012 to 18 months post-launch of FP/FOR. The rate per 1000 person years of patients prescribed each FDC ICS/LABA was estimated for (a) the total population in the CPRD, (b) patients aged ≥18 years with asthma in the CPRD, (c) patients aged 12-18 years with asthma in the CPRD, (d) patients aged 4-11 years with asthma in the CPRD and (e) patients with COPD and no asthma in the CPRD. The first occurrence of an adverse event and also multiple occurrences of adverse events per patient was evaluated

1.6 Setting

The extracted cohort consists of all patients ≥4 years old captured in CPRD during the period from 1st January 2012 until 24th March 2014 (i.e. 18-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 evaluation of prescribing incidence considers those patients who initiated or switched FDC ICS/LABA during the 18 months post UK launch of FP/FOR (25th September 2012 – 24th March 2014). The evaluation of adverse events and patient characteristics considers

those patients who initiated or switched FDC ICS/LABA during the period from 1st January 2012 until 24th March 2014. For each patient, the initiation on FDC ICS/LABA or first switch to a different FDC ICS/LABA during the study period was considered as the index date.*

The analyses considered licensed and off-label subgroups which were patients aged ≥18 years with asthma, patients aged ≥ 12 years and <18 years with asthma, pediatric asthma patients 4–11 years, 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 Seretide DPI, Seretide MDI, Symbicort Turbohaler and Fostair MDI/NEXThaler.

This study was a preliminary study to evaluate all patients in the CPRD initiating on FP/FOR in the 18 months post FP/FOR launch. The feasibility count from CPRD GOLD identified 3,774 research quality (acceptable) patients with a first prescription for FP/FOR during the period 1st January 2012 to 31st March 2014 whilst registered at a research quality (up to standard) practices. Approximately 55% (~2000) of these patients were estimated to be eligible for linkage to HES and ONS.

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.

* Initiation and switch refer to an initiation or switch in FDC ICS/LABA device and not a change in dose or dosing instructions on the same device

1.9 Results

The CPRD database contained a large number of patients aged ≥18 years with asthma prescribed FP/FOR (n=2127) and other licensed comparators (n>7000 for all licensed comparators). However, all other subgroups revealed very low numbers of patients prescribed FP/FOR. For patients with asthma aged ≥12 and <18 years, 77 were prescribed FP/FOR on-label and only 8 off-label, compared to at least 334 patients in the licensed comparator groups. Similarly, for patients with asthma aged 4-11 years, only 12 patients were prescribed FP/FOR, compared to between 150 and 971 patients in the licensed comparator groups. For patients with COPD only, there were 193, 143 and 129 patients prescribed FP/FOR for definitions 1, 2 and 3 respectively with comparator groups FP/SAL DPI and BUD/FOR containing at least 2000 patients each. Lastly for "MART" regimen subgroups, 66 and 6 patients were prescribed FP/FOR for definitions 1 and 2 respectively compared to between 66 and 379 patients for the licensed comparators. Overall, 2204 patients were prescribed FP/FOR on-label and 279 patients prescribed FP/FOR off-label (when considering patients with asthma aged ≥12 and <18 years, patients with asthma aged 4-11 years, definition 1 of COPD and definition 1 of MART regimen). There were also 272 patients prescribed FP/FOR who did not have a diagnosis of asthma or COPD and therefore were not considered in the analyses. The duration of exposure for each adverse event was also lower for FP/FOR versus the licensed comparators in the majority of analyses and subgroups.

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 between half to a third of that of the comparators (4.85 per 1000 person years for FP/FOR compared to 12.10, 16.85, 15.53 and 10.74 per 1000 person years for FP/SAL DPI, FP/SAL MDI, BUD/FOR and BDP/FOR respectively). For patients with COPD, the prescribing rate was less than 10% that of its on-label comparators, with the exception of BDP/FOR (4.66 per 1000 person years for FP/FOR compared to 71.78, 44.08 and 8.27 per 1000 person years for FP/SAL DPI, BUD/FOR and BDP/FOR respectively. The prescribing rate was particularly low for patients with asthma aged 4-11 years and patients with asthma aged 12-17 years who were prescribed FP/FOR off-label (0.33 per 1000 person years and 0.17 per 1000 person years respectively).

We observed a higher rate of patients experiencing LRTIs, in patients with asthma aged 12-18 years (16.0 per 100 person years for FP/FOR prescribed on-label versus 6.4-8.3 per 100 person years for licensed comparators) and patients with COPD (50.9 per 100 person years

for FP/FOR versus 36.3-42.0 per 100 person years for licensed comparators, for definition 1 of COPD), although rates of patients with occurrence of LRTI were less than double that of FP/SAL DPI and MDI for both subgroups. Furthermore, the time to first event was not significantly different between FP/FOR and licensed comparators for patients with COPD and could not be calculated for patients with asthma aged 12-18 due to low numbers of events. Rates of patients experiencing hyperglycaemia for those with no hyperglycaemia or type 2 diabetes in the baseline period were higher for FP/FOR than other FDC ICS/LABAs for patients with COPD definition 1 only, although these rates were less than double the rates for FP/SAL DPI and BUD/FOR (7.7 per 100 person years for FP/FOR versus 4.8, 4.6 and 3.0 per 100 person years for FP/SAL DPI, FP/SAL MDI and BDP/FOR respectively).

For patients with at least 1 year of baseline and 1 year of outcome period and also for those at least 6 months of baseline and 6 months of outcome period, there were <5 patients in the FP/FOR group and so annualised rates of COPD exacerbations could not be compared. For all other adverse events considered, rates were similar, too low for reporting (n<5) or zero for FP/FOR compared to other FDC ICS/LABAs.

The annualised rate of patients with adverse events that result in hospitalisation were broadly similar, too low for reporting (n<5) or zero for FP/FOR compared to other FDC ICS/LABAs in all subgroups. Hospitalisations relating to COPD were slightly higher for patients prescribed FP/FOR compared to other FDC ICS/LABA treatments for definitions 2 and 3 of COPD (35.3 per 100 person years for FP/FOR versus 20.8-28.6 per 100 person years for comparators for definition 2 and 37.6 per 100 person years for FP/FOR versus 21.1-28.3 per 100 person years for comparators for definition 3), although this difference was not observed for COPD definition 1. For all other serious adverse events presented, patients prescribed FP/FOR had similar rates of SAEs to FDC ICS/LABA comparators. For all subgroups, adverse events causing death were low (n<5) or zero for FP/FOR.

Patients were broadly similar between FDC ICS/LABA treatments within each subgroup. However, FP/FOR patients were more likely to be switchers rather than initiators of their FDC ICS/LABA therapy for all subgroups except patients with asthma aged 4-11 years. For example, patients with asthma aged ≥18 years, 66.4% of FP/FOR patients had prescription of an FDC ICS/LABA prior to the index date compared to 23.4-49.3% of comparators and for patients with COPD (definition 1), 57% of FP/FOR patients had prescription of an FDC ICS/LABA prior to the index date compared to 22.1-38.1% of comparators.

1.10 Discussion

The analyses were limited by low numbers of patients prescribed FP/FOR, particularly in certain subgroups such as children with asthma aged 4-11 years and 12-17 years and patients on the MART regimen. Additionally, the outcome period available for FP/FOR patients was often substantially shorter than that of its comparators, likely due to the period of study being post-launch therefore being limited by the rate of uptake after launch. The limited the study period over which adverse events could be assessed and for the COPD exacerbations analysis, limited the number of patients to be included in the analysis. 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.

Our interpretation of the results is that there are no safety signals of concern observed, within the context of the exploratory nature of the study. In the majority of adverse events studied, rates of events were low and in no instances were the rates of adverse events for FP/FOR more than double those of other FDC ICS/LABA treatments. Stage 2 will be conducted to confirm these results using a fully adjusted analysis to make direct comparisons between FP/FOR and other FDC ICS/LABA therapies and as it will be conducted over the 36 months post launch we envisage a longer observation period. Additionally, the patient characterisation revealed that there may be differences between the treatment groups at baseline that need to be accounted for in the analysis during stage 2 of the study.

1.11 Marketing authorisation holder

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1.0 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 will characterise 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 1: 18 months post-launch. The results for Stage 2 (36 month evaluation) have been described in a separate report.

2 Research question and objectives

2.1 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.

2.2 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 18 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 18 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 18 months post FP/FOR launch

3 Amendments and updates to the protocol

A protocol was submitted for this stage of the study to ISAC in order to be granted CPRD data.

We have made one amendment to the protocol and statistical analysis plan. 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, we have changed the analysis of COPD exacerbations to require twelve months of follow-up data and we have also considered a less stringent requirement of six months data, as is often judged clinically appropriate.

4 Research methods

4.1 Study design

This study was a descriptive, historical cohort database study of patients initiating on FP/FOR and other FDC ICS/LABA therapy on or after 1st January 2012 to 18 months post-launch of FP/FOR. The rate per 1000 person years of patients prescribed each FDC ICS/LABA was estimated for (a) the total population in the CPRD, (b) patients aged ≥18 years with asthma in the CPRD, (c) patients aged 12-18 years with asthma in the CPRD, (d) patients aged 4-11 years with asthma in the CPRD and (e) patients with COPD and no asthma in the CPRD. The first occurrence of an adverse event and also multiple occurrences of adverse events per patient was evaluated

4.2 Setting

The extracted cohort consists of all patients ≥4 years old captured in CPRD during the period from 1st January 2012 until 24th March 2014 (i.e. 18-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)].

4.3 Subjects

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. initiated a new FDC ICS/LABA during the study period, having been prescribed an FDC ICS/LABA previously). Each patient only appears 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 incidence considers those patients who initiated or switched FDC ICS/LABA during the 18 months post UK launch of FP/FOR (25th September 2012 – 24th March 2014). The evaluation of adverse events and patient characteristics considers those patients who initiated or switched FDC ICS/LABA during the period from 1st January 2012 until 24th March 2014. For each patient, the initiation on FDC ICS/LABA or first switch to a different FDC ICS/LABA during the study period was considered as the index date. 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 will be included in this category
- Patients aged ≥ 12 years and <18 years with asthma
- Paediatric asthma patients 4–11 years
- 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 (most recent value recorded at any time)†
    - Definition 3) definition 2 plus blood eosinophil count ≤0.4x109/L (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 indication in the UK.

* Considered for patient characterisation and adverse events analyses only

(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

(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) Paediatric asthma patients 4–11 years

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
† This analysis will exclude anyone <31 years of age
‡ Licensed use of Fostair MDI 100/6 in COPD from April 2014
§ Licensed use of Fostair NEXThaler 100/6 in COPD from December 2015
** To be investigated in patients with asthma (+/- comorbid COPD) aged ≥18 years as comparator drugs only licensed for MART in this cohort

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

4.4 Variables

Patient characterisation will be 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 PEF† and percent predicted 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).

‡ This study did not have a baseline period prior to the index date (initiation with FDC ICS/LABA) but data may be available prior to initiation for assessment of these variables

- 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 will be 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 asthma/COPD (as appropriate for the subgroup) hospital outpatient attendances (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 lower respiratory hospital outpatient attendances**Error! Bookmark not defined.** (year prior to the index date)
- Number of lower respiratory 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

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 will be classified as such. Hospital admission and emergency room attendance will be 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 assumed to be the same event, and were classified as such. Hospital admission and emergency room attendance will be 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

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 and 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. Decrease in 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

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):

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 will be classified as such

† Events within four weeks of each other are assumed to be the same event, and will be 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)

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

(i) Result in death

(ii) Require inpatient hospitalisation

Serious adverse events will be identified from primary and secondary cause ICD-10 codes linked to inpatient hospitalisations and deaths occurring in the cohort.

4.5 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 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; 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. 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 related to an adverse event 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 related to an adverse event. CPRD estimated that 55% of the patients in CPRD who meet the inclusion and exclusion criteria for this study would be eligible for linkage.

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 18 month period post launch of FP/FOR (25th September 2012 to 24th March 2014). 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 18 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 was as follows. 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 RiRL'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.

4.6 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 we have reported this and considered rates of adverse events in order to account for any differences. Misclassification may have occurred but as the data used was historical and routinely recorded we did not expect any differential misclassification between groups.

4.7 Study size

This study was a preliminary study to evaluate all patients in the CPRD initiating on FP/FOR in the 18 months post FP/FOR launch. The feasibility count from CPRD GOLD identified 3,774 research quality (acceptable) patients with a first prescription for FP/FOR during the period 1st January 2012 to 31st March 2014 whilst registered at a research quality (up to standard) practices. Approximately 55% (~2000) of these patients were estimated to be eligible for linkage to HES and ONS.

4.8 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.

4.9 Statistical methods

Data preparation 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 was be checked and inaccurately coded data labelled as missing). Skewed data were categorised, as appropriate.

Patient characterisation was carried out as follows:

- Patients were characterised according to variables listed in section Variables4.4
- Summary statistics were produced for patients prescribed FP/FOR and other FDC ICS/LABA therapies, for the licensed/off-label subgroups
- Variables measured on the interval or ratio scale were summarised using the following summary statistics: number of non-missing records (n), mean/median/standard deviation (SD)/interquartile range (IQR) (as appropriate), minimum and maximum
- Categorical data was summarised as the number and percentage of patients in each category
- Treatment arms were compared using F-test, Kruskal Wallis or Chi-squared test, as appropriate
- Patient characterisation analyses, which require data on hospital-related events, were performed only for the cohort who have linkage to HES, using data on hospitalisations from HES

Table 1 summarises the statistical tests used in the analysis.

Test	Use
Kruskal Wallis test	Non-parametric test to compare impact of two or more groups on a continuous outcome.
Chi-squared test	Tests for the association between 2 categorical variables (data presented in contingency tables).

Table 1 Summary of Statistical Tests

Prescription incidence evaluation was carried out as follows:

- The rate per 1000 person years of patients prescribed each FDC ICS/LABA was estimated for (a) the total population in the CPRD, (b) patients aged ≥18 years with asthma in the CPRD, (c) patients aged 12-18 years with asthma in the CPRD, (d) patients aged 4-11 years with asthma in the CPRD and (e) patients with COPD and no asthma in the CPRD (definition 1)
- 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 from CPRD for each subgroup over the time period of interest

Adverse events evaluation was carried out as follows.
First occurrence of an adverse event per patient:

- Annualised rate of adverse events
    - Annualised rate of each adverse event per 100 patients = $\frac{Number\ of\ patients\ having\ adverse\ event\ X}{Total\ duration\ of\ exposure\ of\ all\ patients\ in\ subgroup\ who\ are\ eligible\ for\ analysis} * 100$
    - This was calculated for each FDC ICS/LABA within the licensed/off-label subgroups and conducted for each type of adverse event (listed in section K)
    - When evaluating COPD exacerbations, lower respiratory tract infections, pneumonia, pulmonary embolism and tuberculosis, the number of adverse events after the index date was counted regardless of the number of events before the index date and therefore annualised rates of adverse events were evaluated both for the year prior to the index date and the period post the index date. The exception to this was for COPD exacerbations in which the same follow-up period requirement that was applied to the outcome was applied to the baseline (i.e. requirement of 6 month or 12 month data) for those patients that were eligible for the outcome analysis
    - For all other adverse events (vi-xix), the occurrence of adverse events after the index date was only considered for those patients without occurrence of the adverse event in the year prior to the index date and therefore annualised rates of adverse events were evaluated only in the period post the index date
    - Any adverse event that occurred on index date was classed as occurring in baseline
    - The duration of exposure for each adverse event was defined as the time from index date to time of leaving the cohort, which was defined as the earliest of
        - the time of the first adverse event of interest
        - the end of their available records (classified as censored)
        - at the end of the 18 month study period (24th March 2014) (classified as censored)
        - if they die (classified as censored)
        - the end of exposure to medication (classified as censored) 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 combination)
- Time to adverse event
    - This was conducted for the following adverse events only: COPD exacerbations, lower respiratory tract infections, pneumonia, pulmonary embolism and tuberculosis

- Kaplan-Meier (KM) survival curves were plotted and log-rank test calculated to compare FP/FOR versus other FDC ICS/LABAs in the subgroup.
- Hazard ratios (and their 95% confidence intervals) of FP/FOR versus each FDC ICS/LABA will be calculated using Cox proportional hazards regression test if the proportional hazard assumption is met. Hazard ratios are only presented when there are 10 or more events in the FP/FOR cohort
- In this analysis, patients left the cohort at the time of their first adverse event (i.e. for analysis of COPD exacerbations, patients left the cohort when they experienced a COPD exacerbation and so each patient either experienced none or one of these events; patients did not leave the cohort in this analysis if they experience other adverse events). Additionally, patients left the cohort at the end of their available records, at the end of the 18 month study period (24th March 2014), if they died or at the end of exposure to medication. As described in section K, the following were considered as the end of exposure to medication; 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 combination).

Multiple occurrences of an adverse event per patient:

- This was conducted for the following adverse events only: COPD exacerbations, lower respiratory tract infections, pneumonia and all new events
- Events were assumed to be the same event if they occurred within two weeks of each other for COPD exacerbations, within six weeks for LRTIs and within four weeks for pneumonia
- "All new events" were defined as the event (from the list in section 4.4) occurring for the first time ever in the patient's record after initiation of FDC ICS/LABA. For each patient, only one per each adverse event i-xix was counted, therefore a maximum of 19 new adverse events per patient was evaluated
- Mean/median (as appropriate) number of each adverse event per patient and mean/median (as appropriate) duration of exposure was calculated for each FDC ICS/LABA within the licensed/off-label subgroups.
- The duration of exposure for each event was defined as the time from index date to time of leaving the cohort, which was defined as the earliest of:

* Assuming last prescription was for 30 days of FDC ICS/LABA (exposure period was adjusted accordingly if >30 days prescribed at one time), i.e. end of exposure to FDC ICS/LABA +30 days

- the end of their available records (classified as censored)
- at the end of the 18 month study period (24th March 2014) (classified as censored)
- if they die (classified as censored)
- the end of exposure to medication (classified as censored) 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 combination)

Serious adverse events evaluation was carried out as follows:

- All serious adverse events, representative of those listed in section 4.4 were identified and the annualised rate of patients experiencing any of these serious adverse events combined per 100 patients calculated for each FDC ICS/LABA within the licensed/off-label subgroups (split by those resulting in inpatient hospitalisation and death)
- If appropriate, the annualised rate of each serious adverse event individually (listed in section 4.4) was calculated for each FDC ICS/LABA within the licensed/off-label subgroups (split by those resulting in inpatient hospitalisation and death)
- The serious adverse events analyses, which require data on hospital-related events and deaths, were performed for the cohort who have linkage to HES/ONS, using data on inpatient hospitalisations and deaths from HES/ONS
- All serious adverse events during the outcome period were reported regardless of prior serious adverse events

Stage 1 was exploratory and descriptive and therefore confounding was not be directly addressed in this stage. Confounding will be explored and adjusted for in stage 2 (36 months post-launch analysis). Each analysis was stratified according to the initiation status i.e. whether the patient was initiating on their first FDC ICS/LABA or switching to a different FDC ICS/LABA, if possible (for adverse events analysis and patient characterisation only).
We reported the percentage of missing data to show the representativeness of the summary statistics. Missing data was not predicted 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, we did not foresee that there would be any differential misclassification between the groups to be compared.

As this was a study based on secondary use of data, safety monitoring and safety reporting, 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. Additionally, as per CPRD policy, no cells were presented which contain fewer than five events.

All statistical analyses were carried out using STATA version 14 (StataCorp, College Station, TX: StataCorp LP) and SAS version 9.3 (SAS Institute, Cary, NC). Statistically significant results were defined as $p<0.05$.

4.10 Quality control

As mentioned in section 4.5, 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. Additionally, as mentioned in section 4.9, 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 was be checked and inaccurately coded data labelled as missing). Statistical results were confirmed by a second statistician using independently created code for at least 15% of the outcomes.

5 Results

5.1 Participants

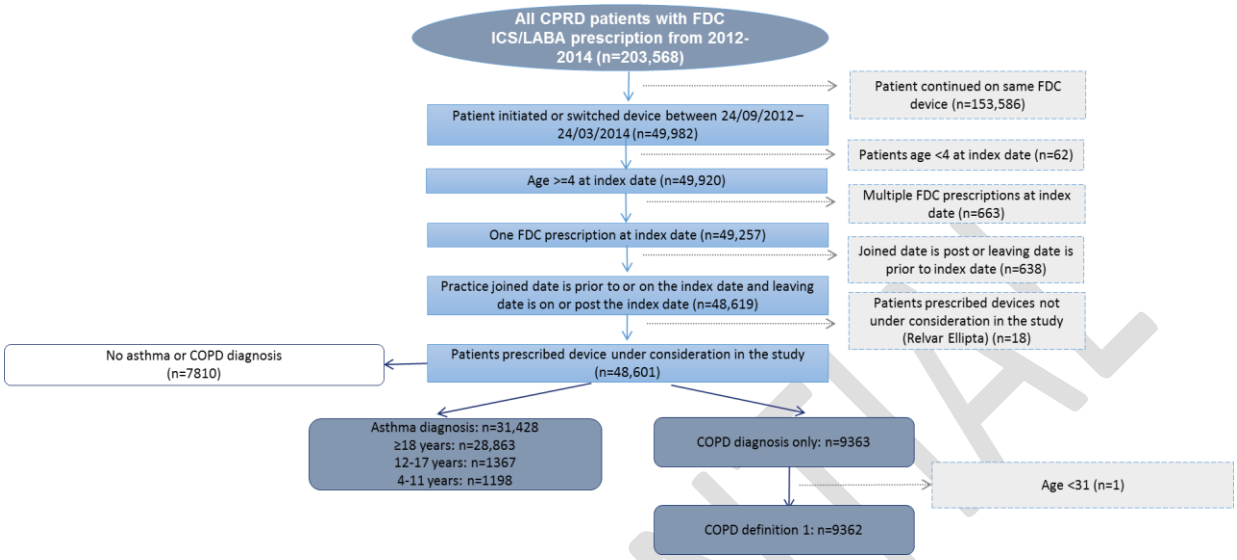

Figure 1 Patient flowchart – Prescribing incidence

For evaluation of prescribing incidence, overall in the asthma subgroups there were 31,428 patients to be analysed who initiated on an FDC ICS/LABA during the study period (n=28,863 age ≥18 years, n=1367 12-17 years and n=1198 age 4-11 years). For evaluation of patients with COPD (definition 1), 9362 patients initiated on an FDC ICS/LABA during the study period. 7810 patients were prescribed a FDC ICS/LABA device under consideration in the study but did not have a record of either asthma or COPD.

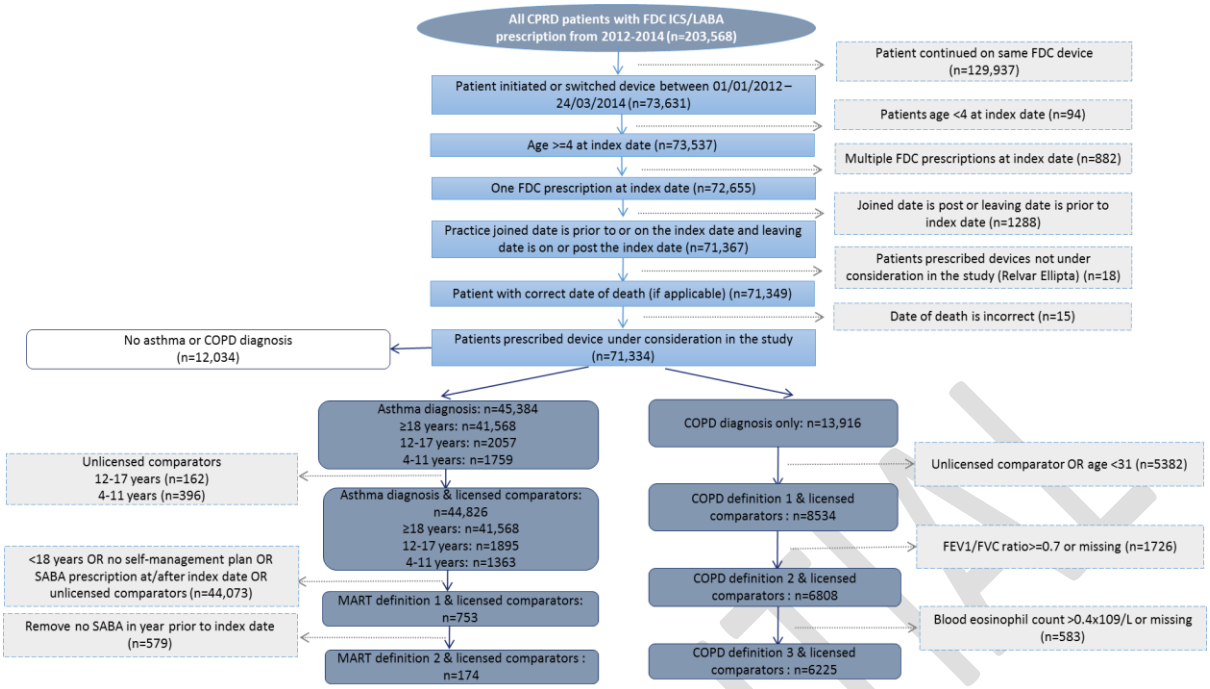

Figure 2 Patient flowchart – Patient characterisation and analysis of adverse events

For patient characterisation and analysis of adverse events, overall in the asthma subgroups there were 44,826 patients to be analysed (n=41,568 in age ≥18 years, n=1895 in 12-17 years and n=1363 in age 4-11 years). For MART definition 1, 753 patients were available for analysis and 174 patients for MART definition 2. For analysis of patients with COPD, 8534 patients were available within definition 1, 6808 patients within definition 2 and 6225 patients within definition 3. 12,034 patients were prescribed a device under consideration in the study but did not have a record of either asthma or COPD.

Of the 15 patients that we decided to exclude from analysis of patient characteristics and adverse events due to an incorrect date of death, 5 did not have a diagnosis of either asthma or COPD, 7 had a diagnosis of asthma and 3 had a diagnosis of COPD. The decision was made to exclude these patients as the death date occurred before the index date so we could not be confident if there were errors in their data. Due to the small number of patients this affected, they were decided to be excluded from analysis.

5.2 Descriptive data

For variables requiring data on hospitalisations, patients with linked HES data will only be analysed (Table 2). For the majority of subgroups, between 50% and 65% of patients had HES/ONS linked data available.

			TOTAL COHORT n=71,334				
Subgroup		Measure	FP/FOR n=2,689	FP/SAL DPI n=18,705	FP/SAL MDI n=21,889	BUD/FOR n=19,194	BDP/FOR n=8,857
Patients aged ≥18 years with asthma	HES link	No, n (%)	1004 (47.2)	3437 (38.6)	5149 (40.8)	4431 (40.7)	2809 (40.1)
		Yes, n (%)	1123 (52.8)	5465 (61.4)	7480 (59.2)	6468 (59.3)	4202 (59.9)
		Total, N (%)	2127 (79.1)	8902 (47.6)	12629 (57.7)	10899 (56.8)	7011 (79.1)
Patients aged ≥12 and <18 years with asthma (licensed Flutiform 50/5, 125/5)	HES link	No, n (%)	33 (42.9)	165 (49.4)	346 (40.1)	261 (42.5)	NA
		Yes, n (%)	44 (57.1)	169 (50.6)	516 (59.9)	353 (57.5)	NA
		Total, N (%)	77 (2.8)	334 (1.8)	862 (3.9)	614 (3.2)	NA
Patients aged ≥12 and <18 years with asthma (off-label Flutiform 250/10)	HES link	No, n (%)	4 (50.0)	165 (49.4)	346 (40.1)	261 (42.5)	NA
		Yes, n (%)	4 (50.0)	169 (50.6)	516 (59.9)	353 (57.5)	NA
		Total, N (%)	8 (0.3)	334 (1.8)	862 (3.9)	614 (3.2)	NA
4-11 years paediatric asthma patients	HES link	No, n (%)	4 (33.3)	61 (40.7)	384 (39.5)	91 (39.6)	NA
		Yes, n (%)	8 (66.7)	89 (59.3)	587 (60.5)	139 (60.4)	NA
		Total, N (%)	12 (0.5)	150 (0.8)	971 (4.4)	230 (1.2)	NA
Patients with COPD only, definition 1	HES link	No, n (%)	104 (53.9)	1954 (38.8)	NA	1098 (39.7)	236 (44.1)
		Yes, n (%)	89 (46.1)	3084 (61.2)	NA	1670 (60.3)	299 (55.9)
		Total, N (%)	193 (7.2)	5038 (26.9)	NA	2768 (14.4)	535 (6.0)
Patients with COPD only, definition 2	HES link	No, n (%)	83 (58.0)	1595 (39.0)	NA	870 (39.8)	164 (41.5)
		Yes, n (%)	60 (42.0)	2490 (61.0)	NA	1315 (60.2)	231 (58.5)
		Total, N (%)	143 (5.3)	4085 (21.8)	NA	2185 (11.4)	395 (4.5)
Patients with COPD only, definition 3	HES link	No, n (%)	73 (56.6)	1472 (39.4)	NA	809 (40.2)	146 (42.1)
		Yes, n (%)	56 (43.4)	2267 (60.6)	NA	1201 (59.8)	201 (57.9)
		Total, N (%)	129 (4.8)	3739 (20)	NA	2010 (10.5)	347 (3.9)
"MART" regimen, definition 1	HES link	No, n (%)	19 (28.8)	NA	NA	126 (33.2)	109 (35.4)
		Yes, n (%)	47 (71.2)	NA	NA	253 (66.8)	199 (64.6)
		Total, N (%)	66 (2.5)	NA	NA	379 (2)	308 (3.5)
"MART" regimen, definition 2	HES link	No, n (%)	2 (33.3)	NA	NA	39 (38.2)	26 (39.4)
		Yes, n (%)	4 (66.7)	NA	NA	63 (61.8)	40 (60.6)
		Total, N (%)	6 (0.2)	NA	NA	102 (0.5)	66 (0.8)

Table 2: Patients with HES/ONS linked data available

Demographic characteristics, prescribed therapies, comorbidities, consultations and hospitalisations are presented by FDC ICS/LABA for each subgroup.

5.2.1 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. Of note, FP/SAL DPI patients appeared to have slightly more severe disease than other groups, had a higher proportion of comorbid COPD diagnosis, had the highest recording of history of ischaemic heart disease and were prescribed higher doses of FDC ICS/LABA. A smaller proportion of FP/FOR patients were prescribed SABA 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 remained similar. FP/FOR patients were more likely to have rhinitis and to be switchers rather than initiators of their FDC ICS/LABA treatment. The year of first diagnosis of asthma/COPD, CCI score, GP consultations and exacerbations were similar across all groups.

5.2.1.1 Demographic characteristics

		TOTAL COHORT					
	Measure	FP/FOR	FP/SAL DPI	FP/SAL MDI	BUD/FOR	BDP/FOR	p-value
Age at index date (years)	N (% not missing)	2127 (100.0)	8902 (100.0)	12629 (100.0)	10899 (100.0)	7011 (100.0)	<0.001‡
	Mean (SD)	53.3 (17.6)	57.4 (18.1)	52.5 (18.9)	49.7 (18.1)	50.4 (17.9)	
	Median (IQR)	53 (41, 67)	59 (44, 71)	52 (38, 67)	49 (35, 64)	50 (37, 64)	
	Min, Max	(18, 100)	(18, 100)	(18, 105)	(18, 103)	(18, 97)	
Gender	N (% not missing)	2127 (100.0)	8902 (100.0)	12629 (100.0)	10899 (100.0)	7011 (100.0)	<0.001*
	Female, n (%)	1302 (61.2)	5297 (59.5)	7794 (61.7)	6529 (59.9)	4364 (62.2)	
	Male, n (%)	825 (38.8)	3605 (40.5)	4835 (38.3)	4370 (40.1)	2647 (37.8)	
Height (m) - closest to index date	N (% not missing)	2080 (97.8)	8558 (96.1)	12060 (95.5)	10386 (95.3)	6821 (97.3)	<0.001‡
	Mean (SD)	1.7 (0.1)	1.7 (0.1)	1.7 (0.1)	1.7 (0.1)	1.7 (0.1)	
	Median (IQR)	1.7 (1.6, 1.7)	1.6 (1.6, 1.7)	1.7 (1.6, 1.7)	1.7 (1.6, 1.8)	1.7 (1.6, 1.7)	
	Min, Max	(1.2, 2.1)	(1.1, 2.0)	(1.1, 2.1)	(1.1, 2.1)	(1.3, 2.0)	
Weight (kg) - closest to index date	N (% not missing)	2080 (97.8)	8543 (96.0)	11936 (94.5)	10330 (94.8)	6773 (96.6)	<0.001‡
	Mean (SD)	81.2 (20.0)	79.6 (20.5)	80.1 (20.3)	80.6 (20.1)	81.2 (20.4)	
	Median (IQR)	78 (67, 93)	77 (65, 91)	77 (65, 91)	78 (66, 92)	78.8 (66.2, 92.5)	
	Min, Max	(40, 177)	(40, 226)	(40, 235)	(40, 216)	(40, 196)	
BMI (kg/m2)	N (% not missing)	2055 (96.6)	8437 (94.8)	11801 (93.4)	10184 (93.4)	6701 (95.6)	<0.001‡
	Mean (SD)	29.2 (6.6)	28.7 (6.8)	28.8 (6.7)	28.7 (6.6)	29.2 (6.8)	
	Median (IQR)	28.0 (24.6, 32.7)	27.8 (24.0, 32.4)	27.8 (24.1, 32.4)	27.5 (24.0, 32.3)	28.0 (24.4, 32.8)	
	Min, Max	(14.7, 55.9)	(13.0, 59.4)	(13.1, 59.5)	(14.3, 59.8)	(14, 60)	

		TOTAL COHORT					
	Measure	FP/FOR	FP/SAL DPI	FP/SAL MDI	BUD/FOR	BDP/FOR	p-value
BMI (kg/m2) (categorised)	N (% not missing)	2055 (96.6)	8437 (94.8)	11801 (93.4)	10184 (93.4)	6701 (95.6)	<0.001*
	Underweight (BMI≤18.5), n (%)	33 (1.6)	228 (2.7)	249 (2.1)	208 (2.0)	120 (1.8)	
	Normal (18.5≤BMI<25), n (%)	534 (26.0)	2438 (28.9)	3465 (29.4)	3076 (30.2)	1833 (27.4)	
	Overweight (25≤BMI<30), n (%)	705 (34.3)	2705 (32.1)	3780 (32.0)	3245 (31.9)	2172 (32.4)	
	Obese (BMI≥30), n (%)	783 (38.1)	3066 (36.3)	4307 (36.5)	3655 (35.9)	2576 (38.4)	
FEV_1 % predicted	N (% not missing)	897 (42.2)	4763 (53.5)	4890 (38.7)	4194 (38.5)	2579 (36.8)	<0.001‡
	Mean (SD)	79.9 (23.8)	68.4 (24.4)	75.8 (23.3)	76.9 (23.3)	80.0 (22.6)	
	Median (IQR)	82 (63, 97)	68 (50, 86)	77 (60, 92)	79 (62, 93)	82 (66, 95)	
	Min, Max	(6, 169)	(1, 193)	(1, 194)	(1, 183)	(11, 163)	
FEV_1 % predicted (categorised)	N (% not missing)	897 (42.2)	4763 (53.5)	4890 (38.7)	4194 (38.5)	2579 (36.8)	<0.001*
	<30 (very severe), n (%)	22 (2.5)	226 (4.7)	150 (3.1)	103 (2.5)	66 (2.6)	
	30-49 (severe), n (%)	75 (8.4)	915 (19.2)	534 (10.9)	482 (11.5)	184 (7.1)	
	50-79 (moderate), n (%)	325 (36.2)	2049 (43.0)	1944 (39.8)	1560 (37.2)	900 (34.9)	
	≥80 (mild), n (%)	475 (53.0)	1573 (33.0)	2262 (46.3)	2049 (48.9)	1429 (55.4)	
PEF % predicted	N (% not missing)	1861 (87.5)	6645 (74.6)	8911 (70.6)	7450 (68.4)	5707 (81.4)	<0.001‡
	Mean (SD)	96.9 (25.6)	85.2 (28.6)	93.2 (27.0)	95.1 (26.9)	96.7 (25.7)	
	Median (IQR)	97.4 (79.4, 115.9)	85.0 (64.2, 105.9)	94.1 (73.5, 113.3)	97.1 (76.5, 115.6)	98.6 (79.3, 115.6)	
	Min, Max	(21.2, 150.0)	(20.0, 150.0)	(20.4, 150.0)	(20.1, 150.0)	(20, 150)	
Smoking Status	N (% not missing)	2126 (100.0)	8879 (99.7)	12593 (99.7)	10880 (99.8)	7008 (100.0)	<0.001*
	Non-smoker, n (%)	1085 (51.0)	3531 (39.8)	6005 (47.7)	5500 (50.6)	3482 (49.7)	
	Current smoker, n (%)	366 (17.2)	2246 (25.3)	2704 (21.5)	2277 (20.9)	1518 (21.7)	
	Ex-smoker, n (%)	675 (31.7)	3102 (34.9)	3884 (30.8)	3103 (28.5)	2008 (28.7)	

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

5.2.1.2 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)	2127 (100.0)	8902 (100.0)	12629 (100.0)	10899 (100.0)	7011 (100.0)	<0.001‡
	Mean (SD)	17.5 (14.1)	16.0 (15.9)	14.1 (15.1)	13.2 (14.3)	16.4 (15.1)	
	Median (IQR)	15.3 (6.6, 24.8)	12.7 (2.0, 23.8)	9.8 (1.0, 21.8)	9.1 (0.8, 20.9)	13.3 (4.0, 24.0)	
	Min, Max	(0, 83)	(0, 91)	(0, 87)	(0, 94)	(0, 90)	
Prescribed FDC ICS/LABA inhaler dose (dose per puff)	N (% not missing)	2127 (100.0)	8902 (100.0)	12629 (100.0)	10899 (100.0)	7011 (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 dosing instructions (FP equivalent dose per day)	N (% not missing)	1861 (87.5)	4102 (46.1)	10844 (85.9)	8109 (74.4)	5171 (73.8)	<0.001‡
	Mean (SD)	647.3 (289.4)	777.2 (348.5)	607.9 (296.1)	295.2 (143.2)	439.7 (106.5)	
	Median (IQR)	500 (500, 1000)	1000 (500, 1000)	500 (500, 1000)	200 (200, 400)	500 (375, 500)	
	Min, Max	(100, 2000)	(100, 2250)	(50, 2000)	(50, 1600)	(125, 1000)	
Prescribed FDC ICS/LABA dosing instructions (FP equivalent dose per day) (categorised)	N (% not missing)	1861 (87.5)	4102 (46.1)	10844 (85.9)	8109 (74.4)	5171 (73.8)	<0.001*
	≥50 & ≤100, n (%)	n<5	n<5	45 (0.4)	n≥5	n<5	
	>100 & ≤200, n (%)	n≥5	n≥5	1749 (16.1)	n≥5	n≥5	
	>200 & ≤400, n (%)	n≥5	n≥5	328 (3.0)	n≥5	n≥5	
	>400 & <600, n (%)	n≥5	n≥5	5131 (47.3)	n≥5	n≥5	
	≥600 & <1000, n (%)	n≥5	n≥5	57 (0.5)	n≥5	n≥5	
	≥1000, n (%)	n≥5	n≥5	3534 (32.6)	n<5	n≥5	
Duration of FDC ICS/LABA prescription (outcome), (months)	N (% not missing)	2127 (100.0)	8902 (100.0)	12629 (100.0)	10899 (100.0)	7011 (100.0)	<0.001‡
	Mean (SD)	15.8 (12.1)	16.2 (14.9)	16.5 (14.2)	17.5 (14.7)	16.7 (14.5)	
	Median (IQR)	14.9 (2.7, 26.5)	12 (2, 28)	13 (3, 28)	14.8 (2.3, 29.1)	13.2 (2.2, 28.2)	
	Min, Max	(0, 40)	(0, 54)	(0, 55)	(0, 53)	(0, 58)	

		TOTAL COHORT					
	Measure	FP/FOR	FP/SAL DPI	FP/SAL MDI	BUD/FOR	BDP/FOR	p-value
SABA prescriptions	N (% not missing)	2127 (100.0)	8902 (100.0)	12629 (100.0)	10899 (100.0)	7011 (100.0)	<0.001*
	No, n (%)	1810 (85.1)	7026 (78.9)	10080 (79.8)	8863 (81.3)	5687 (81.1)	
	Yes, n (%)	317 (14.9)	1876 (21.1)	2549 (20.2)	2036 (18.7)	1324 (18.9)	
SAMA prescriptions	N (% not missing)	2127 (100.0)	8902 (100.0)	12629 (100.0)	10899 (100.0)	7011 (100.0)	<0.001*
	No, n (%)	2112 (99.3)	8778 (98.6)	12496 (98.9)	10830 (99.4)	6971 (99.4)	
	Yes, n (%)	15 (0.7)	124 (1.4)	133 (1.1)	69 (0.6)	40 (0.6)	
LABA prescriptions	N (% not missing)	2127 (100.0)	8902 (100.0)	12629 (100.0)	10899 (100.0)	7011 (100.0)	0.269*
	No, n (%)	2122 (99.8)	8882 (99.8)	12609 (99.8)	10887 (99.9)	6996 (99.8)	
	Yes, n (%)	5 (0.2)	20 (0.2)	20 (0.2)	12 (0.1)	15 (0.2)	
LAMA prescriptions	N (% not missing)	2127 (100.0)	8902 (100.0)	12629 (100.0)	10899 (100.0)	7011 (100.0)	<0.001*
	No, n (%)	2062 (96.9)	7905 (88.8)	12190 (96.5)	10514 (96.5)	6912 (98.6)	
	Yes, n (%)	65 (3.1)	997 (11.2)	439 (3.5)	385 (3.5)	99 (1.4)	
ICS only prescriptions	N (% not missing)	2127 (100.0)	8902 (100.0)	12629 (100.0)	10899 (100.0)	7011 (100.0)	0.067*
	No, n (%)	2107 (99.1)	8819 (99.1)	12498 (99.0)	10787 (99.0)	6914 (98.6)	
	Yes, n (%)	20 (0.9)	83 (0.9)	131 (1.0)	112 (1.0)	97 (1.4)	
Theophylline prescriptions	N (% not missing)	2127 (100.0)	8902 (100.0)	12629 (100.0)	10899 (100.0)	7011 (100.0)	<0.001*
	No, n (%)	2105 (99.0)	8761 (98.4)	12551 (99.4)	10819 (99.3)	6974 (99.5)	
	Yes, n (%)	22 (1.0)	141 (1.6)	78 (0.6)	80 (0.7)	37 (0.5)	
LTRA prescriptions	N (% not missing)	2127 (100.0)	8902 (100.0)	12629 (100.0)	10899 (100.0)	7011 (100.0)	<0.001*
	No, n (%)	2041 (96.0)	8541 (95.9)	12261 (97.1)	10503 (96.4)	6817 (97.2)	
	Yes, n (%)	86 (4.0)	361 (4.1)	368 (2.9)	396 (3.6)	194 (2.8)	

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

5.2.1.3 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)	2127 (100.0)	8902 (100.0)	12629 (100.0)	10899 (100.0)	7011 (100.0)	<0.001*
	Asthma only, n (%)	1931 (90.8)	6221 (69.9)	11070 (87.7)	9634 (88.4)	6594 (94.1)	
	Asthma & COPD, n (%)	196 (9.2)	2681 (30.1)	1559 (12.3)	1265 (11.6)	417 (5.9)	
Year of first asthma diagnosis	N (% not missing)	2127 (100.0)	8902 (100.0)	12629 (100.0)	10899 (100.0)	7011 (100.0)	<0.001‡
	Mean (SD)	1996.1 (12.8)	1996.3 (13.2)	1997.2 (12.9)	1997.5 (12.9)	1997.3 (12.7)	
	Median (IQR)	1998 (1990, 2005)	1999 (1991, 2006)	1999 (1991, 2007)	2000 (1991, 2008)	1999 (1991, 2007)	
	Min, Max	(1923, 2014)	(1919, 2014)	(1932, 2014)	(1919, 2014)	(1927, 2014)	
Duration of asthma (years)	N (% not missing)	2127 (100.0)	8902 (100.0)	12629 (100.0)	10899 (100.0)	7011 (100.0)	<0.001‡
	Mean (SD)	17.2 (12.9)	16.3 (13.3)	15.4 (13.0)	15.2 (13.0)	15.5 (12.8)	
	Median (IQR)	14.9 (8.3, 23.0)	13.5 (6.8, 22.0)	13.1 (5.6, 21.7)	13.0 (5.1, 21.6)	13.5 (5.4, 21.9)	
	Min, Max	(0, 90)	(0, 94)	(0, 82)	(0, 94)	(0, 86)	
Year of first COPD diagnosis	N (% not missing)	196 (9.2)	2675 (30.0)	1563 (12.4)	1262 (11.6)	415 (5.9)	<0.001‡
	Mean (SD)	2005.3 (7.9)	2005.0 (6.9)	2005.2 (7.2)	2006.0 (6.7)	2006.0 (6.5)	
	Median (IQR)	2007 (2003, 2010)	2006 (2002, 2010)	2007 (2002, 2011)	2008 (2003, 2011)	2007 (2003, 2011)	
	Min, Max	(1962, 2014)	(1933, 2014)	(1946, 2014)	(1947, 2014)	(1972, 2014)	
Duration of COPD (years)	N (% not missing)	196 (9.2)	2675 (30.0)	1563 (12.4)	1262 (11.6)	415 (5.9)	<0.001‡
	Mean (SD)	7.8 (8.0)	7.5 (6.9)	7.3 (7.2)	6.6 (6.7)	6.6 (6.5)	
	Median (IQR)	6.2 (2.7, 9.9)	6.3 (2.5, 10.5)	5.7 (2.0, 10.2)	5.2 (1.5, 9.3)	5.0 (1.5, 9.4)	
	Min, Max	(0, 51)	(0, 79)	(0, 66)	(0, 66)	(0, 40)	
Comorbid rhinitis	N (% not missing)	2127 (100.0)	8902 (100.0)	12629 (100.0)	10899 (100.0)	7011 (100.0)	<0.001*
	No, n (%)	1823 (85.7)	7998 (89.8)	11397 (90.2)	9795 (89.9)	6109 (87.1)	
	Yes, n (%)	304 (14.3)	904 (10.2)	1232 (9.8)	1104 (10.1)	902 (12.9)	
Comorbid eczema	N (% not missing)	2127 (100.0)	8902 (100.0)	12629 (100.0)	10899 (100.0)	7011 (100.0)	0.004*
	No, n (%)	1966 (92.4)	8264 (92.8)	11738 (92.9)	10216 (93.7)	6473 (92.3)	
	Yes, n (%)	161 (7.6)	638 (7.2)	891 (7.1)	683 (6.3)	538 (7.7)	
Comorbid GERD	N (% not missing)	2127 (100.0)	8902 (100.0)	12629 (100.0)	10899 (100.0)	7011 (100.0)	<0.001*
	No, n (%)	1858 (87.4)	7797 (87.6)	11344 (89.8)	9828 (90.2)	6224 (88.8)	
	Yes, n (%)	269 (12.6)	1105 (12.4)	1285 (10.2)	1071 (9.8)	787 (11.2)	
History of ischemic heart disease	N (% not missing)	2127 (100.0)	8902 (100.0)	12629 (100.0)	10899 (100.0)	7011 (100.0)	<0.001*
	No, n (%)	1972 (92.7)	7808 (87.7)	11503 (91.1)	10128 (92.9)	6565 (93.6)	
	Yes, n (%)	155 (7.3)	1094 (12.3)	1126 (8.9)	771 (7.1)	446 (6.4)	
History of hypertension	N (% not missing)	2127 (100.0)	8902 (100.0)	12629 (100.0)	10899 (100.0)	7011 (100.0)	<0.001*
	No, n (%)	1536 (72.2)	6157 (69.2)	9435 (74.7)	8505 (78.0)	5345 (76.2)	
	Yes, n (%)	591 (27.8)	2745 (30.8)	3194 (25.3)	2394 (22.0)	1666 (23.8)	

		TOTAL COHORT					
	Measure	FP/FOR	FP/SAL DPI	FP/SAL MDI	BUD/FOR	BDP/FOR	p-value
History of ischemic heart disease and hypertension	N (% not missing)	2127 (100.0)	8902 (100.0)	12629 (100.0)	10899 (100.0)	7011 (100.0)	
	No, n (%)	2024 (95.2)	8257 (92.8)	11963 (94.7)	10478 (96.1)	6768 (96.5)	<0.001*
	Yes, n (%)	103 (4.8)	645 (7.2)	666 (5.3)	421 (3.9)	243 (3.5)	
Charlson Comorbidity Index (CCI)	N (% not missing)	2127 (100.0)	8902 (100.0)	12628 (100.0)	10898 (100.0)	7011 (100.0)	
	Mean (SD)	3.7 (2.5)	3.4 (3.4)	3.4 (2.9)	3.3 (2.8)	3.7 (2.5)	
	Median (IQR)	4 (4, 4)	4 (0, 4)	4 (0, 4)	4 (0, 4)	4 (4, 4)	<0.001‡
	Min, Max	(0, 23)	(0, 34)	(0, 31)	(0, 31)	(0, 30)	
Charlson Comorbidity Index (CCI) (categorised)	N (% not missing)	2127 (100.0)	8902 (100.0)	12628 (100.0)	10898 (100.0)	7011 (100.0)	
	0, n (%)	380 (17.9)	2862 (32.2)	3493 (27.7)	2970 (27.3)	1259 (18.0)	
	1-4, n (%)	1585 (74.5)	5090 (57.2)	8129 (64.4)	7131 (65.4)	5271 (75.2)	<0.001*
	≥5, n (%)	162 (7.6)	950 (10.7)	1006 (8.0)	797 (7.3)	481 (6.9)	

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

5.2.1.4 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	N (% not missing)	2127 (100.0)	8902 (100.0)	12629 (100.0)	10899 (100.0)	7011 (100.0)	
	Mean (SD)	1.6 (1.8)	1.7 (1.8)	1.5 (1.8)	1.5 (1.8)	1.7 (1.8)	
	Median (IQR)	1 (0, 2)	1 (0, 2)	1 (0, 2)	1 (0, 2)	1 (0, 2)	<0.001‡
	Min, Max	(0, 17)	(0, 19)	(0, 24)	(0, 23)	(0, 14)	
Respiratory GP consultations without prescription for an oral corticosteroid (categorised)	N (% not missing)	2127 (100.0)	8902 (100.0)	12629 (100.0)	10899 (100.0)	7011 (100.0)	
	0, n (%)	611 (28.7)	2872 (32.3)	4513 (35.7)	3881 (35.6)	1975 (28.2)	
	1, n (%)	664 (31.2)	2280 (25.6)	3292 (26.1)	2815 (25.8)	2047 (29.2)	<0.001*
	2, n (%)	406 (19.1)	1538 (17.3)	2033 (16.1)	1866 (17.1)	1320 (18.8)	
	≥3, n (%)	446 (21.0)	2212 (24.8)	2791 (22.1)	2337 (21.4)	1669 (23.8)	
Asthma GP consultations without prescription for an oral corticosteroid	N (% not missing)	2127 (100.0)	8902 (100.0)	12629 (100.0)	10899 (100.0)	7011 (100.0)	
	Mean (SD)	0.8 (1.0)	0.6 (0.9)	0.7 (1.0)	0.7 (1.0)	0.8 (1.0)	
	Median (IQR)	1 (0, 1)	0 (0, 1)	0 (0, 1)	0 (0, 1)	1 (0, 1)	<0.001‡
	Min, Max	(0, 8)	(0, 8)	(0, 10)	(0, 10)	(0, 13)	
Asthma GP consultations without prescription for an oral corticosteroid (categorised)	N (% not missing)	2127 (100.0)	8902 (100.0)	12629 (100.0)	10899 (100.0)	7011 (100.0)	
	0, n (%)	956 (44.9)	5033 (56.5)	6852 (54.3)	6089 (55.9)	3189 (45.5)	
	1, n (%)	797 (37.5)	2684 (30.2)	3884 (30.8)	3217 (29.5)	2526 (36.0)	<0.001*
	2, n (%)	253 (11.9)	831 (9.3)	1251 (9.9)	1040 (9.5)	890 (12.7)	
	≥3, n (%)	121 (5.7)	354 (4.0)	642 (5.1)	553 (5.1)	406 (5.8)	
COPD GP consultations without	N (% not missing)	2127 (100.0)	8902 (100.0)	12629 (100.0)	10899 (100.0)	7011 (100.0)	
	Mean (SD)	0.1 (0.3)	0.2 (0.6)	0.1 (0.4)	0.1 (0.4)	0.1 (0.3)	<0.001‡

		TOTAL COHORT					
	Measure	FP/FOR	FP/SAL DPI	FP/SAL MDI	BUD/FOR	BDP/FOR	p-value
prescription for an oral corticosteroid	Median (IQR)	0 (0, 0)	0 (0, 0)	0 (0, 0)	0 (0, 0)	0 (0, 0)	
	Min, Max	(0, 4)	(0, 7)	(0, 6)	(0, 6)	(0, 7)	
COPD GP consultations without prescription for an oral corticosteroid (categorised)	N (% not missing)	2127 (100.0)	8902 (100.0)	12629 (100.0)	10899 (100.0)	7011 (100.0)	<0.001*
	0, n (%)	2026 (95.3)	7401 (83.1)	11788 (93.3)	10185 (93.4)	6744 (96.2)	
	1, n (%)	72 (3.4)	1044 (11.7)	575 (4.6)	497 (4.6)	191 (2.7)	
	2, n (%)	24 (1.1)	348 (3.9)	187 (1.5)	161 (1.5)	56 (0.8)	
	≥3, n (%)	5 (0.2)	109 (1.2)	79 (0.6)	56 (0.5)	20 (0.3)	
Lower respiratory hospital outpatient attendances	N (% not missing)	1123 (100.0)	5465 (100.0)	7480 (100.0)	6468 (100.0)	4202 (100.0)	.579‡
	Mean (SD)	0.0 (0.0)	0.0 (0.1)	0.0 (0.0)	0.0 (0.0)	0.0 (0.0)	
	Median (IQR)	0 (0, 0)	0 (0, 0)	0 (0, 0)	0 (0, 0)	0 (0, 0)	
	Min, Max	(0, 0)	(0, 3)	(0, 1)	(0, 1)	(0, 1)	
Lower respiratory hospital outpatient attendances (categorised)	N (% not missing)	1123 (100.0)	5465 (100.0)	7480 (100.0)	6468 (100.0)	4202 (100.0)	0.478*
	0, n (%)	n≥5	n≥5	n≥5	n≥5	n≥5	
	1, n (%)	n<5	n<5	n<5	n<5	n<5	
	≥2, n (%)	n<5	n<5	n<5	n<5	n<5	
Asthma hospital outpatient attendances	N (% not missing)	1123 (100.0)	5465 (100.0)	7480 (100.0)	6468 (100.0)	4202 (100.0)	NA
	Mean (SD)	0.0 (0.0)	0.0 (0.0)	0.0 (0.0)	0.0 (0.0)	0.0 (0.0)	
	Median (IQR)	0 (0, 0)	0 (0, 0)	0 (0, 0)	0 (0, 0)	0 (0, 0)	
	Min, Max	(0, 0)	(0, 0)	(0, 0)	(0, 0)	(0, 0)	
Asthma hospital outpatient attendances (categorised)	N (% not missing)	1123 (100.0)	5465 (100.0)	7480 (100.0)	6468 (100.0)	4202 (100.0)	NA
	0, n (%)	1123 (100.0)	5465 (100.0)	7480 (100.0)	6468 (100.0)	4202 (100.0)	
COPD hospital outpatient attendances	N (% not missing)	1123 (100.0)	5465 (100.0)	7480 (100.0)	6468 (100.0)	4202 (100.0)	.545‡
	Mean (SD)	0.0 (0.3)	0.0 (0.0)	0.0 (0.0)	0.0 (0.0)	0.0 (0.0)	
	Median (IQR)	0 (0, 0)	0 (0, 0)	0 (0, 0)	0 (0, 0)	0 (0, 0)	
	Min, Max	(0, 9)	(0, 1)	(0, 3)	(0, 2)	(0, 2)	
COPD hospital outpatient attendances (categorised)	N (% not missing)	1123 (100.0)	5465 (100.0)	7480 (100.0)	6468 (100.0)	4202 (100.0)	0.353*
	0, n (%)	n≥5	n≥5	n≥5	n≥5	n≥5	
	1, n (%)	n<5	n≥5	n<5	n≥5	n<5	
	≥2, n (%)	n<5	n<5	n<5	n<5	n<5	
Lower respiratory inpatient hospitalisations	N (% not missing)	1123 (100.0)	5465 (100.0)	7480 (100.0)	6468 (100.0)	4202 (100.0)	<0.001‡
	Mean (SD)	0.0 (0.1)	0.1 (0.5)	0.1 (0.3)	0.1 (0.3)	0.0 (0.2)	
	Median (IQR)	0 (0, 0)	0 (0, 0)	0 (0, 0)	0 (0, 0)	0 (0, 0)	
	Min, Max	(0, 1)	(0, 8)	(0, 8)	(0, 12)	(0, 4)	
Lower respiratory inpatient hospitalisations (categorised)	N (% not missing)	1123 (100.0)	5465 (100.0)	7480 (100.0)	6468 (100.0)	4202 (100.0)	<0.001*
	0, n (%)	n≥5	5075 (92.9)	7213 (96.4)	6225 (96.2)	4125 (98.2)	
	1, n (%)	n≥5	282 (5.2)	191 (2.6)	194 (3.0)	67 (1.6)	
	≥2, n (%)	n<5	108 (2.0)	76 (1.0)	49 (0.8)	10 (0.2)	
	N (% not missing)	1123 (100.0)	5465 (100.0)	7480 (100.0)	6468 (100.0)	4202 (100.0)	<0.001‡

		TOTAL COHORT					
	Measure	FP/FOR	FP/SAL DPI	FP/SAL MDI	BUD/FOR	BDP/FOR	p-value
Asthma inpatient hospitalisations	Mean (SD)	0.0 (0.2)	0.0 (0.2)	0.0 (0.2)	0.1 (0.3)	0.0 (0.2)	
	Median (IQR)	0 (0, 0)	0 (0, 0)	0 (0, 0)	0 (0, 0)	0 (0, 0)	
	Min, Max	(0, 4)	(0, 5)	(0, 12)	(0, 11)	(0, 7)	
Asthma inpatient hospitalisations (categorised)	N (% not missing)	1123 (100.0)	5465 (100.0)	7480 (100.0)	6468 (100.0)	4202 (100.0)	<0.001*
	0, n (%)	n≥5	5315 (97.3)	7275 (97.3)	6183 (95.6)	4118 (98.0)	
	1, n (%)	n≥5	129 (2.4)	183 (2.4)	242 (3.7)	74 (1.8)	
	≥2, n (%)	n<5	21 (0.4)	22 (0.3)	43 (0.7)	10 (0.2)	
COPD inpatient hospitalisations	N (% not missing)	1123 (100.0)	5465 (100.0)	7480 (100.0)	6468 (100.0)	4202 (100.0)	<0.001‡
	Mean (SD)	0.0 (0.1)	0.1 (0.4)	0.0 (0.3)	0.0 (0.3)	0.0 (0.1)	
	Median (IQR)	0 (0, 0)	0 (0, 0)	0 (0, 0)	0 (0, 0)	0 (0, 0)	
	Min, Max	(0, 1)	(0, 9)	(0, 8)	(0, 13)	(0, 2)	
COPD inpatient hospitalisations (categorised)	N (% not missing)	1123 (100.0)	5465 (100.0)	7480 (100.0)	6468 (100.0)	4202 (100.0)	<0.001*
	0, n (%)	n≥5	5223 (95.6)	7331 (98.0)	6338 (98.0)	n≥5	
	1, n (%)	n<5	174 (3.2)	106 (1.4)	99 (1.5)	n≥5	
	≥2, n (%)	n<5	68 (1.2)	43 (0.6)	31 (0.5)	n<5	
Asthma exacerbations	N (% not missing)	1123 (100.0)	5465 (100.0)	7480 (100.0)	6468 (100.0)	4202 (100.0)	<0.001‡
	Mean (SD)	1.1 (1.4)	1.3 (1.7)	1.0 (1.3)	1.0 (1.4)	1.0 (1.3)	
	Median (IQR)	1 (0, 2)	1 (0, 2)	1 (0, 2)	1 (0, 2)	1 (0, 1)	
	Min, Max	(0, 8)	(0, 14)	(0, 11)	(0, 11)	(0, 11)	
Asthma exacerbations (categorised)	N (% not missing)	1123 (100.0)	5465 (100.0)	7480 (100.0)	6468 (100.0)	4202 (100.0)	<0.001*
	0, n (%)	502 (44.7)	2262 (41.4)	3616 (48.3)	3101 (47.9)	2031 (48.3)	
	1, n (%)	297 (26.4)	1313 (24.0)	1919 (25.7)	1656 (25.6)	1134 (27.0)	
	≥2, n (%)	324 (28.9)	1890 (34.6)	1945 (26.0)	1711 (26.5)	1037 (24.7)	
COPD exacerbations	N (% not missing)	1123 (100.0)	5465 (100.0)	7480 (100.0)	6468 (100.0)	4202 (100.0)	<0.001‡
	Mean (SD)	1.1 (1.4)	1.4 (1.7)	1.0 (1.4)	1.0 (1.4)	0.9 (1.3)	
	Median (IQR)	1 (0, 2)	1 (0, 2)	1 (0, 2)	1 (0, 2)	1 (0, 1)	
	Min, Max	(0, 8)	(0, 14)	(0, 11)	(0, 11)	(0, 11)	
COPD exacerbations (categorised)	N (% not missing)	1123 (100.0)	5465 (100.0)	7480 (100.0)	6468 (100.0)	4202 (100.0)	<0.001*
	0, n (%)	504 (44.9)	2253 (41.2)	3622 (48.4)	3139 (48.5)	2040 (48.5)	
	1, n (%)	298 (26.5)	1317 (24.1)	1922 (25.7)	1642 (25.4)	1134 (27.0)	
	≥2, n (%)	321 (28.6)	1895 (34.7)	1936 (25.9)	1687 (26.1)	1028 (24.5)	

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

5.2.1.5 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 prescriptions	N (% not missing)	2127 (100.0)	8902 (100.0)	12629 (100.0)	10899 (100.0)	7011 (100.0)	<0.001‡
	Mean (SD)	5.3 (5.4)	4.2 (5.7)	1.9 (4.3)	1.9 (4.2)	2.6 (4.9)	
	Median (IQR)	4 (0, 10)	0 (0, 8)	0 (0, 0)	0 (0, 0)	0 (0, 4)	
	Min, Max	(0, 38)	(0, 45)	(0, 44)	(0, 39)	(0, 92)	
FDC ICS+LABA prescriptions (categorised)	N (% not missing)	2127 (100.0)	8902 (100.0)	12629 (100.0)	10899 (100.0)	7011 (100.0)	<0.001*
	0, n (%)	715 (33.6)	4510 (50.7)	9652 (76.4)	8345 (76.6)	4707 (67.1)	
	1, n (%)	78 (3.7)	253 (2.8)	298 (2.4)	172 (1.6)	155 (2.2)	
	≥2, n (%)	1334 (62.7)	4139 (46.5)	2679 (21.2)	2382 (21.9)	2149 (30.7)	
SABA prescriptions	N (% not missing)	2127 (100.0)	8902 (100.0)	12629 (100.0)	10899 (100.0)	7011 (100.0)	<0.001‡
	Mean (SD)	2.5 (5.7)	3.5 (6.8)	2.8 (5.8)	2.7 (5.6)	3.2 (5.9)	
	Median (IQR)	0 (0, 3)	0 (0, 4)	0 (0, 3)	0 (0, 3)	1 (0, 4)	
	Min, Max	(0, 82)	(0, 86)	(0, 188)	(0, 149)	(0, 80)	
SABA prescriptions (categorised)	N (% not missing)	2127 (100.0)	8902 (100.0)	12629 (100.0)	10899 (100.0)	7011 (100.0)	<0.001*
	0, n (%)	1314 (61.8)	4895 (55.0)	7082 (56.1)	6084 (55.8)	3447 (49.2)	
	1, n (%)	135 (6.3)	571 (6.4)	1050 (8.3)	981 (9.0)	584 (8.3)	
	≥2, n (%)	678 (31.9)	3436 (38.6)	4497 (35.6)	3834 (35.2)	2980 (42.5)	
SAMA prescriptions	N (% not missing)	2127 (100.0)	8902 (100.0)	12629 (100.0)	10899 (100.0)	7011 (100.0)	<0.001‡
	Mean (SD)	0.3 (3.2)	0.5 (3.1)	0.2 (1.8)	0.2 (2.2)	0.2 (1.6)	
	Median (IQR)	0 (0, 0)	0 (0, 0)	0 (0, 0)	0 (0, 0)	0 (0, 0)	
	Min, Max	(0, 104)	(0, 71)	(0, 56)	(0, 103)	(0, 60)	
SAMA prescriptions (categorised)	N (% not missing)	2127 (100.0)	8902 (100.0)	12629 (100.0)	10899 (100.0)	7011 (100.0)	<0.001*
	0, n (%)	2065 (97.1)	8428 (94.7)	12254 (97.0)	10609 (97.3)	6873 (98.0)	
	1, n (%)	16 (0.8)	64 (0.7)	76 (0.6)	77 (0.7)	34 (0.5)	
	≥2, n (%)	46 (2.2)	410 (4.6)	299 (2.4)	213 (2.0)	104 (1.5)	
LABA prescriptions	N (% not missing)	2127 (100.0)	8902 (100.0)	12629 (100.0)	10899 (100.0)	7011 (100.0)	<0.001‡
	Mean (SD)	0.3 (1.6)	0.5 (2.3)	0.6 (2.3)	0.4 (2.0)	0.6 (2.4)	
	Median (IQR)	0 (0, 0)	0 (0, 0)	0 (0, 0)	0 (0, 0)	0 (0, 0)	
	Min, Max	(0, 28)	(0, 40)	(0, 28)	(0, 53)	(0, 35)	
LABA prescriptions (categorised)	N (% not missing)	2127 (100.0)	8902 (100.0)	12629 (100.0)	10899 (100.0)	7011 (100.0)	<0.001*
	0, n (%)	2036 (95.7)	8167 (91.7)	11252 (89.1)	10163 (93.2)	6319 (90.1)	
	1, n (%)	13 (0.6)	127 (1.4)	332 (2.6)	143 (1.3)	165 (2.4)	
	≥2, n (%)	78 (3.7)	608 (6.8)	1045 (8.3)	593 (5.4)	527 (7.5)	
LAMA prescriptions	N (% not missing)	2127 (100.0)	8902 (100.0)	12629 (100.0)	10899 (100.0)	7011 (100.0)	<0.001‡
	Mean (SD)	1.0 (4.7)	3.1 (7.8)	1.0 (4.6)	1.0 (4.5)	0.6 (3.8)	
	Median (IQR)	0 (0, 0)	0 (0, 0)	0 (0, 0)	0 (0, 0)	0 (0, 0)	
	Min, Max	(0, 54)	(0, 88)	(0, 60)	(0, 64)	(0, 96)	
	N (% not missing)	2127 (100.0)	8902 (100.0)	12629 (100.0)	10899 (100.0)	7011 (100.0)	<0.001*

		TOTAL COHORT					
	Measure	FP/FOR	FP/SAL DPI	FP/SAL MDI	BUD/FOR	BDP/FOR	p-value
LAMA prescriptions (categorised)	0, n (%)	n≥5	7098 (79.7)	11689 (92.6)	10057 (92.3)	n≥5	
	1, n (%)	n<5	13 (0.1)	11 (0.1)	6 (0.1)	n<5	
	≥2, n (%)	n≥5	1791 (20.1)	929 (7.4)	836 (7.7)	n≥5	
ICS only prescriptions	N (% not missing)	2127 (100.0)	8902 (100.0)	12629 (100.0)	10899 (100.0)	7011 (100.0)	
	Mean (SD)	1.3 (3.0)	1.4 (3.3)	2.4 (3.8)	1.9 (3.5)	2.7 (3.8)	<0.001‡
	Median (IQR)	0 (0, 1)	0 (0, 1)	0 (0, 4)	0 (0, 2)	1 (0, 4)	
	Min, Max	(0, 42)	(0, 48)	(0, 64)	(0, 46)	(0, 36)	
ICS only prescriptions (categorised)	N (% not missing)	2127 (100.0)	8902 (100.0)	12629 (100.0)	10899 (100.0)	7011 (100.0)	
	0, n (%)	1502 (70.6)	6571 (73.8)	6490 (51.4)	6417 (58.9)	3144 (44.8)	<0.001*
	1, n (%)	132 (6.2)	410 (4.6)	1124 (8.9)	901 (8.3)	696 (9.9)	
	≥2, n (%)	493 (23.2)	1921 (21.6)	5015 (39.7)	3581 (32.9)	3171 (45.2)	
Theophylline prescriptions	N (% not missing)	2127 (100.0)	8902 (100.0)	12629 (100.0)	10899 (100.0)	7011 (100.0)	
	Mean (SD)	0.2 (1.7)	0.3 (1.8)	0.1 (1.4)	0.1 (1.2)	0.1 (1.0)	<0.001‡
	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, 23)	
Theophylline prescriptions (categorised)	N (% not missing)	2127 (100.0)	8902 (100.0)	12629 (100.0)	10899 (100.0)	7011 (100.0)	
	0, n (%)	2081 (97.8)	8561 (96.2)	12430 (98.4)	10729 (98.4)	6911 (98.6)	<0.001*
	1, n (%)	6 (0.3)	42 (0.5)	31 (0.2)	32 (0.3)	11 (0.2)	
	≥2, n (%)	40 (1.9)	299 (3.4)	168 (1.3)	138 (1.3)	89 (1.3)	
LTRA prescriptions	N (% not missing)	2127 (100.0)	8902 (100.0)	12629 (100.0)	10899 (100.0)	7011 (100.0)	
	Mean (SD)	0.7 (2.4)	0.5 (2.4)	0.3 (2.0)	0.4 (1.8)	0.4 (1.8)	<0.001‡
	Median (IQR)	0 (0, 0)	0 (0, 0)	0 (0, 0)	0 (0, 0)	0 (0, 0)	
	Min, Max	(0, 17)	(0, 57)	(0, 52)	(0, 49)	(0, 48)	
LTRA prescriptions (categorised)	N (% not missing)	2127 (100.0)	8902 (100.0)	12629 (100.0)	10899 (100.0)	7011 (100.0)	
	0, n (%)	1890 (88.9)	8165 (91.7)	11918 (94.4)	10126 (92.9)	6531 (93.2)	<0.001*
	1, n (%)	52 (2.4)	147 (1.7)	196 (1.6)	250 (2.3)	106 (1.5)	
	≥2, n (%)	185 (8.7)	590 (6.6)	515 (4.1)	523 (4.8)	374 (5.3)	
Spacer prescription	N (% not missing)	2127 (100.0)	8902 (100.0)	12629 (100.0)	10899 (100.0)	7011 (100.0)	
	No, n (%)	1447 (68.0)	7404 (83.2)	8517 (67.4)	9371 (86.0)	4697 (67.0)	<0.001*
	Yes, n (%)	680 (32.0)	1498 (16.8)	4112 (32.6)	1528 (14.0)	2314 (33.0)	
Pain-relief medication prescriptions	N (% not missing)	2127 (100.0)	8902 (100.0)	12629 (100.0)	10899 (100.0)	7011 (100.0)	
	Mean (SD)	2.9 (5.7)	3.2 (7.1)	2.4 (5.6)	2.0 (4.9)	2.5 (5.1)	<0.001‡
	Median (IQR)	0 (0, 3)	0 (0, 3)	0 (0, 2)	0 (0, 1)	0 (0, 2)	
	Min, Max	(0, 61)	(0, 319)	(0, 192)	(0, 73)	(0, 77)	
Pain-relief medication prescriptions (categorised)	N (% not missing)	2127 (100.0)	8902 (100.0)	12629 (100.0)	10899 (100.0)	7011 (100.0)	
	0, n (%)	1235 (58.1)	4854 (54.5)	7630 (60.4)	7055 (64.7)	4264 (60.8)	<0.001*
	1-4, n (%)	454 (21.3)	2036 (22.9)	2835 (22.4)	2320 (21.3)	1486 (21.2)	
	≥5, n (%)	438 (20.6)	2012 (22.6)	2164 (17.1)	1524 (14.0)	1261 (18.0)	

		TOTAL COHORT					
	Measure	FP/FOR	FP/SAL DPI	FP/SAL MDI	BUD/FOR	BDP/FOR	p-value
Non-steroidal anti-inflammatory drugs (NSAIDs) prescriptions	N (% not missing)	2127 (100.0)	8902 (100.0)	12629 (100.0)	10899 (100.0)	7011 (100.0)	<0.001‡
	Mean (SD)	0.7 (2.4)	0.7 (2.5)	0.6 (2.0)	0.6 (2.0)	0.7 (2.2)	
	Median (IQR)	0 (0, 0)	0 (0, 0)	0 (0, 0)	0 (0, 0)	0 (0, 0)	
	Min, Max	(0, 52)	(0, 63)	(0, 50)	(0, 53)	(0, 54)	
Non-steroidal anti-inflammatory drugs (NSAIDs) prescriptions (categorised)	N (% not missing)	2127 (100.0)	8902 (100.0)	12629 (100.0)	10899 (100.0)	7011 (100.0)	<0.001*
	0, n (%)	1692 (79.5)	7219 (81.1)	10345 (81.9)	8925 (81.9)	5490 (78.3)	
	1-2, n (%)	272 (12.8)	1064 (12.0)	1539 (12.2)	1324 (12.1)	986 (14.1)	
	3-4, n (%)	58 (2.7)	205 (2.3)	291 (2.3)	258 (2.4)	195 (2.8)	
	≥5, n (%)	105 (4.9)	414 (4.7)	454 (3.6)	392 (3.6)	340 (4.8)	
Beta-blocker prescriptions	N (% not missing)	2127 (100.0)	8902 (100.0)	12629 (100.0)	10899 (100.0)	7011 (100.0)	.023‡
	Mean (SD)	0.4 (2.3)	0.5 (2.4)	0.4 (2.6)	0.5 (2.5)	0.4 (2.3)	
	Median (IQR)	0 (0, 0)	0 (0, 0)	0 (0, 0)	0 (0, 0)	0 (0, 0)	
	Min, Max	(0, 54)	(0, 50)	(0, 83)	(0, 59)	(0, 55)	
Beta-blocker prescriptions (categorised)	N (% not missing)	2127 (100.0)	8902 (100.0)	12629 (100.0)	10899 (100.0)	7011 (100.0)	0.007*
	0, n (%)	2024 (95.2)	8345 (93.7)	11936 (94.5)	10248 (94.0)	6631 (94.6)	
	1-4, n (%)	26 (1.2)	165 (1.9)	241 (1.9)	221 (2.0)	108 (1.5)	
	5-9, n (%)	38 (1.8)	191 (2.1)	230 (1.8)	231 (2.1)	120 (1.7)	
	≥10, n (%)	39 (1.8)	201 (2.3)	222 (1.8)	199 (1.8)	152 (2.2)	

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

5.2.2 Patients aged ⩾12 and <18 years with asthma (licensed FP/FOR: 50/5, 125/5; off-label FP/FOR: 250/10)

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. Dose per day of ICS/LABA and LTRA prescription at the index date was highest for the FP/FOR group; SABA prescription was similar across all treatment groups. FP/FOR patients had a higher proportion of rhinitis and eczema recorded and were more likely to be FDC ICS/LABA switchers rather than initiators. First diagnosis of asthma, CCI score, GP consultations, hospitalisations and exacerbations were broadly similar across treatment groups.

5.2.2.1 Demographic characteristics

		TOTAL COHORT						
	Measure	FP/FOR licensed	FP/FOR offlabel	FP/SAL DPI	FP/SAL MDI	BUD/FOR	BDP/FOR	p-value
Age at index date (years)	N (% not missing)	77 (100.0)	8 (100.0)	334 (100.0)	862 (100.0)	614 (100.0)	NA	<0.001‡
	Mean (SD)	14.7 (1.6)	15.8 (1.5)	14.4 (1.7)	14.3 (1.7)	14.6 (1.7)	NA	
	Median (IQR)	15 (13, 16)	16 (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)	77 (100.0)	8 (100.0)	334 (100.0)	862 (100.0)	614 (100.0)	NA	0.071*
	Female, n (%)	33 (42.9)	n≥5	150 (44.9)	433 (50.2)	301 (49.0)	NA	
	Male, n (%)	44 (57.1)	n<5	184 (55.1)	429 (49.8)	313 (51.0)	NA	
Height (m) - closest to index date	N (% not missing)	64 (83.1)	7 (87.5)	266 (79.6)	719 (83.4)	496 (80.8)	NA	.041‡
	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 (1.5, 1.7)	1.6 (1.6, 1.7)	1.6 (1.5, 1.7)	1.6 (1.5, 1.7)	1.6 (1.6, 1.7)	NA	
	Min, Max	(1.4, 1.8)	(1.4, 1.7)	(1.3, 2.0)	(1.2, 1.9)	(1.2, 1.9)	NA	
Weight (kg) - closest to index date	N (% not missing)	59 (76.6)	6 (75.0)	214 (64.1)	562 (65.2)	400 (65.1)	NA	.098‡
	Mean (SD)	61.5 (16.5)	88.2 (30.6)	60.3 (15.9)	60.1 (15.6)	61.3 (16.3)	NA	
	Median (IQR)	57 (50, 71)	79 (67, 112)	58 (49, 69)	58 (50, 69)	58 (51, 68)	NA	
	Min, Max	(37, 113)	(54.9, 136.5)	(26, 125)	(26, 145)	(28, 140)	NA	
CHILD BMI (kg/m2) (categorised)	N (% not missing)	58 (75.3)	6 (75.0)	213 (63.8)	570 (66.1)	401 (65.3)	NA	0.731*
	Normal, n (%)	n≥5	n<5	125 (58.7)	333 (58.4)	230 (57.4)	NA	
	Obese, n (%)	n≥5	n<5	31 (14.6)	94 (16.5)	75 (18.7)	NA	

		TOTAL COHORT						
	Measure	FP/FOR licensed	FP/FOR offlabel	FP/SAL DPI	FP/SAL MDI	BUD/FOR	BDP/FOR	p-value
	Overweight, n (%)	n≥5	n<5	45 (21.1)	118 (20.7)	75 (18.7)	NA	
	Underweight, n (%)	n<5	n<5	12 (5.6)	25 (4.4)	21 (5.2)	NA	
PEF % predicted	N (% not missing)	50 (64.9)	5 (62.5)	200 (59.9)	517 (60.0)	365 (59.4)	NA	.473‡
	Mean (SD)	94.5 (20.4)	85.6 (20.6)	95.3 (21.5)	97.7 (20.3)	97.5 (22.1)	NA	
	Median (IQR)	95.4 (79.6, 107.9)	79.6 (69.4, 105.9)	97.1 (84.9, 108.8)	97.7 (85.0, 111.8)	100.0 (82.2, 113.4)	NA	
	Min, Max	(44.1, 138.2)	(64.2, 108.8)	(20.4, 139.4)	(26.0, 150.0)	(25.7, 147.0)	NA	
Smoking Status	N (% not missing)	77 (100.0)	8 (100.0)	321 (96.1)	811 (94.1)	592 (96.4)	NA	<0.001*
	Non-smoker, n (%)	n≥5	n≥5	n≥5	744 (91.7)	556 (93.9)	NA	
	Current smoker, n (%)	n<5	n<5	n≥5	55 (6.8)	29 (4.9)	NA	
	Ex-smoker, n (%)	n<5	n<5	n<5	12 (1.5)	7 (1.2)	NA	

Table 8: Demographic characteristics by FDC/ICS LABA (patients aged ≥12 and <18 years with asthma)
‡ Kruskal-Wallis test, * Chi-square test, NA – not applicable

5.2.2.2 Medication prescribed at index date

		TOTAL COHORT						
	Measure	FP/FOR licensed	FP/FOR offlabel	FP/SAL DPI	FP/SAL MDI	BUD/FOR	BDP/FOR	p-value
Continuous data available prior index date (years)	N (% not missing)	77 (100.0)	8 (100.0)	334 (100.0)	862 (100.0)	614 (100.0)	NA	<0.001‡
	Mean (SD)	10.7 (4.9)	14.2 (2.8)	8.9 (5.8)	8.7 (5.7)	9.6 (5.9)	NA	
	Median (IQR)	12.4 (7.7, 14.1)	14.6 (12.1, 16.6)	10.9 (2.6, 13.7)	10.6 (2.6, 13.3)	11.6 (4.0, 14.7)	NA	
	Min, Max	(0.0, 17.2)	(9.5, 17.7)	(0, 18)	(0, 18)	(0, 18)	NA	
Prescribed FDC ICS/LABA inhaler dose (dose per puff)	N (% not missing)	77 (100.0)	8 (100.0)	334 (100.0)	862 (100.0)	614 (100.0)	NA	<0.001*
	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	

		TOTAL COHORT						
	Measure	FP/FOR licensed	FP/FOR offlabel	FP/SAL DPI	FP/SAL MDI	BUD/FOR	BDP/FOR	p-value
	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 dosing instructions (FP equivalent dose per day)	N (% not missing)	71 (92.2)	7 (87.5)	172 (51.5)	749 (86.9)	459 (74.8)	NA	<0.001‡
	Mean (SD)	409.2 (132.7)	1000.0 (0.0)	370.3 (294.0)	375.5 (216.1)	205.0 (115.9)	NA	
	Median (IQR)	500 (250, 500)	1000 (1000, 1000)	200 (200, 500)	250 (200, 500)	200 (100, 200)	NA	
	Min, Max	(100, 500)	(1000, 1000)	(200, 2000)	(50, 1000)	(100, 1200)	NA	
Prescribed FDC ICS/LABA dosing instructions (FP equivalent dose per day) (categorised)	N (% not missing)	71 (92.2)	7 (87.5)	172 (51.5)	749 (86.9)	459 (74.8)	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	
Duration of FDC ICS/LABA prescription (outcome), (months)	N (% not missing)	77 (100.0)	8 (100.0)	334 (100.0)	862 (100.0)	614 (100.0)	NA	.175‡
	Mean (SD)	18.3 (11.9)	16.0 (13.9)	15.5 (14.5)	16.7 (13.9)	16.2 (14.6)	NA	
	Median (IQR)	19 (5, 27)	12.1 (3.6, 29.9)	10 (2, 27)	13.6 (3.1, 27.2)	12 (2, 27)	NA	
	Min, Max	(0.6, 39.0)	(1.1, 35.6)	(0, 51)	(0, 50)	(0, 50)	NA	
SABA prescriptions	N (% not missing)	77 (100.0)	8 (100.0)	334 (100.0)	862 (100.0)	614 (100.0)	NA	0.405*
	No, n (%)	62 (80.5)	n≥5	245 (73.4)	651 (75.5)	477 (77.7)	NA	
	Yes, n (%)	15 (19.5)	n<5	89 (26.6)	211 (24.5)	137 (22.3)	NA	
SAMA prescriptions	N (% not missing)	77 (100.0)	8 (100.0)	334 (100.0)	862 (100.0)	614 (100.0)	NA	NA
	No, n (%)	77 (100.0)	8 (100.0)	334 (100.0)	862 (100.0)	614 (100.0)	NA	
LABA prescriptions	N (% not missing)	77 (100.0)	8 (100.0)	334 (100.0)	862 (100.0)	614 (100.0)	NA	0.663*
	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)	77 (100.0)	8 (100.0)	334 (100.0)	862 (100.0)	614 (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)	77 (100.0)	8 (100.0)	334 (100.0)	862 (100.0)	614 (100.0)	NA	0.545*
	No, n (%)	n≥5	n≥5	328 (98.2)	845 (98.0)	607 (98.9)	NA	

		TOTAL COHORT						
	Measure	FP/FOR licensed	FP/FOR offlabel	FP/SAL DPI	FP/SAL MDI	BUD/FOR	BDP/FOR	p-value
	Yes, n (%)	n<5	n<5	6 (1.8)	17 (2.0)	7 (1.1)	NA	
Theophylline prescriptions	N (% not missing)	77 (100.0)	8 (100.0)	334 (100.0)	862 (100.0)	614 (100.0)	NA	0.040*
	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)	77 (100.0)	8 (100.0)	334 (100.0)	862 (100.0)	614 (100.0)	NA	<0.001*
	No, n (%)	65 (84.4)	n<5	306 (91.6)	813 (94.3)	571 (93.0)	NA	
	Yes, n (%)	12 (15.6)	n<5	28 (8.4)	49 (5.7)	43 (7.0)	NA	

Table 9: 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

5.2.2.3 Comorbidities

		TOTAL COHORT						
	Measure	FP/FOR licensed	FP/FOR offlabel	FP/SAL DPI	FP/SAL MDI	BUD/FOR	BDP/FOR	p-value
Year of first asthma diagnosis	N (% not missing)	77 (100.0)	8 (100.0)	334 (100.0)	862 (100.0)	614 (100.0)	NA	.005‡
	Mean (SD)	2004.4 (4.4)	2002.5 (3.6)	2004.3 (4.8)	2005.2 (4.8)	2004.5 (4.7)	NA	
	Median (IQR)	2004 (2001, 2007)	2003 (1999, 2005)	2004 (2000, 2009)	2004 (2001, 2010)	2004 (2001, 2008)	NA	
	Min, Max	(1997, 2014)	(1999, 2009)	(1995, 2014)	(1996, 2014)	(1996, 2014)	NA	
Duration of asthma (years)	N (% not missing)	77 (100.0)	8 (100.0)	334 (100.0)	862 (100.0)	614 (100.0)	NA	.002‡
	Mean (SD)	8.8 (4.3)	10.8 (3.5)	8.1 (4.8)	7.4 (4.8)	8.1 (4.6)	NA	
	Median (IQR)	9.4 (5.9, 12.0)	10.8 (8.6, 13.8)	9.0 (3.9, 12.1)	8.1 (2.9, 11.2)	9.0 (4.4, 11.7)	NA	
	Min, Max	(0, 16)	(4.7, 14.9)	(0, 17)	(0, 17)	(0, 17)	NA	
Comorbid rhinitis	N (% not missing)	77 (100.0)	8 (100.0)	334 (100.0)	862 (100.0)	614 (100.0)	NA	<0.001*
	No, n (%)	55 (71.4)	n≥5	261 (78.1)	741 (86.0)	501 (81.6)	NA	
	Yes, n (%)	22 (28.6)	n<5	73 (21.9)	121 (14.0)	113 (18.4)	NA	
Comorbid eczema	N (% not missing)	77 (100.0)	8 (100.0)	334 (100.0)	862 (100.0)	614 (100.0)	NA	0.215*
	No, n (%)	63 (81.8)	n≥5	301 (90.1)	774 (89.8)	556 (90.6)	NA	
	Yes, n (%)	14 (18.2)	n<5	33 (9.9)	88 (10.2)	58 (9.4)	NA	
Comorbid GERD	N (% not missing)	77 (100.0)	8 (100.0)	334 (100.0)	862 (100.0)	614 (100.0)	NA	0.523*
	No, n (%)	n≥5	n≥5	n≥5	856 (99.3)	n≥5	NA	
	Yes, n (%)	n<5	n<5	n<5	6 (0.7)	n<5	NA	

		TOTAL COHORT						
	Measure	FP/FOR licensed	FP/FOR offlabel	FP/SAL DPI	FP/SAL MDI	BUD/FOR	BDP/FOR	p-value
Charlson Comorbidity Index (CCI)	N (% not missing)	77 (100.0)	8 (100.0)	334 (100.0)	862 (100.0)	614 (100.0)	NA	.109‡
	Mean (SD)	3.5 (1.4)	3.0 (1.9)	3.1 (1.7)	3.3 (1.6)	3.3 (1.5)	NA	
	Median (IQR)	4 (4, 4)	4 (2, 4)	4 (4, 4)	4 (4, 4)	4 (4, 4)	NA	
	Min, Max	(0, 4)	(0, 4)	(0, 4)	(0, 7)	(0, 7)	NA	
Charlson Comorbidity Index (CCI) (categorised)	N (% not missing)	77 (100.0)	8 (100.0)	334 (100.0)	862 (100.0)	614 (100.0)	NA	0.463*
	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 10: Comorbidities by FDC/ICS LABA (patients aged ≥12 and <18 years with asthma)
‡ Kruskal-Wallis test, * Chi-square test, NA – not applicable

5.2.2.4 Consultations and hospitalisations in year prior to index date

		TOTAL COHORT						
	Measure	FP/FOR licensed	FP/FOR offlabel	FP/SAL DPI	FP/SAL MDI	BUD/FOR	BDP/FOR	p-value
Respiratory GP consultations without prescription for an oral corticosteroid	N (% not missing)	77 (100.0)	8 (100.0)	334 (100.0)	862 (100.0)	614 (100.0)	NA	.037‡
	Mean (SD)	1.2 (1.4)	3.0 (3.7)	1.3 (1.4)	1.6 (1.7)	1.5 (1.6)	NA	
	Median (IQR)	1 (0, 2)	2 (0, 5)	1 (0, 2)	1 (0, 2)	1 (0, 2)	NA	
	Min, Max	(0, 5)	(0, 10)	(0, 7)	(0, 13)	(0, 10)	NA	
Respiratory GP consultations without prescription for an oral corticosteroid (categorised)	N (% not missing)	77 (100.0)	8 (100.0)	334 (100.0)	862 (100.0)	614 (100.0)	NA	0.018*
	0, n (%)	32 (41.6)	n<5	115 (34.4)	268 (31.1)	185 (30.1)	NA	
	1, n (%)	21 (27.3)	n<5	105 (31.4)	229 (26.6)	177 (28.8)	NA	
	2, n (%)	6 (7.8)	n<5	60 (18.0)	159 (18.4)	131 (21.3)	NA	
	≥3, n (%)	18 (23.4)	n<5	54 (16.2)	206 (23.9)	121 (19.7)	NA	
Asthma GP consultations without prescription for an oral corticosteroid	N (% not missing)	77 (100.0)	8 (100.0)	334 (100.0)	862 (100.0)	614 (100.0)	NA	.182‡
	Mean (SD)	0.7 (0.9)	1.4 (1.4)	0.9 (1.0)	0.9 (1.1)	0.9 (1.1)	NA	
	Median (IQR)	0 (0, 1)	2 (0, 2)	1 (0, 1)	1 (0, 1)	1 (0, 1)	NA	
	Min, Max	(0, 4)	(0, 4)	(0, 5)	(0, 8)	(0, 8)	NA	
Asthma GP consultations without prescription for an oral corticosteroid (categorised)	N (% not missing)	77 (100.0)	8 (100.0)	334 (100.0)	862 (100.0)	614 (100.0)	NA	0.514*
	0, n (%)	n≥5	n<5	152 (45.5)	378 (43.9)	261 (42.5)	NA	
	1, n (%)	n≥5	n<5	110 (32.9)	280 (32.5)	215 (35.0)	NA	
	2, n (%)	n≥5	n<5	50 (15.0)	130 (15.1)	92 (15.0)	NA	
	≥3, n (%)	n<5	n<5	22 (6.6)	74 (8.6)	46 (7.5)	NA	
Lower respiratory hospital outpatient attendances	N (% not missing)	44 (100.0)	n<5	169 (100.0)	516 (100.0)	353 (100.0)	NA	NA
	Mean (SD)	0.0 (0.0)	n<5	0.0 (0.0)	0.0 (0.0)	0.0 (0.0)	NA	
	Median (IQR)	0 (0, 0)	n<5	0 (0, 0)	0 (0, 0)	0 (0, 0)	NA	

		TOTAL COHORT						
	Measure	FP/FOR licensed	FP/FOR offlabel	FP/SAL DPI	FP/SAL MDI	BUD/FOR	BDP/FOR	p-value
	Min, Max	(0, 0)	n<5	(0, 0)	(0, 0)	(0, 0)	NA	
Lower respiratory hospital outpatient attendances (categorised)	N (% not missing)	44 (100.0)	n<5	169 (100.0)	516 (100.0)	353 (100.0)	NA	NA
	0, n (%)	44 (100.0)	n<5	169 (100.0)	516 (100.0)	353 (100.0)	NA	
Asthma hospital outpatient attendances	N (% not missing)	44 (100.0)	n<5	169 (100.0)	516 (100.0)	353 (100.0)	NA	NA
	Mean (SD)	0.0 (0.0)	n<5	0.0 (0.0)	0.0 (0.0)	0.0 (0.0)	NA	
	Median (IQR)	0 (0, 0)	n<5	0 (0, 0)	0 (0, 0)	0 (0, 0)	NA	
	Min, Max	(0, 0)	n<5	(0, 0)	(0, 0)	(0, 0)	NA	
Asthma hospital outpatient attendances (categorised)	N (% not missing)	44 (100.0)	n<5	169 (100.0)	516 (100.0)	353 (100.0)	NA	NA
	0, n (%)	44 (100.0)	n<5	169 (100.0)	516 (100.0)	353 (100.0)	NA	
Lower respiratory inpatient hospitalisations	N (% not missing)	44 (100.0)	n<5	169 (100.0)	516 (100.0)	353 (100.0)	NA	<0.001‡
	Mean (SD)	0.0 (0.0)	n<5	0.0 (0.1)	0.0 (0.0)	0.0 (0.1)	NA	
	Median (IQR)	0 (0, 0)	n<5	0 (0, 0)	0 (0, 0)	0 (0, 0)	NA	
	Min, Max	(0, 0)	n<5	(0, 1)	(0, 0)	(0, 1)	NA	
Lower respiratory inpatient hospitalisations (categorised)	N (% not missing)	44 (100.0)	n<5	169 (100.0)	516 (100.0)	353 (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	N (% not missing)	44 (100.0)	n<5	169 (100.0)	516 (100.0)	353 (100.0)	NA	.492‡
	Mean (SD)	0.0 (0.0)	n<5	0.1 (0.8)	0.1 (0.4)	0.1 (0.5)	NA	
	Median (IQR)	0 (0, 0)	n<5	0 (0, 0)	0 (0, 0)	0 (0, 0)	NA	
	Min, Max	(0, 0)	n<5	(0, 7)	(0, 6)	(0, 5)	NA	
Asthma inpatient hospitalisations (categorised)	N (% not missing)	44 (100.0)	n<5	169 (100.0)	516 (100.0)	353 (100.0)	NA	0.338*
	0, n (%)	n≥5	n<5	n≥5	488 (94.6)	338 (95.8)	NA	
	1, n (%)	n<5	n<5	n≥5	23 (4.5)	7 (2.0)	NA	
	≥2, n (%)	n<5	n<5	n<5	5 (1.0)	8 (2.3)	NA	
Asthma exacerbations	N (% not missing)	44 (100.0)	n<5	169 (100.0)	516 (100.0)	353 (100.0)	NA	.465‡
	Mean (SD)	0.6 (0.8)	n<5	0.7 (1.2)	0.8 (1.1)	0.9 (1.2)	NA	
	Median (IQR)	0 (0, 1)	n<5	0 (0, 1)	0 (0, 1)	0 (0, 1)	NA	
	Min, Max	(0, 3)	n<5	(0, 7)	(0, 6)	(0, 6)	NA	
Asthma exacerbations (categorised)	N (% not missing)	44 (100.0)	n<5	169 (100.0)	516 (100.0)	353 (100.0)	NA	0.612*
	0, n (%)	24 (54.5)	n<5	99 (58.6)	275 (53.3)	182 (51.6)	NA	
	1, n (%)	13 (29.5)	n<5	41 (24.3)	133 (25.8)	91 (25.8)	NA	
	≥2, n (%)	7 (15.9)	n<5	29 (17.2)	108 (20.9)	80 (22.7)	NA	

Table 11: 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

5.2.2.5 Prescriptions for therapy in year prior to index date

		TOTAL COHORT						
	Measure	FP/FOR licensed	FP/FOR offlabel	FP/SAL DPI	FP/SAL MDI	BUD/FOR	BDP/FOR	p-value
FDC ICS+LABA prescriptions	N (% not missing)	77 (100.0)	8 (100.0)	334 (100.0)	862 (100.0)	614 (100.0)	NA	<0.001‡
	Mean (SD)	2.8 (5.5)	5.9 (3.9)	2.3 (4.1)	0.7 (2.4)	1.5 (3.7)	NA	
	Median (IQR)	0 (0, 4)	5.5 (3.5, 8.5)	0 (0, 4)	0 (0, 0)	0 (0, 0)	NA	
	Min, Max	(0, 40)	(0, 12)	(0, 23)	(0, 18)	(0, 37)	NA	
FDC ICS+LABA prescriptions (categorised)	N (% not missing)	77 (100.0)	8 (100.0)	334 (100.0)	862 (100.0)	614 (100.0)	NA	<0.001*
	0, n (%)	n≥5	n<5	212 (63.5)	764 (88.6)	485 (79.0)	NA	
	1, n (%)	n<5	n<5	11 (3.3)	11 (1.3)	14 (2.3)	NA	
	≥2, n (%)	n≥5	n≥5	111 (33.2)	87 (10.1)	115 (18.7)	NA	
SABA prescriptions	N (% not missing)	77 (100.0)	8 (100.0)	334 (100.0)	862 (100.0)	614 (100.0)	NA	.055‡
	Mean (SD)	2.4 (4.9)	7.0 (7.9)	3.6 (5.9)	3.1 (5.4)	3.5 (6.4)	NA	
	Median (IQR)	0 (0, 3)	5 (0, 12)	1 (0, 4)	1 (0, 4)	1 (0, 4)	NA	
	Min, Max	(0, 28)	(0, 22)	(0, 32)	(0, 58)	(0, 66)	NA	
SABA prescriptions (categorised)	N (% not missing)	77 (100.0)	8 (100.0)	334 (100.0)	862 (100.0)	614 (100.0)	NA	0.003*
	0, n (%)	n≥5	n<5	149 (44.6)	402 (46.6)	261 (42.5)	NA	
	1, n (%)	n<5	n<5	23 (6.9)	70 (8.1)	76 (12.4)	NA	
	≥2, n (%)	n≥5	n≥5	162 (48.5)	390 (45.2)	277 (45.1)	NA	
SAMA prescriptions	N (% not missing)	77 (100.0)	8 (100.0)	334 (100.0)	862 (100.0)	614 (100.0)	NA	.477‡
	Mean (SD)	0.0 (0.0)	0.0 (0.0)	0.0 (0.0)	0.0 (0.1)	0.0 (0.3)	NA	
	Median (IQR)	0 (0, 0)	0 (0, 0)	0 (0, 0)	0 (0, 0)	0 (0, 0)	NA	
	Min, Max	(0, 0)	(0, 0)	(0, 0)	(0, 2)	(0, 5)	NA	
SAMA prescriptions (categorised)	N (% not missing)	77 (100.0)	8 (100.0)	334 (100.0)	862 (100.0)	614 (100.0)	NA	0.792*
	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	
	≥2, n (%)	n<5	n<5	n<5	n<5	n<5	NA	
LABA prescriptions	N (% not missing)	77 (100.0)	8 (100.0)	334 (100.0)	862 (100.0)	614 (100.0)	NA	.090‡
	Mean (SD)	0.6 (3.4)	0.0 (0.0)	0.3 (1.4)	0.4 (1.6)	0.3 (1.8)	NA	
	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, 16)	(0, 24)	NA	
LABA prescriptions (categorised)	N (% not missing)	77 (100.0)	8 (100.0)	334 (100.0)	862 (100.0)	614 (100.0)	NA	0.307*
	0, n (%)	n≥5	n≥5	308 (92.2)	774 (89.8)	572 (93.2)	NA	
	1, n (%)	n<5	n<5	8 (2.4)	30 (3.5)	13 (2.1)	NA	
	≥2, n (%)	n<5	n<5	18 (5.4)	58 (6.7)	29 (4.7)	NA	
LAMA prescriptions	N (% not missing)	77 (100.0)	8 (100.0)	334 (100.0)	862 (100.0)	614 (100.0)	NA	<0.001‡
	Mean (SD)	0.0 (0.0)	0.3 (0.7)	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)	0 (0, 0)	NA	
	Min, Max	(0, 0)	(0, 2)	(0, 0)	(0, 0)	(0, 0)	NA	

		TOTAL COHORT						
	Measure	FP/FOR licensed	FP/FOR offlabel	FP/SAL DPI	FP/SAL MDI	BUD/FOR	BDP/FOR	p-value
LAMA prescriptions (categorised)	N (% not missing)	77 (100.0)	8 (100.0)	334 (100.0)	862 (100.0)	614 (100.0)	NA	<0.001*
	0, n (%)	n≥5	n≥5	n≥5	n≥5	n≥5	NA	
	≥2, n (%)	n<5	n<5	n<5	n<5	n<5	NA	
ICS only prescriptions	N (% not missing)	77 (100.0)	8 (100.0)	334 (100.0)	862 (100.0)	614 (100.0)	NA	<0.001‡
	Mean (SD)	2.2 (3.6)	0.3 (0.7)	1.9 (3.2)	2.9 (3.4)	2.1 (2.9)	NA	
	Median (IQR)	0 (0, 3)	0 (0, 0)	0 (0, 3)	2 (0, 4)	1 (0, 3)	NA	
	Min, Max	(0, 14)	(0, 2)	(0, 18)	(0, 22)	(0, 22)	NA	
ICS only prescriptions (categorised)	N (% not missing)	77 (100.0)	8 (100.0)	334 (100.0)	862 (100.0)	614 (100.0)	NA	<0.001*
	0, n (%)	n≥5	n≥5	182 (54.5)	276 (32.0)	278 (45.3)	NA	
	1, n (%)	n<5	n<5	37 (11.1)	109 (12.6)	75 (12.2)	NA	
	≥2, n (%)	n≥5	n<5	115 (34.4)	477 (55.3)	261 (42.5)	NA	
Theophylline prescriptions	N (% not missing)	77 (100.0)	8 (100.0)	334 (100.0)	862 (100.0)	614 (100.0)	NA	.213‡
	Mean (SD)	0.0 (0.0)	0.0 (0.0)	0.0 (0.5)	0.0 (0.4)	0.0 (0.0)	NA	
	Median (IQR)	0 (0, 0)	0 (0, 0)	0 (0, 0)	0 (0, 0)	0 (0, 0)	NA	
	Min, Max	(0, 0)	(0, 0)	(0, 8)	(0, 9)	(0, 0)	NA	
Theophylline prescriptions (categorised)	N (% not missing)	77 (100.0)	8 (100.0)	334 (100.0)	862 (100.0)	614 (100.0)	NA	0.667*
	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	
	≥2, n (%)	n<5	n<5	n<5	n<5	n<5	NA	
LTRA prescriptions	N (% not missing)	77 (100.0)	8 (100.0)	334 (100.0)	862 (100.0)	614 (100.0)	NA	<0.001‡
	Mean (SD)	1.3 (2.6)	2.4 (3.4)	1.0 (2.6)	0.5 (1.7)	0.8 (2.3)	NA	
	Median (IQR)	0 (0, 1)	1 (0, 5)	0 (0, 0)	0 (0, 0)	0 (0, 0)	NA	
	Min, Max	(0, 12)	(0, 9)	(0, 13)	(0, 13)	(0, 16)	NA	
LTRA prescriptions (categorised)	N (% not missing)	77 (100.0)	8 (100.0)	334 (100.0)	862 (100.0)	614 (100.0)	NA	<0.001*
	0, n (%)	n≥5	n<5	269 (80.5)	763 (88.5)	505 (82.2)	NA	
	1, n (%)	n<5	n<5	7 (2.1)	24 (2.8)	26 (4.2)	NA	
	≥2, n (%)	n≥5	n<5	58 (17.4)	75 (8.7)	83 (13.5)	NA	
Spacer prescription	N (% not missing)	77 (100.0)	8 (100.0)	334 (100.0)	862 (100.0)	614 (100.0)	NA	<0.001*
	No, n (%)	49 (63.6)	n<5	251 (75.1)	456 (52.9)	461 (75.1)	NA	
	Yes, n (%)	28 (36.4)	n≥5	83 (24.9)	406 (47.1)	153 (24.9)	NA	
Pain-relief medication prescriptions	N (% not missing)	77 (100.0)	8 (100.0)	334 (100.0)	862 (100.0)	614 (100.0)	NA	.791‡
	Mean (SD)	0.2 (0.8)	0.5 (1.1)	0.3 (1.0)	0.2 (0.6)	0.2 (0.6)	NA	
	Median (IQR)	0 (0, 0)	0 (0, 1)	0 (0, 0)	0 (0, 0)	0 (0, 0)	NA	
	Min, Max	(0, 5)	(0, 3)	(0, 9)	(0, 8)	(0, 7)	NA	
Pain-relief medication prescriptions (categorised)	N (% not missing)	77 (100.0)	8 (100.0)	334 (100.0)	862 (100.0)	614 (100.0)	NA	0.331*
	0, n (%)	n≥5	n≥5	290 (86.8)	n≥5	n≥5	NA	
	1-4, n (%)	n≥5	n<5	39 (11.7)	n≥5	n≥5	NA	
	≥5, n (%)	n<5	n<5	5 (1.5)	n<5	n<5	NA	

		TOTAL COHORT						
	Measure	FP/FOR licensed	FP/FOR offlabel	FP/SAL DPI	FP/SAL MDI	BUD/FOR	BDP/FOR	p-value
Non-steroidal anti-inflammatory drugs (NSAIDs) prescriptions	N (% not missing)	77 (100.0)	8 (100.0)	334 (100.0)	862 (100.0)	614 (100.0)	NA	.078‡
	Mean (SD)	0.1 (0.4)	0.8 (1.4)	0.2 (0.6)	0.1 (0.5)	0.1 (0.4)	NA	
	Median (IQR)	0 (0, 0)	0 (0, 1)	0 (0, 0)	0 (0, 0)	0 (0, 0)	NA	
	Min, Max	(0, 2)	(0, 4)	(0, 5)	(0, 6)	(0, 2)	NA	
Non-steroidal anti-inflammatory drugs (NSAIDs) prescriptions (categorised)	N (% not missing)	77 (100.0)	8 (100.0)	334 (100.0)	862 (100.0)	614 (100.0)	NA	<0.001*
	0, n (%)	n≥5	n≥5	n≥5	n≥5	n≥5	NA	
	1-2, n (%)	n≥5	n<5	n≥5	n≥5	n≥5	NA	
	3-4, 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 12: 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

5.2.3 4-11 years paediatric asthma patients

The FP/FOR group was small for this subgroup. For patients with asthma aged 4-11 years, demographic characteristics were broadly similar across treatment groups. Respiratory prescriptions at and prior to index date were similar between groups as were date of first diagnosis of asthma, comorbidities, GP consultations, hospitalisations and exacerbations. The daily dose prescribed at index date was similar across treatment groups but FP/SAL MDI patients were more likely to be initiators than the other treatment groups.

5.2.3.1 Demographic characteristics

		TOTAL COHORT					
	Measure	FP/FOR	FP/SAL DPI	FP/SAL MDI	BUD/FOR	BDP/FOR	p-value
Age at index date (years)	N (% not missing)	12 (100.0)	150 (100.0)	971 (100.0)	230 (100.0)	NA	<0.001‡
	Mean (SD)	8.1 (2.4)	8.6 (2.1)	7.6 (2.1)	9.2 (1.6)	NA	
	Median (IQR)	8.5 (5.5, 10.5)	9 (7, 10)	7 (6, 9)	10 (8, 11)	NA	
	Min, Max	(5, 11)	(4, 11)	(4, 11)	(4, 11)	NA	
Gender	N (% not missing)	12 (100.0)	150 (100.0)	971 (100.0)	230 (100.0)	NA	0.468*
	Female, n (%)	5 (41.7)	63 (42.0)	381 (39.2)	103 (44.8)	NA	
	Male, n (%)	7 (58.3)	87 (58.0)	590 (60.8)	127 (55.2)	NA	
Height (m) - closest to index date	N (% not missing)	8 (66.7)	116 (77.3)	770 (79.3)	191 (83.0)	NA	<0.001‡
	Mean (SD)	1.3 (0.1)	1.3 (0.2)	1.3 (0.1)	1.4 (0.1)	NA	
	Median (IQR)	1.2 (1.2, 1.3)	1.3 (1.2, 1.4)	1.3 (1.1, 1.4)	1.4 (1.3, 1.4)	NA	
	Min, Max	(1.2, 1.4)	(0.9, 1.7)	(0.9, 1.8)	(1.0, 1.7)	NA	
Weight (kg) - closest to index date	N (% not missing)	10 (83.3)	109 (72.7)	701 (72.2)	158 (68.7)	NA	<0.001‡
	Mean (SD)	26.4 (6.7)	31.4 (11.0)	27.5 (9.9)	35.3 (11.6)	NA	
	Median (IQR)	24.4 (21.7, 29.5)	29 (23, 39)	25 (20, 33)	34 (27, 42)	NA	
	Min, Max	(19, 42)	(14, 64)	(11, 66)	(16, 80)	NA	
CHILD BMI (kg/m2) (categorised)	N (% not missing)	8 (66.7)	95 (63.3)	630 (64.9)	148 (64.3)	NA	0.145*
	Normal, n (%)	n<5	56 (58.9)	372 (59.0)	96 (64.9)	NA	
	Obese, n (%)	n<5	17 (17.9)	92 (14.6)	29 (19.6)	NA	
	Overweight, n (%)	n<5	11 (11.6)	105 (16.7)	17 (11.5)	NA	
	Underweight, n (%)	n<5	11 (11.6)	61 (9.7)	6 (4.1)	NA	
PEF % predicted	N (% not missing)	n<5	63 (42.0)	371 (38.2)	139 (60.4)	NA	.771‡
	Mean (SD)	n<5	96.0 (23.6)	93.9 (23.0)	94.5 (22.5)	NA	
	Median (IQR)	n<5	95.6 (80.4, 107.5)	94.5 (78.2, 107.5)	95.6 (79.9, 109.5)	NA	
	Min, Max	n<5	(28.4, 148.4)	(34.0, 148.4)	(23.9, 146.5)	NA	

Table 13: Demographic characteristics by FDC/ICS LABA (4-11 years paediatric asthma patients)
‡ Kruskal-Wallis test, * Chi-square test, NA – not applicable

5.2.3.2 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)	12 (100.0)	150 (100.0)	971 (100.0)	230 (100.0)	NA	.005‡
	Mean (SD)	5.5 (3.9)	5.7 (3.6)	5.5 (3.2)	6.3 (3.5)	NA	
	Median (IQR)	5.1 (2.4, 8.8)	5.8 (2.3, 9.0)	5.5 (3.1, 8.0)	6.9 (3.2, 9.2)	NA	
	Min, Max	(0.2, 11.5)	(0, 12)	(0, 12)	(0.0, 11.8)	NA	
Prescribed FDC ICS/LABA inhaler dose (dose per puff)	N (% not missing)	12 (100.0)	150 (100.0)	971 (100.0)	230 (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 dosing instructions (FP equivalent dose per day)	N (% not missing)	9 (75.0)	72 (48.0)	821 (84.6)	187 (81.3)	NA	<0.001‡
	Mean (SD)	305.6 (132.7)	219.4 (62.0)	193.4 (24.2)	151.7 (50.3)	NA	
	Median (IQR)	200 (200, 375)	200 (200, 200)	200 (200, 200)	150 (100, 200)	NA	
	Min, Max	(200, 500)	(100, 400)	(100, 300)	(50, 400)	NA	
Prescribed FDC ICS/LABA dosing instructions (FP equivalent dose per day) (categorised)	N (% not missing)	9 (75.0)	72 (48.0)	821 (84.6)	187 (81.3)	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	
Duration of FDC ICS/LABA prescription (outcome), (months)	N (% not missing)	12 (100.0)	150 (100.0)	971 (100.0)	230 (100.0)	NA	<0.001‡
	Mean (SD)	4.2 (8.4)	15.9 (14.6)	19.2 (14.1)	17.1 (14.1)	NA	
	Median (IQR)	1.8 (0.2, 3.6)	12 (2, 27)	19 (5, 30)	13.1 (3.2, 28.7)	NA	
	Min, Max	(0, 30)	(0, 48)	(0, 50)	(0, 48)	NA	
SABA prescriptions	N (% not missing)	12 (100.0)	150 (100.0)	971 (100.0)	230 (100.0)	NA	0.070*
	No, n (%)	7 (58.3)	115 (76.7)	795 (81.9)	180 (78.3)	NA	
	Yes, n (%)	5 (41.7)	35 (23.3)	176 (18.1)	50 (21.7)	NA	
SAMA prescriptions	N (% not missing)	12 (100.0)	150 (100.0)	971 (100.0)	230 (100.0)	NA	NA
	No, n (%)	12 (100.0)	150 (100.0)	971 (100.0)	230 (100.0)	NA	
LABA prescriptions	N (% not missing)	12 (100.0)	150 (100.0)	971 (100.0)	230 (100.0)	NA	0.838*
	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)	12 (100.0)	150 (100.0)	971 (100.0)	230 (100.0)	NA	NA
	No, n (%)	12 (100.0)	150 (100.0)	971 (100.0)	230 (100.0)	NA	
ICS only prescriptions	N (% not missing)	12 (100.0)	150 (100.0)	971 (100.0)	230 (100.0)	NA	<0.001*
	No, n (%)	n≥5	n≥5	953 (98.1)	n≥5	NA	

		TOTAL COHORT					
	Measure	FP/FOR	FP/SAL DPI	FP/SAL MDI	BUD/FOR	BDP/FOR	p-value
	Yes, n (%)	n<5	n<5	18 (1.9)	n<5	NA	
Theophylline prescriptions	N (% not missing)	12 (100.0)	150 (100.0)	971 (100.0)	230 (100.0)	NA	0.644*
	No, n (%)	n≥5	n≥5	n≥5	n≥5	NA	
	Yes, n (%)	n<5	n<5	n<5	n<5	NA	
LTRA prescriptions	N (% not missing)	12 (100.0)	150 (100.0)	971 (100.0)	230 (100.0)	NA	0.344*
	No, n (%)	n≥5	126 (84.0)	851 (87.6)	200 (87.0)	NA	
	Yes, n (%)	n<5	24 (16.0)	120 (12.4)	30 (13.0)	NA	

Table 14: Medication prescribed at index date by FDC/ICS LABA (4-11 years paediatric asthma patients)
‡ Kruskal-Wallis test, * Chi-square test, NA – not applicable

5.2.3.3 Comorbidities

		TOTAL COHORT					
	Measure	FP/FOR	FP/SAL DPI	FP/SAL MDI	BUD/FOR	BDP/FOR	p-value
Year of first asthma diagnosis	N (% not missing)	12 (100.0)	150 (100.0)	971 (100.0)	230 (100.0)	NA	<0.001‡
	Mean (SD)	2009.2 (2.9)	2008.5 (2.9)	2009.3 (2.6)	2008.4 (2.9)	NA	
	Median (IQR)	2009 (2007, 2012)	2009 (2006, 2011)	2010 (2007, 2012)	2008 (2006, 2011)	NA	
	Min, Max	(2005, 2013)	(2002, 2013)	(2002, 2014)	(2002, 2014)	NA	
Duration of asthma (years)	N (% not missing)	12 (100.0)	150 (100.0)	971 (100.0)	230 (100.0)	NA	<0.001‡
	Mean (SD)	3.9 (3.0)	4.0 (3.0)	3.2 (2.5)	4.2 (2.8)	NA	
	Median (IQR)	4.2 (0.8, 6.5)	3.6 (1.4, 6.4)	2.8 (1.0, 5.0)	4.4 (1.9, 6.1)	NA	
	Min, Max	(0, 8)	(0, 11)	(0, 11)	(0, 11)	NA	
Comorbid rhinitis	N (% not missing)	12 (100.0)	150 (100.0)	971 (100.0)	230 (100.0)	NA	0.058*
	No, n (%)	n≥5	131 (87.3)	851 (87.6)	186 (80.9)	NA	
	Yes, n (%)	n<5	19 (12.7)	120 (12.4)	44 (19.1)	NA	
Comorbid eczema	N (% not missing)	12 (100.0)	150 (100.0)	971 (100.0)	230 (100.0)	NA	0.249*
	No, n (%)	n≥5	123 (82.0)	829 (85.4)	190 (82.6)	NA	
	Yes, n (%)	n<5	27 (18.0)	142 (14.6)	40 (17.4)	NA	
Comorbid GERD	N (% not missing)	12 (100.0)	150 (100.0)	971 (100.0)	230 (100.0)	NA	0.417*
	No, n (%)	n≥5	n≥5	964 (99.3)	n≥5	NA	
	Yes, n (%)	n<5	n<5	7 (0.7)	n<5	NA	
Charlson Comorbidity Index (CCI)	N (% not missing)	12 (100.0)	150 (100.0)	971 (100.0)	230 (100.0)	NA	.298‡
	Mean (SD)	3.3 (1.6)	3.1 (1.7)	3.3 (1.5)	3.3 (1.5)	NA	

		TOTAL COHORT					
	Measure	FP/FOR	FP/SAL DPI	FP/SAL MDI	BUD/FOR	BDP/FOR	p-value
	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)	12 (100.0)	150 (100.0)	971 (100.0)	230 (100.0)	NA	
	0, n (%)	n<5	n≥5	n≥5	n≥5	NA	0.049*
	1-4, n (%)	n≥5	n≥5	n≥5	n≥5	NA	
	≥5, n (%)	n<5	n<5	n<5	n<5	NA	

Table 15: Comorbidities by FDC/ICS LABA (4-11 years paediatric asthma patients)
‡ Kruskal-Wallis test, * Chi-square test, NA – not applicable

5.2.3.4 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	N (% not missing)	12 (100.0)	150 (100.0)	971 (100.0)	230 (100.0)	NA	
	Mean (SD)	1.6 (2.4)	1.9 (1.8)	2.1 (2.0)	2.0 (2.1)	NA	.221‡
	Median (IQR)	1 (0, 3)	1 (1, 3)	2 (1, 3)	1 (1, 3)	NA	
	Min, Max	(0, 8)	(0, 7)	(0, 12)	(0, 12)	NA	
Respiratory GP consultations without prescription for an oral corticosteroid (categorised)	N (% not missing)	12 (100.0)	150 (100.0)	971 (100.0)	230 (100.0)	NA	
	0, n (%)	n≥5	35 (23.3)	224 (23.1)	56 (24.3)	NA	
	1, n (%)	n<5	49 (32.7)	237 (24.4)	65 (28.3)	NA	0.236*
	2, n (%)	n<5	23 (15.3)	191 (19.7)	40 (17.4)	NA	
	≥3, n (%)	n<5	43 (28.7)	319 (32.9)	69 (30.0)	NA	
Asthma GP consultations without prescription for an oral corticosteroid	N (% not missing)	12 (100.0)	150 (100.0)	971 (100.0)	230 (100.0)	NA	
	Mean (SD)	0.8 (1.1)	0.9 (1.1)	1.1 (1.2)	1.1 (1.4)	NA	.160‡
	Median (IQR)	0 (0, 1)	1 (0, 1)	1 (0, 2)	1 (0, 2)	NA	
	Min, Max	(0, 3)	(0, 6)	(0, 8)	(0, 8)	NA	
Asthma GP consultations without prescription for an oral corticosteroid (categorised)	N (% not missing)	12 (100.0)	150 (100.0)	971 (100.0)	230 (100.0)	NA	
	0, n (%)	n≥5	70 (46.7)	375 (38.6)	92 (40.0)	NA	
	1, n (%)	n<5	44 (29.3)	321 (33.1)	77 (33.5)	NA	0.424*
	2, n (%)	n<5	25 (16.7)	155 (16.0)	36 (15.7)	NA	
	≥3, n (%)	n<5	11 (7.3)	120 (12.4)	25 (10.9)	NA	
Lower respiratory hospital outpatient attendances	N (% not missing)	8 (100.0)	89 (100.0)	587 (100.0)	139 (100.0)	NA	
	Mean (SD)	0.0 (0.0)	0.0 (0.0)	0.0 (0.0)	0.0 (0.0)	NA	NA
	Median (IQR)	0 (0, 0)	0 (0, 0)	0 (0, 0)	0 (0, 0)	NA	
	Min, Max	(0, 0)	(0, 0)	(0, 0)	(0, 0)	NA	
	N (% not missing)	8 (100.0)	89 (100.0)	587 (100.0)	139 (100.0)	NA	NA

		TOTAL COHORT					
	Measure	FP/FOR	FP/SAL DPI	FP/SAL MDI	BUD/FOR	BDP/FOR	p-value
Lower respiratory hospital outpatient attendances (categorised)	0, n (%)	8 (100.0)	89 (100.0)	587 (100.0)	139 (100.0)	NA	
Asthma hospital outpatient attendances	N (% not missing)	8 (100.0)	89 (100.0)	587 (100.0)	139 (100.0)	NA	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	
	Min, Max	(0, 0)	(0, 0)	(0, 0)	(0, 0)	NA	
Asthma hospital outpatient attendances (categorised)	N (% not missing)	8 (100.0)	89 (100.0)	587 (100.0)	139 (100.0)	NA	NA
	0, n (%)	8 (100.0)	89 (100.0)	587 (100.0)	139 (100.0)	NA	
Lower respiratory inpatient hospitalisations	N (% not missing)	8 (100.0)	89 (100.0)	587 (100.0)	139 (100.0)	NA	.741‡
	Mean (SD)	0.0 (0.0)	0.0 (0.1)	0.0 (0.2)	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, 3)	(0, 1)	NA	
Lower respiratory inpatient hospitalisations (categorised)	N (% not missing)	8 (100.0)	89 (100.0)	587 (100.0)	139 (100.0)	NA	0.897*
	0, n (%)	n≥5	n≥5	576 (98.1)	n≥5	NA	
	1, n (%)	n<5	n<5	6 (1.0)	n<5	NA	
	≥2, n (%)	n<5	n<5	5 (0.9)	n<5	NA	
Asthma inpatient hospitalisations	N (% not missing)	8 (100.0)	89 (100.0)	587 (100.0)	139 (100.0)	NA	.286‡
	Mean (SD)	0.0 (0.0)	0.2 (0.7)	0.2 (0.6)	0.1 (0.5)	NA	
	Median (IQR)	0 (0, 0)	0 (0, 0)	0 (0, 0)	0 (0, 0)	NA	
	Min, Max	(0, 0)	(0, 4)	(0, 4)	(0, 5)	NA	
Asthma inpatient hospitalisations (categorised)	N (% not missing)	8 (100.0)	89 (100.0)	587 (100.0)	139 (100.0)	NA	0.699*
	0, n (%)	n≥5	n≥5	521 (88.8)	n≥5	NA	
	1, n (%)	n<5	n≥5	41 (7.0)	n≥5	NA	
	≥2, n (%)	n<5	n<5	25 (4.3)	n<5	NA	
Asthma exacerbations	N (% not missing)	8 (100.0)	89 (100.0)	587 (100.0)	139 (100.0)	NA	.337‡
	Mean (SD)	0.6 (0.9)	1.1 (1.3)	1.2 (1.4)	1.0 (1.3)	NA	
	Median (IQR)	0 (0, 2)	1 (0, 2)	1 (0, 2)	1 (0, 2)	NA	
	Min, Max	(0, 2)	(0, 8)	(0, 8)	(0, 9)	NA	
Asthma exacerbations (categorised)	N (% not missing)	8 (100.0)	89 (100.0)	587 (100.0)	139 (100.0)	NA	0.257*
	0, n (%)	n≥5	33 (37.1)	250 (42.6)	64 (46.0)	NA	
	1, n (%)	n<5	30 (33.7)	139 (23.7)	38 (27.3)	NA	
	≥2, n (%)	n<5	26 (29.2)	198 (33.7)	37 (26.6)	NA	

Table 16: Consultations and hospitalisations in year prior to index date by FDC/ICS LABA (4-11 years paediatric asthma patients)

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

5.2.3.5 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 prescriptions	N (% not missing)	12 (100.0)	150 (100.0)	971 (100.0)	230 (100.0)	NA	<0.001‡
	Mean (SD)	1.0 (2.5)	0.9 (2.4)	0.1 (0.9)	1.0 (2.8)	NA	
	Median (IQR)	0 (0, 0)	0 (0, 0)	0 (0, 0)	0 (0, 0)	NA	
	Min, Max	(0, 8)	(0, 16)	(0, 12)	(0, 16)	NA	
FDC ICS+LABA prescriptions (categorised)	N (% not missing)	12 (100.0)	150 (100.0)	971 (100.0)	230 (100.0)	NA	<0.001*
	0, n (%)	n≥5	n≥5	n≥5	195 (84.8)	NA	
	1, n (%)	n<5	n<5	n<5	5 (2.2)	NA	
	≥2, n (%)	n<5	n≥5	n≥5	30 (13.0)	NA	
SABA prescriptions	N (% not missing)	12 (100.0)	150 (100.0)	971 (100.0)	230 (100.0)	NA	.141‡
	Mean (SD)	1.3 (3.3)	2.7 (4.3)	2.7 (4.6)	2.6 (4.6)	NA	
	Median (IQR)	0 (0, 0)	0 (0, 4)	1 (0, 4)	1 (0, 4)	NA	
	Min, Max	(0, 11)	(0, 20)	(0, 57)	(0, 38)	NA	
SABA prescriptions (categorised)	N (% not missing)	12 (100.0)	150 (100.0)	971 (100.0)	230 (100.0)	NA	<0.001*
	0, n (%)	n≥5	77 (51.3)	482 (49.6)	92 (40.0)	NA	
	1, n (%)	n<5	15 (10.0)	59 (6.1)	31 (13.5)	NA	
	≥2, n (%)	n<5	58 (38.7)	430 (44.3)	107 (46.5)	NA	
SAMA prescriptions	N (% not missing)	12 (100.0)	150 (100.0)	971 (100.0)	230 (100.0)	NA	.350‡
	Mean (SD)	0.0 (0.0)	0.0 (0.1)	0.0 (0.5)	0.0 (0.0)	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, 0)	NA	
SAMA prescriptions (categorised)	N (% not missing)	12 (100.0)	150 (100.0)	971 (100.0)	230 (100.0)	NA	0.647*
	0, n (%)	n≥5	n≥5	959 (98.8)	n≥5	NA	
	1, n (%)	n<5	n<5	5 (0.5)	n<5	NA	
	≥2, n (%)	n<5	n<5	7 (0.7)	n<5	NA	
LABA prescriptions	N (% not missing)	12 (100.0)	150 (100.0)	971 (100.0)	230 (100.0)	NA	.608‡
	Mean (SD)	0.0 (0.0)	0.4 (1.8)	0.4 (1.7)	0.5 (1.6)	NA	
	Median (IQR)	0 (0, 0)	0 (0, 0)	0 (0, 0)	0 (0, 0)	NA	
	Min, Max	(0, 0)	(0, 12)	(0, 16)	(0, 10)	NA	
LABA prescriptions (categorised)	N (% not missing)	12 (100.0)	150 (100.0)	971 (100.0)	230 (100.0)	NA	0.531*
	0, n (%)	n≥5	135 (90.0)	861 (88.7)	n≥5	NA	
	1, n (%)	n<5	6 (4.0)	40 (4.1)	n<5	NA	
	≥2, n (%)	n<5	9 (6.0)	70 (7.2)	n≥5	NA	
LAMA prescriptions	N (% not missing)	12 (100.0)	150 (100.0)	971 (100.0)	230 (100.0)	NA	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	
	Min, Max	(0, 0)	(0, 0)	(0, 0)	(0, 0)	NA	

		TOTAL COHORT					
	Measure	FP/FOR	FP/SAL DPI	FP/SAL MDI	BUD/FOR	BDP/FOR	p-value
LAMA prescriptions (categorised)	N (% not missing)	12 (100.0)	150 (100.0)	971 (100.0)	230 (100.0)	NA	NA
	0, n (%)	12 (100.0)	150 (100.0)	971 (100.0)	230 (100.0)	NA	
ICS only prescriptions	N (% not missing)	12 (100.0)	150 (100.0)	971 (100.0)	230 (100.0)	NA	<0.001‡
	Mean (SD)	2.6 (3.2)	3.0 (3.2)	4.0 (3.3)	2.6 (2.8)	NA	
	Median (IQR)	2 (0, 4)	2 (0, 5)	3 (2, 6)	2 (0, 4)	NA	
	Min, Max	(0, 11)	(0, 15)	(0, 24)	(0, 19)	NA	
ICS only prescriptions (categorised)	N (% not missing)	12 (100.0)	150 (100.0)	971 (100.0)	230 (100.0)	NA	<0.001*
	0, n (%)	n<5	45 (30.0)	125 (12.9)	67 (29.1)	NA	
	1, n (%)	n<5	19 (12.7)	102 (10.5)	36 (15.7)	NA	
	≥2, n (%)	n≥5	86 (57.3)	744 (76.6)	127 (55.2)	NA	
Theophylline prescriptions	N (% not missing)	12 (100.0)	150 (100.0)	971 (100.0)	230 (100.0)	NA	.939‡
	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	
	Min, Max	(0, 0)	(0, 0)	(0, 1)	(0, 0)	NA	
Theophylline prescriptions (categorised)	N (% not missing)	12 (100.0)	150 (100.0)	971 (100.0)	230 (100.0)	NA	0.939*
	0, n (%)	n≥5	n≥5	n≥5	n≥5	NA	
	1, n (%)	n<5	n<5	n<5	n<5	NA	
LTRA prescriptions	N (% not missing)	12 (100.0)	150 (100.0)	971 (100.0)	230 (100.0)	NA	.468‡
	Mean (SD)	1.2 (3.7)	1.4 (3.0)	1.6 (3.1)	1.7 (3.1)	NA	
	Median (IQR)	0 (0, 0)	0 (0, 1)	0 (0, 1)	0 (0, 2)	NA	
	Min, Max	(0, 13)	(0, 14)	(0, 16)	(0, 13)	NA	
LTRA prescriptions (categorised)	N (% not missing)	12 (100.0)	150 (100.0)	971 (100.0)	230 (100.0)	NA	0.653*
	0, n (%)	n≥5	108 (72.0)	661 (68.1)	151 (65.7)	NA	
	1, n (%)	n<5	7 (4.7)	71 (7.3)	18 (7.8)	NA	
	≥2, n (%)	n<5	35 (23.3)	239 (24.6)	61 (26.5)	NA	
Spacer prescription	N (% not missing)	12 (100.0)	150 (100.0)	971 (100.0)	230 (100.0)	NA	<0.001*
	No, n (%)	6 (50.0)	84 (56.0)	306 (31.5)	124 (53.9)	NA	
	Yes, n (%)	6 (50.0)	66 (44.0)	665 (68.5)	106 (46.1)	NA	
Pain-relief medication prescriptions	N (% not missing)	12 (100.0)	150 (100.0)	971 (100.0)	230 (100.0)	NA	.393‡
	Mean (SD)	0.3 (0.5)	0.2 (0.7)	0.3 (0.8)	0.2 (0.9)	NA	
	Median (IQR)	0 (0, 1)	0 (0, 0)	0 (0, 0)	0 (0, 0)	NA	
	Min, Max	(0, 1)	(0, 6)	(0, 10)	(0, 9)	NA	
Pain-relief medication prescriptions (categorised)	N (% not missing)	12 (100.0)	150 (100.0)	971 (100.0)	230 (100.0)	NA	0.692*
	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	
	N (% not missing)	12 (100.0)	150 (100.0)	971 (100.0)	230 (100.0)	NA	.209‡
	Mean (SD)	0.0 (0.0)	0.1 (0.3)	0.1 (0.4)	0.1 (0.7)	NA	

		TOTAL COHORT					
	Measure	FP/FOR	FP/SAL DPI	FP/SAL MDI	BUD/FOR	BDP/FOR	p-value
Non-steroidal anti-inflammatory drugs (NSAIDs) prescriptions	Median (IQR)	0 (0, 0)	0 (0, 0)	0 (0, 0)	0 (0, 0)	NA	
	Min, Max	(0, 0)	(0, 3)	(0, 5)	(0, 9)	NA	
Non-steroidal anti-inflammatory drugs (NSAIDs) prescriptions (categorised)	N (% not missing)	12 (100.0)	150 (100.0)	971 (100.0)	230 (100.0)	NA	0.627*
	0, n (%)	n≥5	n≥5	n≥5	n≥5	NA	
	1-2, n (%)	n<5	n≥5	n≥5	n≥5	NA	
	3-4, n (%)	n<5	n<5	n<5	n<5	NA	
	≥5, n (%)	n<5	n<5	n<5	n<5	NA	

Table 17: Prescriptions for therapy in year prior to index date by FDC/ICS LABA (4-11 years paediatric asthma patients)

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

5.2.4 Patients with COPD only, definition 1

Patients with COPD only (definition 1) had similar demographic characteristics, disease severity, year of first diagnosis, GP consultations, hospitalisations, exacerbations and prior respiratory prescriptions across the treatment groups. Dose of ICS/LABA at the index date was higher for FP/SAL DPI and FP/FOR; SAMA and LAMA prescriptions were higher for FP/FOR and FP/SAL DPI at the index date, respectively. FP/FOR had slightly higher proportion of patients with eczema, rhinitis, GERD than other treatment groups; CCI score was similar. FP/FOR group were more likely to be switchers than the other treatment groups.

5.2.4.1 Demographic characteristics

		TOTAL COHORT					
	Measure	FP/FOR	FP/SAL DPI	FP/SAL MDI	BUD/FOR	BDP/FOR	p-value
Age at index date (years)	N (% not missing)	193 (100.0)	5038 (100.0)	NA	2768 (100.0)	535 (100.0)	.005‡
	Mean (SD)	69.4 (11.6)	69.8 (10.6)	NA	68.8 (11.0)	69.2 (11.8)	
	Median (IQR)	70 (62, 78)	70 (63, 77)	NA	69 (62, 77)	69 (61, 78)	
	Min, Max	(42, 94)	(35, 98)	NA	(32, 97)	(35, 95)	
Gender	N (% not missing)	193 (100.0)	5038 (100.0)	NA	2768 (100.0)	535 (100.0)	0.001*
	Female, n (%)	94 (48.7)	2155 (42.8)	NA	1250 (45.2)	271 (50.7)	
	Male, n (%)	99 (51.3)	2883 (57.2)	NA	1518 (54.8)	264 (49.3)	
Height (m) - closest to index date	N (% not missing)	191 (99.0)	4907 (97.4)	NA	2700 (97.5)	523 (97.8)	.242‡
	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, 1.8)	1.6 (1.6, 1.7)	
	Min, Max	(1.4, 2.0)	(1, 2)	NA	(1.2, 2.1)	(1.4, 2.0)	
Weight (kg) - closest to index date	N (% not missing)	190 (98.4)	4840 (96.1)	NA	2685 (97.0)	522 (97.6)	.594‡
	Mean (SD)	77.7 (22.0)	75.9 (19.7)	NA	76.2 (19.3)	76.7 (19.9)	
	Median (IQR)	73 (62, 89)	74 (62, 88)	NA	74 (63, 88)	75 (62, 89)	
	Min, Max	(41.4, 159.4)	(40, 250)	NA	(40, 177)	(41, 180)	
BMI (kg/m2)	N (% not missing)	190 (98.4)	4859 (96.4)	NA	2684 (97.0)	520 (97.2)	.071‡
	Mean (SD)	27.8 (6.8)	27.0 (6.4)	NA	27.0 (6.2)	27.6 (6.5)	
	Median (IQR)	26.5 (23.3, 30.7)	26.2 (22.5, 30.5)	NA	26.4 (22.6, 30.7)	26.8 (23.0, 31.2)	
	Min, Max	(13.3, 53.3)	(13.1, 58.6)	NA	(13.5, 54.1)	(13.5, 56.8)	
BMI (kg/m2) (categorised)	N (% not missing)	190 (98.4)	4859 (96.4)	NA	2684 (97.0)	520 (97.2)	0.138*
	Underweight (BMI≤18.5), n (%)	7 (3.7)	328 (6.8)	NA	167 (6.2)	27 (5.2)	
	Normal (18.5≤BMI<25), n (%)	61 (32.1)	1707 (35.1)	NA	898 (33.5)	158 (30.4)	
	Overweight (25≤BMI<30), n (%)	64 (33.7)	1482 (30.5)	NA	858 (32.0)	172 (33.1)	
	Obese (BMI≥30), n (%)	58 (30.5)	1342 (27.6)	NA	761 (28.4)	163 (31.3)	

		TOTAL COHORT					
	Measure	FP/FOR	FP/SAL DPI	FP/SAL MDI	BUD/FOR	BDP/FOR	p-value
FEV_1 % predicted	N (% not missing)	174 (90.2)	4570 (90.7)	NA	2477 (89.5)	487 (91.0)	<0.001‡
	Mean (SD)	59.3 (19.3)	56.1 (20.4)	NA	58.8 (20.2)	61.3 (22.3)	
	Median (IQR)	58 (46, 73)	54 (42, 69)	NA	58 (44, 72)	61 (46, 74)	
	Min, Max	(19, 123)	(5, 190)	NA	(1, 169)	(9, 151)	
FEV_1 % predicted (categorised)	N (% not missing)	174 (90.2)	4570 (90.7)	NA	2477 (89.5)	487 (91.0)	<0.001*
	<30 (very severe), n (%)	9 (5.2)	381 (8.3)	NA	148 (6.0)	33 (6.8)	
	30-49 (severe), n (%)	45 (25.9)	1466 (32.1)	NA	718 (29.0)	121 (24.8)	
	50-79 (moderate), n (%)	94 (54.0)	2194 (48.0)	NA	1233 (49.8)	251 (51.5)	
	≥80 (mild), n (%)	26 (14.9)	529 (11.6)	NA	378 (15.3)	82 (16.8)	
Smoking Status	N (% not missing)	193 (100.0)	5022 (99.7)	NA	2761 (99.7)	534 (99.8)	0.009*
	Non-smoker, n (%)	18 (9.3)	351 (7.0)	NA	236 (8.5)	59 (11.0)	
	Current smoker, n (%)	65 (33.7)	1951 (38.8)	NA	1067 (38.6)	193 (36.1)	
	Ex-smoker, n (%)	110 (57.0)	2720 (54.2)	NA	1458 (52.8)	282 (52.8)	

Table 18: Demographic characteristics by FDC/ICS LABA (patients with COPD only, definition 1)
‡ Kruskal-Wallis test, * Chi-square test, NA – not applicable

5.2.4.2 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)	193 (100.0)	5038 (100.0)	NA	2768 (100.0)	535 (100.0)	<0.001‡
	Mean (SD)	19.4 (14.0)	21.6 (18.6)	NA	19.2 (17.5)	18.8 (16.3)	
	Median (IQR)	17.5 (9.3, 25.7)	18.8 (5.8, 31.7)	NA	16.7 (4.2, 27.3)	16.9 (4.8, 25.4)	
	Min, Max	(0.0, 65.3)	(0, 93)	NA	(0, 97)	(0, 89)	
Prescribed FDC ICS/LABA inhaler dose (dose per puff)	N (% not missing)	193 (100.0)	5038 (100.0)	NA	2768 (100.0)	535 (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 dosing instructions (FP equivalent dose per day)	N (% not missing)	142 (73.6)	2194 (43.5)	NA	2294 (82.9)	416 (77.8)	<0.001‡
	Mean (SD)	791.9 (273.8)	1020.3 (147.7)	NA	377.8 (115.6)	448.2 (103.9)	
	Median (IQR)	1000 (500, 1000)	1000 (1000, 1000)	NA	400 (400, 400)	500 (500, 500)	

		TOTAL COHORT					
	Measure	FP/FOR	FP/SAL DPI	FP/SAL MDI	BUD/FOR	BDP/FOR	p-value
	Min, Max	(150, 1000)	(500, 2000)	NA	(100, 800)	(188, 1000)	
Prescribed FDC ICS/LABA dosing instructions (FP equivalent dose per day) (categorised)	N (% not missing)	142 (73.6)	2194 (43.5)	NA	2294 (82.9)	416 (77.8)	<0.001*
	≥50 & ≤100, n (%)	n<5	n<5	NA	n<5	n<5	
	>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)	193 (100.0)	5038 (100.0)	NA	2768 (100.0)	535 (100.0)	<0.001‡
	Mean (SD)	17.4 (13.2)	19.0 (14.6)	NA	18.4 (14.2)	16.6 (13.9)	
	Median (IQR)	20.0 (2.7, 28.5)	17.9 (4.4, 30.6)	NA	16.7 (4.4, 29.4)	13.8 (3.0, 27.0)	
	Min, Max	(0, 41)	(0, 59)	NA	(0, 51)	(0, 50)	
SABA prescriptions	N (% not missing)	193 (100.0)	5038 (100.0)	NA	2768 (100.0)	535 (100.0)	0.335*
	No, n (%)	155 (80.3)	4053 (80.4)	NA	2254 (81.4)	418 (78.1)	
	Yes, n (%)	38 (19.7)	985 (19.6)	NA	514 (18.6)	117 (21.9)	
SAMA prescriptions	N (% not missing)	193 (100.0)	5038 (100.0)	NA	2768 (100.0)	535 (100.0)	0.003*
	No, n (%)	183 (94.8)	4931 (97.9)	NA	2726 (98.5)	525 (98.1)	
	Yes, n (%)	10 (5.2)	107 (2.1)	NA	42 (1.5)	10 (1.9)	
LABA prescriptions	N (% not missing)	193 (100.0)	5038 (100.0)	NA	2768 (100.0)	535 (100.0)	0.295*
	No, n (%)	n≥5	5024 (99.7)	NA	2760 (99.7)	n≥5	
	Yes, n (%)	n<5	14 (0.3)	NA	8 (0.3)	n<5	
LAMA prescriptions	N (% not missing)	193 (100.0)	5038 (100.0)	NA	2768 (100.0)	535 (100.0)	<0.001*
	No, n (%)	156 (80.8)	3398 (67.4)	NA	2086 (75.4)	429 (80.2)	
	Yes, n (%)	37 (19.2)	1640 (32.6)	NA	682 (24.6)	106 (19.8)	
ICS only prescriptions	N (% not missing)	193 (100.0)	5038 (100.0)	NA	2768 (100.0)	535 (100.0)	0.149*
	No, n (%)	n≥5	5026 (99.8)	NA	2758 (99.6)	n≥5	
	Yes, n (%)	n<5	12 (0.2)	NA	10 (0.4)	n<5	
Theophylline prescriptions	N (% not missing)	193 (100.0)	5038 (100.0)	NA	2768 (100.0)	535 (100.0)	0.108*
	No, n (%)	n≥5	4933 (97.9)	NA	2729 (98.6)	528 (98.7)	
	Yes, n (%)	n<5	105 (2.1)	NA	39 (1.4)	7 (1.3)	
LTRA prescriptions	N (% not missing)	193 (100.0)	5038 (100.0)	NA	2768 (100.0)	535 (100.0)	0.762*
	No, n (%)	n≥5	5013 (99.5)	NA	2749 (99.3)	n≥5	
	Yes, n (%)	n<5	25 (0.5)	NA	19 (0.7)	n<5	

Table 19: Medication prescribed at index date by FDC/ICS LABA (patients with COPD only, definition 1)
‡ Kruskal-Wallis test, * Chi-square test, NA – not applicable

5.2.4.3 Comorbidities

		TOTAL COHORT					
	Measure	FP/FOR	FP/SAL DPI	FP/SAL MDI	BUD/FOR	BDP/FOR	p-value
Year of first COPD diagnosis	N (% not missing)	192 (99.5)	5022 (99.7)	NA	2758 (99.6)	531 (99.3)	<0.001‡
	Mean (SD)	2006.5 (7.5)	2007.3 (5.7)	NA	2008.1 (5.7)	2007.6 (6.0)	
	Median (IQR)	2008 (2004, 2011)	2009 (2005, 2012)	NA	2010 (2006, 2012)	2010 (2005, 2011)	
	Min, Max	(1940, 2014)	(1960, 2014)	NA	(1950, 2014)	(1965, 2014)	
Duration of COPD (years)	N (% not missing)	192 (99.5)	5022 (99.7)	NA	2758 (99.6)	531 (99.3)	<0.001‡
	Mean (SD)	6.7 (7.5)	5.2 (5.7)	NA	4.6 (5.7)	5.0 (6.0)	
	Median (IQR)	5.4 (1.7, 9.2)	3.7 (0.8, 7.8)	NA	2.6 (0.4, 6.8)	3.0 (1.0, 7.1)	
	Min, Max	(0, 74)	(0, 52)	NA	(0, 63)	(0, 48)	
Comorbid rhinitis	N (% not missing)	193 (100.0)	5038 (100.0)	NA	2768 (100.0)	535 (100.0)	0.725*
	No, n (%)	183 (94.8)	4856 (96.4)	NA	2666 (96.3)	516 (96.4)	
	Yes, n (%)	10 (5.2)	182 (3.6)	NA	102 (3.7)	19 (3.6)	
Comorbid eczema	N (% not missing)	193 (100.0)	5038 (100.0)	NA	2768 (100.0)	535 (100.0)	0.659*
	No, n (%)	179 (92.7)	4755 (94.4)	NA	2601 (94.0)	501 (93.6)	
	Yes, n (%)	14 (7.3)	283 (5.6)	NA	167 (6.0)	34 (6.4)	
Comorbid GERD	N (% not missing)	193 (100.0)	5038 (100.0)	NA	2768 (100.0)	535 (100.0)	0.001*
	No, n (%)	158 (81.9)	4440 (88.1)	NA	2452 (88.6)	449 (83.9)	
	Yes, n (%)	35 (18.1)	598 (11.9)	NA	316 (11.4)	86 (16.1)	
History of ischemic heart disease	N (% not missing)	193 (100.0)	5038 (100.0)	NA	2768 (100.0)	535 (100.0)	0.253*
	No, n (%)	153 (79.3)	3955 (78.5)	NA	2221 (80.2)	432 (80.7)	
	Yes, n (%)	40 (20.7)	1083 (21.5)	NA	547 (19.8)	103 (19.3)	
History of hypertension	N (% not missing)	193 (100.0)	5038 (100.0)	NA	2768 (100.0)	535 (100.0)	0.446*
	No, n (%)	105 (54.4)	2897 (57.5)	NA	1625 (58.7)	300 (56.1)	
	Yes, n (%)	88 (45.6)	2141 (42.5)	NA	1143 (41.3)	235 (43.9)	
History of ischemic heart disease and hypertension	N (% not missing)	193 (100.0)	5038 (100.0)	NA	2768 (100.0)	535 (100.0)	0.591*
	No, n (%)	166 (86.0)	4465 (88.6)	NA	2464 (89.0)	478 (89.3)	
	Yes, n (%)	27 (14.0)	573 (11.4)	NA	304 (11.0)	57 (10.7)	
Charlson Comorbidity Index (CCI)	N (% not missing)	193 (100.0)	5035 (99.9)	NA	2766 (99.9)	535 (100.0)	.099‡
	Mean (SD)	2.6 (4.6)	2.5 (4.0)	NA	2.5 (4.0)	2.2 (3.9)	
	Median (IQR)	0 (0, 4)	0 (0, 4)	NA	0 (0, 4)	0 (0, 4)	
	Min, Max	(0, 34)	(0, 34)	NA	(0, 29)	(0, 35)	

		TOTAL COHORT					
	Measure	FP/FOR	FP/SAL DPI	FP/SAL MDI	BUD/FOR	BDP/FOR	p-value
Charlson Comorbidity Index (CCI) (categorised)	N (% not missing)	193 (100.0)	5035 (99.9)	NA	2766 (99.9)	535 (100.0)	0.166*
	0, n (%)	117 (60.6)	2895 (57.5)	NA	1613 (58.3)	335 (62.6)	
	1-4, n (%)	51 (26.4)	1498 (29.8)	NA	774 (28.0)	142 (26.5)	
	≥5, n (%)	25 (13.0)	642 (12.8)	NA	379 (13.7)	58 (10.8)	

Table 20: Comorbidities by FDC/ICS LABA (patients with COPD only, definition 1)
‡ Kruskal-Wallis test, * Chi-square test, NA – not applicable

5.2.4.4 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	N (% not missing)	193 (100.0)	5038 (100.0)	NA	2768 (100.0)	535 (100.0)	.084‡
	Mean (SD)	1.5 (1.6)	1.8 (1.9)	NA	1.9 (2.3)	1.9 (1.9)	
	Median (IQR)	1 (0, 3)	1 (0, 3)	NA	1 (0, 3)	2 (0, 3)	
	Min, Max	(0, 9)	(0, 20)	NA	(0, 67)	(0, 15)	
Respiratory GP consultations without prescription for an oral corticosteroid (categorised)	N (% not missing)	193 (100.0)	5038 (100.0)	NA	2768 (100.0)	535 (100.0)	0.090*
	0, n (%)	57 (29.5)	1403 (27.8)	NA	755 (27.3)	134 (25.0)	
	1, n (%)	62 (32.1)	1305 (25.9)	NA	685 (24.7)	133 (24.9)	
	2, n (%)	25 (13.0)	966 (19.2)	NA	541 (19.5)	122 (22.8)	
	≥3, n (%)	49 (25.4)	1364 (27.1)	NA	787 (28.4)	146 (27.3)	
COPD GP consultations without prescription for an oral corticosteroid	N (% not missing)	193 (100.0)	5038 (100.0)	NA	2768 (100.0)	535 (100.0)	.005‡
	Mean (SD)	0.5 (0.7)	0.7 (0.9)	NA	0.7 (1.0)	0.7 (0.9)	
	Median (IQR)	0 (0, 1)	0 (0, 1)	NA	0 (0, 1)	1 (0, 1)	
	Min, Max	(0, 4)	(0, 8)	NA	(0, 12)	(0, 5)	
COPD GP consultations without prescription for an oral corticosteroid (categorised)	N (% not missing)	193 (100.0)	5038 (100.0)	NA	2768 (100.0)	535 (100.0)	0.031*
	0, n (%)	n≥5	2549 (50.6)	NA	1391 (50.3)	263 (49.2)	
	1, n (%)	n≥5	1668 (33.1)	NA	913 (33.0)	189 (35.3)	
	2, n (%)	n≥5	582 (11.6)	NA	321 (11.6)	52 (9.7)	
	≥3, n (%)	n<5	239 (4.7)	NA	143 (5.2)	31 (5.8)	
Lower respiratory hospital outpatient attendances	N (% not missing)	89 (100.0)	3084 (100.0)	NA	1670 (100.0)	299 (100.0)	.856‡
	Mean (SD)	0.0 (0.0)	0.0 (0.0)	NA	0.0 (0.0)	0.0 (0.0)	
	Median (IQR)	0 (0, 0)	0 (0, 0)	NA	0 (0, 0)	0 (0, 0)	
	Min, Max	(0, 0)	(0, 1)	NA	(0, 1)	(0, 0)	
Lower respiratory hospital outpatient attendances (categorised)	N (% not missing)	89 (100.0)	3084 (100.0)	NA	1670 (100.0)	299 (100.0)	0.856*
	0, n (%)	n≥5	n≥5	NA	n≥5	n≥5	
	1, n (%)	n<5	n<5	NA	n<5	n<5	
	N (% not missing)	89 (100.0)	3084 (100.0)	NA	1670 (100.0)	299 (100.0)	.252‡

		TOTAL COHORT					
	Measure	FP/FOR	FP/SAL DPI	FP/SAL MDI	BUD/FOR	BDP/FOR	p-value
COPD hospital outpatient attendances	Mean (SD)	0.0 (0.1)	0.0 (0.1)	NA	0.0 (0.0)	0.0 (0.1)	
	Median (IQR)	0 (0, 0)	0 (0, 0)	NA	0 (0, 0)	0 (0, 0)	
	Min, Max	(0, 1)	(0, 2)	NA	(0, 1)	(0, 1)	
COPD hospital outpatient attendances (categorised)	N (% not missing)	89 (100.0)	3084 (100.0)	NA	1670 (100.0)	299 (100.0)	0.450*
	0, n (%)	n≥5	n≥5	NA	n≥5	n≥5	
	1, n (%)	n<5	n<5	NA	n<5	n<5	
	≥2, n (%)	n<5	n<5	NA	n<5	n<5	
Lower respiratory inpatient hospitalisations	N (% not missing)	89 (100.0)	3084 (100.0)	NA	1670 (100.0)	299 (100.0)	.002‡
	Mean (SD)	0.2 (0.8)	0.2 (0.7)	NA	0.2 (0.6)	0.1 (0.5)	
	Median (IQR)	0 (0, 0)	0 (0, 0)	NA	0 (0, 0)	0 (0, 0)	
	Min, Max	(0, 5)	(0, 10)	NA	(0, 8)	(0, 5)	
Lower respiratory inpatient hospitalisations (categorised)	N (% not missing)	89 (100.0)	3084 (100.0)	NA	1670 (100.0)	299 (100.0)	0.007*
	0, n (%)	n≥5	2595 (84.1)	NA	1442 (86.3)	274 (91.6)	
	1, n (%)	n≥5	369 (12.0)	NA	183 (11.0)	18 (6.0)	
	≥2, n (%)	n<5	120 (3.9)	NA	45 (2.7)	7 (2.3)	
COPD inpatient hospitalisations	N (% not missing)	89 (100.0)	3084 (100.0)	NA	1670 (100.0)	299 (100.0)	<0.001‡
	Mean (SD)	0.2 (0.6)	0.2 (0.6)	NA	0.1 (0.5)	0.1 (0.4)	
	Median (IQR)	0 (0, 0)	0 (0, 0)	NA	0 (0, 0)	0 (0, 0)	
	Min, Max	(0, 4)	(0, 9)	NA	(0, 7)	(0, 5)	
COPD inpatient hospitalisations (categorised)	N (% not missing)	89 (100.0)	3084 (100.0)	NA	1670 (100.0)	299 (100.0)	<0.001*
	0, n (%)	n≥5	2688 (87.2)	NA	1507 (90.2)	287 (96.0)	
	1, n (%)	n≥5	303 (9.8)	NA	129 (7.7)	7 (2.3)	
	≥2, n (%)	n<5	93 (3.0)	NA	34 (2.0)	5 (1.7)	
COPD exacerbations	N (% not missing)	89 (100.0)	3084 (100.0)	NA	1670 (100.0)	299 (100.0)	.007‡
	Mean (SD)	1.8 (1.6)	1.6 (1.8)	NA	1.5 (1.6)	1.4 (1.6)	
	Median (IQR)	1 (1, 3)	1 (0, 2)	NA	1 (0, 2)	1 (0, 2)	
	Min, Max	(0, 8)	(0, 13)	NA	(0, 14)	(0, 8)	
COPD exacerbations (categorised)	N (% not missing)	89 (100.0)	3084 (100.0)	NA	1670 (100.0)	299 (100.0)	0.059*
	0, n (%)	19 (21.3)	965 (31.3)	NA	578 (34.6)	106 (35.5)	
	1, n (%)	26 (29.2)	819 (26.6)	NA	425 (25.4)	79 (26.4)	
	≥2, n (%)	44 (49.4)	1300 (42.2)	NA	667 (39.9)	114 (38.1)	

Table 21: Consultations and hospitalisations in year prior to index date by FDC/ICS LABA (patients with COPD only, definition 1)

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

5.2.4.5 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 prescriptions	N (% not missing)	193 (100.0)	5038 (100.0)	NA	2768 (100.0)	535 (100.0)	<0.001‡
	Mean (SD)	5.5 (6.1)	3.6 (5.5)	NA	1.9 (4.3)	2.6 (4.6)	
	Median (IQR)	4 (0, 11)	0 (0, 7)	NA	0 (0, 0)	0 (0, 4)	
	Min, Max	(0, 32)	(0, 50)	NA	(0, 45)	(0, 26)	
FDC ICS+LABA prescriptions (categorised)	N (% not missing)	193 (100.0)	5038 (100.0)	NA	2768 (100.0)	535 (100.0)	<0.001*
	0, n (%)	n≥5	3117 (61.9)	NA	2155 (77.9)	350 (65.4)	
	1, n (%)	n<5	73 (1.4)	NA	47 (1.7)	21 (3.9)	
	≥2, n (%)	n≥5	1848 (36.7)	NA	566 (20.4)	164 (30.7)	
SABA prescriptions	N (% not missing)	193 (100.0)	5038 (100.0)	NA	2768 (100.0)	535 (100.0)	<0.001‡
	Mean (SD)	3.3 (6.1)	3.6 (6.6)	NA	3.2 (5.9)	4.6 (7.7)	
	Median (IQR)	0 (0, 5)	0 (0, 4)	NA	0 (0, 4)	1 (0, 7)	
	Min, Max	(0, 34)	(0, 62)	NA	(0, 57)	(0, 74)	
SABA prescriptions (categorised)	N (% not missing)	193 (100.0)	5038 (100.0)	NA	2768 (100.0)	535 (100.0)	<0.001*
	0, n (%)	111 (57.5)	2705 (53.7)	NA	1507 (54.4)	228 (42.6)	
	1, n (%)	13 (6.7)	383 (7.6)	NA	215 (7.8)	41 (7.7)	
	≥2, n (%)	69 (35.8)	1950 (38.7)	NA	1046 (37.8)	266 (49.7)	
SAMA prescriptions	N (% not missing)	193 (100.0)	5038 (100.0)	NA	2768 (100.0)	535 (100.0)	.401‡
	Mean (SD)	0.8 (2.7)	0.8 (4.0)	NA	0.6 (3.6)	0.7 (2.9)	
	Median (IQR)	0 (0, 0)	0 (0, 0)	NA	0 (0, 0)	0 (0, 0)	
	Min, Max	(0, 14)	(0, 96)	NA	(0, 88)	(0, 28)	
SAMA prescriptions (categorised)	N (% not missing)	193 (100.0)	5038 (100.0)	NA	2768 (100.0)	535 (100.0)	0.033*
	0, n (%)	n≥5	4619 (91.7)	NA	2552 (92.2)	n≥5	
	1, n (%)	n<5	54 (1.1)	NA	46 (1.7)	n<5	
	≥2, n (%)	n≥5	365 (7.2)	NA	170 (6.1)	n≥5	
LABA prescriptions	N (% not missing)	193 (100.0)	5038 (100.0)	NA	2768 (100.0)	535 (100.0)	.002‡
	Mean (SD)	0.2 (1.3)	0.7 (2.7)	NA	0.6 (2.3)	0.8 (2.7)	
	Median (IQR)	0 (0, 0)	0 (0, 0)	NA	0 (0, 0)	0 (0, 0)	
	Min, Max	(0, 12)	(0, 41)	NA	(0, 24)	(0, 20)	
LABA prescriptions (categorised)	N (% not missing)	193 (100.0)	5038 (100.0)	NA	2768 (100.0)	535 (100.0)	<0.001*
	0, n (%)	182 (94.3)	4554 (90.4)	NA	2521 (91.1)	462 (86.4)	
	1, n (%)	5 (2.6)	56 (1.1)	NA	41 (1.5)	13 (2.4)	
	≥2, n (%)	6 (3.1)	428 (8.5)	NA	206 (7.4)	60 (11.2)	
LAMA prescriptions	N (% not missing)	193 (100.0)	5038 (100.0)	NA	2768 (100.0)	535 (100.0)	<0.001‡
	Mean (SD)	8.5 (10.5)	7.8 (10.2)	NA	6.3 (9.4)	5.9 (9.3)	
	Median (IQR)	2 (0, 16)	2 (0, 14)	NA	0 (0, 11)	0 (0, 10)	
	Min, Max	(0, 52)	(0, 88)	NA	(0, 66)	(0, 58)	

		TOTAL COHORT					
	Measure	FP/FOR	FP/SAL DPI	FP/SAL MDI	BUD/FOR	BDP/FOR	p-value
LAMA prescriptions (categorised)	N (% not missing)	193 (100.0)	5038 (100.0)	NA	2768 (100.0)	535 (100.0)	<0.001*
	0, n (%)	n≥5	2289 (45.4)	NA	1444 (52.2)	n≥5	
	1, n (%)	n<5	26 (0.5)	NA	13 (0.5)	n<5	
	≥2, n (%)	n≥5	2723 (54.0)	NA	1311 (47.4)	n≥5	
ICS only prescriptions	N (% not missing)	193 (100.0)	5038 (100.0)	NA	2768 (100.0)	535 (100.0)	<0.001‡
	Mean (SD)	0.6 (2.2)	0.6 (2.5)	NA	0.8 (2.4)	1.4 (3.5)	
	Median (IQR)	0 (0, 0)	0 (0, 0)	NA	0 (0, 0)	0 (0, 0)	
	Min, Max	(0, 15)	(0, 46)	NA	(0, 26)	(0, 28)	
ICS only prescriptions (categorised)	N (% not missing)	193 (100.0)	5038 (100.0)	NA	2768 (100.0)	535 (100.0)	<0.001*
	0, n (%)	167 (86.5)	4462 (88.6)	NA	2327 (84.1)	404 (75.5)	
	1, n (%)	9 (4.7)	124 (2.5)	NA	92 (3.3)	24 (4.5)	
	≥2, n (%)	17 (8.8)	452 (9.0)	NA	349 (12.6)	107 (20.0)	
Theophylline prescriptions	N (% not missing)	193 (100.0)	5038 (100.0)	NA	2768 (100.0)	535 (100.0)	.032‡
	Mean (SD)	0.5 (2.2)	0.3 (2.3)	NA	0.2 (1.7)	0.2 (1.7)	
	Median (IQR)	0 (0, 0)	0 (0, 0)	NA	0 (0, 0)	0 (0, 0)	
	Min, Max	(0, 14)	(0, 51)	NA	(0, 52)	(0, 23)	
Theophylline prescriptions (categorised)	N (% not missing)	193 (100.0)	5038 (100.0)	NA	2768 (100.0)	535 (100.0)	0.020*
	0, n (%)	n≥5	4843 (96.1)	NA	2687 (97.1)	n≥5	
	1, n (%)	n<5	21 (0.4)	NA	15 (0.5)	n<5	
	≥2, n (%)	n≥5	174 (3.5)	NA	66 (2.4)	n≥5	
LTRA prescriptions	N (% not missing)	193 (100.0)	5038 (100.0)	NA	2768 (100.0)	535 (100.0)	.085‡
	Mean (SD)	0.3 (2.7)	0.1 (0.9)	NA	0.1 (0.8)	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, 13)	(0, 13)	
LTRA prescriptions (categorised)	N (% not missing)	193 (100.0)	5038 (100.0)	NA	2768 (100.0)	535 (100.0)	0.019*
	0, n (%)	n≥5	4977 (98.8)	NA	2739 (99.0)	524 (97.9)	
	1, n (%)	n<5	9 (0.2)	NA	6 (0.2)	5 (0.9)	
	≥2, n (%)	n<5	52 (1.0)	NA	23 (0.8)	6 (1.1)	
Spacer prescription	N (% not missing)	193 (100.0)	5038 (100.0)	NA	2768 (100.0)	535 (100.0)	<0.001*
	No, n (%)	127 (65.8)	4084 (81.1)	NA	2317 (83.7)	366 (68.4)	
	Yes, n (%)	66 (34.2)	954 (18.9)	NA	451 (16.3)	169 (31.6)	
Pain-relief medication prescriptions	N (% not missing)	193 (100.0)	5038 (100.0)	NA	2768 (100.0)	535 (100.0)	.011‡
	Mean (SD)	4.4 (5.9)	3.7 (6.3)	NA	3.7 (6.7)	4.1 (6.7)	
	Median (IQR)	1 (0, 8)	1 (0, 6)	NA	1 (0, 5)	1 (0, 6)	
	Min, Max	(0, 31)	(0, 66)	NA	(0, 102)	(0, 50)	
Pain-relief medication prescriptions (categorised)	N (% not missing)	193 (100.0)	5038 (100.0)	NA	2768 (100.0)	535 (100.0)	0.040*
	0, n (%)	83 (43.0)	2502 (49.7)	NA	1381 (49.9)	235 (43.9)	
	1-4, n (%)	43 (22.3)	1171 (23.2)	NA	658 (23.8)	139 (26.0)	

		TOTAL COHORT					
	Measure	FP/FOR	FP/SAL DPI	FP/SAL MDI	BUD/FOR	BDP/FOR	p-value
	≥5, n (%)	67 (34.7)	1365 (27.1)	NA	729 (26.3)	161 (30.1)	
Non-steroidal anti-inflammatory drugs (NSAIDs) prescriptions	N (% not missing)	193 (100.0)	5038 (100.0)	NA	2768 (100.0)	535 (100.0)	.077‡
	Mean (SD)	0.8 (2.5)	0.6 (2.3)	NA	0.7 (2.1)	0.8 (2.4)	
	Median (IQR)	0 (0, 0)	0 (0, 0)	NA	0 (0, 0)	0 (0, 0)	
	Min, Max	(0, 15)	(0, 49)	NA	(0, 40)	(0, 19)	
Non-steroidal anti-inflammatory drugs (NSAIDs) prescriptions (categorised)	N (% not missing)	193 (100.0)	5038 (100.0)	NA	2768 (100.0)	535 (100.0)	0.190*
	0, n (%)	154 (79.8)	4170 (82.8)	NA	2244 (81.1)	426 (79.6)	
	1-2, n (%)	20 (10.4)	533 (10.6)	NA	309 (11.2)	61 (11.4)	
	3-4, n (%)	5 (2.6)	100 (2.0)	NA	76 (2.7)	18 (3.4)	
	≥5, n (%)	14 (7.3)	235 (4.7)	NA	139 (5.0)	30 (5.6)	
Beta-blocker prescriptions	N (% not missing)	193 (100.0)	5038 (100.0)	NA	2768 (100.0)	535 (100.0)	.365‡
	Mean (SD)	2.3 (6.3)	1.5 (4.5)	NA	1.5 (4.2)	1.7 (5.1)	
	Median (IQR)	0 (0, 0)	0 (0, 0)	NA	0 (0, 0)	0 (0, 0)	
	Min, Max	(0, 52)	(0, 58)	NA	(0, 54)	(0, 54)	
Beta-blocker prescriptions (categorised)	N (% not missing)	193 (100.0)	5038 (100.0)	NA	2768 (100.0)	535 (100.0)	0.228*
	0, n (%)	153 (79.3)	4192 (83.2)	NA	2276 (82.2)	444 (83.0)	
	1-4, n (%)	5 (2.6)	185 (3.7)	NA	108 (3.9)	22 (4.1)	
	5-9, n (%)	15 (7.8)	300 (6.0)	NA	201 (7.3)	29 (5.4)	
	≥10, n (%)	20 (10.4)	361 (7.2)	NA	183 (6.6)	40 (7.5)	

Table 22: Prescriptions for therapy in year prior to index date by FDC/ICS LABA (patients with COPD only, definition 1)

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

5.2.5 Patients with COPD only, definition 2

The number of COPD patients (definition 2) prescribed FP/FOR was low. Patients had similar demographic characteristics, disease severity, comorbidities, GP consultations and hospitalisations across the treatment groups. Dose of ICS/LABA at the index date was higher for FP/SAL DPI and FP/FOR; Theophylline prescriptions were higher for FP/FOR prior to the index date than other treatment groups and LABA and LAMA prescriptions were lower. FP/FOR group were more likely to be switchers than the other treatment groups, had more exacerbations during baseline, were more likely to be prescribed a spacer and had an earlier date of first diagnosis.

5.2.5.1 Demographic characteristics

		TOTAL COHORT					
	Measure	FP/FOR	FP/SAL DPI	FP/SAL MDI	BUD/FOR	BDP/FOR	p-value
Age at index date (years)	N (% not missing)	143 (100.0)	4085 (100.0)	NA	2185 (100.0)	395 (100.0)	.002‡
	Mean (SD)	70.3 (10.5)	69.7 (10.2)	NA	68.7 (10.5)	68.4 (11.4)	
	Median (IQR)	71 (63, 78)	70 (63, 77)	NA	69 (62, 76)	68 (61, 77)	
	Min, Max	(43, 94)	(37, 98)	NA	(32, 96)	(35, 94)	
Gender	N (% not missing)	143 (100.0)	4085 (100.0)	NA	2185 (100.0)	395 (100.0)	0.042*
	Female, n (%)	67 (46.9)	1689 (41.3)	NA	941 (43.1)	189 (47.8)	
	Male, n (%)	76 (53.1)	2396 (58.7)	NA	1244 (56.9)	206 (52.2)	
Height (m) - closest to index date	N (% not missing)	143 (100.0)	4050 (99.1)	NA	2170 (99.3)	392 (99.2)	.486‡
	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, 1.8)	1.7 (1.6, 1.8)	
	Min, Max	(1.4, 1.9)	(1, 2)	NA	(1.2, 2.1)	(1.4, 2.0)	
Weight (kg) - closest to index date	N (% not missing)	141 (98.6)	3985 (97.6)	NA	2147 (98.3)	388 (98.2)	.099‡
	Mean (SD)	74.6 (20.6)	75.3 (19.1)	NA	75.8 (19.0)	77.2 (19.7)	
	Median (IQR)	71 (60, 88)	73 (61, 87)	NA	73 (62, 87)	76 (63, 90)	
	Min, Max	(41.4, 146.2)	(40, 179)	NA	(40, 177)	(41, 180)	
BMI (kg/m2)	N (% not missing)	142 (99.3)	4017 (98.3)	NA	2157 (98.7)	390 (98.7)	.023‡
	Mean (SD)	26.6 (6.0)	26.7 (6.1)	NA	26.8 (6.0)	27.6 (6.3)	
	Median (IQR)	26.2 (22.6, 29.6)	26.0 (22.4, 30.1)	NA	26.2 (22.6, 30.2)	26.9 (23.2, 30.9)	
	Min, Max	(13.3, 46.4)	(13.1, 58.6)	NA	(13.8, 54.1)	(13.5, 53.8)	
BMI (kg/m2) (categorised)	N (% not missing)	142 (99.3)	4017 (98.3)	NA	2157 (98.7)	390 (98.7)	0.074*
	Underweight (BMI≤18.5), n (%)	7 (4.9)	271 (6.7)	NA	128 (5.9)	20 (5.1)	
	Normal (18.5≤BMI<25), n (%)	50 (35.2)	1459 (36.3)	NA	756 (35.0)	113 (29.0)	

		TOTAL COHORT					
	Measure	FP/FOR	FP/SAL DPI	FP/SAL MDI	BUD/FOR	BDP/FOR	p-value
	Overweight (25≤BMI<30), n (%)	51 (35.9)	1257 (31.3)	NA	707 (32.8)	135 (34.6)	
	Obese (BMI≥30), n (%)	34 (23.9)	1030 (25.6)	NA	566 (26.2)	122 (31.3)	
FEV_1 % predicted	N (% not missing)	134 (93.7)	3930 (96.2)	NA	2087 (95.5)	384 (97.2)	<0.001‡
	Mean (SD)	56.6 (18.4)	54.8 (19.7)	NA	56.9 (19.4)	58.6 (21.1)	
	Median (IQR)	55 (43, 70)	53 (41, 67)	NA	56 (43, 69)	59 (44, 71)	
	Min, Max	(19, 104)	(5, 190)	NA	(1, 169)	(9, 148)	
FEV_1 % predicted (categorised)	N (% not missing)	134 (93.7)	3930 (96.2)	NA	2087 (95.5)	384 (97.2)	<0.001*
	<30 (very severe), n (%)	8 (6.0)	339 (8.6)	NA	134 (6.4)	31 (8.1)	
	30-49 (severe), n (%)	40 (29.9)	1334 (33.9)	NA	661 (31.7)	106 (27.6)	
	50-79 (moderate), n (%)	71 (53.0)	1878 (47.8)	NA	1035 (49.6)	196 (51.0)	
	≥80 (mild), n (%)	15 (11.2)	379 (9.6)	NA	257 (12.3)	51 (13.3)	
Smoking Status	N (% not missing)	143 (100.0)	4085 (100.0)	NA	2184 (100.0)	395 (100.0)	0.069*
	Non-smoker, n (%)	13 (9.1)	243 (5.9)	NA	154 (7.1)	37 (9.4)	
	Current smoker, n (%)	48 (33.6)	1638 (40.1)	NA	870 (39.8)	155 (39.2)	
	Ex-smoker, n (%)	82 (57.3)	2204 (54.0)	NA	1160 (53.1)	203 (51.4)	

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

5.2.5.2 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)	143 (100.0)	4085 (100.0)	NA	2185 (100.0)	395 (100.0)	<0.001‡
	Mean (SD)	20.9 (14.7)	22.7 (18.3)	NA	20.2 (17.0)	19.6 (15.0)	
	Median (IQR)	18.0 (10.1, 27.4)	19.8 (7.9, 33.2)	NA	17.8 (6.6, 28.5)	17.6 (7.3, 26.0)	
	Min, Max	(0.1, 65.3)	(0, 92)	NA	(0, 86)	(0, 81)	
Prescribed FDC ICS/LABA inhaler dose (dose per puff)	N (% not missing)	143 (100.0)	4085 (100.0)	NA	2185 (100.0)	395 (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 dosing instructions (FP	N (% not missing)	104 (72.7)	1799 (44.0)	NA	1811 (82.9)	306 (77.5)	<0.001‡
	Mean (SD)	812.3 (267.9)	1021.1 (149.5)	NA	379.8 (111.6)	453.6 (102.5)	

		TOTAL COHORT					
	Measure	FP/FOR	FP/SAL DPI	FP/SAL MDI	BUD/FOR	BDP/FOR	p-value
equivalent dose per day)	Median (IQR)	1000 (500, 1000)	1000 (1000, 1000)	NA	400 (400, 400)	500 (500, 500)	
	Min, Max	(200, 1000)	(500, 2000)	NA	(200, 800)	(188, 1000)	
Prescribed FDC ICS/LABA dosing instructions (FP equivalent dose per day) (categorised)	N (% not missing)	104 (72.7)	1799 (44.0)	NA	1811 (82.9)	306 (77.5)	<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)	143 (100.0)	4085 (100.0)	NA	2185 (100.0)	395 (100.0)	.002‡
	Mean (SD)	17.4 (13.3)	19.6 (14.7)	NA	18.9 (14.3)	17.0 (14.1)	
	Median (IQR)	20.5 (2.7, 28.5)	19.2 (4.7, 31.4)	NA	18 (5, 30)	15 (3, 27)	
	Min, Max	(0, 41)	(0, 59)	NA	(0, 51)	(0, 50)	
SABA prescriptions	N (% not missing)	143 (100.0)	4085 (100.0)	NA	2185 (100.0)	395 (100.0)	0.069*
	No, n (%)	111 (77.6)	3307 (81.0)	NA	1815 (83.1)	313 (79.2)	
	Yes, n (%)	32 (22.4)	778 (19.0)	NA	370 (16.9)	82 (20.8)	
SAMA prescriptions	N (% not missing)	143 (100.0)	4085 (100.0)	NA	2185 (100.0)	395 (100.0)	0.015*
	No, n (%)	136 (95.1)	4004 (98.0)	NA	2155 (98.6)	387 (98.0)	
	Yes, n (%)	7 (4.9)	81 (2.0)	NA	30 (1.4)	8 (2.0)	
LABA prescriptions	N (% not missing)	143 (100.0)	4085 (100.0)	NA	2185 (100.0)	395 (100.0)	0.132*
	No, n (%)	n≥5	4072 (99.7)	NA	2178 (99.7)	n≥5	
	Yes, n (%)	n<5	13 (0.3)	NA	7 (0.3)	n<5	
LAMA prescriptions	N (% not missing)	143 (100.0)	4085 (100.0)	NA	2185 (100.0)	395 (100.0)	<0.001*
	No, n (%)	112 (78.3)	2814 (68.9)	NA	1689 (77.3)	321 (81.3)	
	Yes, n (%)	31 (21.7)	1271 (31.1)	NA	496 (22.7)	74 (18.7)	
ICS only prescriptions	N (% not missing)	143 (100.0)	4085 (100.0)	NA	2185 (100.0)	395 (100.0)	0.193*
	No, n (%)	n≥5	4078 (99.8)	NA	2176 (99.6)	n≥5	
	Yes, n (%)	n<5	7 (0.2)	NA	9 (0.4)	n<5	
Theophylline prescriptions	N (% not missing)	143 (100.0)	4085 (100.0)	NA	2185 (100.0)	395 (100.0)	0.227*
	No, n (%)	n≥5	4009 (98.1)	NA	2156 (98.7)	n≥5	
	Yes, n (%)	n<5	76 (1.9)	NA	29 (1.3)	n<5	
LTRA prescriptions	N (% not missing)	143 (100.0)	4085 (100.0)	NA	2185 (100.0)	395 (100.0)	0.519*
	No, n (%)	n≥5	4071 (99.7)	NA	2174 (99.5)	n≥5	
	Yes, n (%)	n<5	14 (0.3)	NA	11 (0.5)	n<5	

Table 24: Medication prescribed at index date by FDC/ICS LABA (patients with COPD only, definition 2)
‡ Kruskal-Wallis test, * Chi-square test, NA – not applicable

5.2.5.3 Comorbidities

		TOTAL COHORT					
	Measure	FP/FOR	FP/SAL DPI	FP/SAL MDI	BUD/FOR	BDP/FOR	p-value
Year of first COPD diagnosis	N (% not missing)	142 (99.3)	4077 (99.8)	NA	2178 (99.7)	394 (99.7)	<0.001‡
	Mean (SD)	2006.2 (7.8)	2007.2 (5.7)	NA	2008.1 (5.4)	2007.4 (6.3)	
	Median (IQR)	2007 (2004, 2011)	2009 (2005, 2011)	NA	2010 (2006, 2012)	2010 (2005, 2011)	
	Min, Max	(1940, 2014)	(1960, 2014)	NA	(1956, 2014)	(1965, 2014)	
Duration of COPD (years)	N (% not missing)	142 (99.3)	4077 (99.8)	NA	2178 (99.7)	394 (99.7)	<0.001‡
	Mean (SD)	7.0 (7.7)	5.4 (5.7)	NA	4.6 (5.4)	5.2 (6.3)	
	Median (IQR)	5.9 (2.1, 9.4)	3.9 (1.0, 7.9)	NA	2.7 (0.5, 6.8)	3.0 (1.0, 7.3)	
	Min, Max	(0, 74)	(0, 52)	NA	(0, 57)	(0, 48)	
Comorbid rhinitis	N (% not missing)	143 (100.0)	4085 (100.0)	NA	2185 (100.0)	395 (100.0)	0.250*
	No, n (%)	133 (93.0)	3933 (96.3)	NA	2097 (96.0)	379 (95.9)	
	Yes, n (%)	10 (7.0)	152 (3.7)	NA	88 (4.0)	16 (4.1)	
Comorbid eczema	N (% not missing)	143 (100.0)	4085 (100.0)	NA	2185 (100.0)	395 (100.0)	0.620*
	No, n (%)	133 (93.0)	3845 (94.1)	NA	2039 (93.3)	371 (93.9)	
	Yes, n (%)	10 (7.0)	240 (5.9)	NA	146 (6.7)	24 (6.1)	
Comorbid GERD	N (% not missing)	143 (100.0)	4085 (100.0)	NA	2185 (100.0)	395 (100.0)	0.059*
	No, n (%)	117 (81.8)	3611 (88.4)	NA	1931 (88.4)	340 (86.1)	
	Yes, n (%)	26 (18.2)	474 (11.6)	NA	254 (11.6)	55 (13.9)	
History of ischemic heart disease	N (% not missing)	143 (100.0)	4085 (100.0)	NA	2185 (100.0)	395 (100.0)	0.156*
	No, n (%)	111 (77.6)	3242 (79.4)	NA	1756 (80.4)	331 (83.8)	
	Yes, n (%)	32 (22.4)	843 (20.6)	NA	429 (19.6)	64 (16.2)	
History of hypertension	N (% not missing)	143 (100.0)	4085 (100.0)	NA	2185 (100.0)	395 (100.0)	0.566*
	No, n (%)	76 (53.1)	2386 (58.4)	NA	1283 (58.7)	225 (57.0)	
	Yes, n (%)	67 (46.9)	1699 (41.6)	NA	902 (41.3)	170 (43.0)	
History of ischemic heart disease and hypertension	N (% not missing)	143 (100.0)	4085 (100.0)	NA	2185 (100.0)	395 (100.0)	0.121*
	No, n (%)	121 (84.6)	3653 (89.4)	NA	1945 (89.0)	362 (91.6)	
	Yes, n (%)	22 (15.4)	432 (10.6)	NA	240 (11.0)	33 (8.4)	
Charlson Comorbidity Index (CCI)	N (% not missing)	143 (100.0)	4084 (100.0)	NA	2183 (99.9)	395 (100.0)	.020‡
	Mean (SD)	2.2 (4.3)	2.5 (3.8)	NA	2.5 (3.8)	2.1 (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, 35)	

		TOTAL COHORT					
	Measure	FP/FOR	FP/SAL DPI	FP/SAL MDI	BUD/FOR	BDP/FOR	p-value
Charlson Comorbidity Index (CCI) (categorised)	N (% not missing)	143 (100.0)	4084 (100.0)	NA	2183 (99.9)	395 (100.0)	0.033*
	0, n (%)	92 (64.3)	2310 (56.6)	NA	1252 (57.4)	247 (62.5)	
	1-4, n (%)	37 (25.9)	1278 (31.3)	NA	635 (29.1)	111 (28.1)	
	≥5, n (%)	14 (9.8)	496 (12.1)	NA	296 (13.6)	37 (9.4)	

Table 25: Comorbidities by FDC/ICS LABA (patients with COPD only, definition 2)
‡ Kruskal-Wallis test, * Chi-square test, NA – not applicable

5.2.5.4 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	N (% not missing)	143 (100.0)	4085 (100.0)	NA	2185 (100.0)	395 (100.0)	.077‡
	Mean (SD)	1.6 (1.6)	1.9 (1.9)	NA	2.0 (2.0)	1.9 (1.9)	
	Median (IQR)	1 (0, 2)	1 (1, 3)	NA	2 (1, 3)	2 (1, 3)	
	Min, Max	(0, 9)	(0, 20)	NA	(0, 16)	(0, 15)	
Respiratory GP consultations without prescription for an oral corticosteroid (categorised)	N (% not missing)	143 (100.0)	4085 (100.0)	NA	2185 (100.0)	395 (100.0)	0.272*
	0, n (%)	40 (28.0)	996 (24.4)	NA	515 (23.6)	93 (23.5)	
	1, n (%)	46 (32.2)	1079 (26.4)	NA	562 (25.7)	97 (24.6)	
	2, n (%)	22 (15.4)	837 (20.5)	NA	447 (20.5)	96 (24.3)	
	≥3, n (%)	35 (24.5)	1173 (28.7)	NA	661 (30.3)	109 (27.6)	
COPD GP consultations without prescription for an oral corticosteroid	N (% not missing)	143 (100.0)	4085 (100.0)	NA	2185 (100.0)	395 (100.0)	.023‡
	Mean (SD)	0.5 (0.7)	0.8 (1.0)	NA	0.8 (1.0)	0.8 (1.0)	
	Median (IQR)	0 (0, 1)	1 (0, 1)	NA	1 (0, 1)	1 (0, 1)	
	Min, Max	(0, 4)	(0, 8)	NA	(0, 12)	(0, 5)	
COPD GP consultations without prescription for an oral corticosteroid (categorised)	N (% not missing)	143 (100.0)	4085 (100.0)	NA	2185 (100.0)	395 (100.0)	0.109*
	0, n (%)	n≥5	1915 (46.9)	NA	1010 (46.2)	189 (47.8)	
	1, n (%)	n≥5	1434 (35.1)	NA	759 (34.7)	140 (35.4)	
	2, n (%)	n≥5	517 (12.7)	NA	291 (13.3)	40 (10.1)	
	≥3, n (%)	n<5	219 (5.4)	NA	125 (5.7)	26 (6.6)	
Lower respiratory hospital outpatient attendances	N (% not missing)	60 (100.0)	2490 (100.0)	NA	1315 (100.0)	231 (100.0)	.767‡
	Mean (SD)	0.0 (0.0)	0.0 (0.0)	NA	0.0 (0.0)	0.0 (0.0)	
	Median (IQR)	0 (0, 0)	0 (0, 0)	NA	0 (0, 0)	0 (0, 0)	
	Min, Max	(0, 0)	(0, 1)	NA	(0, 1)	(0, 0)	
Lower respiratory hospital outpatient attendances (categorised)	N (% not missing)	60 (100.0)	2490 (100.0)	NA	1315 (100.0)	231 (100.0)	0.767*
	0, n (%)	n≥5	n≥5	NA	n≥5	n≥5	
	1, n (%)	n<5	n<5	NA	n<5	n<5	
	N (% not missing)	60 (100.0)	2490 (100.0)	NA	1315 (100.0)	231 (100.0)	.052‡

		TOTAL COHORT					
	Measure	FP/FOR	FP/SAL DPI	FP/SAL MDI	BUD/FOR	BDP/FOR	p-value
COPD hospital outpatient attendances	Mean (SD)	0.0 (0.1)	0.0 (0.0)	NA	0.0 (0.1)	0.0 (0.1)	
	Median (IQR)	0 (0, 0)	0 (0, 0)	NA	0 (0, 0)	0 (0, 0)	
	Min, Max	(0, 1)	(0, 2)	NA	(0, 1)	(0, 1)	
COPD hospital outpatient attendances (categorised)	N (% not missing)	60 (100.0)	2490 (100.0)	NA	1315 (100.0)	231 (100.0)	0.106*
	0, n (%)	n≥5	n≥5	NA	n≥5	n≥5	
	1, n (%)	n<5	n<5	NA	n<5	n<5	
	≥2, n (%)	n<5	n<5	NA	n<5	n<5	
Lower respiratory inpatient hospitalisations	N (% not missing)	60 (100.0)	2490 (100.0)	NA	1315 (100.0)	231 (100.0)	.028‡
	Mean (SD)	0.2 (0.6)	0.2 (0.6)	NA	0.2 (0.6)	0.1 (0.5)	
	Median (IQR)	0 (0, 0)	0 (0, 0)	NA	0 (0, 0)	0 (0, 0)	
	Min, Max	(0, 4)	(0, 10)	NA	(0, 8)	(0, 5)	
Lower respiratory inpatient hospitalisations (categorised)	N (% not missing)	60 (100.0)	2490 (100.0)	NA	1315 (100.0)	231 (100.0)	0.074*
	0, n (%)	n≥5	2151 (86.4)	NA	1145 (87.1)	216 (93.5)	
	1, n (%)	n≥5	270 (10.8)	NA	137 (10.4)	9 (3.9)	
	≥2, n (%)	n<5	69 (2.8)	NA	33 (2.5)	6 (2.6)	
COPD inpatient hospitalisations	N (% not missing)	60 (100.0)	2490 (100.0)	NA	1315 (100.0)	231 (100.0)	<0.001‡
	Mean (SD)	0.2 (0.6)	0.2 (0.6)	NA	0.1 (0.4)	0.1 (0.4)	
	Median (IQR)	0 (0, 0)	0 (0, 0)	NA	0 (0, 0)	0 (0, 0)	
	Min, Max	(0, 4)	(0, 9)	NA	(0, 5)	(0, 5)	
COPD inpatient hospitalisations (categorised)	N (% not missing)	60 (100.0)	2490 (100.0)	NA	1315 (100.0)	231 (100.0)	0.004*
	0, n (%)	n≥5	2212 (88.8)	NA	1200 (91.3)	n≥5	
	1, n (%)	n≥5	223 (9.0)	NA	89 (6.8)	n<5	
	≥2, n (%)	n<5	55 (2.2)	NA	26 (2.0)	n<5	
COPD exacerbations	N (% not missing)	60 (100.0)	2490 (100.0)	NA	1315 (100.0)	231 (100.0)	.009‡
	Mean (SD)	2.0 (1.7)	1.7 (1.8)	NA	1.5 (1.6)	1.5 (1.6)	
	Median (IQR)	2 (1, 3)	1 (0, 3)	NA	1 (0, 2)	1 (0, 2)	
	Min, Max	(0, 8)	(0, 13)	NA	(0, 14)	(0, 7)	
COPD exacerbations (categorised)	N (% not missing)	60 (100.0)	2490 (100.0)	NA	1315 (100.0)	231 (100.0)	0.174*
	0, n (%)	12 (20.0)	763 (30.6)	NA	445 (33.8)	78 (33.8)	
	1, n (%)	16 (26.7)	644 (25.9)	NA	329 (25.0)	60 (26.0)	
	≥2, n (%)	32 (53.3)	1083 (43.5)	NA	541 (41.1)	93 (40.3)	

Table 26: 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

5.2.5.5 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 prescriptions	N (% not missing)	143 (100.0)	4085 (100.0)	NA	2185 (100.0)	395 (100.0)	<0.001‡
	Mean (SD)	6.2 (6.4)	3.9 (5.7)	NA	2.2 (4.6)	2.9 (4.7)	
	Median (IQR)	6 (0, 11)	0 (0, 8)	NA	0 (0, 0)	0 (0, 5)	
	Min, Max	(0, 32)	(0, 50)	NA	(0, 45)	(0, 26)	
FDC ICS+LABA prescriptions (categorised)	N (% not missing)	143 (100.0)	4085 (100.0)	NA	2185 (100.0)	395 (100.0)	<0.001*
	0, n (%)	n≥5	2397 (58.7)	NA	1649 (75.5)	245 (62.0)	
	1, n (%)	n<5	61 (1.5)	NA	39 (1.8)	17 (4.3)	
	≥2, n (%)	n≥5	1627 (39.8)	NA	497 (22.7)	133 (33.7)	
SABA prescriptions	N (% not missing)	143 (100.0)	4085 (100.0)	NA	2185 (100.0)	395 (100.0)	<0.001‡
	Mean (SD)	3.9 (6.6)	3.8 (6.8)	NA	3.5 (6.2)	5.2 (8.3)	
	Median (IQR)	0 (0, 6)	0 (0, 5)	NA	0 (0, 5)	2 (0, 7)	
	Min, Max	(0, 34)	(0, 58)	NA	(0, 57)	(0, 74)	
SABA prescriptions (categorised)	N (% not missing)	143 (100.0)	4085 (100.0)	NA	2185 (100.0)	395 (100.0)	<0.001*
	0, n (%)	74 (51.7)	2092 (51.2)	NA	1137 (52.0)	152 (38.5)	
	1, n (%)	9 (6.3)	302 (7.4)	NA	162 (7.4)	31 (7.8)	
	≥2, n (%)	60 (42.0)	1691 (41.4)	NA	886 (40.5)	212 (53.7)	
SAMA prescriptions	N (% not missing)	143 (100.0)	4085 (100.0)	NA	2185 (100.0)	395 (100.0)	.663‡
	Mean (SD)	0.8 (2.5)	0.8 (4.3)	NA	0.7 (3.9)	0.8 (3.1)	
	Median (IQR)	0 (0, 0)	0 (0, 0)	NA	0 (0, 0)	0 (0, 0)	
	Min, Max	(0, 14)	(0, 96)	NA	(0, 88)	(0, 28)	
SAMA prescriptions (categorised)	N (% not missing)	143 (100.0)	4085 (100.0)	NA	2185 (100.0)	395 (100.0)	0.118*
	0, n (%)	n≥5	3736 (91.5)	NA	2006 (91.8)	n≥5	
	1, n (%)	n<5	37 (0.9)	NA	34 (1.6)	n<5	
	≥2, n (%)	n≥5	312 (7.6)	NA	145 (6.6)	n≥5	
LABA prescriptions	N (% not missing)	143 (100.0)	4085 (100.0)	NA	2185 (100.0)	395 (100.0)	.003‡
	Mean (SD)	0.3 (1.5)	0.8 (2.8)	NA	0.6 (2.5)	0.9 (3.0)	
	Median (IQR)	0 (0, 0)	0 (0, 0)	NA	0 (0, 0)	0 (0, 0)	
	Min, Max	(0, 12)	(0, 41)	NA	(0, 24)	(0, 20)	
LABA prescriptions (categorised)	N (% not missing)	143 (100.0)	4085 (100.0)	NA	2185 (100.0)	395 (100.0)	0.003*
	0, n (%)	n≥5	3653 (89.4)	NA	1975 (90.4)	336 (85.1)	
	1, n (%)	n<5	48 (1.2)	NA	32 (1.5)	10 (2.5)	
	≥2, n (%)	n≥5	384 (9.4)	NA	178 (8.1)	49 (12.4)	
LAMA prescriptions	N (% not missing)	143 (100.0)	4085 (100.0)	NA	2185 (100.0)	395 (100.0)	<0.001‡
	Mean (SD)	10.0 (11.1)	8.5 (10.6)	NA	7.1 (9.8)	6.4 (9.7)	
	Median (IQR)	6 (0, 20)	4 (0, 14)	NA	2 (0, 12)	0 (0, 11)	
	Min, Max	(0, 52)	(0, 88)	NA	(0, 66)	(0, 58)	

		TOTAL COHORT					
	Measure	FP/FOR	FP/SAL DPI	FP/SAL MDI	BUD/FOR	BDP/FOR	p-value
LAMA prescriptions (categorised)	N (% not missing)	143 (100.0)	4085 (100.0)	NA	2185 (100.0)	395 (100.0)	<0.001*
	0, n (%)	n≥5	1702 (41.7)	NA	1043 (47.7)	n≥5	
	1, n (%)	n<5	23 (0.6)	NA	11 (0.5)	n<5	
	≥2, n (%)	n≥5	2360 (57.8)	NA	1131 (51.8)	n≥5	
ICS only prescriptions	N (% not missing)	143 (100.0)	4085 (100.0)	NA	2185 (100.0)	395 (100.0)	<0.001‡
	Mean (SD)	0.5 (2.1)	0.6 (2.4)	NA	0.9 (2.6)	1.4 (3.5)	
	Median (IQR)	0 (0, 0)	0 (0, 0)	NA	0 (0, 0)	0 (0, 0)	
	Min, Max	(0, 14)	(0, 32)	NA	(0, 26)	(0, 28)	
ICS only prescriptions (categorised)	N (% not missing)	143 (100.0)	4085 (100.0)	NA	2185 (100.0)	395 (100.0)	<0.001*
	0, n (%)	126 (88.1)	3618 (88.6)	NA	1817 (83.2)	300 (75.9)	
	1, n (%)	7 (4.9)	105 (2.6)	NA	71 (3.2)	17 (4.3)	
	≥2, n (%)	10 (7.0)	362 (8.9)	NA	297 (13.6)	78 (19.7)	
Theophylline prescriptions	N (% not missing)	143 (100.0)	4085 (100.0)	NA	2185 (100.0)	395 (100.0)	.027‡
	Mean (SD)	0.6 (2.4)	0.4 (2.4)	NA	0.2 (1.9)	0.3 (1.9)	
	Median (IQR)	0 (0, 0)	0 (0, 0)	NA	0 (0, 0)	0 (0, 0)	
	Min, Max	(0, 14)	(0, 51)	NA	(0, 52)	(0, 23)	
Theophylline prescriptions (categorised)	N (% not missing)	143 (100.0)	4085 (100.0)	NA	2185 (100.0)	395 (100.0)	0.035*
	0, n (%)	n≥5	3914 (95.8)	NA	2119 (97.0)	n≥5	
	1, n (%)	n<5	17 (0.4)	NA	11 (0.5)	n<5	
	≥2, n (%)	n≥5	154 (3.8)	NA	55 (2.5)	n≥5	
LTRA prescriptions	N (% not missing)	143 (100.0)	4085 (100.0)	NA	2185 (100.0)	395 (100.0)	.102‡
	Mean (SD)	0.4 (3.1)	0.1 (0.9)	NA	0.1 (0.9)	0.1 (1.0)	
	Median (IQR)	0 (0, 0)	0 (0, 0)	NA	0 (0, 0)	0 (0, 0)	
	Min, Max	(0, 35)	(0, 14)	NA	(0, 13)	(0, 13)	
LTRA prescriptions (categorised)	N (% not missing)	143 (100.0)	4085 (100.0)	NA	2185 (100.0)	395 (100.0)	0.307*
	0, n (%)	n≥5	4033 (98.7)	NA	n≥5	n≥5	
	1, n (%)	n<5	6 (0.1)	NA	n<5	n<5	
	≥2, n (%)	n<5	46 (1.1)	NA	n≥5	n<5	
Spacer prescription	N (% not missing)	143 (100.0)	4085 (100.0)	NA	2185 (100.0)	395 (100.0)	<0.001*
	No, n (%)	90 (62.9)	3275 (80.2)	NA	1819 (83.2)	271 (68.6)	
	Yes, n (%)	53 (37.1)	810 (19.8)	NA	366 (16.8)	124 (31.4)	
Pain-relief medication prescriptions	N (% not missing)	143 (100.0)	4085 (100.0)	NA	2185 (100.0)	395 (100.0)	.255‡
	Mean (SD)	4.0 (5.7)	3.7 (6.1)	NA	3.6 (6.5)	3.7 (6.1)	
	Median (IQR)	1 (0, 7)	0 (0, 6)	NA	0 (0, 5)	1 (0, 6)	
	Min, Max	(0, 31)	(0, 61)	NA	(0, 57)	(0, 46)	
Pain-relief medication prescriptions (categorised)	N (% not missing)	143 (100.0)	4085 (100.0)	NA	2185 (100.0)	395 (100.0)	0.377*
	0, n (%)	64 (44.8)	2076 (50.8)	NA	1121 (51.3)	183 (46.3)	
	1-4, n (%)	33 (23.1)	891 (21.8)	NA	481 (22.0)	100 (25.3)	

		TOTAL COHORT					
	Measure	FP/FOR	FP/SAL DPI	FP/SAL MDI	BUD/FOR	BDP/FOR	p-value
	≥5, n (%)	46 (32.2)	1118 (27.4)	NA	583 (26.7)	112 (28.4)	
Non-steroidal anti-inflammatory drugs (NSAIDs) prescriptions	N (% not missing)	143 (100.0)	4085 (100.0)	NA	2185 (100.0)	395 (100.0)	.196‡
	Mean (SD)	0.8 (2.6)	0.6 (2.1)	NA	0.7 (2.1)	0.8 (2.3)	
	Median (IQR)	0 (0, 0)	0 (0, 0)	NA	0 (0, 0)	0 (0, 0)	
	Min, Max	(0, 15)	(0, 23)	NA	(0, 40)	(0, 14)	
Non-steroidal anti-inflammatory drugs (NSAIDs) prescriptions (categorised)	N (% not missing)	143 (100.0)	4085 (100.0)	NA	2185 (100.0)	395 (100.0)	0.270*
	0, n (%)	n≥5	3370 (82.5)	NA	1766 (80.8)	314 (79.5)	
	1-2, n (%)	n≥5	445 (10.9)	NA	251 (11.5)	42 (10.6)	
	3-4, n (%)	n<5	86 (2.1)	NA	64 (2.9)	14 (3.5)	
	≥5, n (%)	n≥5	184 (4.5)	NA	104 (4.8)	25 (6.3)	
Beta-blocker prescriptions	N (% not missing)	143 (100.0)	4085 (100.0)	NA	2185 (100.0)	395 (100.0)	.253‡
	Mean (SD)	1.8 (4.1)	1.5 (4.6)	NA	1.5 (4.0)	1.6 (5.3)	
	Median (IQR)	0 (0, 0)	0 (0, 0)	NA	0 (0, 0)	0 (0, 0)	
	Min, Max	(0, 16)	(0, 58)	NA	(0, 54)	(0, 54)	
Beta-blocker prescriptions (categorised)	N (% not missing)	143 (100.0)	4085 (100.0)	NA	2185 (100.0)	395 (100.0)	0.207*
	0, n (%)	n≥5	3432 (84.0)	NA	1798 (82.3)	333 (84.3)	
	1-4, n (%)	n<5	121 (3.0)	NA	71 (3.2)	14 (3.5)	
	5-9, n (%)	n≥5	239 (5.9)	NA	165 (7.6)	18 (4.6)	
	≥10, n (%)	n≥5	293 (7.2)	NA	151 (6.9)	30 (7.6)	

Table 27: 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

5.2.6 Patients with COPD only, definition 3

The number of COPD patients (definition 3) prescribed FP/FOR and BDP/FOR was low. Patients had similar demographic characteristics, disease severity, GP consultations and hospitalisations across the treatment groups. Dose of ICS/LABA at the index date was higher for FP/SAL DPI and FP/FOR. There were no differences in comorbidities or CCI score across the treatment groups. Prescriptions prior to the index date were similar except for lower LABA prescription and higher LAMA prescription for the FP/FOR group. FP/FOR patients had a slightly earlier date of COPD diagnosis and higher proportion of exacerbations prior to the index date. FP/FOR group were more likely to be switchers than the other treatment groups.

5.2.6.1 Demographic characteristics

		TOTAL COHORT					
	Measure	FP/FOR	FP/SAL DPI	FP/SAL MDI	BUD/FOR	BDP/FOR	p-value
Age at index date (years)	N (% not missing)	129 (100.0)	3739 (100.0)	NA	2010 (100.0)	347 (100.0)	.002‡
	Mean (SD)	70.5 (10.7)	69.5 (10.3)	NA	68.6 (10.6)	68.1 (11.4)	
	Median (IQR)	72 (63, 78)	70 (63, 77)	NA	69 (62, 76)	68 (61, 77)	
	Min, Max	(43, 94)	(37, 98)	NA	(32, 94)	(35, 94)	
Gender	N (% not missing)	129 (100.0)	3739 (100.0)	NA	2010 (100.0)	347 (100.0)	0.038*
	Female, n (%)	61 (47.3)	1593 (42.6)	NA	885 (44.0)	174 (50.1)	
	Male, n (%)	68 (52.7)	2146 (57.4)	NA	1125 (56.0)	173 (49.9)	
Height (m) - closest to index date	N (% not missing)	129 (100.0)	3706 (99.1)	NA	1996 (99.3)	344 (99.1)	.427‡
	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, 1.8)	1.7 (1.6, 1.8)	
	Min, Max	(1.4, 1.9)	(1, 2)	NA	(1.2, 2.1)	(1.4, 1.9)	
Weight (kg) - closest to index date	N (% not missing)	128 (99.2)	3654 (97.7)	NA	1973 (98.2)	341 (98.3)	.238‡
	Mean (SD)	74.5 (20.7)	75.2 (19.3)	NA	75.7 (19.1)	76.8 (20.2)	
	Median (IQR)	71 (60, 87)	73 (61, 87)	NA	73 (62, 87)	75 (61, 88)	
	Min, Max	(41.4, 146.2)	(40, 179)	NA	(40, 177)	(41, 180)	
BMI (kg/m2)	N (% not missing)	129 (100.0)	3681 (98.4)	NA	1984 (98.7)	342 (98.6)	.099‡
	Mean (SD)	26.6 (6.1)	26.7 (6.2)	NA	26.8 (6.1)	27.5 (6.5)	
	Median (IQR)	26.2 (22.4, 29.0)	26.0 (22.4, 30.1)	NA	26.1 (22.5, 30.2)	26.7 (22.9, 31.2)	
	Min, Max	(13.3, 46.4)	(13.1, 58.6)	NA	(13.8, 54.1)	(13.5, 53.8)	
BMI (kg/m2) (categorised)	N (% not missing)	129 (100.0)	3681 (98.4)	NA	1984 (98.7)	342 (98.6)	0.177*
	Underweight (BMI≤18.5), n (%)	5 (3.9)	253 (6.9)	NA	122 (6.1)	19 (5.6)	
	Normal (18.5≤BMI<25), n (%)	46 (35.7)	1331 (36.2)	NA	698 (35.2)	103 (30.1)	

		TOTAL COHORT					
	Measure	FP/FOR	FP/SAL DPI	FP/SAL MDI	BUD/FOR	BDP/FOR	p-value
	Overweight (25≤BMI<30), n (%)	48 (37.2)	1148 (31.2)	NA	643 (32.4)	112 (32.7)	
	Obese (BMI≥30), n (%)	30 (23.3)	949 (25.8)	NA	521 (26.3)	108 (31.6)	
FEV_1 % predicted	N (% not missing)	121 (93.8)	3593 (96.1)	NA	1918 (95.4)	336 (96.8)	
	Mean (SD)	55.8 (18.4)	54.7 (19.6)	NA	56.9 (19.4)	58.3 (21.4)	<0.001‡
	Median (IQR)	54 (43, 67)	53 (41, 67)	NA	56 (43, 69)	59 (44, 71)	
	Min, Max	(19, 104)	(5, 167)	NA	(1, 169)	(9, 148)	
FEV_1 % predicted (categorised)	N (% not missing)	121 (93.8)	3593 (96.1)	NA	1918 (95.4)	336 (96.8)	
	<30 (very severe), n (%)	8 (6.6)	312 (8.7)	NA	123 (6.4)	30 (8.9)	
	30-49 (severe), n (%)	37 (30.6)	1220 (34.0)	NA	601 (31.3)	91 (27.1)	0.001*
	50-79 (moderate), n (%)	63 (52.1)	1717 (47.8)	NA	959 (50.0)	171 (50.9)	
	≥80 (mild), n (%)	13 (10.7)	344 (9.6)	NA	235 (12.3)	44 (13.1)	
Smoking Status	N (% not missing)	129 (100.0)	3739 (100.0)	NA	2009 (100.0)	347 (100.0)	
	Non-smoker, n (%)	13 (10.1)	220 (5.9)	NA	136 (6.8)	31 (8.9)	
	Current smoker, n (%)	43 (33.3)	1516 (40.5)	NA	818 (40.7)	141 (40.6)	0.093*
	Ex-smoker, n (%)	73 (56.6)	2003 (53.6)	NA	1055 (52.5)	175 (50.4)	

Table 28: Demographic characteristics by FDC/ICS LABA (patients with COPD only, definition 3)
‡ Kruskal-Wallis test, * Chi-square test, NA – not applicable

5.2.6.2 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)	129 (100.0)	3739 (100.0)	NA	2010 (100.0)	347 (100.0)	
	Mean (SD)	21.3 (14.7)	22.4 (18.3)	NA	20.0 (17.0)	19.4 (15.2)	
	Median (IQR)	18.0 (11.6, 27.4)	19.6 (7.6, 32.9)	NA	17.7 (6.3, 28.4)	17.6 (6.7, 25.5)	<0.001‡
	Min, Max	(0.1, 65.3)	(0, 88)	NA	(0, 86)	(0, 81)	
Prescribed FDC ICS/LABA inhaler dose (dose per puff)	N (% not missing)	129 (100.0)	3739 (100.0)	NA	2010 (100.0)	347 (100.0)	
	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	<0.001*
	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 dosing instructions (FP	N (% not missing)	95 (73.6)	1642 (43.9)	NA	1663 (82.7)	265 (76.4)	
	Mean (SD)	805.0 (271.9)	1021.6 (150.1)	NA	379.6 (110.6)	454.0 (103.0)	<0.001‡

		TOTAL COHORT					
	Measure	FP/FOR	FP/SAL DPI	FP/SAL MDI	BUD/FOR	BDP/FOR	p-value
equivalent dose per day)	Median (IQR)	1000 (500, 1000)	1000 (1000, 1000)	NA	400 (400, 400)	500 (500, 500)	
	Min, Max	(200, 1000)	(500, 2000)	NA	(200, 800)	(188, 1000)	
Prescribed FDC ICS/LABA dosing instructions (FP equivalent dose per day) (categorised)	N (% not missing)	95 (73.6)	1642 (43.9)	NA	1663 (82.7)	265 (76.4)	<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)	129 (100.0)	3739 (100.0)	NA	2010 (100.0)	347 (100.0)	.001‡
	Mean (SD)	17.1 (13.3)	19.6 (14.7)	NA	18.9 (14.4)	16.7 (14.1)	
	Median (IQR)	20.0 (2.6, 28.5)	19.2 (4.6, 31.2)	NA	18 (5, 30)	14.3 (3.0, 26.4)	
	Min, Max	(0, 41)	(0, 54)	NA	(0, 51)	(0, 50)	
SABA prescriptions	N (% not missing)	129 (100.0)	3739 (100.0)	NA	2010 (100.0)	347 (100.0)	0.111*
	No, n (%)	98 (76.0)	3029 (81.0)	NA	1664 (82.8)	277 (79.8)	
	Yes, n (%)	31 (24.0)	710 (19.0)	NA	346 (17.2)	70 (20.2)	
SAMA prescriptions	N (% not missing)	129 (100.0)	3739 (100.0)	NA	2010 (100.0)	347 (100.0)	0.145*
	No, n (%)	n≥5	3666 (98.0)	NA	1985 (98.8)	340 (98.0)	
	Yes, n (%)	n<5	73 (2.0)	NA	25 (1.2)	7 (2.0)	
LABA prescriptions	N (% not missing)	129 (100.0)	3739 (100.0)	NA	2010 (100.0)	347 (100.0)	0.086*
	No, n (%)	n≥5	3726 (99.7)	NA	2004 (99.7)	n≥5	
	Yes, n (%)	n<5	13 (0.3)	NA	6 (0.3)	n<5	
LAMA prescriptions	N (% not missing)	129 (100.0)	3739 (100.0)	NA	2010 (100.0)	347 (100.0)	<0.001*
	No, n (%)	101 (78.3)	2561 (68.5)	NA	1549 (77.1)	285 (82.1)	
	Yes, n (%)	28 (21.7)	1178 (31.5)	NA	461 (22.9)	62 (17.9)	
ICS only prescriptions	N (% not missing)	129 (100.0)	3739 (100.0)	NA	2010 (100.0)	347 (100.0)	0.238*
	No, n (%)	n≥5	3732 (99.8)	NA	2002 (99.6)	n≥5	
	Yes, n (%)	n<5	7 (0.2)	NA	8 (0.4)	n<5	
Theophylline prescriptions	N (% not missing)	129 (100.0)	3739 (100.0)	NA	2010 (100.0)	347 (100.0)	0.311*
	No, n (%)	n≥5	3667 (98.1)	NA	1982 (98.6)	n≥5	
	Yes, n (%)	n<5	72 (1.9)	NA	28 (1.4)	n<5	
LTRA prescriptions	N (% not missing)	129 (100.0)	3739 (100.0)	NA	2010 (100.0)	347 (100.0)	0.490*
	No, n (%)	n≥5	3725 (99.6)	NA	1999 (99.5)	n≥5	
	Yes, n (%)	n<5	14 (0.4)	NA	11 (0.5)	n<5	

Table 29: Medication prescribed at index date by FDC/ICS LABA (patients with COPD only, definition 3)
‡ Kruskal-Wallis test, * Chi-square test, NA – not applicable

5.2.6.3 Comorbidities

		TOTAL COHORT					
	Measure	FP/FOR	FP/SAL DPI	FP/SAL MDI	BUD/FOR	BDP/FOR	p-value
Year of first COPD diagnosis	N (% not missing)	128 (99.2)	3732 (99.8)	NA	2003 (99.7)	346 (99.7)	<0.001‡
	Mean (SD)	2006.2 (7.8)	2007.2 (5.7)	NA	2008.0 (5.5)	2007.5 (5.9)	
	Median (IQR)	2007 (2004, 2011)	2009 (2005, 2011)	NA	2010 (2006, 2012)	2010 (2005, 2011)	
	Min, Max	(1940, 2014)	(1963, 2014)	NA	(1956, 2014)	(1966, 2014)	
Duration of COPD (years)	N (% not missing)	128 (99.2)	3732 (99.8)	NA	2003 (99.7)	346 (99.7)	<0.001‡
	Mean (SD)	6.9 (7.8)	5.4 (5.7)	NA	4.6 (5.5)	5.1 (5.9)	
	Median (IQR)	5.8 (2.2, 9.2)	3.9 (1.0, 7.8)	NA	2.8 (0.5, 6.8)	3.0 (1.0, 7.4)	
	Min, Max	(0, 74)	(0, 51)	NA	(0, 57)	(0, 46)	
Comorbid rhinitis	N (% not missing)	129 (100.0)	3739 (100.0)	NA	2010 (100.0)	347 (100.0)	0.499*
	No, n (%)	122 (94.6)	3608 (96.5)	NA	1929 (96.0)	336 (96.8)	
	Yes, n (%)	7 (5.4)	131 (3.5)	NA	81 (4.0)	11 (3.2)	
Comorbid eczema	N (% not missing)	129 (100.0)	3739 (100.0)	NA	2010 (100.0)	347 (100.0)	0.269*
	No, n (%)	120 (93.0)	3536 (94.6)	NA	1877 (93.4)	329 (94.8)	
	Yes, n (%)	9 (7.0)	203 (5.4)	NA	133 (6.6)	18 (5.2)	
Comorbid GERD	N (% not missing)	129 (100.0)	3739 (100.0)	NA	2010 (100.0)	347 (100.0)	0.048*
	No, n (%)	104 (80.6)	3312 (88.6)	NA	1774 (88.3)	303 (87.3)	
	Yes, n (%)	25 (19.4)	427 (11.4)	NA	236 (11.7)	44 (12.7)	
History of ischemic heart disease	N (% not missing)	129 (100.0)	3739 (100.0)	NA	2010 (100.0)	347 (100.0)	0.159*
	No, n (%)	99 (76.7)	2985 (79.8)	NA	1625 (80.8)	292 (84.1)	
	Yes, n (%)	30 (23.3)	754 (20.2)	NA	385 (19.2)	55 (15.9)	
History of hypertension	N (% not missing)	129 (100.0)	3739 (100.0)	NA	2010 (100.0)	347 (100.0)	0.487*
	No, n (%)	68 (52.7)	2206 (59.0)	NA	1195 (59.5)	201 (57.9)	
	Yes, n (%)	61 (47.3)	1533 (41.0)	NA	815 (40.5)	146 (42.1)	
History of ischemic heart disease and hypertension	N (% not missing)	129 (100.0)	3739 (100.0)	NA	2010 (100.0)	347 (100.0)	0.094*
	No, n (%)	108 (83.7)	3351 (89.6)	NA	1796 (89.4)	318 (91.6)	
	Yes, n (%)	21 (16.3)	388 (10.4)	NA	214 (10.6)	29 (8.4)	
Charlson Comorbidity Index (CCI)	N (% not missing)	129 (100.0)	3738 (100.0)	NA	2008 (99.9)	347 (100.0)	.051‡
	Mean (SD)	2.1 (4.4)	2.5 (3.8)	NA	2.5 (3.9)	2.2 (3.8)	
	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, 35)	

		TOTAL COHORT					
	Measure	FP/FOR	FP/SAL DPI	FP/SAL MDI	BUD/FOR	BDP/FOR	p-value
Charlson Comorbidity Index (CCI) (categorised)	N (% not missing)	129 (100.0)	3738 (100.0)	NA	2008 (99.9)	347 (100.0)	0.029*
	0, n (%)	84 (65.1)	2118 (56.7)	NA	1171 (58.3)	214 (61.7)	
	1-4, n (%)	33 (25.6)	1175 (31.4)	NA	568 (28.3)	100 (28.8)	
	≥5, n (%)	12 (9.3)	445 (11.9)	NA	269 (13.4)	33 (9.5)	

Table 30: Comorbidities by FDC/ICS LABA (patients with COPD only, definition 3)
‡ Kruskal-Wallis test, * Chi-square test, NA – not applicable

5.2.6.4 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	N (% not missing)	129 (100.0)	3739 (100.0)	NA	2010 (100.0)	347 (100.0)	.127‡
	Mean (SD)	1.5 (1.5)	1.9 (1.9)	NA	2.0 (1.9)	1.9 (1.9)	
	Median (IQR)	1 (0, 2)	1 (1, 3)	NA	2 (1, 3)	2 (1, 3)	
	Min, Max	(0, 9)	(0, 20)	NA	(0, 15)	(0, 15)	
Respiratory GP consultations without prescription for an oral corticosteroid (categorised)	N (% not missing)	129 (100.0)	3739 (100.0)	NA	2010 (100.0)	347 (100.0)	0.460*
	0, n (%)	36 (27.9)	921 (24.6)	NA	485 (24.1)	80 (23.1)	
	1, n (%)	42 (32.6)	986 (26.4)	NA	515 (25.6)	87 (25.1)	
	2, n (%)	21 (16.3)	763 (20.4)	NA	412 (20.5)	83 (23.9)	
	≥3, n (%)	30 (23.3)	1069 (28.6)	NA	598 (29.8)	97 (28.0)	
COPD GP consultations without prescription for an oral corticosteroid	N (% not missing)	129 (100.0)	3739 (100.0)	NA	2010 (100.0)	347 (100.0)	.091‡
	Mean (SD)	0.6 (0.7)	0.8 (1.0)	NA	0.8 (1.0)	0.8 (1.0)	
	Median (IQR)	0 (0, 1)	1 (0, 1)	NA	1 (0, 1)	1 (0, 1)	
	Min, Max	(0, 4)	(0, 8)	NA	(0, 6)	(0, 5)	
COPD GP consultations without prescription for an oral corticosteroid (categorised)	N (% not missing)	129 (100.0)	3739 (100.0)	NA	2010 (100.0)	347 (100.0)	0.223*
	0, n (%)	n≥5	1757 (47.0)	NA	940 (46.8)	168 (48.4)	
	1, n (%)	n≥5	1308 (35.0)	NA	697 (34.7)	119 (34.3)	
	2, n (%)	n≥5	472 (12.6)	NA	264 (13.1)	35 (10.1)	
	≥3, n (%)	n<5	202 (5.4)	NA	109 (5.4)	25 (7.2)	
Lower respiratory hospital outpatient attendances	N (% not missing)	56 (100.0)	2267 (100.0)	NA	1201 (100.0)	201 (100.0)	.862‡
	Mean (SD)	0.0 (0.0)	0.0 (0.0)	NA	0.0 (0.0)	0.0 (0.0)	
	Median (IQR)	0 (0, 0)	0 (0, 0)	NA	0 (0, 0)	0 (0, 0)	
	Min, Max	(0, 0)	(0, 1)	NA	(0, 1)	(0, 0)	
Lower respiratory hospital outpatient attendances (categorised)	N (% not missing)	56 (100.0)	2267 (100.0)	NA	1201 (100.0)	201 (100.0)	0.862*
	0, n (%)	n≥5	n≥5	NA	n≥5	n≥5	
	1, n (%)	n<5	n<5	NA	n<5	n<5	
	N (% not missing)	56 (100.0)	2267 (100.0)	NA	1201 (100.0)	201 (100.0)	.046‡

		TOTAL COHORT					
	Measure	FP/FOR	FP/SAL DPI	FP/SAL MDI	BUD/FOR	BDP/FOR	p-value
COPD hospital outpatient attendances	Mean (SD)	0.0 (0.1)	0.0 (0.1)	NA	0.0 (0.0)	0.0 (0.1)	
	Median (IQR)	0 (0, 0)	0 (0, 0)	NA	0 (0, 0)	0 (0, 0)	
	Min, Max	(0, 1)	(0, 2)	NA	(0, 1)	(0, 1)	
COPD hospital outpatient attendances (categorised)	N (% not missing)	56 (100.0)	2267 (100.0)	NA	1201 (100.0)	201 (100.0)	0.097*
	0, n (%)	n≥5	n≥5	NA	n≥5	n≥5	
	1, n (%)	n<5	n<5	NA	n<5	n<5	
	≥2, n (%)	n<5	n<5	NA	n<5	n<5	
Lower respiratory inpatient hospitalisations	N (% not missing)	56 (100.0)	2267 (100.0)	NA	1201 (100.0)	201 (100.0)	.019‡
	Mean (SD)	0.2 (0.7)	0.2 (0.6)	NA	0.2 (0.6)	0.1 (0.3)	
	Median (IQR)	0 (0, 0)	0 (0, 0)	NA	0 (0, 0)	0 (0, 0)	
	Min, Max	(0, 4)	(0, 10)	NA	(0, 8)	(0, 2)	
Lower respiratory inpatient hospitalisations (categorised)	N (% not missing)	56 (100.0)	2267 (100.0)	NA	1201 (100.0)	201 (100.0)	0.085*
	0, n (%)	n≥5	1955 (86.2)	NA	1049 (87.3)	n≥5	
	1, n (%)	n≥5	252 (11.1)	NA	124 (10.3)	n≥5	
	≥2, n (%)	n<5	60 (2.6)	NA	28 (2.3)	n<5	
COPD inpatient hospitalisations	N (% not missing)	56 (100.0)	2267 (100.0)	NA	1201 (100.0)	201 (100.0)	<0.001‡
	Mean (SD)	0.2 (0.6)	0.2 (0.6)	NA	0.1 (0.4)	0.0 (0.3)	
	Median (IQR)	0 (0, 0)	0 (0, 0)	NA	0 (0, 0)	0 (0, 0)	
	Min, Max	(0, 4)	(0, 9)	NA	(0, 5)	(0, 3)	
COPD inpatient hospitalisations (categorised)	N (% not missing)	56 (100.0)	2267 (100.0)	NA	1201 (100.0)	201 (100.0)	0.003*
	0, n (%)	n≥5	2012 (88.8)	NA	1098 (91.4)	n≥5	
	1, n (%)	n≥5	206 (9.1)	NA	83 (6.9)	n<5	
	≥2, n (%)	n<5	49 (2.2)	NA	20 (1.7)	n<5	
COPD exacerbations	N (% not missing)	56 (100.0)	2267 (100.0)	NA	1201 (100.0)	201 (100.0)	.015‡
	Mean (SD)	1.9 (1.6)	1.7 (1.8)	NA	1.5 (1.6)	1.4 (1.5)	
	Median (IQR)	2 (1, 3)	1 (0, 2)	NA	1 (0, 2)	1 (0, 2)	
	Min, Max	(0, 5)	(0, 13)	NA	(0, 14)	(0, 7)	
COPD exacerbations (categorised)	N (% not missing)	56 (100.0)	2267 (100.0)	NA	1201 (100.0)	201 (100.0)	0.190*
	0, n (%)	12 (21.4)	703 (31.0)	NA	407 (33.9)	71 (35.3)	
	1, n (%)	14 (25.0)	590 (26.0)	NA	300 (25.0)	55 (27.4)	
	≥2, n (%)	30 (53.6)	974 (43.0)	NA	494 (41.1)	75 (37.3)	

Table 31: Consultations and hospitalisations in year prior to index date by FDC/ICS LABA (patients with COPD only, definition 3)

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

5.2.6.5 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 prescriptions	N (% not missing)	129 (100.0)	3739 (100.0)	NA	2010 (100.0)	347 (100.0)	<0.001‡
	Mean (SD)	6.1 (6.3)	3.8 (5.6)	NA	2.1 (4.5)	2.9 (4.8)	
	Median (IQR)	5 (0, 11)	0 (0, 8)	NA	0 (0, 0)	0 (0, 5)	
	Min, Max	(0, 32)	(0, 50)	NA	(0, 45)	(0, 26)	
FDC ICS+LABA prescriptions (categorised)	N (% not missing)	129 (100.0)	3739 (100.0)	NA	2010 (100.0)	347 (100.0)	<0.001*
	0, n (%)	n≥5	2221 (59.4)	NA	1526 (75.9)	219 (63.1)	
	1, n (%)	n<5	56 (1.5)	NA	38 (1.9)	12 (3.5)	
	≥2, n (%)	n≥5	1462 (39.1)	NA	446 (22.2)	116 (33.4)	
SABA prescriptions	N (% not missing)	129 (100.0)	3739 (100.0)	NA	2010 (100.0)	347 (100.0)	<0.001‡
	Mean (SD)	4.1 (6.7)	3.8 (6.8)	NA	3.4 (6.0)	5.1 (8.5)	
	Median (IQR)	1 (0, 6)	0 (0, 5)	NA	0 (0, 4)	2 (0, 7)	
	Min, Max	(0, 34)	(0, 58)	NA	(0, 57)	(0, 74)	
SABA prescriptions (categorised)	N (% not missing)	129 (100.0)	3739 (100.0)	NA	2010 (100.0)	347 (100.0)	0.009*
	0, n (%)	64 (49.6)	1928 (51.6)	NA	1045 (52.0)	142 (40.9)	
	1, n (%)	9 (7.0)	272 (7.3)	NA	148 (7.4)	25 (7.2)	
	≥2, n (%)	56 (43.4)	1539 (41.2)	NA	817 (40.6)	180 (51.9)	
SAMA prescriptions	N (% not missing)	129 (100.0)	3739 (100.0)	NA	2010 (100.0)	347 (100.0)	.640‡
	Mean (SD)	0.7 (2.4)	0.8 (3.8)	NA	0.7 (4.0)	0.8 (3.2)	
	Median (IQR)	0 (0, 0)	0 (0, 0)	NA	0 (0, 0)	0 (0, 0)	
	Min, Max	(0, 14)	(0, 66)	NA	(0, 88)	(0, 28)	
SAMA prescriptions (categorised)	N (% not missing)	129 (100.0)	3739 (100.0)	NA	2010 (100.0)	347 (100.0)	0.121*
	0, n (%)	n≥5	3426 (91.6)	NA	1846 (91.8)	n≥5	
	1, n (%)	n<5	33 (0.9)	NA	32 (1.6)	n<5	
	≥2, n (%)	n≥5	280 (7.5)	NA	132 (6.6)	n≥5	
LABA prescriptions	N (% not missing)	129 (100.0)	3739 (100.0)	NA	2010 (100.0)	347 (100.0)	.003‡
	Mean (SD)	0.3 (1.6)	0.8 (2.8)	NA	0.6 (2.5)	0.9 (3.0)	
	Median (IQR)	0 (0, 0)	0 (0, 0)	NA	0 (0, 0)	0 (0, 0)	
	Min, Max	(0, 12)	(0, 30)	NA	(0, 24)	(0, 20)	
LABA prescriptions (categorised)	N (% not missing)	129 (100.0)	3739 (100.0)	NA	2010 (100.0)	347 (100.0)	0.002*
	0, n (%)	n≥5	3337 (89.2)	NA	1817 (90.4)	294 (84.7)	
	1, n (%)	n<5	41 (1.1)	NA	29 (1.4)	10 (2.9)	
	≥2, n (%)	n≥5	361 (9.7)	NA	164 (8.2)	43 (12.4)	
LAMA prescriptions	N (% not missing)	129 (100.0)	3739 (100.0)	NA	2010 (100.0)	347 (100.0)	<0.001‡
	Mean (SD)	10.3 (11.3)	8.5 (10.6)	NA	7.1 (9.7)	6.3 (9.8)	
	Median (IQR)	8 (0, 20)	4 (0, 14)	NA	2 (0, 12)	0 (0, 10)	
	Min, Max	(0, 52)	(0, 88)	NA	(0, 66)	(0, 58)	

		TOTAL COHORT					
	Measure	FP/FOR	FP/SAL DPI	FP/SAL MDI	BUD/FOR	BDP/FOR	p-value
LAMA prescriptions (categorised)	N (% not missing)	129 (100.0)	3739 (100.0)	NA	2010 (100.0)	347 (100.0)	<0.001*
	0, n (%)	n≥5	1579 (42.2)	NA	971 (48.3)	n≥5	
	1, n (%)	n<5	18 (0.5)	NA	9 (0.4)	n<5	
	≥2, n (%)	n≥5	2142 (57.3)	NA	1030 (51.2)	n≥5	
ICS only prescriptions	N (% not missing)	129 (100.0)	3739 (100.0)	NA	2010 (100.0)	347 (100.0)	<0.001‡
	Mean (SD)	0.6 (2.2)	0.6 (2.5)	NA	0.9 (2.6)	1.5 (3.6)	
	Median (IQR)	0 (0, 0)	0 (0, 0)	NA	0 (0, 0)	0 (0, 0)	
	Min, Max	(0, 14)	(0, 32)	NA	(0, 26)	(0, 28)	
ICS only prescriptions (categorised)	N (% not missing)	129 (100.0)	3739 (100.0)	NA	2010 (100.0)	347 (100.0)	<0.001*
	0, n (%)	113 (87.6)	3315 (88.7)	NA	1673 (83.2)	262 (75.5)	
	1, n (%)	6 (4.7)	94 (2.5)	NA	64 (3.2)	15 (4.3)	
	≥2, n (%)	10 (7.8)	330 (8.8)	NA	273 (13.6)	70 (20.2)	
Theophylline prescriptions	N (% not missing)	129 (100.0)	3739 (100.0)	NA	2010 (100.0)	347 (100.0)	.050‡
	Mean (SD)	0.5 (2.3)	0.4 (2.5)	NA	0.2 (1.9)	0.3 (2.0)	
	Median (IQR)	0 (0, 0)	0 (0, 0)	NA	0 (0, 0)	0 (0, 0)	
	Min, Max	(0, 14)	(0, 51)	NA	(0, 52)	(0, 23)	
Theophylline prescriptions (categorised)	N (% not missing)	129 (100.0)	3739 (100.0)	NA	2010 (100.0)	347 (100.0)	0.058*
	0, n (%)	n≥5	3593 (96.1)	NA	1951 (97.1)	n≥5	
	1, n (%)	n<5	14 (0.4)	NA	10 (0.5)	n<5	
	≥2, n (%)	n≥5	132 (3.5)	NA	49 (2.4)	n≥5	
LTRA prescriptions	N (% not missing)	129 (100.0)	3739 (100.0)	NA	2010 (100.0)	347 (100.0)	.620‡
	Mean (SD)	0.3 (3.2)	0.1 (0.9)	NA	0.1 (0.9)	0.1 (0.8)	
	Median (IQR)	0 (0, 0)	0 (0, 0)	NA	0 (0, 0)	0 (0, 0)	
	Min, Max	(0, 35)	(0, 14)	NA	(0, 13)	(0, 13)	
LTRA prescriptions (categorised)	N (% not missing)	129 (100.0)	3739 (100.0)	NA	2010 (100.0)	347 (100.0)	0.556*
	0, n (%)	n≥5	3696 (98.8)	NA	n≥5	n≥5	
	1, n (%)	n<5	5 (0.1)	NA	n<5	n<5	
	≥2, n (%)	n<5	38 (1.0)	NA	n≥5	n<5	
Spacer prescription	N (% not missing)	129 (100.0)	3739 (100.0)	NA	2010 (100.0)	347 (100.0)	<0.001*
	No, n (%)	80 (62.0)	3006 (80.4)	NA	1681 (83.6)	241 (69.5)	
	Yes, n (%)	49 (38.0)	733 (19.6)	NA	329 (16.4)	106 (30.5)	
Pain-relief medication prescriptions	N (% not missing)	129 (100.0)	3739 (100.0)	NA	2010 (100.0)	347 (100.0)	.246‡
	Mean (SD)	4.1 (5.8)	3.6 (6.0)	NA	3.7 (6.5)	3.8 (6.3)	
	Median (IQR)	1 (0, 7)	0 (0, 5)	NA	0 (0, 5)	1 (0, 6)	
	Min, Max	(0, 31)	(0, 61)	NA	(0, 57)	(0, 46)	
Pain-relief medication prescriptions (categorised)	N (% not missing)	129 (100.0)	3739 (100.0)	NA	2010 (100.0)	347 (100.0)	0.425*
	0, n (%)	57 (44.2)	1904 (50.9)	NA	1031 (51.3)	160 (46.1)	
	1-4, n (%)	31 (24.0)	823 (22.0)	NA	437 (21.7)	88 (25.4)	

		TOTAL COHORT					
	Measure	FP/FOR	FP/SAL DPI	FP/SAL MDI	BUD/FOR	BDP/FOR	p-value
	≥5, n (%)	41 (31.8)	1012 (27.1)	NA	542 (27.0)	99 (28.5)	
Non-steroidal anti-inflammatory drugs (NSAIDs) prescriptions	N (% not missing)	129 (100.0)	3739 (100.0)	NA	2010 (100.0)	347 (100.0)	.323‡
	Mean (SD)	0.6 (2.1)	0.6 (2.0)	NA	0.7 (2.1)	0.8 (2.2)	
	Median (IQR)	0 (0, 0)	0 (0, 0)	NA	0 (0, 0)	0 (0, 0)	
	Min, Max	(0, 15)	(0, 23)	NA	(0, 40)	(0, 13)	
Non-steroidal anti-inflammatory drugs (NSAIDs) prescriptions (categorised)	N (% not missing)	129 (100.0)	3739 (100.0)	NA	2010 (100.0)	347 (100.0)	0.541*
	0, n (%)	n≥5	3087 (82.6)	NA	1628 (81.0)	278 (80.1)	
	1-2, n (%)	n≥5	407 (10.9)	NA	227 (11.3)	36 (10.4)	
	3-4, n (%)	n<5	81 (2.2)	NA	59 (2.9)	12 (3.5)	
	≥5, n (%)	n≥5	164 (4.4)	NA	96 (4.8)	21 (6.1)	
Beta-blocker prescriptions	N (% not missing)	129 (100.0)	3739 (100.0)	NA	2010 (100.0)	347 (100.0)	.450‡
	Mean (SD)	1.7 (4.0)	1.5 (4.6)	NA	1.5 (4.0)	1.6 (5.5)	
	Median (IQR)	0 (0, 0)	0 (0, 0)	NA	0 (0, 0)	0 (0, 0)	
	Min, Max	(0, 16)	(0, 58)	NA	(0, 54)	(0, 54)	
Beta-blocker prescriptions (categorised)	N (% not missing)	129 (100.0)	3739 (100.0)	NA	2010 (100.0)	347 (100.0)	0.688*
	0, n (%)	n≥5	3145 (84.1)	NA	1662 (82.7)	294 (84.7)	
	1-4, n (%)	n<5	113 (3.0)	NA	65 (3.2)	11 (3.2)	
	5-9, n (%)	n≥5	216 (5.8)	NA	143 (7.1)	17 (4.9)	
	≥10, n (%)	n≥5	265 (7.1)	NA	140 (7.0)	25 (7.2)	

Table 32: Prescriptions for therapy in year prior to index date by FDC/ICS LABA (patients with COPD only, definition 3)

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

5.2.7 "MART" regimen, definition 1

For MART regimen patients (definition 1), demographic characteristics, disease severity, comorbidities, presence of comorbid COPD, GP consultations, hospitalisations and prescriptions at the index date were similar across treatment groups. The FP/FOR group had an earlier first diagnosis of asthma and a greater proportion had asthma exacerbations than other treatment groups. The FP/FOR group also had a lower prescription of SABA and ICS prior to the index date and were more likely to be switchers than the other FDC ICS/LABA groups.

5.2.7.1 Demographic characteristics

		TOTAL COHORT					
	Measure	FP/FOR	FP/SAL DPI	FP/SAL MDI	BUD/FOR	BDP/FOR	p-value
Age at index date (years)	N (% not missing)	66 (100.0)	NA	NA	379 (100.0)	308 (100.0)	.054‡
	Mean (SD)	52.0 (17.5)	NA	NA	45.9 (16.3)	46.8 (17.6)	
	Median (IQR)	50 (39, 65)	NA	NA	45 (33, 57)	45 (33, 59)	
	Min, Max	(19, 87)	NA	NA	(18, 92)	(18, 95)	
Gender	N (% not missing)	66 (100.0)	NA	NA	379 (100.0)	308 (100.0)	0.034*
	Female, n (%)	50 (75.8)	NA	NA	226 (59.6)	182 (59.1)	
	Male, n (%)	16 (24.2)	NA	NA	153 (40.4)	126 (40.9)	
Height (m) - closest to index date	N (% not missing)	64 (97.0)	NA	NA	356 (93.9)	297 (96.4)	.208‡
	Mean (SD)	1.7 (0.1)	NA	NA	1.7 (0.1)	1.7 (0.1)	
	Median (IQR)	1.7 (1.6, 1.7)	NA	NA	1.7 (1.6, 1.8)	1.7 (1.6, 1.7)	
	Min, Max	(1.5, 1.9)	NA	NA	(1.5, 2.0)	(1.4, 2.0)	
Weight (kg) - closest to index date	N (% not missing)	64 (97.0)	NA	NA	354 (93.4)	295 (95.8)	.214‡
	Mean (SD)	75.5 (16.7)	NA	NA	79.6 (19.9)	80.8 (20.6)	
	Median (IQR)	72 (61, 89)	NA	NA	75 (66, 90)	77.5 (65.3, 92.1)	
	Min, Max	(45, 118)	NA	NA	(42, 163)	(47, 169)	
BMI (kg/m2)	N (% not missing)	64 (97.0)	NA	NA	346 (91.3)	289 (93.8)	.319‡
	Mean (SD)	27.6 (6.4)	NA	NA	28.1 (6.5)	28.7 (6.7)	
	Median (IQR)	25.7 (22.3, 31.7)	NA	NA	26.9 (23.8, 30.8)	27.8 (23.8, 32.5)	
	Min, Max	(17.0, 47.8)	NA	NA	(16.2, 53.7)	(17.2, 55.4)	
BMI (kg/m2) (categorised)	N (% not missing)	64 (97.0)	NA	NA	346 (91.3)	289 (93.8)	0.213*
	Underweight (BMI≤18.5), n (%)	n<5	NA	NA	7 (2.0)	n<5	
	Normal (18.5≤BMI<25), n (%)	n≥5	NA	NA	119 (34.4)	n≥5	
	Overweight (25≤BMI<30), n (%)	n≥5	NA	NA	118 (34.1)	n≥5	
	Obese (BMI≥30), n (%)	n≥5	NA	NA	102 (29.5)	n≥5	

		TOTAL COHORT					
	Measure	FP/FOR	FP/SAL DPI	FP/SAL MDI	BUD/FOR	BDP/FOR	p-value
FEV_1 % predicted	N (% not missing)	15 (22.7)	NA	NA	122 (32.2)	83 (26.9)	.257‡
	Mean (SD)	72.9 (24.7)	NA	NA	83.0 (23.5)	82.9 (23.7)	
	Median (IQR)	83 (51, 90)	NA	NA	88 (71, 99)	86 (70, 98)	
	Min, Max	(20, 109)	NA	NA	(20, 131)	(30, 144)	
FEV_1 % predicted (categorised)	N (% not missing)	15 (22.7)	NA	NA	122 (32.2)	83 (26.9)	0.288*
	<30 (very severe), n (%)	n<5	NA	NA	7 (5.7)	n<5	
	30-49 (severe), n (%)	n<5	NA	NA	5 (4.1)	n≥5	
	50-79 (moderate), n (%)	n<5	NA	NA	30 (24.6)	n≥5	
	≥80 (mild), n (%)	n≥5	NA	NA	80 (65.6)	n≥5	
PEF % predicted	N (% not missing)	54 (81.8)	NA	NA	245 (64.6)	249 (80.8)	.067‡
	Mean (SD)	96.1 (26.8)	NA	NA	98.0 (24.3)	101.9 (26.9)	
	Median (IQR)	96.4 (79.7, 113.1)	NA	NA	97.7 (81.6, 116.3)	102.9 (88.1, 123.5)	
	Min, Max	(32.1, 149.0)	NA	NA	(30.2, 149.0)	(23.8, 149.6)	
Smoking Status	N (% not missing)	66 (100.0)	NA	NA	377 (99.5)	308 (100.0)	0.223*
	Non-smoker, n (%)	40 (60.6)	NA	NA	209 (55.4)	149 (48.4)	
	Current smoker, n (%)	11 (16.7)	NA	NA	80 (21.2)	80 (26.0)	
	Ex-smoker, n (%)	15 (22.7)	NA	NA	88 (23.3)	79 (25.6)	

Table 33: Demographic characteristics by FDC/ICS LABA ("MART" regimen definition 1)
‡ Kruskal-Wallis test, * Chi-square test, NA – not applicable

5.2.7.2 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)	66 (100.0)	NA	NA	379 (100.0)	308 (100.0)	<0.001‡
	Mean (SD)	16.5 (13.0)	NA	NA	12.0 (14.0)	17.1 (16.1)	
	Median (IQR)	13.3 (7.0, 23.5)	NA	NA	6.7 (0.4, 20.1)	14.4 (3.1, 25.2)	
	Min, Max	(0.0, 64.8)	NA	NA	(0, 75)	(0, 83)	
Prescribed FDC ICS/LABA inhaler dose (dose per puff)	N (% not missing)	66 (100.0)	NA	NA	379 (100.0)	308 (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)	66 (100.0)	NA	NA	379 (100.0)	308 (100.0)	<0.001‡
	Mean (SD)	15.4 (12.0)	NA	NA	18.3 (15.1)	13.0 (12.7)	
	Median (IQR)	14 (2, 28)	NA	NA	17.1 (2.8, 28.9)	8 (2, 23)	

		TOTAL COHORT					
	Measure	FP/FOR	FP/SAL DPI	FP/SAL MDI	BUD/FOR	BDP/FOR	p-value
	Min, Max	(0, 36)	NA	NA	(0, 52)	(0, 46)	
SABA prescriptions	N (% not missing)	66 (100.0)	NA	NA	379 (100.0)	308 (100.0)	NA
	No, n (%)	66 (100.0)	NA	NA	379 (100.0)	308 (100.0)	
SAMA prescriptions	N (% not missing)	66 (100.0)	NA	NA	379 (100.0)	308 (100.0)	0.848*
	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)	66 (100.0)	NA	NA	379 (100.0)	308 (100.0)	0.235*
	No, n (%)	n≥5	NA	NA	n≥5	n≥5	
	Yes, n (%)	n<5	NA	NA	n<5	n<5	
LAMA prescriptions	N (% not missing)	66 (100.0)	NA	NA	379 (100.0)	308 (100.0)	0.803*
	No, n (%)	n≥5	NA	NA	n≥5	303 (98.4)	
	Yes, n (%)	n<5	NA	NA	n<5	5 (1.6)	
ICS only prescriptions	N (% not missing)	66 (100.0)	NA	NA	379 (100.0)	308 (100.0)	0.624*
	No, n (%)	n≥5	NA	NA	n≥5	302 (98.1)	
	Yes, n (%)	n<5	NA	NA	n<5	6 (1.9)	
Theophylline prescriptions	N (% not missing)	66 (100.0)	NA	NA	379 (100.0)	308 (100.0)	0.629*
	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)	66 (100.0)	NA	NA	379 (100.0)	308 (100.0)	0.470*
	No, n (%)	n≥5	NA	NA	371 (97.9)	303 (98.4)	
	Yes, n (%)	n<5	NA	NA	8 (2.1)	5 (1.6)	

Table 34: Medication prescribed at index date by FDC/ICS LABA ("MART" regimen definition 1)
‡ Kruskal-Wallis test, * Chi-square test, NA – not applicable

5.2.7.3 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)	66 (100.0)	NA	NA	379 (100.0)	308 (100.0)	0.865*
	Asthma only, n (%)	n≥5	NA	NA	365 (96.3)	298 (96.8)	
	Asthma & COPD, n (%)	n<5	NA	NA	14 (3.7)	10 (3.2)	
Year of first asthma diagnosis	N (% not missing)	66 (100.0)	NA	NA	379 (100.0)	308 (100.0)	.040‡
	Mean (SD)	1995.0 (9.3)	NA	NA	1997.1 (13.2)	1996.2 (12.7)	
	Median (IQR)	1994 (1989, 2001)	NA	NA	2000 (1990, 2007)	1998 (1990, 2006)	
	Min, Max	(1967, 2013)	NA	NA	(1949, 2014)	(1940, 2014)	
Duration of asthma (years)	N (% not missing)	66 (100.0)	NA	NA	379 (100.0)	308 (100.0)	.004‡
	Mean (SD)	18.4 (9.4)	NA	NA	15.4 (13.3)	16.8 (12.8)	

		TOTAL COHORT					
	Measure	FP/FOR	FP/SAL DPI	FP/SAL MDI	BUD/FOR	BDP/FOR	p-value
	Median (IQR)	19.1 (12.2, 23.9)	NA	NA	12.4 (5.4, 22.4)	15.5 (7.8, 23.2)	
	Min, Max	(0.1, 46.9)	NA	NA	(0, 64)	(0, 73)	
Year of first COPD diagnosis	N (% not missing)	n<5	NA	NA	14 (3.7)	10 (3.2)	.447‡
	Mean (SD)	n<5	NA	NA	2004.9 (7.2)	2004.6 (5.7)	
	Median (IQR)	n<5	NA	NA	2007 (2000, 2009)	2007 (2000, 2010)	
	Min, Max	n<5	NA	NA	(1990, 2014)	(1995, 2011)	
Duration of COPD (years)	N (% not missing)	n<5	NA	NA	14 (3.7)	10 (3.2)	.530‡
	Mean (SD)	n<5	NA	NA	7.5 (7.2)	8.1 (5.6)	
	Median (IQR)	n<5	NA	NA	5.6 (2.6, 12.1)	6.8 (3.2, 12.5)	
	Min, Max	n<5	NA	NA	(0, 22)	(2.4, 18.0)	
Comorbid rhinitis	N (% not missing)	66 (100.0)	NA	NA	379 (100.0)	308 (100.0)	0.075*
	No, n (%)	55 (83.3)	NA	NA	341 (90.0)	261 (84.7)	
	Yes, n (%)	11 (16.7)	NA	NA	38 (10.0)	47 (15.3)	
Comorbid eczema	N (% not missing)	66 (100.0)	NA	NA	379 (100.0)	308 (100.0)	0.680*
	No, n (%)	n≥5	NA	NA	354 (93.4)	285 (92.5)	
	Yes, n (%)	n<5	NA	NA	25 (6.6)	23 (7.5)	
Comorbid GERD	N (% not missing)	66 (100.0)	NA	NA	379 (100.0)	308 (100.0)	0.258*
	No, n (%)	56 (84.8)	NA	NA	346 (91.3)	276 (89.6)	
	Yes, n (%)	10 (15.2)	NA	NA	33 (8.7)	32 (10.4)	
History of ischemic heart disease	N (% not missing)	66 (100.0)	NA	NA	379 (100.0)	308 (100.0)	0.087*
	No, n (%)	n≥5	NA	NA	369 (97.4)	290 (94.2)	
	Yes, n (%)	n<5	NA	NA	10 (2.6)	18 (5.8)	
History of hypertension	N (% not missing)	66 (100.0)	NA	NA	379 (100.0)	308 (100.0)	0.274*
	No, n (%)	51 (77.3)	NA	NA	321 (84.7)	252 (81.8)	
	Yes, n (%)	15 (22.7)	NA	NA	58 (15.3)	56 (18.2)	
History of ischemic heart disease and hypertension	N (% not missing)	66 (100.0)	NA	NA	379 (100.0)	308 (100.0)	0.041*
	No, n (%)	n≥5	NA	NA	n≥5	299 (97.1)	
	Yes, n (%)	n<5	NA	NA	n<5	9 (2.9)	
Charlson Comorbidity Index (CCI)	N (% not missing)	66 (100.0)	NA	NA	379 (100.0)	308 (100.0)	.004‡
	Mean (SD)	3.6 (2.2)	NA	NA	3.1 (2.5)	3.6 (2.3)	
	Median (IQR)	4 (4, 4)	NA	NA	4 (0, 4)	4 (4, 4)	
	Min, Max	(0, 12)	NA	NA	(0, 20)	(0, 19)	
Charlson Comorbidity Index (CCI) (categorised)	N (% not missing)	66 (100.0)	NA	NA	379 (100.0)	308 (100.0)	0.017*
	0, n (%)	n≥5	NA	NA	107 (28.2)	55 (17.9)	
	1-4, n (%)	n≥5	NA	NA	255 (67.3)	236 (76.6)	
	≥5, n (%)	n<5	NA	NA	17 (4.5)	17 (5.5)	

Table 35: Comorbidities by FDC/ICS LABA ("MART" regimen definition 1)
‡ Kruskal-Wallis test, * Chi-square test, NA – not applicable

5.2.7.4 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	N (% not missing)	66 (100.0)	NA	NA	379 (100.0)	308 (100.0)	.025‡
	Mean (SD)	1.8 (2.1)	NA	NA	1.3 (1.4)	1.6 (1.8)	
	Median (IQR)	1 (0, 3)	NA	NA	1 (0, 2)	1 (0, 2)	
	Min, Max	(0, 12)	NA	NA	(0, 8)	(0, 11)	
Respiratory GP consultations without prescription for an oral corticosteroid (categorised)	N (% not missing)	66 (100.0)	NA	NA	379 (100.0)	308 (100.0)	0.335*
	0, n (%)	17 (25.8)	NA	NA	140 (36.9)	96 (31.2)	
	1, n (%)	19 (28.8)	NA	NA	104 (27.4)	79 (25.6)	
	2, n (%)	13 (19.7)	NA	NA	67 (17.7)	63 (20.5)	
	≥3, n (%)	17 (25.8)	NA	NA	68 (17.9)	70 (22.7)	
Asthma GP consultations without prescription for an oral corticosteroid	N (% not missing)	66 (100.0)	NA	NA	379 (100.0)	308 (100.0)	.004‡
	Mean (SD)	0.8 (0.8)	NA	NA	0.7 (0.9)	0.9 (1.0)	
	Median (IQR)	1 (0, 1)	NA	NA	0 (0, 1)	1 (0, 1)	
	Min, Max	(0, 4)	NA	NA	(0, 4)	(0, 5)	
Asthma GP consultations without prescription for an oral corticosteroid (categorised)	N (% not missing)	66 (100.0)	NA	NA	379 (100.0)	308 (100.0)	0.018*
	0, n (%)	n≥5	NA	NA	204 (53.8)	131 (42.5)	
	1, n (%)	n≥5	NA	NA	114 (30.1)	106 (34.4)	
	2, n (%)	n≥5	NA	NA	41 (10.8)	47 (15.3)	
	≥3, n (%)	n<5	NA	NA	20 (5.3)	24 (7.8)	
COPD GP consultations without prescription for an oral corticosteroid	N (% not missing)	66 (100.0)	NA	NA	379 (100.0)	308 (100.0)	.804‡
	Mean (SD)	0.0 (0.2)	NA	NA	0.0 (0.1)	0.0 (0.2)	
	Median (IQR)	0 (0, 0)	NA	NA	0 (0, 0)	0 (0, 0)	
	Min, Max	(0, 2)	NA	NA	(0, 2)	(0, 3)	
COPD GP consultations without prescription for an oral corticosteroid (categorised)	N (% not missing)	66 (100.0)	NA	NA	379 (100.0)	308 (100.0)	0.597*
	0, n (%)	n≥5	NA	NA	n≥5	n≥5	
	1, n (%)	n<5	NA	NA	n<5	n<5	
	2, n (%)	n<5	NA	NA	n<5	n<5	
	≥3, n (%)	n<5	NA	NA	n<5	n<5	
Lower respiratory hospital outpatient attendances	N (% not missing)	47 (100.0)	NA	NA	253 (100.0)	199 (100.0)	NA
	Mean (SD)	0.0 (0.0)	NA	NA	0.0 (0.0)	0.0 (0.0)	
	Median (IQR)	0 (0, 0)	NA	NA	0 (0, 0)	0 (0, 0)	
	Min, Max	(0, 0)	NA	NA	(0, 0)	(0, 0)	
Lower respiratory hospital outpatient attendances (categorised)	N (% not missing)	47 (100.0)	NA	NA	253 (100.0)	199 (100.0)	NA
	0, n (%)	47 (100.0)	NA	NA	253 (100.0)	199 (100.0)	
Asthma hospital outpatient attendances	N (% not missing)	47 (100.0)	NA	NA	253 (100.0)	199 (100.0)	NA
	Mean (SD)	0.0 (0.0)	NA	NA	0.0 (0.0)	0.0 (0.0)	

		TOTAL COHORT					
	Measure	FP/FOR	FP/SAL DPI	FP/SAL MDI	BUD/FOR	BDP/FOR	p-value
	Median (IQR)	0 (0, 0)	NA	NA	0 (0, 0)	0 (0, 0)	
	Min, Max	(0, 0)	NA	NA	(0, 0)	(0, 0)	
Asthma hospital outpatient attendances (categorised)	N (% not missing)	47 (100.0)	NA	NA	253 (100.0)	199 (100.0)	NA
	0, n (%)	47 (100.0)	NA	NA	253 (100.0)	199 (100.0)	
COPD hospital outpatient attendances	N (% not missing)	47 (100.0)	NA	NA	253 (100.0)	199 (100.0)	NA
	Mean (SD)	0.0 (0.0)	NA	NA	0.0 (0.0)	0.0 (0.0)	
	Median (IQR)	0 (0, 0)	NA	NA	0 (0, 0)	0 (0, 0)	
	Min, Max	(0, 0)	NA	NA	(0, 0)	(0, 0)	
COPD hospital outpatient attendances (categorised)	N (% not missing)	47 (100.0)	NA	NA	253 (100.0)	199 (100.0)	NA
	0, n (%)	47 (100.0)	NA	NA	253 (100.0)	199 (100.0)	
Lower respiratory inpatient hospitalisations	N (% not missing)	47 (100.0)	NA	NA	253 (100.0)	199 (100.0)	.476‡
	Mean (SD)	0.0 (0.0)	NA	NA	0.0 (0.2)	0.0 (0.2)	
	Median (IQR)	0 (0, 0)	NA	NA	0 (0, 0)	0 (0, 0)	
	Min, Max	(0, 0)	NA	NA	(0, 2)	(0, 1)	
Lower respiratory inpatient hospitalisations (categorised)	N (% not missing)	47 (100.0)	NA	NA	253 (100.0)	199 (100.0)	0.549*
	0, n (%)	n≥5	NA	NA	n≥5	n≥5	
	1, n (%)	n<5	NA	NA	n<5	n≥5	
	≥2, n (%)	n<5	NA	NA	n<5	n<5	
Asthma inpatient hospitalisations	N (% not missing)	47 (100.0)	NA	NA	253 (100.0)	199 (100.0)	.303‡
	Mean (SD)	0.0 (0.0)	NA	NA	0.0 (0.3)	0.0 (0.2)	
	Median (IQR)	0 (0, 0)	NA	NA	0 (0, 0)	0 (0, 0)	
	Min, Max	(0, 0)	NA	NA	(0, 3)	(0, 2)	
Asthma inpatient hospitalisations (categorised)	N (% not missing)	47 (100.0)	NA	NA	253 (100.0)	199 (100.0)	0.611*
	0, n (%)	n≥5	NA	NA	n≥5	n≥5	
	1, n (%)	n<5	NA	NA	n≥5	n<5	
	≥2, n (%)	n<5	NA	NA	n<5	n<5	
COPD inpatient hospitalisations	N (% not missing)	47 (100.0)	NA	NA	253 (100.0)	199 (100.0)	.584‡
	Mean (SD)	0.0 (0.0)	NA	NA	0.0 (0.2)	0.0 (0.1)	
	Median (IQR)	0 (0, 0)	NA	NA	0 (0, 0)	0 (0, 0)	
	Min, Max	(0, 0)	NA	NA	(0, 2)	(0, 1)	
COPD inpatient hospitalisations (categorised)	N (% not missing)	47 (100.0)	NA	NA	253 (100.0)	199 (100.0)	0.836*
	0, n (%)	n≥5	NA	NA	n≥5	n≥5	
	1, n (%)	n<5	NA	NA	n<5	n<5	
	≥2, n (%)	n<5	NA	NA	n<5	n<5	
Asthma exacerbations	N (% not missing)	47 (100.0)	NA	NA	253 (100.0)	199 (100.0)	.344‡
	Mean (SD)	1.0 (1.1)	NA	NA	0.9 (1.2)	0.9 (1.2)	
	Median (IQR)	1 (0, 1)	NA	NA	0 (0, 1)	0 (0, 2)	

		TOTAL COHORT					
	Measure	FP/FOR	FP/SAL DPI	FP/SAL MDI	BUD/FOR	BDP/FOR	p-value
	Min, Max	(0, 4)	NA	NA	(0, 6)	(0, 6)	
Asthma exacerbations (categorised)	N (% not missing)	47 (100.0)	NA	NA	253 (100.0)	199 (100.0)	0.008*
	0, n (%)	17 (36.2)	NA	NA	140 (55.3)	106 (53.3)	
	1, n (%)	20 (42.6)	NA	NA	52 (20.6)	38 (19.1)	
	≥2, n (%)	10 (21.3)	NA	NA	61 (24.1)	55 (27.6)	
COPD exacerbations	N (% not missing)	47 (100.0)	NA	NA	253 (100.0)	199 (100.0)	.289‡
	Mean (SD)	1.0 (1.1)	NA	NA	0.9 (1.2)	0.9 (1.2)	
	Median (IQR)	1 (0, 1)	NA	NA	0 (0, 1)	0 (0, 2)	
	Min, Max	(0, 4)	NA	NA	(0, 5)	(0, 6)	
COPD exacerbations (categorised)	N (% not missing)	47 (100.0)	NA	NA	253 (100.0)	199 (100.0)	0.005*
	0, n (%)	17 (36.2)	NA	NA	143 (56.5)	107 (53.8)	
	1, n (%)	20 (42.6)	NA	NA	49 (19.4)	37 (18.6)	
	≥2, n (%)	10 (21.3)	NA	NA	61 (24.1)	55 (27.6)	

Table 36: Consultations and hospitalisations in year prior to index date by FDC/ICS LABA ("MART" regimen definition 1)
‡ Kruskal-Wallis test, * Chi-square test, NA – not applicable

5.2.7.5 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 prescriptions	N (% not missing)	66 (100.0)	NA	NA	379 (100.0)	308 (100.0)	<0.001‡
	Mean (SD)	4.2 (4.7)	NA	NA	1.5 (3.6)	2.6 (5.2)	
	Median (IQR)	3 (0, 8)	NA	NA	0 (0, 0)	0 (0, 4)	
	Min, Max	(0, 20)	NA	NA	(0, 18)	(0, 44)	
FDC ICS+LABA prescriptions (categorised)	N (% not missing)	66 (100.0)	NA	NA	379 (100.0)	308 (100.0)	<0.001*
	0, n (%)	n≥5	NA	NA	299 (78.9)	205 (66.6)	
	1, n (%)	n<5	NA	NA	7 (1.8)	9 (2.9)	
	≥2, n (%)	n≥5	NA	NA	73 (19.3)	94 (30.5)	
SABA prescriptions	N (% not missing)	66 (100.0)	NA	NA	379 (100.0)	308 (100.0)	.005‡
	Mean (SD)	0.2 (0.8)	NA	NA	0.9 (2.4)	0.9 (3.3)	
	Median (IQR)	0 (0, 0)	NA	NA	0 (0, 1)	0 (0, 0)	
	Min, Max	(0, 4)	NA	NA	(0, 22)	(0, 36)	
SABA prescriptions (categorised)	N (% not missing)	66 (100.0)	NA	NA	379 (100.0)	308 (100.0)	0.027*
	0, n (%)	n≥5	NA	NA	277 (73.1)	242 (78.6)	
	1, n (%)	n<5	NA	NA	28 (7.4)	19 (6.2)	
	≥2, n (%)	n<5	NA	NA	74 (19.5)	47 (15.3)	
SAMA prescriptions	N (% not missing)	66 (100.0)	NA	NA	379 (100.0)	308 (100.0)	.869‡

		TOTAL COHORT					
	Measure	FP/FOR	FP/SAL DPI	FP/SAL MDI	BUD/FOR	BDP/FOR	p-value
	Mean (SD)	0.0 (0.2)	NA	NA	0.3 (2.6)	0.2 (2.5)	
	Median (IQR)	0 (0, 0)	NA	NA	0 (0, 0)	0 (0, 0)	
	Min, Max	(0, 1)	NA	NA	(0, 40)	(0, 36)	
SAMA prescriptions (categorised)	N (% not missing)	66 (100.0)	NA	NA	379 (100.0)	308 (100.0)	0.096*
	0, n (%)	n≥5	NA	NA	n≥5	n≥5	
	1, n (%)	n<5	NA	NA	n<5	n<5	
	≥2, n (%)	n<5	NA	NA	n≥5	n<5	
LABA prescriptions	N (% not missing)	66 (100.0)	NA	NA	379 (100.0)	308 (100.0)	.009‡
	Mean (SD)	0.3 (1.6)	NA	NA	0.1 (0.9)	0.8 (3.5)	
	Median (IQR)	0 (0, 0)	NA	NA	0 (0, 0)	0 (0, 0)	
	Min, Max	(0, 10)	NA	NA	(0, 12)	(0, 32)	
LABA prescriptions (categorised)	N (% not missing)	66 (100.0)	NA	NA	379 (100.0)	308 (100.0)	0.056*
	0, n (%)	n≥5	NA	NA	n≥5	280 (90.9)	
	1, n (%)	n<5	NA	NA	n<5	7 (2.3)	
	≥2, n (%)	n<5	NA	NA	n≥5	21 (6.8)	
LAMA prescriptions	N (% not missing)	66 (100.0)	NA	NA	379 (100.0)	308 (100.0)	.744‡
	Mean (SD)	0.2 (1.5)	NA	NA	0.4 (3.2)	0.7 (4.4)	
	Median (IQR)	0 (0, 0)	NA	NA	0 (0, 0)	0 (0, 0)	
	Min, Max	(0, 12)	NA	NA	(0, 44)	(0, 44)	
LAMA prescriptions (categorised)	N (% not missing)	66 (100.0)	NA	NA	379 (100.0)	308 (100.0)	0.750*
	0, n (%)	n≥5	NA	NA	368 (97.1)	298 (96.8)	
	≥2, n (%)	n<5	NA	NA	11 (2.9)	10 (3.2)	
ICS only prescriptions	N (% not missing)	66 (100.0)	NA	NA	379 (100.0)	308 (100.0)	<0.001‡
	Mean (SD)	0.9 (1.7)	NA	NA	1.7 (3.4)	2.6 (4.0)	
	Median (IQR)	0 (0, 1)	NA	NA	0 (0, 2)	1 (0, 4)	
	Min, Max	(0, 7)	NA	NA	(0, 26)	(0, 26)	
ICS only prescriptions (categorised)	N (% not missing)	66 (100.0)	NA	NA	379 (100.0)	308 (100.0)	<0.001*
	0, n (%)	n≥5	NA	NA	226 (59.6)	137 (44.5)	
	1, n (%)	n<5	NA	NA	42 (11.1)	29 (9.4)	
	≥2, n (%)	n≥5	NA	NA	111 (29.3)	142 (46.1)	
Theophylline prescriptions	N (% not missing)	66 (100.0)	NA	NA	379 (100.0)	308 (100.0)	.368‡
	Mean (SD)	0.0 (0.0)	NA	NA	0.1 (1.0)	0.1 (1.1)	
	Median (IQR)	0 (0, 0)	NA	NA	0 (0, 0)	0 (0, 0)	
	Min, Max	(0, 0)	NA	NA	(0, 13)	(0, 11)	
Theophylline prescriptions (categorised)	N (% not missing)	66 (100.0)	NA	NA	379 (100.0)	308 (100.0)	0.367*
	0, n (%)	n≥5	NA	NA	n≥5	302 (98.1)	
	≥2, n (%)	n<5	NA	NA	n<5	6 (1.9)	
LTRA prescriptions	N (% not missing)	66 (100.0)	NA	NA	379 (100.0)	308 (100.0)	.871‡

		TOTAL COHORT					
	Measure	FP/FOR	FP/SAL DPI	FP/SAL MDI	BUD/FOR	BDP/FOR	p-value
	Mean (SD)	0.3 (1.4)	NA	NA	0.2 (1.0)	0.4 (1.9)	
	Median (IQR)	0 (0, 0)	NA	NA	0 (0, 0)	0 (0, 0)	
	Min, Max	(0, 7)	NA	NA	(0, 9)	(0, 13)	
LTRA prescriptions (categorised)	N (% not missing)	66 (100.0)	NA	NA	379 (100.0)	308 (100.0)	0.240*
	0, n (%)	n≥5	NA	NA	356 (93.9)	n≥5	
	1, n (%)	n<5	NA	NA	11 (2.9)	n<5	
	≥2, n (%)	n<5	NA	NA	12 (3.2)	n≥5	
Spacer prescription	N (% not missing)	66 (100.0)	NA	NA	379 (100.0)	308 (100.0)	<0.001*
	No, n (%)	46 (69.7)	NA	NA	340 (89.7)	226 (73.4)	
	Yes, n (%)	20 (30.3)	NA	NA	39 (10.3)	82 (26.6)	
Pain-relief medication prescriptions	N (% not missing)	66 (100.0)	NA	NA	379 (100.0)	308 (100.0)	.060‡
	Mean (SD)	3.6 (10.7)	NA	NA	1.4 (4.1)	2.2 (5.5)	
	Median (IQR)	0 (0, 2)	NA	NA	0 (0, 1)	0 (0, 1)	
	Min, Max	(0, 61)	NA	NA	(0, 48)	(0, 47)	
Pain-relief medication prescriptions (categorised)	N (% not missing)	66 (100.0)	NA	NA	379 (100.0)	308 (100.0)	0.197*
	0, n (%)	41 (62.1)	NA	NA	278 (73.4)	210 (68.2)	
	1-4, n (%)	14 (21.2)	NA	NA	65 (17.2)	55 (17.9)	
	≥5, n (%)	11 (16.7)	NA	NA	36 (9.5)	43 (14.0)	
Non-steroidal anti-inflammatory drugs (NSAIDs) prescriptions	N (% not missing)	66 (100.0)	NA	NA	379 (100.0)	308 (100.0)	.014‡
	Mean (SD)	1.6 (6.7)	NA	NA	0.5 (1.5)	0.7 (2.3)	
	Median (IQR)	0 (0, 1)	NA	NA	0 (0, 0)	0 (0, 0)	
	Min, Max	(0, 52)	NA	NA	(0, 13)	(0, 26)	
Non-steroidal anti-inflammatory drugs (NSAIDs) prescriptions (categorised)	N (% not missing)	66 (100.0)	NA	NA	379 (100.0)	308 (100.0)	0.027*
	0, n (%)	n≥5	NA	NA	325 (85.8)	243 (78.9)	
	1-2, n (%)	n≥5	NA	NA	31 (8.2)	45 (14.6)	
	3-4, n (%)	n<5	NA	NA	9 (2.4)	9 (2.9)	
	≥5, n (%)	n≥5	NA	NA	14 (3.7)	11 (3.6)	
Beta-blocker prescriptions	N (% not missing)	66 (100.0)	NA	NA	379 (100.0)	308 (100.0)	.489‡
	Mean (SD)	0.2 (1.4)	NA	NA	0.4 (3.0)	0.3 (1.7)	
	Median (IQR)	0 (0, 0)	NA	NA	0 (0, 0)	0 (0, 0)	
	Min, Max	(0, 8)	NA	NA	(0, 54)	(0, 13)	
Beta-blocker prescriptions (categorised)	N (% not missing)	66 (100.0)	NA	NA	379 (100.0)	308 (100.0)	0.705*
	0, n (%)	n≥5	NA	NA	n≥5	n≥5	
	1-4, n (%)	n<5	NA	NA	n≥5	n≥5	
	5-9, n (%)	n<5	NA	NA	n≥5	n≥5	
	≥10, n (%)	n<5	NA	NA	n<5	n<5	

Table 37: Prescriptions for therapy in year prior to index date by FDC/ICS LABA ("MART" regimen definition 1)

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

5.2.8 "MART" regimen, definition 2

The number of MART patients (definition 2) prescribed FP/FOR was very low. For MART regimen patients (definition 2), demographic characteristics, disease severity, comorbidities, GP consultations, hospitalisations, exacerbations and prescriptions at the index date were similar across treatment groups. The FP/FOR group had an earlier first diagnosis of asthma than other treatment groups. The FP/FOR group also had a lower prescription of ICS prior to the index date; other prior respiratory prescriptions were similar but were more likely to be switchers than the other FDC ICS/LABA groups.

5.2.8.1 Demographic characteristics

		TOTAL COHORT					
	Measure	FP/FOR	FP/SAL DPI	FP/SAL MDI	BUD/FOR	BDP/FOR	p-value
Age at index date (years)	N (% not missing)	6 (100.0)	NA	NA	102 (100.0)	66 (100.0)	.144‡
	Mean (SD)	48.2 (12.5)	NA	NA	43.0 (15.8)	48.1 (18.2)	
	Median (IQR)	46 (41, 52)	NA	NA	42 (32, 52)	46 (37, 63)	
	Min, Max	(34, 70)	NA	NA	(18, 87)	(19, 88)	
Gender	N (% not missing)	6 (100.0)	NA	NA	102 (100.0)	66 (100.0)	0.268*
	Female, n (%)	n<5	NA	NA	57 (55.9)	45 (68.2)	
	Male, n (%)	n<5	NA	NA	45 (44.1)	21 (31.8)	
Height (m) - closest to index date	N (% not missing)	6 (100.0)	NA	NA	97 (95.1)	66 (100.0)	.706‡
	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)	1.7 (1.6, 1.7)	
	Min, Max	(1.6, 1.8)	NA	NA	(1.5, 2.0)	(1.5, 1.9)	
Weight (kg) - closest to index date	N (% not missing)	6 (100.0)	NA	NA	93 (91.2)	65 (98.5)	.218‡
	Mean (SD)	91.0 (19.1)	NA	NA	77.8 (18.3)	80.6 (21.7)	
	Median (IQR)	91 (74, 104)	NA	NA	75 (65, 87)	73 (64, 90)	
	Min, Max	(69.9, 117.8)	NA	NA	(48, 140)	(49, 142)	
BMI (kg/m2)	N (% not missing)	6 (100.0)	NA	NA	92 (90.2)	65 (98.5)	.237‡
	Mean (SD)	33.0 (9.9)	NA	NA	27.2 (6.1)	28.8 (7.8)	
	Median (IQR)	30.7 (25.6, 41.5)	NA	NA	25.7 (23.4, 28.9)	26.5 (23.3, 31.2)	
	Min, Max	(22.0, 47.8)	NA	NA	(17.9, 52.7)	(17.2, 55.4)	
BMI (kg/m2) (categorised)	N (% not missing)	6 (100.0)	NA	NA	92 (90.2)	65 (98.5)	0.578*
	Underweight (BMI≤18.5), n (%)	n<5	NA	NA	n<5	n<5	
	Normal (18.5≤BMI<25), n (%)	n<5	NA	NA	n≥5	n≥5	
	Overweight (25≤BMI<30), n (%)	n<5	NA	NA	n≥5	n≥5	

		TOTAL COHORT					
	Measure	FP/FOR	FP/SAL DPI	FP/SAL MDI	BUD/FOR	BDP/FOR	p-value
	Obese (BMI≥30), n (%)	n<5	NA	NA	n≥5	n≥5	
FEV_1 % predicted	N (% not missing)	n<5	NA	NA	37 (36.3)	21 (31.8)	.916‡
	Mean (SD)	n<5	NA	NA	81.6 (22.8)	83.9 (19.9)	
	Median (IQR)	n<5	NA	NA	86 (70, 97)	88 (75, 93)	
	Min, Max	n<5	NA	NA	(23, 113)	(44, 124)	
FEV_1 % predicted (categorised)	N (% not missing)	n<5	NA	NA	37 (36.3)	21 (31.8)	0.919*
	<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)	5 (83.3)	NA	NA	84 (82.4)	56 (84.8)	.290‡
	Mean (SD)	91.5 (36.5)	NA	NA	98.3 (22.8)	103.6 (25.7)	
	Median (IQR)	82.2 (64.2, 102.9)	NA	NA	97.0 (83.5, 117.7)	104.4 (89.2, 119.5)	
	Min, Max	(58.8, 149.0)	NA	NA	(40.8, 141.2)	(41.1, 149.6)	
Smoking Status	N (% not missing)	6 (100.0)	NA	NA	102 (100.0)	66 (100.0)	0.767*
	Non-smoker, n (%)	n<5	NA	NA	66 (64.7)	36 (54.5)	
	Current smoker, n (%)	n<5	NA	NA	19 (18.6)	16 (24.2)	
	Ex-smoker, n (%)	n<5	NA	NA	17 (16.7)	14 (21.2)	

Table 38: Demographic characteristics by FDC/ICS LABA ("MART" regimen definition 2)
‡ Kruskal-Wallis test, * Chi-square test, NA – not applicable

5.2.8.2 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)	6 (100.0)	NA	NA	102 (100.0)	66 (100.0)	.183‡
	Mean (SD)	20.8 (17.9)	NA	NA	14.2 (12.5)	20.3 (18.3)	
	Median (IQR)	16.0 (6.1, 33.0)	NA	NA	11.2 (4.3, 21.7)	17.4 (5.0, 28.6)	
	Min, Max	(3.4, 50.3)	NA	NA	(0.1, 75.0)	(0.0, 82.9)	
Prescribed FDC ICS/LABA inhaler dose (dose per puff)	N (% not missing)	6 (100.0)	NA	NA	102 (100.0)	66 (100.0)	<0.001*
	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)	6 (100.0)	NA	NA	102 (100.0)	66 (100.0)	.047‡
	Mean (SD)	12.1 (9.6)	NA	NA	17.4 (15.2)	11.8 (12.0)	
	Median (IQR)	12 (2, 22)	NA	NA	13 (2, 29)	7 (2, 22)	

		TOTAL COHORT					
	Measure	FP/FOR	FP/SAL DPI	FP/SAL MDI	BUD/FOR	BDP/FOR	p-value
	Min, Max	(1.5, 23.4)	NA	NA	(0, 50)	(0, 45)	
SABA prescriptions	N (% not missing)	6 (100.0)	NA	NA	102 (100.0)	66 (100.0)	NA
	No, n (%)	6 (100.0)	NA	NA	102 (100.0)	66 (100.0)	
SAMA prescriptions	N (% not missing)	6 (100.0)	NA	NA	102 (100.0)	66 (100.0)	<0.001*
	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)	6 (100.0)	NA	NA	102 (100.0)	66 (100.0)	0.191*
	No, n (%)	n≥5	NA	NA	n≥5	n≥5	
	Yes, n (%)	n<5	NA	NA	n<5	n<5	
LAMA prescriptions	N (% not missing)	6 (100.0)	NA	NA	102 (100.0)	66 (100.0)	0.701*
	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)	6 (100.0)	NA	NA	102 (100.0)	66 (100.0)	0.576*
	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)	6 (100.0)	NA	NA	102 (100.0)	66 (100.0)	NA
	No, n (%)	6 (100.0)	NA	NA	102 (100.0)	66 (100.0)	
LTRA prescriptions	N (% not missing)	6 (100.0)	NA	NA	102 (100.0)	66 (100.0)	0.340*
	No, n (%)	n≥5	NA	NA	n≥5	n≥5	
	Yes, n (%)	n<5	NA	NA	n<5	n<5	

Table 39: Medication prescribed at index date by FDC/ICS LABA ("MART" regimen definition 2)
‡ Kruskal-Wallis test, * Chi-square test, NA – not applicable

5.2.8.3 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)	6 (100.0)	NA	NA	102 (100.0)	66 (100.0)	0.917*
	Asthma only, n (%)	n≥5	NA	NA	n≥5	n≥5	
	Asthma & COPD, n (%)	n<5	NA	NA	n<5	n<5	
Year of first asthma diagnosis	N (% not missing)	6 (100.0)	NA	NA	102 (100.0)	66 (100.0)	.691‡
	Mean (SD)	1994.3 (6.8)	NA	NA	1996.9 (14.2)	1996.8 (14.0)	
	Median (IQR)	1994 (1993, 1999)	NA	NA	1998 (1989, 2010)	2001 (1992, 2009)	
	Min, Max	(1983, 2003)	NA	NA	(1950, 2014)	(1953, 2013)	
Duration of asthma (years)	N (% not missing)	6 (100.0)	NA	NA	102 (100.0)	66 (100.0)	.548‡
	Mean (SD)	19.3 (7.0)	NA	NA	15.7 (14.3)	16.0 (14.1)	

		TOTAL COHORT					
	Measure	FP/FOR	FP/SAL DPI	FP/SAL MDI	BUD/FOR	BDP/FOR	p-value
	Median (IQR)	19.4 (15.1, 21.1)	NA	NA	14.6 (2.6, 23.4)	12.6 (4.1, 21.0)	
	Min, Max	(9.9, 31.0)	NA	NA	(0, 63)	(0.0, 60.5)	
Year of first COPD diagnosis	N (% not missing)	n<5	NA	NA	n<5	n<5	NA
	Mean (SD)	n<5	NA	NA	n<5	n<5	
	Median (IQR)	n<5	NA	NA	n<5	n<5	
	Min, Max	n<5	NA	NA	n<5	n<5	
Duration of COPD (years)	N (% not missing)	n<5	NA	NA	n<5	n<5	NA
	Mean (SD)	n<5	NA	NA	n<5	n<5	
	Median (IQR)	n<5	NA	NA	n<5	n<5	
	Min, Max	n<5	NA	NA	n<5	n<5	
Comorbid rhinitis	N (% not missing)	6 (100.0)	NA	NA	102 (100.0)	66 (100.0)	0.409*
	No, n (%)	n≥5	NA	NA	90 (88.2)	55 (83.3)	
	Yes, n (%)	n<5	NA	NA	12 (11.8)	11 (16.7)	
Comorbid eczema	N (% not missing)	6 (100.0)	NA	NA	102 (100.0)	66 (100.0)	0.243*
	No, n (%)	n≥5	NA	NA	95 (93.1)	57 (86.4)	
	Yes, n (%)	n<5	NA	NA	7 (6.9)	9 (13.6)	
Comorbid GERD	N (% not missing)	6 (100.0)	NA	NA	102 (100.0)	66 (100.0)	0.806*
	No, n (%)	n≥5	NA	NA	92 (90.2)	58 (87.9)	
	Yes, n (%)	n<5	NA	NA	10 (9.8)	8 (12.1)	
History of ischemic heart disease	N (% not missing)	6 (100.0)	NA	NA	102 (100.0)	66 (100.0)	0.839*
	No, n (%)	n≥5	NA	NA	n≥5	n≥5	
	Yes, n (%)	n<5	NA	NA	n<5	n<5	
History of hypertension	N (% not missing)	6 (100.0)	NA	NA	102 (100.0)	66 (100.0)	0.294*
	No, n (%)	n≥5	NA	NA	93 (91.2)	55 (83.3)	
	Yes, n (%)	n<5	NA	NA	9 (8.8)	11 (16.7)	
History of ischemic heart disease and hypertension	N (% not missing)	6 (100.0)	NA	NA	102 (100.0)	66 (100.0)	0.925*
	No, n (%)	n≥5	NA	NA	n≥5	n≥5	
	Yes, n (%)	n<5	NA	NA	n<5	n<5	
Charlson Comorbidity Index (CCI)	N (% not missing)	6 (100.0)	NA	NA	102 (100.0)	66 (100.0)	.002‡
	Mean (SD)	5.3 (3.3)	NA	NA	3.5 (1.9)	4.2 (1.2)	
	Median (IQR)	4 (4, 4)	NA	NA	4 (4, 4)	4 (4, 4)	
	Min, Max	(4, 12)	NA	NA	(0, 14)	(0, 10)	
Charlson Comorbidity Index (CCI) (categorised)	N (% not missing)	6 (100.0)	NA	NA	102 (100.0)	66 (100.0)	0.007*
	0, n (%)	n<5	NA	NA	n≥5	n<5	
	1-4, n (%)	n≥5	NA	NA	n≥5	n≥5	
	≥5, n (%)	n<5	NA	NA	n<5	n<5	

Table 40: Comorbidities by FDC/ICS LABA ("MART" regimen definition 2)
‡ Kruskal-Wallis test, * Chi-square test, NA – not applicable

5.2.8.4 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	N (% not missing)	6 (100.0)	NA	NA	102 (100.0)	66 (100.0)	.110‡
	Mean (SD)	3.7 (2.6)	NA	NA	1.7 (1.4)	2.4 (2.4)	
	Median (IQR)	4 (2, 6)	NA	NA	2 (1, 3)	2 (1, 4)	
	Min, Max	(0, 7)	NA	NA	(0, 7)	(0, 11)	
Respiratory GP consultations without prescription for an oral corticosteroid (categorised)	N (% not missing)	6 (100.0)	NA	NA	102 (100.0)	66 (100.0)	0.316*
	0, n (%)	n<5	NA	NA	20 (19.6)	15 (22.7)	
	1, n (%)	n<5	NA	NA	29 (28.4)	14 (21.2)	
	2, n (%)	n<5	NA	NA	27 (26.5)	14 (21.2)	
	≥3, n (%)	n<5	NA	NA	26 (25.5)	23 (34.8)	
Asthma GP consultations without prescription for an oral corticosteroid	N (% not missing)	6 (100.0)	NA	NA	102 (100.0)	66 (100.0)	.562‡
	Mean (SD)	1.0 (1.1)	NA	NA	0.9 (0.9)	1.2 (1.2)	
	Median (IQR)	1 (0, 2)	NA	NA	1 (0, 1)	1 (0, 2)	
	Min, Max	(0, 2)	NA	NA	(0, 4)	(0, 4)	
Asthma GP consultations without prescription for an oral corticosteroid (categorised)	N (% not missing)	6 (100.0)	NA	NA	102 (100.0)	66 (100.0)	0.007*
	0, n (%)	n<5	NA	NA	37 (36.3)	26 (39.4)	
	1, n (%)	n<5	NA	NA	45 (44.1)	16 (24.2)	
	2, n (%)	n<5	NA	NA	13 (12.7)	12 (18.2)	
	≥3, n (%)	n<5	NA	NA	7 (6.9)	12 (18.2)	
COPD GP consultations without prescription for an oral corticosteroid	N (% not missing)	6 (100.0)	NA	NA	102 (100.0)	66 (100.0)	.441‡
	Mean (SD)	0.0 (0.0)	NA	NA	0.0 (0.0)	0.0 (0.4)	
	Median (IQR)	0 (0, 0)	NA	NA	0 (0, 0)	0 (0, 0)	
	Min, Max	(0, 0)	NA	NA	(0, 0)	(0, 3)	
COPD GP consultations without prescription for an oral corticosteroid (categorised)	N (% not missing)	6 (100.0)	NA	NA	102 (100.0)	66 (100.0)	0.439*
	0, n (%)	n≥5	NA	NA	n≥5	n≥5	
	≥3, n (%)	n<5	NA	NA	n<5	n<5	
Lower respiratory hospital outpatient attendances	N (% not missing)	n<5	NA	NA	63 (100.0)	40 (100.0)	NA
	Mean (SD)	n<5	NA	NA	0.0 (0.0)	0.0 (0.0)	
	Median (IQR)	n<5	NA	NA	0 (0, 0)	0 (0, 0)	
	Min, Max	n<5	NA	NA	(0, 0)	(0, 0)	
Lower respiratory hospital outpatient attendances (categorised)	N (% not missing)	n<5	NA	NA	63 (100.0)	40 (100.0)	NA
	0, n (%)	n<5	NA	NA	63 (100.0)	40 (100.0)	
Asthma hospital outpatient attendances	N (% not missing)	n<5	NA	NA	63 (100.0)	40 (100.0)	NA
	Mean (SD)	n<5	NA	NA	0.0 (0.0)	0.0 (0.0)	
	Median (IQR)	n<5	NA	NA	0 (0, 0)	0 (0, 0)	
	Min, Max	n<5	NA	NA	(0, 0)	(0, 0)	

		TOTAL COHORT					
	Measure	FP/FOR	FP/SAL DPI	FP/SAL MDI	BUD/FOR	BDP/FOR	p-value
Asthma hospital outpatient attendances (categorised)	N (% not missing)	n<5	NA	NA	63 (100.0)	40 (100.0)	NA
	0, n (%)	n<5	NA	NA	63 (100.0)	40 (100.0)	
COPD hospital outpatient attendances	N (% not missing)	n<5	NA	NA	63 (100.0)	40 (100.0)	NA
	Mean (SD)	n<5	NA	NA	0.0 (0.0)	0.0 (0.0)	
	Median (IQR)	n<5	NA	NA	0 (0, 0)	0 (0, 0)	
	Min, Max	n<5	NA	NA	(0, 0)	(0, 0)	
COPD hospital outpatient attendances (categorised)	N (% not missing)	n<5	NA	NA	63 (100.0)	40 (100.0)	NA
	0, n (%)	n<5	NA	NA	63 (100.0)	40 (100.0)	
Lower respiratory inpatient hospitalisations	N (% not missing)	n<5	NA	NA	63 (100.0)	40 (100.0)	.910‡
	Mean (SD)	n<5	NA	NA	0.0 (0.1)	0.0 (0.2)	
	Median (IQR)	n<5	NA	NA	0 (0, 0)	0 (0, 0)	
	Min, Max	n<5	NA	NA	(0, 1)	(0, 1)	
Lower respiratory inpatient hospitalisations (categorised)	N (% not missing)	n<5	NA	NA	63 (100.0)	40 (100.0)	0.909*
	0, n (%)	n<5	NA	NA	n≥5	n≥5	
	1, n (%)	n<5	NA	NA	n<5	n<5	
Asthma inpatient hospitalisations	N (% not missing)	n<5	NA	NA	63 (100.0)	40 (100.0)	.471‡
	Mean (SD)	n<5	NA	NA	0.1 (0.3)	0.1 (0.3)	
	Median (IQR)	n<5	NA	NA	0 (0, 0)	0 (0, 0)	
	Min, Max	n<5	NA	NA	(0, 1)	(0, 2)	
Asthma inpatient hospitalisations (categorised)	N (% not missing)	n<5	NA	NA	63 (100.0)	40 (100.0)	0.262*
	0, n (%)	n<5	NA	NA	n≥5	n≥5	
	1, n (%)	n<5	NA	NA	n≥5	n<5	
	≥2, n (%)	n<5	NA	NA	n<5	n<5	
COPD inpatient hospitalisations	N (% not missing)	n<5	NA	NA	63 (100.0)	40 (100.0)	.910‡
	Mean (SD)	n<5	NA	NA	0.0 (0.1)	0.0 (0.2)	
	Median (IQR)	n<5	NA	NA	0 (0, 0)	0 (0, 0)	
	Min, Max	n<5	NA	NA	(0, 1)	(0, 1)	
COPD inpatient hospitalisations (categorised)	N (% not missing)	n<5	NA	NA	63 (100.0)	40 (100.0)	0.909*
	0, n (%)	n<5	NA	NA	n≥5	n≥5	
	1, n (%)	n<5	NA	NA	n<5	n<5	
Asthma exacerbations	N (% not missing)	n<5	NA	NA	63 (100.0)	40 (100.0)	.959‡
	Mean (SD)	n<5	NA	NA	1.1 (1.1)	1.2 (1.3)	
	Median (IQR)	n<5	NA	NA	1 (0, 2)	1 (0, 2)	
	Min, Max	n<5	NA	NA	(0, 4)	(0, 5)	
Asthma exacerbations (categorised)	N (% not missing)	n<5	NA	NA	63 (100.0)	40 (100.0)	0.254*
	0, n (%)	n<5	NA	NA	22 (34.9)	18 (45.0)	
	1, n (%)	n<5	NA	NA	22 (34.9)	7 (17.5)	

		TOTAL COHORT					
	Measure	FP/FOR	FP/SAL DPI	FP/SAL MDI	BUD/FOR	BDP/FOR	p-value
	≥2, n (%)	n<5	NA	NA	19 (30.2)	15 (37.5)	
COPD exacerbations	N (% not missing)	n<5	NA	NA	63 (100.0)	40 (100.0)	.963‡
	Mean (SD)	n<5	NA	NA	1.1 (1.1)	1.2 (1.3)	
	Median (IQR)	n<5	NA	NA	1 (0, 2)	1 (0, 2)	
	Min, Max	n<5	NA	NA	(0, 4)	(0, 5)	
COPD exacerbations (categorised)	N (% not missing)	n<5	NA	NA	63 (100.0)	40 (100.0)	0.271*
	0, n (%)	n<5	NA	NA	24 (38.1)	18 (45.0)	
	1, n (%)	n<5	NA	NA	20 (31.7)	6 (15.0)	
	≥2, n (%)	n<5	NA	NA	19 (30.2)	16 (40.0)	

Table 41: 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

5.2.8.5 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 prescriptions	N (% not missing)	6 (100.0)	NA	NA	102 (100.0)	66 (100.0)	.045‡
	Mean (SD)	3.7 (4.0)	NA	NA	1.6 (4.1)	1.9 (3.8)	
	Median (IQR)	3 (0, 8)	NA	NA	0 (0, 0)	0 (0, 2)	
	Min, Max	(0, 9)	NA	NA	(0, 18)	(0, 16)	
FDC ICS+LABA prescriptions (categorised)	N (% not missing)	6 (100.0)	NA	NA	102 (100.0)	66 (100.0)	0.028*
	0, n (%)	n<5	NA	NA	n≥5	n≥5	
	1, n (%)	n<5	NA	NA	n<5	n<5	
	≥2, n (%)	n<5	NA	NA	n≥5	n≥5	
SABA prescriptions	N (% not missing)	6 (100.0)	NA	NA	102 (100.0)	66 (100.0)	.982‡
	Mean (SD)	2.5 (1.4)	NA	NA	3.4 (3.5)	4.4 (6.1)	
	Median (IQR)	3 (1, 4)	NA	NA	2 (1, 4)	2 (1, 4)	
	Min, Max	(1, 4)	NA	NA	(1, 22)	(1, 36)	
SABA prescriptions (categorised)	N (% not missing)	6 (100.0)	NA	NA	102 (100.0)	66 (100.0)	0.943*
	1, n (%)	n<5	NA	NA	28 (27.5)	19 (28.8)	
	≥2, n (%)	n<5	NA	NA	74 (72.5)	47 (71.2)	
SAMA prescriptions	N (% not missing)	6 (100.0)	NA	NA	102 (100.0)	66 (100.0)	.703‡
	Mean (SD)	0.0 (0.0)	NA	NA	0.0 (0.1)	0.0 (0.0)	
	Median (IQR)	0 (0, 0)	NA	NA	0 (0, 0)	0 (0, 0)	
	Min, Max	(0, 0)	NA	NA	(0, 1)	(0, 0)	
SAMA prescriptions (categorised)	N (% not missing)	6 (100.0)	NA	NA	102 (100.0)	66 (100.0)	0.701*
	0, n (%)	n≥5	NA	NA	n≥5	n≥5	

		TOTAL COHORT					
	Measure	FP/FOR	FP/SAL DPI	FP/SAL MDI	BUD/FOR	BDP/FOR	p-value
	1, n (%)	n<5	NA	NA	n<5	n<5	
LABA prescriptions	N (% not missing)	6 (100.0)	NA	NA	102 (100.0)	66 (100.0)	.162‡
	Mean (SD)	0.0 (0.0)	NA	NA	0.2 (1.3)	1.0 (3.2)	
	Median (IQR)	0 (0, 0)	NA	NA	0 (0, 0)	0 (0, 0)	
	Min, Max	(0, 0)	NA	NA	(0, 12)	(0, 14)	
LABA prescriptions (categorised)	N (% not missing)	6 (100.0)	NA	NA	102 (100.0)	66 (100.0)	0.454*
	0, n (%)	n≥5	NA	NA	n≥5	n≥5	
	1, n (%)	n<5	NA	NA	n<5	n<5	
	≥2, n (%)	n<5	NA	NA	n<5	n≥5	
LAMA prescriptions	N (% not missing)	6 (100.0)	NA	NA	102 (100.0)	66 (100.0)	.918‡
	Mean (SD)	0.0 (0.0)	NA	NA	0.2 (2.4)	0.4 (3.0)	
	Median (IQR)	0 (0, 0)	NA	NA	0 (0, 0)	0 (0, 0)	
	Min, Max	(0, 0)	NA	NA	(0, 24)	(0, 24)	
LAMA prescriptions (categorised)	N (% not missing)	6 (100.0)	NA	NA	102 (100.0)	66 (100.0)	0.917*
	0, n (%)	n≥5	NA	NA	n≥5	n≥5	
	≥2, n (%)	n<5	NA	NA	n<5	n<5	
ICS only prescriptions	N (% not missing)	6 (100.0)	NA	NA	102 (100.0)	66 (100.0)	.016‡
	Mean (SD)	0.3 (0.8)	NA	NA	2.1 (2.8)	3.4 (4.1)	
	Median (IQR)	0 (0, 0)	NA	NA	1 (0, 3)	2 (0, 5)	
	Min, Max	(0, 2)	NA	NA	(0, 16)	(0, 17)	
ICS only prescriptions (categorised)	N (% not missing)	6 (100.0)	NA	NA	102 (100.0)	66 (100.0)	0.078*
	0, n (%)	n≥5	NA	NA	34 (33.3)	21 (31.8)	
	1, n (%)	n<5	NA	NA	21 (20.6)	9 (13.6)	
	≥2, n (%)	n<5	NA	NA	47 (46.1)	36 (54.5)	
Theophylline prescriptions	N (% not missing)	6 (100.0)	NA	NA	102 (100.0)	66 (100.0)	.570‡
	Mean (SD)	0.0 (0.0)	NA	NA	0.0 (0.4)	0.2 (1.3)	
	Median (IQR)	0 (0, 0)	NA	NA	0 (0, 0)	0 (0, 0)	
	Min, Max	(0, 0)	NA	NA	(0, 4)	(0, 8)	
Theophylline prescriptions (categorised)	N (% not missing)	6 (100.0)	NA	NA	102 (100.0)	66 (100.0)	0.576*
	0, n (%)	n≥5	NA	NA	n≥5	n≥5	
	≥2, n (%)	n<5	NA	NA	n<5	n<5	
LTRA prescriptions	N (% not missing)	6 (100.0)	NA	NA	102 (100.0)	66 (100.0)	.035‡
	Mean (SD)	2.3 (3.6)	NA	NA	0.2 (1.0)	0.4 (2.1)	
	Median (IQR)	0 (0, 7)	NA	NA	0 (0, 0)	0 (0, 0)	
	Min, Max	(0, 7)	NA	NA	(0, 7)	(0, 12)	
LTRA prescriptions (categorised)	N (% not missing)	6 (100.0)	NA	NA	102 (100.0)	66 (100.0)	0.009*
	0, n (%)	n<5	NA	NA	n≥5	n≥5	
	1, n (%)	n<5	NA	NA	n≥5	n<5	

		TOTAL COHORT					
	Measure	FP/FOR	FP/SAL DPI	FP/SAL MDI	BUD/FOR	BDP/FOR	p-value
	≥2, n (%)	n<5	NA	NA	n<5	n<5	
Spacer prescription	N (% not missing)	6 (100.0)	NA	NA	102 (100.0)	66 (100.0)	0.270*
	No, n (%)	n<5	NA	NA	86 (84.3)	50 (75.8)	
	Yes, n (%)	n<5	NA	NA	16 (15.7)	16 (24.2)	
Pain-relief medication prescriptions	N (% not missing)	6 (100.0)	NA	NA	102 (100.0)	66 (100.0)	.061‡
	Mean (SD)	12.7 (23.4)	NA	NA	1.0 (2.8)	3.0 (7.6)	
	Median (IQR)	1 (0, 15)	NA	NA	0 (0, 0)	0 (0, 1)	
	Min, Max	(0, 59)	NA	NA	(0, 16)	(0, 47)	
Pain-relief medication prescriptions (categorised)	N (% not missing)	6 (100.0)	NA	NA	102 (100.0)	66 (100.0)	0.242*
	0, n (%)	n<5	NA	NA	78 (76.5)	43 (65.2)	
	1-4, n (%)	n<5	NA	NA	15 (14.7)	12 (18.2)	
	≥5, n (%)	n<5	NA	NA	9 (8.8)	11 (16.7)	
Non-steroidal anti-inflammatory drugs (NSAIDs) prescriptions	N (% not missing)	6 (100.0)	NA	NA	102 (100.0)	66 (100.0)	.197‡
	Mean (SD)	1.2 (2.4)	NA	NA	0.5 (1.6)	1.1 (3.7)	
	Median (IQR)	0 (0, 1)	NA	NA	0 (0, 0)	0 (0, 1)	
	Min, Max	(0, 6)	NA	NA	(0, 11)	(0, 26)	
Non-steroidal anti-inflammatory drugs (NSAIDs) prescriptions (categorised)	N (% not missing)	6 (100.0)	NA	NA	102 (100.0)	66 (100.0)	0.502*
	0, n (%)	n<5	NA	NA	n≥5	n≥5	
	1-2, n (%)	n<5	NA	NA	n≥5	n≥5	
	3-4, n (%)	n<5	NA	NA	n<5	n<5	
	≥5, n (%)	n<5	NA	NA	n<5	n<5	
Beta-blocker prescriptions	N (% not missing)	6 (100.0)	NA	NA	102 (100.0)	66 (100.0)	.858‡
	Mean (SD)	0.0 (0.0)	NA	NA	0.2 (1.4)	0.3 (1.7)	
	Median (IQR)	0 (0, 0)	NA	NA	0 (0, 0)	0 (0, 0)	
	Min, Max	(0, 0)	NA	NA	(0, 13)	(0, 13)	
Beta-blocker prescriptions (categorised)	N (% not missing)	6 (100.0)	NA	NA	102 (100.0)	66 (100.0)	0.984*
	0, n (%)	n≥5	NA	NA	n≥5	n≥5	
	1-4, n (%)	n<5	NA	NA	n<5	n<5	
	5-9, n (%)	n<5	NA	NA	n<5	n<5	
	≥10, n (%)	n<5	NA	NA	n<5	n<5	

Table 42: 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

5.2.8.6 Availability of height data for asthma cohorts <18 years

Only 36% and 39% of patients have 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.

5.3 Outcome data

Please see section 5.1 for a breakdown of the patients available for analysis.

5.4 Main results

5.4.1 Prescribing incidence

Prescribing incidence of FP/FOR was lower compared to the licensed comparators for all subgroups studied. The prescribing rate was highest in patients with asthma ≥18 years and COPD patients (definition 1). Prescribing was particularly low in the two off-label asthma groups.

Total cohort, N= 48,601	COMPARATOR GROUPS				
Prescribing rate per 1000 person years	FP/FOR	DPI FP/SAL	MDI FP/SAL	BUD/FOR	BDP/FOR
Total CPRD Population*	0.71	2.95	3.39	3.18	1.56
Patients aged ≥18 years with asthma	4.85	12.10	16.85	15.53	10.74
Patients aged ≥12 and <18 years with asthma	1.56 0.17 ŀ	4.10	10.15	7.40	1.99 ŀ
4-11 years paediatric asthma patients	0.33 ŀ	2.34 0.24 ŀ	15.41 4.95 ŀ	3.66 0.73 ŀ	0.61ŀ
Patients with COPD and no asthma, definition 1	4.66 ŀ	71.78 19.94 ŀ	50.21 ŀ	44.08 4.83 ŀ	8.27

Table 43: Prescribing incidence rate (18 months post launch of FP/FOR – starting September 2012) by FDC ICS/LABA

ŀ - Off-label dosage annualized rate, unlabelled – licensed dosage annualized rate (refer Section 1.1.3 for licensed dosages)

* This includes 7810 patients without a recorded diagnosis of asthma or COPD
FP/FOR: 288 (9.8), FP/SAL: n=3947 (15.1), BUD/FOR: 2826 (21.5), BDP/FOR: 750 (11.7)

5.4.2 Adverse events

5.4.2.1 COPD exacerbations*

For patients with at least 1 year of baseline and 1 year of outcome period, there were <5 patients in the FP/FOR group and so annualised rates could not be compared.

Subgroup	Measure	FP/FOR	FP/SAL DPI	FP/SAL MDI	BUD/FOR	BDP/FOR
Patients with COPD only, definition 1	Number of patients at risk in subgroup, N (%)	n<5	334 (100)	-	186 (100)	23 (100)
	Occurrence of AE (baseline), N (%)	n<5	116 (30.9)	-	77 (33.8)	12 (41.4)
	Total exposure to AE (baseline), years	n<5	334	-	186	23
	Annualized rate of AE (baseline)/100 person years	n<5	55.4	-	58.6	60.9
	Number of patients at risk in subgroup, N (%)	n<5	375 (100)	-	228 (100)	29 (100)
	Occurrence of AE (outcome), N (%)	n<5	116 (30.9)	-	77 (33.8)	12 (41.4)
	Total exposure to AE (outcome), years	n<5	555	-	318	42
	Annualized rate of AE (outcome)/100 person years	n<5	20.9	-	24.2	28.7
	Number of times AE occurred per patient, median (IQR)	n<5	0.5 (0.9)	-	0.5 (0.9)	0.7 (0.9)
	Number of times AE occurred per patient, mean (SD)	n<5	0 (0, 1)	-	0 (0, 1)	0 (0, 1)
	Number of times AE occurred per patient, (min,max)	n<5	(0, 6)	-	(0, 5)	(0, 3)
	Duration of exposure, months, median (IQR)	n<5	17.7 (4.2)	-	16.7 (3.8)	17.3 (4.2)
	Duration of exposure, months, mean (SD)	n<5	17.7 (13.7, 21.1)	-	16.1 (13.5, 19.3)	16.9 (13.4, 20.2)
	Duration of exposure, months, (min,max)	n<5	(12.1, 26.6)	-	(12.1, 26.2)	(12.2, 26.5)
Patients with COPD only, definition 2	Number of patients at risk in subgroup, N (%)	n<5	284 (100)	-	154 (100)	20 (100)
	Occurrence of AE (baseline), N (%)	n<5	99 (31.1)	-	63 (34.2)	11 (44.0)
	Total exposure to AE (baseline), years	n<5	284	-	154	20
	Annualized rate of AE (baseline)/100 person years	n<5	54.6	-	55.2	60
	Number of patients at risk in subgroup, N (%)	n<5	318 (100)	-	184 (100)	25 (100)
	Occurrence of AE (outcome), N (%)	n<5	99 (31.1)	-	63 (34.2)	11 (44.0)
	Total exposure to AE (outcome), years	n<5	467	-	260	36
	Annualized rate of AE (outcome)/100 person years	n<5	21.2	-	24.3	30.5
	Number of times AE occurred per patient, median (IQR)	n<5	0.5 (1.0)	-	0.5 (0.9)	0.6 (0.9)
	Number of times AE occurred per patient, mean (SD)	n<5	0 (0, 1)	-	0 (0, 1)	0 (0, 1)
	Number of times AE occurred per patient, (min,max)	n<5	(0, 6)	-	(0, 5)	(0, 3)
	Duration of exposure, months, median (IQR)	n<5	17.6 (4.2)	-	16.9 (3.8)	17.3 (4.1)
	Duration of exposure, months, mean (SD)	n<5	17.1 (13.5, 21.1)	-	16.5 (13.5, 19.5)	17.0 (14.3, 20.2)
	Duration of exposure, months, (min,max)	n<5	(12.1, 26.6)	-	(12.1, 26.2)	(12.2, 26.5)
Patients with COPD	Number of patients at risk in subgroup, N (%)	n<5	258 (100)	-	134 (100)	13 (100)
	Occurrence of AE (baseline), N (%)	n<5	90 (30.9)	-	56 (34.1)	8 (44.4)

* COPD exacerbations (moderate and severe): COPD-related unscheduled hospital admission/emergency room attendance OR antibiotics prescribed with lower respiratory consultations OR an acute course of oral steroids.

Subgroup	Measure	FP/FOR	FP/SAL DPI	FP/SAL MDI	BUD/FOR	BDP/FOR
only, definition 3	Total exposure to AE (baseline), years	n<5	258	-	134	13
	Annualized rate of AE (baseline)/100 person years	n<5	54.7	-	54.5	53.8
	Number of patients at risk in subgroup, N (%)	n<5	291 (100)	-	164 (100)	18 (100)
	Occurrence of AE (outcome), N (%)	n<5	90 (30.9)	-	56 (34.1)	8 (44.4)
	Total exposure to AE (outcome), years	n<5	426	-	230	26
	Annualized rate of AE (outcome)/100 person years	n<5	21.1	-	24.3	30.4
	Number of times AE occurred per patient, median (IQR)	n<5	0.5 (1.0)	-	0.5 (0.9)	0.7 (1.0)
	Number of times AE occurred per patient, mean (SD)	n<5	0 (0, 1)	-	0 (0, 1)	0 (0, 1)
	Number of times AE occurred per patient, (min,max)	n<5	(0, 6)	-	(0, 5)	(0, 3)
	Duration of exposure, months, median (IQR)	n<5	17.6 (4.2)	-	16.8 (3.8)	17.5 (3.6)
	Duration of exposure, months, mean (SD)	n<5	17.1 (13.5, 20.9)	-	16.3 (13.5, 19.6)	17.3 (14.8, 20.2)
	Duration of exposure, months, (min,max)	n<5	(12.1, 26.6)	-	(12.1, 26.2)	(12.4, 23.6)

Table 44 COPD exacerbations evaluation by FDC ICS/LABA (at least 1 year for baseline and outcome periods)

For patients with at least 6 months of baseline and 6 months of outcome period, there were <5 patients in the FP/FOR group and so annualised rates could not be compared.

Subgroup	Measure	FP/FOR	FP/SAL DPI	FP/SAL MDI	BUD/FOR	BDP/FOR
Patients with COPD only, definition 1	Number of patients at risk in subgroup, N (%)	8 (100)	873 (100)	-	432 (100)	69 (100)
	Occurrence of AE (baseline), N (%)	6 (75.0)	425 (44.2)	-	215 (42.7)	37 (46.8)
	Total exposure to AE (baseline), years	8	866	-	429	68
	Annualized rate of AE (baseline)/100 person years	75	63.5	-	63.9	64.6
	Number of patients at risk in subgroup, N (%)	8 (100)	962 (100)	-	504 (100)	79 (100)
	Occurrence of AE (outcome), N (%)	n<5	425 (44.2)	-	215 (42.7)	37 (46.8)
	Total exposure to AE (outcome), years	n<5	976	-	517	77
	Annualized rate of AE (outcome)/100 person years	n<5	43.6	-	41.6	48.1
	Number of times AE occurred per patient, median (IQR)	0.3 (0.5)	0.9 (1.4)	-	0.8 (1.2)	0.9 (1.5)
	Number of times AE occurred per patient, mean (SD)	0 (0, 1)	0 (0, 1)	-	0 (0, 1)	0 (0, 1)
	Number of times AE occurred per patient, (min,max)	(0, 1)	(0, 13)	-	(0, 12)	(0, 10)
	Duration of exposure, months, median (IQR)	8.2 (1.9)	12.2 (5.3)	-	12.3 (4.9)	11.7 (5.2)
	Duration of exposure, months, mean (SD)	7.9 (6.9, 8.4)	10.5 (7.9, 15.1)	-	11.2 (8.2, 15.4)	10.3 (7.6, 14.4)
	Duration of exposure, months, (min,max)	(6.4, 12.6)	(6.0, 26.6)	-	(6.0, 26.2)	(6.0, 26.5)
Patients with COPD only, definition 2	Number of patients at risk in subgroup, N (%)	7 (100)	735 (100)	-	358 (100)	54 (100)
	Occurrence of AE (baseline), N (%)	5 (71.4)	342 (43.1)	-	167 (41.6)	30 (49.2)
	Total exposure to AE (baseline), years	7	730	-	355	54
	Annualized rate of AE (baseline)/100 person years	71.4	62.9	-	62.8	65.4
	Number of patients at risk in subgroup, N (%)	7 (100)	793 (100)	-	401 (100)	61 (100)
	Occurrence of AE (outcome), N (%)	n<5	342 (43.1)	-	167 (41.6)	30 (49.2)
	Total exposure to AE (outcome), years	n<5	808	-	416	62

Subgroup	Measure	FP/FOR	FP/SAL DPI	FP/SAL MDI	BUD/FOR	BDP/FOR
	Annualized rate of AE (outcome)/100 person years	n<5	42.3	-	40.1	48.6
	Number of times AE occurred per patient, median (IQR)	0.3 (0.5)	0.9 (1.4)	-	0.8 (1.3)	1.0 (1.6)
	Number of times AE occurred per patient, mean (SD)	0 (0, 1)	0 (0, 1)	-	0 (0, 1)	0 (0, 1)
	Number of times AE occurred per patient, (min,max)	(0, 1)	(0, 13)	-	(0, 12)	(0, 10)
	Duration of exposure, months, median (IQR)	8.4 (2.0)	12.2 (5.3)	-	12.5 (5.0)	12.2 (5.3)
	Duration of exposure, months, mean (SD)	7.9 (7.3, 8.7)	10.6 (7.9, 15.1)	-	11.3 (8.3, 15.8)	11.1 (7.9, 15.2)
	Duration of exposure, months, (min,max)	(6.5, 12.6)	(6.0, 26.6)	-	(6.0, 26.2)	(6.0, 26.5)
Patients with COPD only, definition 3	Number of patients at risk in subgroup, N (%)	7 (100)	668 (100)	-	320 (100)	38 (100)
	Occurrence of AE (baseline), N (%)	5 (71.4)	313 (43.2)	-	156 (43.0)	22 (48.9)
	Total exposure to AE (baseline), years	7	663	-	317	38
	Annualized rate of AE (baseline)/100 person years	71.4	62	-	63.7	58.6
	Number of patients at risk in subgroup, N (%)	7 (100)	725 (100)	-	363 (100)	45 (100)
	Occurrence of AE (outcome), N (%)	n<5	313 (43.2)	-	156 (43.0)	22 (48.9)
	Total exposure to AE (outcome), years	n<5	737	-	374	46
	Annualized rate of AE (outcome)/100 person years	n<5	42.5	-	41.8	47.7
	Number of times AE occurred per patient, median (IQR)	0.3 (0.5)	0.9 (1.4)	-	0.8 (1.3)	1.0 (1.7)
	Number of times AE occurred per patient, mean (SD)	0 (0, 1)	0 (0, 1)	-	0 (0, 1)	0 (0, 1)
	Number of times AE occurred per patient, (min,max)	(0, 1)	(0, 11)	-	(0, 12)	(0, 10)
	Duration of exposure, months, median (IQR)	8.4 (2.0)	12.2 (5.3)	-	12.3 (5.0)	12.3 (5.1)
	Duration of exposure, months, mean (SD)	7.9 (7.3, 8.7)	10.5 (7.9, 15.1)	-	11.2 (8.2, 15.5)	11.1 (8.3, 15.4)
	Duration of exposure, months, (min,max)	(6.5, 12.6)	(6.0, 26.6)	-	(6.0, 26.2)	(6.2, 23.6)

Table 45 COPD exacerbations evaluation by FDC ICS/LABA (6 months exposure for baseline and outcome)

5.4.2.2 Lower respiratory tract infection (including pneumonia)*

For patients with asthma aged ≥18 years, the rate of LRTIs during the outcome year was similar between treatment groups and the time to first LRTI was not significantly different. The rate of LRTI during the outcome period was higher for on-label FP/FOR than other treatment groups for patients with asthma aged 12-18 years, however the time to first LRTI was not calculated for this subgroup due to low numbers of events. For patients with asthma aged 4-11 years, patients with asthma aged 12-19 years (off-label FP/FOR) and MART regimen patients, events were low (n<5) or zero. For the COPD subgroups, the annualised rate of LRTI was higher than other treatment groups although the time to first LRTI was not significantly different between the treatment groups.

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

		TOTAL COHORT				
Subgroup	Measure	FP/FOR	FP/SAL DPI	FP/SAL MDI	BUD/FOR	BDP/FOR
Patients aged ≥18 years with asthma	Number of patients at risk in subgroup, N (%)	2127	8902	12629	10899	7011
	Occurrence of AE (baseline), N (%)	445 (20.9)	2446 (27.5)	2812 (22.3)	2308 (21.2)	1404 (20.0)
	Total exposure to AE (baseline), years	2024	7389	10146	8691	6404
	Annualized rate of AE (baseline)/100 person years	22.0	33.1	27.7	26.6	21.9
	Occurrence of AE (outcome), N (%)	198 (9.3)	1599 (18.0)	1791 (14.2)	1329 (12.2)	711 (10.1)
	Total exposure to AE (outcome), years	795	5367	8544	7262	4290
	Annualized rate of AE (outcome)/100 person years	24.9	29.8	21.0	18.3	16.6
	Hazard Ratio (95% CI)	1.0	1.3 (1.2, 1.6)	1.0 (0.8, 1.1)	0.8 (0.7, 1.0)	0.7 (0.6, 0.9)
	Number of times AE occurred per patient, mean (SD)	0.1 (0.4)	0.3 (0.7)	0.2 (0.6)	0.2 (0.5)	0.1 (0.4)
	Number of times AE occurred per patient, median (IQR)	0 (0, 0)	0 (0, 0)	0 (0, 0)	0 (0, 0)	0 (0, 0)
	Number of times AE occurred per patient, (min,max)	(0, 5)	(0, 7)	(0, 7)	(0, 9)	(0, 5)
	Duration of exposure, months, mean (SD)	4.5 (4.0)	7.2 (7.2)	8.1 (7.4)	8.0 (7.4)	7.3 (7.0)
	Duration of exposure, months, median (IQR)	3.2 (1.3, 7.0)	4.3 (1.6, 11.7)	5.5 (2.0, 13.2)	5.3 (2.0, 13.0)	4.6 (1.9, 11.6)
	Duration of exposure, months, (min,max)	(0, 17)	(0, 27)	(0, 27)	(0, 27)	(0, 27)
Patients aged ≥12 and <18 years with asthma (licensed Flutiform 50/5, 125/5)	Number of patients at risk in subgroup, N (%)	77	334	862	614	NA
	Occurrence of AE (baseline), N (%)	6 (7.8)	27 (8.1)	111 (12.9)	86 (14.0)	NA
	Total exposure to AE (baseline), years	72	292	751	544	NA
	Annualized rate of AE (baseline)/100 person years	8.3	9.2	14.8	15.8	NA
	Occurrence of AE (outcome), N (%)	5 (6.5)	19 (5.7)	53 (6.1)	28 (4.6)	NA
	Total exposure to AE (outcome), years	31	230	639	437	NA
	Annualized rate of AE (outcome)/100 person years	16.0	8.3	8.3	6.4	NA
	Hazard Ratio (95% CI)	-	-	-	-	NA
	Number of times AE occurred per patient, mean (SD)	0.1 (0.3)	0.1 (0.3)	0.1 (0.3)	0.1 (0.3)	NA
	Number of times AE occurred per patient, median (IQR)	0 (0, 0)	0 (0, 0)	0 (0, 0)	0 (0, 0)	NA
	Number of times AE occurred per patient, (min,max)	(0, 2)	(0, 3)	(0, 3)	(0, 3)	NA
	Duration of exposure, months, mean (SD)	4.9 (4.3)	8.3 (7.8)	8.9 (7.8)	8.5 (7.6)	NA
	Duration of exposure, months, median (IQR)	3.4 (1.5, 7.7)	5.2 (2.0, 13.5)	6.4 (2.0, 14.9)	5.7 (2.0, 13.6)	NA
	Duration of exposure, months, (min,max)	(0, 15)	(0, 27)	(0, 27)	(0, 27)	NA
Patients aged ≥12 and <18 years with asthma	Number of patients at risk in subgroup, N (%)	8	334	862	614	NA
	Occurrence of AE (baseline), N (%)	n<5	27 (8.1)	111 (12.9)	86 (14.0)	NA
	Total exposure to AE (baseline), years	n<5	292	751	544	NA
	Annualized rate of AE (baseline)/100 person years	n<5	9.2	14.8	15.8	NA

		TOTAL COHORT				
Subgroup	Measure	FP/FOR	FP/SAL DPI	FP/SAL MDI	BUD/FOR	BDP/FOR
(off-label Flutiform 250/10)	Occurrence of AE (outcome), N (%)	n<5	19 (5.7)	53 (6.1)	28 (4.6)	NA
	Total exposure to AE (outcome), years	n<5	230	639	437	NA
	Annualized rate of AE (outcome)/100 person years	n<5	8.3	8.3	6.4	NA
	Hazard Ratio (95% CI)	-	-	-	-	NA
	Number of times AE occurred per patient, mean (SD)	0.0 (0.0)	0.1 (0.3)	0.1 (0.3)	0.1 (0.3)	NA
	Number of times AE occurred per patient, median (IQR)	0 (0, 0)	0 (0, 0)	0 (0, 0)	0 (0, 0)	NA
	Number of times AE occurred per patient, (min,max)	(0, 0)	(0, 3)	(0, 3)	(0, 3)	NA
	Duration of exposure, months, mean (SD)	5.8 (4.1)	8.3 (7.8)	8.9 (7.8)	8.5 (7.6)	NA
	Duration of exposure, months, median (IQR)	4.5 (2.5, 9.6)	5.2 (2.0, 13.5)	6.4 (2.0, 14.9)	5.7 (2.0, 13.6)	NA
	Duration of exposure, months, (min,max)	(1.1, 12.2)	(0, 27)	(0, 27)	(0, 27)	NA
Paediatric asthma patients 4-11 years	Number of patients at risk in subgroup, N (%)	12	150	971	230	NA
	Occurrence of AE (baseline), N (%)	n<5	22 (14.7)	141 (14.5)	34 (14.8)	NA
	Total exposure to AE (baseline), years	n<5	136	886	211	NA
	Annualized rate of AE (baseline)/100 person years	n<5	16.2	15.9	16.1	NA
	Occurrence of AE (outcome), N (%)	n<5	15 (10.0)	74 (7.6)	20 (8.7)	NA
	Total exposure to AE (outcome), years	n<5	96	745	168	NA
	Annualized rate of AE (outcome)/100 person years	n<5	15.7	9.9	11.9	NA
	Hazard Ratio (95% CI)	-	-	-	-	NA
	Number of times AE occurred per patient, mean (SD)	0.0 (0.0)	0.1 (0.3)	0.1 (0.4)	0.1 (0.3)	NA
	Number of times AE occurred per patient, median (IQR)	0 (0, 0)	0 (0, 0)	0 (0, 0)	0 (0, 0)	NA
	Number of times AE occurred per patient, (min,max)	(0, 0)	(0, 2)	(0, 4)	(0, 2)	NA
	Duration of exposure, months, mean (SD)	2.1 (2.3)	7.7 (7.7)	9.2 (7.7)	8.8 (7.3)	NA
	Duration of exposure, months, median (IQR)	1.8 (0.2, 3.2)	4.8 (1.1, 12.4)	6.8 (2.3, 15.1)	7.2 (2.0, 13.4)	NA
	Duration of exposure, months, (min,max)	(0, 6)	(0, 26)	(0, 27)	(0, 26)	NA
Patients with COPD only, definition 1	Number of patients at risk in subgroup, N (%)	193	5038	NA	2768	535
	Occurrence of AE (baseline), N (%)	70 (36.3)	1830 (36.3)	NA	985 (35.6)	198 (37.0)
	Total exposure to AE (baseline), years	187	4465	NA	2387	485
	Annualized rate of AE (baseline)/100 person years	37.5	41.0	NA	41.3	40.8
	Occurrence of AE (outcome), N (%)	37 (19.2)	1346 (26.7)	NA	618 (22.3)	124 (23.2)
	Total exposure to AE (outcome), years	73	3202	NA	1700	295
	Annualized rate of AE (outcome)/100 person years	50.9	42.0	NA	36.3	42.0
	Hazard Ratio (95% CI)	1.0	0.9 (0.6, 1.2)	NA	0.8 (0.6, 1.1)	0.9 (0.6, 1.3)
	Number of times AE occurred per patient, mean (SD)	0.3 (0.7)	0.4 (0.8)	NA	0.3 (0.7)	0.3 (0.7)

		TOTAL COHORT				
Subgroup	Measure	FP/FOR	FP/SAL DPI	FP/SAL MDI	BUD/FOR	BDP/FOR
	Number of times AE occurred per patient, median (IQR)	0 (0, 0)	0 (0, 1)	NA	0 (0, 0)	0 (0, 0)
	Number of times AE occurred per patient, (min,max)	(0, 4)	(0, 8)	NA	(0, 7)	(0, 4)
	Duration of exposure, months, mean (SD)	4.5 (4.5)	7.6 (7.1)	NA	7.4 (6.8)	6.6 (6.6)
	Duration of exposure, months, median (IQR)	2.5 (1.2, 7.5)	5.2 (2.0, 11.8)	NA	4.9 (2.0, 11.5)	3.8 (1.8, 10.1)
	Duration of exposure, months, (min,max)	(0, 16)	(0, 27)	NA	(0, 27)	(0, 27)
Patients with COPD only, definition 2	Number of patients at risk in subgroup, N (%)	143	4085	NA	2185	395
	Occurrence of AE (baseline), N (%)	47 (32.9)	1483 (36.3)	NA	804 (36.8)	152 (38.5)
	Total exposure to AE (baseline), years	141	3782	NA	1977	368
	Annualized rate of AE (baseline)/100 person years	33.3	39.2	NA	40.7	41.3
	Occurrence of AE (outcome), N (%)	28 (19.6)	1076 (26.3)	NA	492 (22.5)	96 (24.3)
	Total exposure to AE (outcome), years	54	2672	NA	1372	231
	Annualized rate of AE (outcome)/100 person years	52.1	40.3	NA	35.9	41.6
	Hazard Ratio (95% CI)	1.0	0.8 (0.6, 1.2)	NA	0.7 (0.5, 1.1)	0.9 (0.6, 1.3)
	Number of times AE occurred per patient, mean (SD)	0.3 (0.7)	0.4 (0.8)	NA	0.3 (0.8)	0.3 (0.7)
	Number of times AE occurred per patient, median (IQR)	0 (0, 0)	0 (0, 1)	NA	0 (0, 0)	0 (0, 0)
	Number of times AE occurred per patient, (min,max)	(0, 4)	(0, 7)	NA	(0, 7)	(0, 4)
	Duration of exposure, months, mean (SD)	4.5 (4.5)	7.9 (7.1)	NA	7.5 (6.9)	7.0 (6.9)
	Duration of exposure, months, median (IQR)	2.5 (1.2, 7.5)	5.5 (2.0, 12.2)	NA	5.1 (2.0, 11.8)	4.0 (2.0, 11.1)
	Duration of exposure, months, (min,max)	(0, 16)	(0, 27)	NA	(0, 27)	(0, 27)
Patients with COPD only, definition 3	Number of patients at risk in subgroup, N (%)	129	3739	NA	2010	347
	Occurrence of AE (baseline), N (%)	43 (33.3)	1352 (36.2)	NA	738 (36.7)	133 (38.3)
	Total exposure to AE (baseline), years	127	3444	NA	1807	320
	Annualized rate of AE (baseline)/100 person years	33.8	39.3	NA	40.8	41.6
	Occurrence of AE (outcome), N (%)	25 (19.4)	986 (26.4)	NA	457 (22.7)	82 (23.6)
	Total exposure to AE (outcome), years	46	2439	NA	1259	195
	Annualized rate of AE (outcome)/100 person years	54.3	40.4	NA	36.3	42.1
	Hazard Ratio (95% CI)	1.0	0.8 (0.5, 1.2)	NA	0.7 (0.5, 1.1)	0.8 (0.5, 1.3)
	Number of times AE occurred per patient, mean (SD)	0.3 (0.7)	0.4 (0.8)	NA	0.3 (0.8)	0.3 (0.7)
	Number of times AE occurred per patient, median (IQR)	0 (0, 0)	0 (0, 1)	NA	0 (0, 0)	0 (0, 0)
	Number of times AE occurred per patient, (min,max)	(0, 4)	(0, 7)	NA	(0, 7)	(0, 4)
	Duration of exposure, months, mean (SD)	4.3 (4.3)	7.8 (7.1)	NA	7.5 (7.0)	6.7 (6.9)
	Duration of exposure, months, median (IQR)	2.4 (1.2, 5.7)	5.5 (2.0, 12.1)	NA	5.1 (2.0, 11.8)	3.6 (1.9, 10.2)

		TOTAL COHORT				
Subgroup	Measure	FP/FOR	FP/SAL DPI	FP/SAL MDI	BUD/FOR	BDP/FOR
	Duration of exposure, months, (min,max)	(0, 16)	(0, 27)	NA	(0, 27)	(0, 26)
"MART" regimen definition 1	Number of patients at risk in subgroup, N (%)	66	NA	NA	379	308
	Occurrence of AE (baseline), N (%)	10 (15.2)	NA	NA	70 (18.5)	66 (21.4)
	Total exposure to AE (baseline), years	63	NA	NA	285	275
	Annualized rate of AE (baseline)/100 person years	15.9	NA	NA	24.6	24.0
	Occurrence of AE (outcome), N (%)	n<5	NA	NA	43 (11.3)	19 (6.2)
	Total exposure to AE (outcome), years	n<5	NA	NA	299	146
	Annualized rate of AE (outcome)/100 person years	n<5	NA	NA	14.4	13.1
	Hazard Ratio (95% CI)	-	NA	NA	-	-
	Number of times AE occurred per patient, mean (SD)	0.1 (0.3)	NA	NA	0.1 (0.4)	0.1 (0.3)
	Number of times AE occurred per patient, median (IQR)	0 (0, 0)	NA	NA	0 (0, 0)	0 (0, 0)
	Number of times AE occurred per patient, (min,max)	(0, 2)	NA	NA	(0, 4)	(0, 3)
	Duration of exposure, months, mean (SD)	4.0 (3.6)	NA	NA	9.5 (8.3)	5.7 (6.0)
	Duration of exposure, months, median (IQR)	2.9 (1.2, 6.1)	NA	NA	6.6 (2.0, 16.4)	3.1 (1.4, 8.4)
	Duration of exposure, months, (min,max)	(0, 15)	NA	NA	(0, 27)	(0, 26)
"MART" regimen definition 2	Number of patients at risk in subgroup, N (%)	6	NA	NA	102	66
	Occurrence of AE (baseline), N (%)	n<5	NA	NA	19 (18.6)	20 (30.3)
	Total exposure to AE (baseline), years	n<5	NA	NA	99	62
	Annualized rate of AE (baseline)/100 person years	n<5	NA	NA	19.3	32.2
	Occurrence of AE (outcome), N (%)	n<5	NA	NA	11 (10.8)	n<5
	Total exposure to AE (outcome), years	n<5	NA	NA	77	n<5
	Annualized rate of AE (outcome)/100 person years	n<5	NA	NA	14.4	n<5
	Hazard Ratio (95% CI)	-	NA	NA	-	-
	Number of times AE occurred per patient, mean (SD)	0.2 (0.4)	NA	NA	0.1 (0.4)	0.1 (0.4)
	Number of times AE occurred per patient, median (IQR)	0 (0, 0)	NA	NA	0 (0, 0)	0 (0, 0)
	Number of times AE occurred per patient, (min,max)	(0, 1)	NA	NA	(0, 2)	(0, 3)
	Duration of exposure, months, mean (SD)	3.3 (2.5)	NA	NA	9.0 (8.1)	5.5 (5.9)
	Duration of exposure, months, median (IQR)	2.0 (1.5, 6.4)	NA	NA	6.5 (2.0, 13.8)	2.7 (1.6, 8.0)
	Duration of exposure, months, (min,max)	(1.3, 6.5)	NA	NA	(0, 26)	(0, 22)

Table 46: Lower respiratory tract infection (including pneumonia) evaluation by FDC ICS/LABA

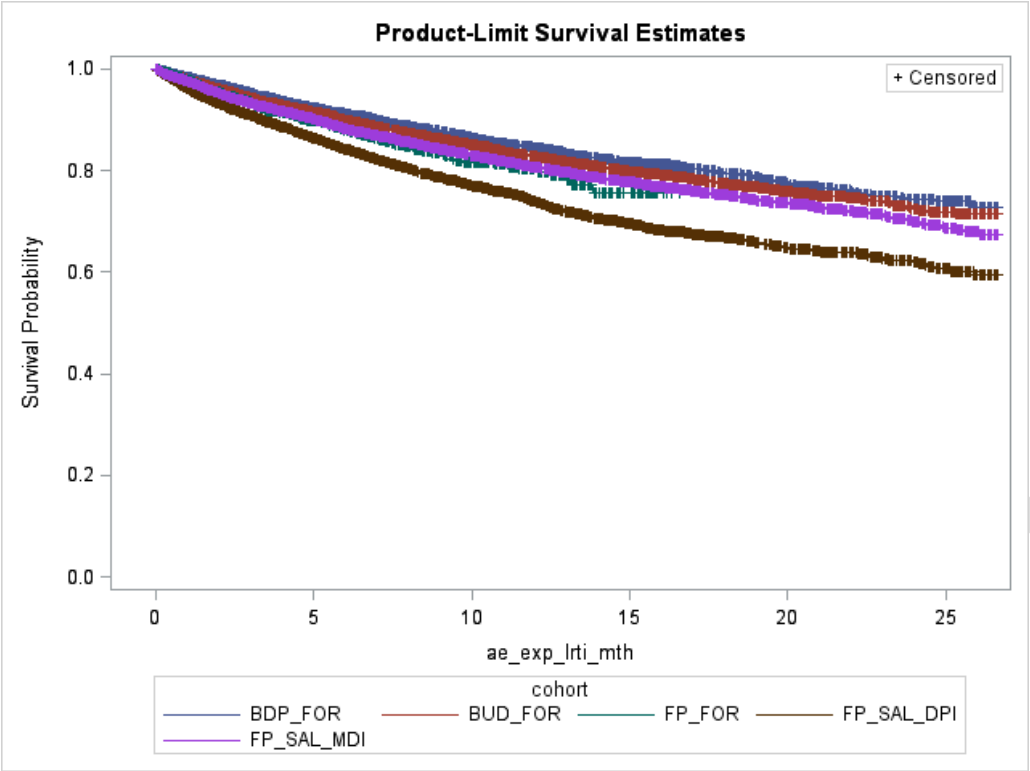

Figure 3: Lower respiratory tract infection (including pneumonia) evaluation by FDC ICS/LABA (asthma patients ≥18 years old)

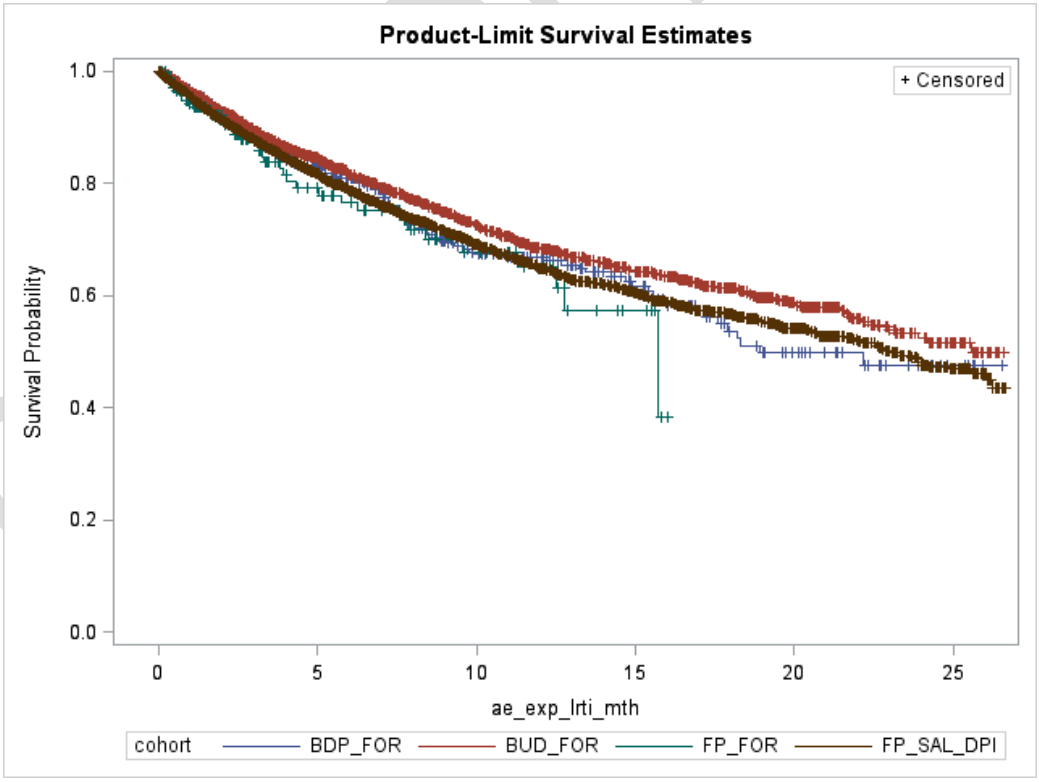

Figure 4: Lower respiratory tract infection (including pneumonia) evaluation by FDC ICS/LABA (COPD only patients, definition 1)

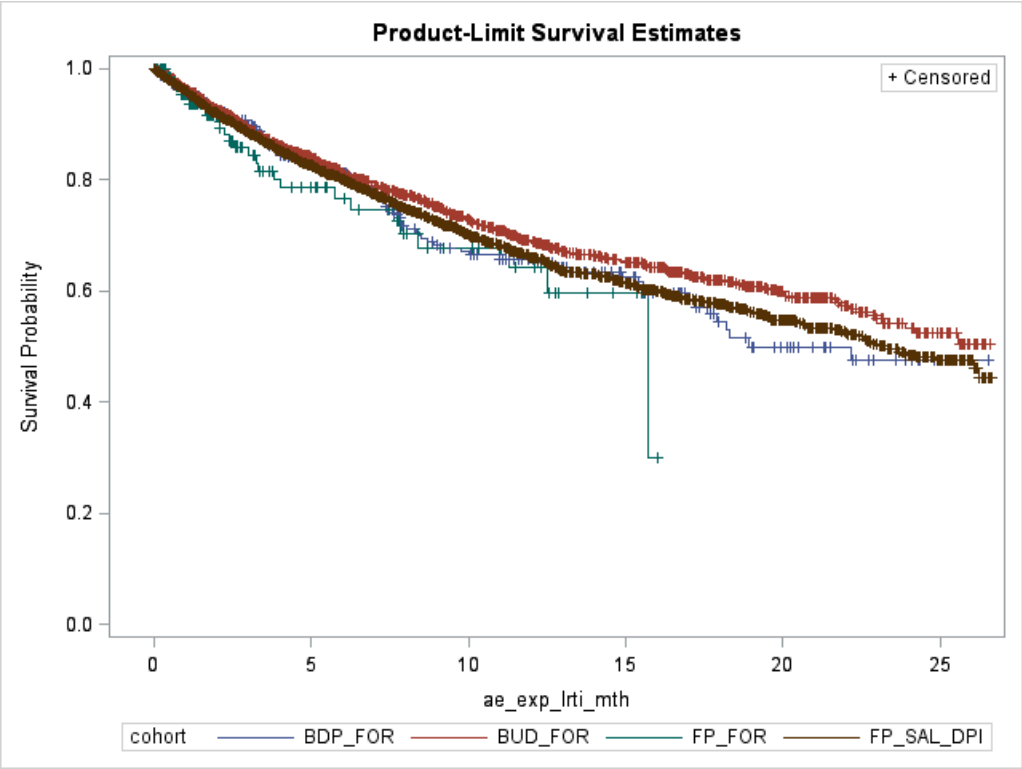

Figure 5: Lower respiratory tract infection (including pneumonia) evaluation by FDC ICS/LABA (COPD only patients, definition 2)

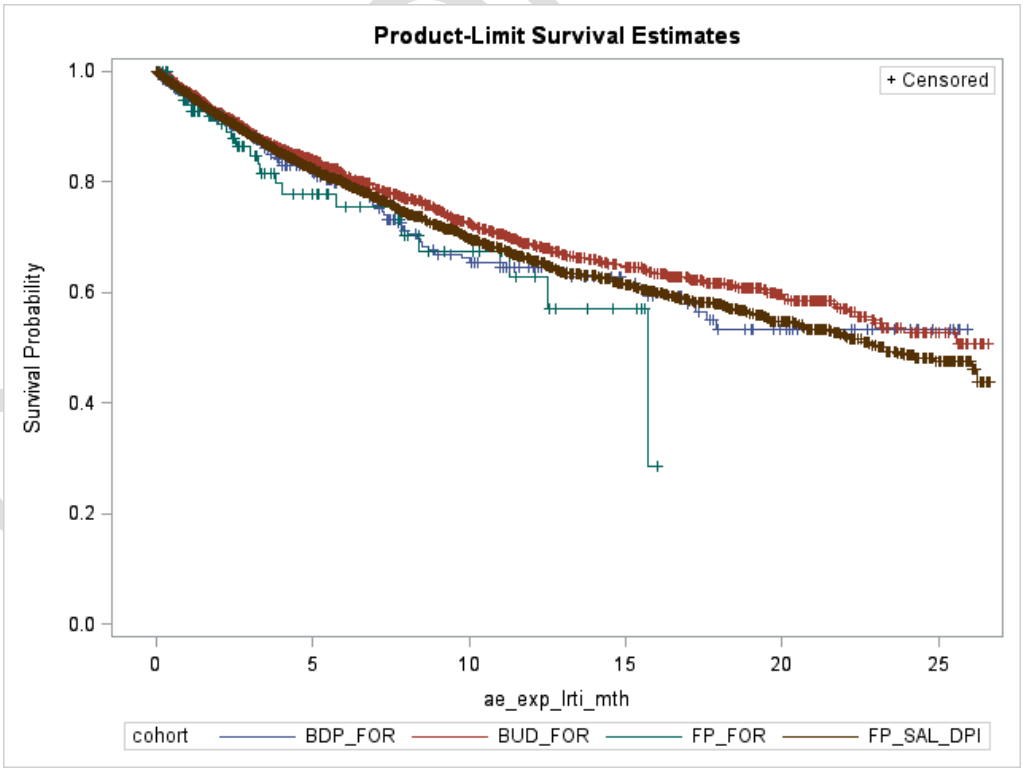

Figure 6: Lower respiratory tract infection (including pneumonia) evaluation by FDC ICS/LABA (COPD only patients, definition 3)

5.4.2.3 Pneumonia*

The annualised rate of patients with pneumonia was broadly similar at outcome across treatment groups for patients with asthma aged ≥18. The number of times pneumonia occurred was similarly low across all treatment groups in all subgroups studied. The hazard ratios were not presented due to <10 events in the FP/FOR group in each of the subgroups. Numbers of events were low in the patients with asthma aged <18 years, COPD definitions 1, 2 and 3 and MART definitions 1 and 2 and so limited comparisons could be made.

		TOTAL COHORT				
Subgroup	Measure	FP/FOR	FP/SAL DPI	FP/SAL MDI	BUD/FOR	BDP/FOR
Patients aged ≥18 years with asthma	Number of patients at risk in subgroup, N (%)	2127	8902	12629	10899	7011
	Occurrence of AE (baseline), N (%)	9 (0.4)	132 (1.5)	109 (0.9)	105 (1.0)	36 (0.5)
	Total exposure to AE (baseline), years	2024	7389	10146	8691	6404
	Annualized rate of AE (baseline)/100 person years	0.4	1.8	1.1	1.2	0.6
	Occurrence of AE (outcome), N (%)	5 (0.2)	69 (0.8)	79 (0.6)	40 (0.4)	24 (0.3)
	Total exposure to AE (outcome), years	859	6417	9731	8126	4700
	Annualized rate of AE (outcome)/100 person years	0.6	1.1	0.8	0.5	0.5
	Hazard Ratio (95% CI)	-	-	-	-	-
	Number of times AE occurred per patient, mean (SD)	0.0 (0.1)	0.0 (0.1)	0.0 (0.1)	0.0 (0.1)	0.0 (0.1)
	Number of times AE occurred per patient, median (IQR)	0 (0, 0)	0 (0, 0)	0 (0, 0)	0 (0, 0)	0 (0, 0)
	Number of times AE occurred per patient, (min,max)	(0, 3)	(0, 2)	(0, 4)	(0, 5)	(0, 2)
	Duration of exposure, months, mean (SD)	4.8 (4.1)	8.7 (7.9)	9.2 (7.9)	8.9 (7.8)	8.0 (7.4)
	Duration of exposure, months, median (IQR)	3.5 (1.5, 7.7)	5.9 (2.0, 14.5)	6.9 (2.0, 15.5)	6.4 (2.0, 15.1)	5.5 (2.0, 13.1)
	Duration of exposure, months, (min,max)	(0, 19)	(0, 27)	(0, 27)	(0, 27)	(0, 27)
Patients aged ≥12 and <18 years with asthma (licensed Flutiform 50/5, 125/5)	Number of patients at risk in subgroup, N (%)	77	334	862	614	NA
	Occurrence of AE (baseline), N (%)	n<5	n<5	n<5	n<5	NA
	Total exposure to AE (baseline), years	n<5	n<5	n<5	n<5	NA
	Annualized rate of AE (baseline)/100 person years	n<5	n<5	n<5	n<5	NA
	Occurrence of AE (outcome), N (%)	n<5	n<5	n<5	n<5	NA
	Total exposure to AE (outcome), years	n<5	n<5	n<5	n<5	NA
	Annualized rate of AE (outcome)/100 person years	n<5	n<5	n<5	n<5	NA
	Hazard Ratio (95% CI)	-	-	-	-	NA
	Number of times AE occurred per patient, mean (SD)	0.0 (0.0)	0.0 (0.1)	0.0 (0.0)	0.0 (0.0)	NA
	Number of times AE occurred per patient, median (IQR)	0 (0, 0)	0 (0, 0)	0 (0, 0)	0 (0, 0)	NA

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

		TOTAL COHORT				
Subgroup	Measure	FP/FOR	FP/SAL DPI	FP/SAL MDI	BUD/FOR	BDP/FOR
	Number of times AE occurred per patient, (min,max)	(0, 0)	(0, 1)	(0, 1)	(0, 1)	NA
	Duration of exposure, months, mean (SD)	5.4 (4.6)	8.6 (8.0)	9.4 (7.9)	9.0 (7.7)	NA
	Duration of exposure, months, median (IQR)	4.2 (1.8, 8.9)	5.3 (2.0, 14.0)	7.1 (2.0, 15.8)	6.2 (2.0, 14.9)	NA
	Duration of exposure, months, (min,max)	(0, 15)	(0, 27)	(0, 27)	(0, 27)	NA
Patients aged ≥12 and <18 years with asthma (off-label Flutiform 250/10)	Number of patients at risk in subgroup, N (%)	8	334	862	614	NA
	Occurrence of AE (baseline), N (%)	n<5	n<5	n<5	n<5	NA
	Total exposure to AE (baseline), years	n<5	n<5	n<5	n<5	NA
	Annualized rate of AE (baseline)/100 person years	n<5	n<5	n<5	n<5	NA
	Occurrence of AE (outcome), N (%)	n<5	n<5	n<5	n<5	NA
	Total exposure to AE (outcome), years	n<5	n<5	n<5	n<5	NA
	Annualized rate of AE (outcome)/100 person years	n<5	n<5	n<5	n<5	NA
	Hazard Ratio (95% CI)	-	-	-	-	NA
	Number of times AE occurred per patient, mean (SD)	0.0 (0.0)	0.0 (0.1)	0.0 (0.0)	0.0 (0.0)	NA
	Number of times AE occurred per patient, median (IQR)	0 (0, 0)	0 (0, 0)	0 (0, 0)	0 (0, 0)	NA
	Number of times AE occurred per patient, (min,max)	(0, 0)	(0, 1)	(0, 1)	(0, 1)	NA
	Duration of exposure, months, mean (SD)	5.8 (4.1)	8.6 (8.0)	9.4 (7.9)	9.0 (7.7)	NA
	Duration of exposure, months, median (IQR)	4.5 (2.5, 9.6)	5.3 (2.0, 14.0)	7.1 (2.0, 15.8)	6.2 (2.0, 14.9)	NA
	Duration of exposure, months, (min,max)	(1.1, 12.2)	(0, 27)	(0, 27)	(0, 27)	NA
Paediatric asthma patients 4-11 years	Number of patients at risk in subgroup, N (%)	12	150	971	230	NA
	Occurrence of AE (baseline), N (%)	n<5	n<5	n<5	n<5	NA
	Total exposure to AE (baseline), years	n<5	n<5	n<5	n<5	NA
	Annualized rate of AE (baseline)/100 person years	n<5	n<5	n<5	n<5	NA
	Occurrence of AE (outcome), N (%)	n<5	n<5	n<5	n<5	NA
	Total exposure to AE (outcome), years	n<5	n<5	n<5	n<5	NA
	Annualized rate of AE (outcome)/100 person years	n<5	n<5	n<5	n<5	NA
	Hazard Ratio (95% CI)	-	-	-	-	NA
	Number of times AE occurred per patient, mean (SD)	0.0 (0.0)	0.0 (0.0)	0.0 (0.0)	0.0 (0.0)	NA
	Number of times AE occurred per patient, median (IQR)	0 (0, 0)	0 (0, 0)	0 (0, 0)	0 (0, 0)	NA
	Number of times AE occurred per patient, (min,max)	(0, 0)	(0, 0)	(0, 1)	(0, 0)	NA
	Duration of exposure, months, mean (SD)	2.1 (2.3)	8.6 (8.1)	9.8 (7.8)	9.3 (7.7)	NA
	Duration of exposure, months, median (IQR)	1.8 (0.2, 3.2)	5.3 (1.8, 14.8)	7.8 (2.7, 16.1)	8.0 (2.0, 15.1)	NA
	Duration of exposure, months, (min,max)	(0, 6)	(0, 26)	(0, 27)	(0, 26)	NA

		TOTAL COHORT				
Subgroup	Measure	FP/FOR	FP/SAL DPI	FP/SAL MDI	BUD/FOR	BDP/FOR
Patients with COPD only, definition 1	Number of patients at risk in subgroup, N (%)	193	5038	NA	2768	535
	Occurrence of AE (baseline), N (%)	n<5	118 (2.3)	NA	68 (2.5)	8 (1.5)
	Total exposure to AE (baseline), years	n<5	4465	NA	2387	485
	Annualized rate of AE (baseline)/100 person years	n<5	2.6	NA	2.8	1.7
	Occurrence of AE (outcome), N (%)	n<5	89 (1.8)	NA	41 (1.5)	n<5
	Total exposure to AE (outcome), years	n<5	4113	NA	2082	n<5
	Annualized rate of AE (outcome)/100 person years	n<5	2.2	NA	2.0	n<5
	Hazard Ratio (95% CI)	-	-	NA	-	-
	Number of times AE occurred per patient, mean (SD)	0.0 (0.2)	0.0 (0.2)	NA	0.0 (0.2)	0.0 (0.1)
	Number of times AE occurred per patient, median (IQR)	0 (0, 0)	0 (0, 0)	NA	0 (0, 0)	0 (0, 0)
	Number of times AE occurred per patient, (min,max)	(0, 3)	(0, 4)	NA	(0, 3)	(0, 1)
	Duration of exposure, months, mean (SD)	5.4 (4.9)	9.8 (8.0)	NA	9.0 (7.6)	8.4 (7.5)
	Duration of exposure, months, median (IQR)	3.2 (1.5, 8.7)	7.8 (2.3, 16.2)	NA	6.8 (2.0, 14.7)	5.5 (2.0, 14.0)
	Duration of exposure, months, (min,max)	(0, 16)	(0, 27)	NA	(0, 27)	(0, 27)
Patients with COPD only, definition 2	Number of patients at risk in subgroup, N (%)	143	4085	NA	2185	395
	Occurrence of AE (baseline), N (%)	n<5	81 (2.0)	NA	54 (2.5)	n<5
	Total exposure to AE (baseline), years	n<5	3782	NA	1977	n<5
	Annualized rate of AE (baseline)/100 person years	n<5	2.1	NA	2.7	n<5
	Occurrence of AE (outcome), N (%)	n<5	66 (1.6)	NA	29 (1.3)	n<5
	Total exposure to AE (outcome), years	n<5	3413	NA	1684	n<5
	Annualized rate of AE (outcome)/100 person years	n<5	1.9	NA	1.7	n<5
	Hazard Ratio (95% CI)	-	-	NA	-	-
	Number of times AE occurred per patient, mean (SD)	0.0 (0.3)	0.0 (0.2)	NA	0.0 (0.1)	0.0 (0.1)
	Number of times AE occurred per patient, median (IQR)	0 (0, 0)	0 (0, 0)	NA	0 (0, 0)	0 (0, 0)
	Number of times AE occurred per patient, (min,max)	(0, 3)	(0, 4)	NA	(0, 2)	(0, 1)
	Duration of exposure, months, mean (SD)	5.4 (5.0)	10.0 (8.0)	NA	9.2 (7.7)	8.9 (7.8)
	Duration of exposure, months, median (IQR)	3.2 (1.4, 9.6)	8.2 (2.5, 16.5)	NA	7.3 (2.0, 15.3)	5.6 (2.0, 15.6)
	Duration of exposure, months, (min,max)	(0, 16)	(0, 27)	NA	(0, 27)	(0, 27)
Patients with COPD only, definition 3	Number of patients at risk in subgroup, N (%)	129	3739	NA	2010	347
	Occurrence of AE (baseline), N (%)	n<5	74 (2.0)	NA	49 (2.4)	n<5
	Total exposure to AE (baseline), years	n<5	3444	NA	1807	n<5
	Annualized rate of AE (baseline)/100 person years	n<5	2.1	NA	2.7	n<5
	Occurrence of AE (outcome), N (%)	n<5	58 (1.6)	NA	28 (1.4)	n<5

		TOTAL COHORT				
Subgroup	Measure	FP/FOR	FP/SAL DPI	FP/SAL MDI	BUD/FOR	BDP/FOR
	Total exposure to AE (outcome), years	n<5	3123	NA	1550	n<5
	Annualized rate of AE (outcome)/100 person years	n<5	1.9	NA	1.8	n<5
	Hazard Ratio (95% CI)	-	-	NA	-	-
	Number of times AE occurred per patient, mean (SD)	0.0 (0.3)	0.0 (0.2)	NA	0.0 (0.1)	0.0 (0.1)
	Number of times AE occurred per patient, median (IQR)	0 (0, 0)	0 (0, 0)	NA	0 (0, 0)	0 (0, 0)
	Number of times AE occurred per patient, (min,max)	(0, 3)	(0, 4)	NA	(0, 2)	(0, 1)
	Duration of exposure, months, mean (SD)	5.2 (4.9)	10.0 (8.0)	NA	9.3 (7.7)	8.7 (7.8)
	Duration of exposure, months, median (IQR)	2.8 (1.4, 8.4)	8.1 (2.5, 16.5)	NA	7.3 (2.0, 15.2)	5.4 (2.0, 15.3)
	Duration of exposure, months, (min,max)	(0, 16)	(0, 27)	NA	(0, 27)	(0, 26)
"MART" regimen definition 1	Number of patients at risk in subgroup, N (%)	66	NA	NA	379	308
	Occurrence of AE (baseline), N (%)	n<5	NA	NA	n<5	n<5
	Total exposure to AE (baseline), years	n<5	NA	NA	n<5	n<5
	Annualized rate of AE (baseline)/100 person years	n<5	NA	NA	n<5	n<5
	Occurrence of AE (outcome), N (%)	n<5	NA	NA	n<5	n<5
	Total exposure to AE (outcome), years	n<5	NA	NA	n<5	n<5
	Annualized rate of AE (outcome)/100 person years	n<5	NA	NA	n<5	n<5
	Hazard Ratio (95% CI)	-	NA	NA	-	-
	Number of times AE occurred per patient, mean (SD)	0.0 (0.0)	NA	NA	0.0 (0.1)	0.0 (0.0)
	Number of times AE occurred per patient, median (IQR)	0 (0, 0)	NA	NA	0 (0, 0)	0 (0, 0)
	Number of times AE occurred per patient, (min,max)	(0, 0)	NA	NA	(0, 1)	(0, 0)
	Duration of exposure, months, mean (SD)	4.3 (3.7)	NA	NA	10.4 (8.6)	6.0 (6.1)
	Duration of exposure, months, median (IQR)	3.3 (1.3, 6.2)	NA	NA	8.7 (2.0, 17.9)	3.3 (1.5, 9.4)
	Duration of exposure, months, (min,max)	(0, 15)	NA	NA	(0, 27)	(0, 26)
"MART" regimen definition 2	Number of patients at risk in subgroup, N (%)	6	NA	NA	102	66
	Occurrence of AE (baseline), N (%)	n<5	NA	NA	n<5	n<5
	Total exposure to AE (baseline), years	n<5	NA	NA	n<5	n<5
	Annualized rate of AE (baseline)/100 person years	n<5	NA	NA	n<5	n<5
	Occurrence of AE (outcome), N (%)	n<5	NA	NA	n<5	n<5
	Total exposure to AE (outcome), years	n<5	NA	NA	n<5	n<5
	Annualized rate of AE (outcome)/100 person years	n<5	NA	NA	n<5	n<5
	Hazard Ratio (95% CI)	-	NA	NA	-	-
	Number of times AE occurred per patient, mean (SD)	0.0 (0.0)	NA	NA	0.0 (0.0)	0.0 (0.0)

		TOTAL COHORT				
Subgroup	Measure	FP/FOR	FP/SAL DPI	FP/SAL MDI	BUD/FOR	BDP/FOR
	Number of times AE occurred per patient, median (IQR)	0 (0, 0)	NA	NA	0 (0, 0)	0 (0, 0)
	Number of times AE occurred per patient, (min,max)	(0, 0)	NA	NA	(0, 0)	(0, 0)
	Duration of exposure, months, mean (SD)	3.4 (2.4)	NA	NA	9.8 (8.4)	5.6 (5.9)
	Duration of exposure, months, median (IQR)	2.0 (2.0, 6.4)	NA	NA	7.4 (2.0, 17.2)	2.8 (1.8, 8.1)
	Duration of exposure, months, (min,max)	(1.5, 6.5)	NA	NA	(0, 26)	(0, 22)

Table 47: Pneumonia evaluation by FDC ICS/LABA

5.4.2.4 Pulmonary embolism

The annualised rate of patients with a pulmonary embolism was low (n<5) or zero for all treatment groups across all subgroups. The hazard ratios were not presented due to <10 events in the FP/FOR group in each of the subgroups.

		TOTAL COHORT				
Subgroup	Measure	FP/FOR	FP/SAL DPI	FP/SAL MDI	BUD/FOR	BDP/FOR
Patients aged ≥18 years with asthma	Number of patients at risk in subgroup, N (%)	2127	8902	12629	10899	7011
	Occurrence of AE (baseline), N (%)	5 (0.2)	22 (0.2)	28 (0.2)	37 (0.3)	10 (0.1)
	Total exposure to AE (baseline), years	2024	7389	10146	8691	6404
	Annualized rate of AE (baseline)/100 person years	0.2	0.3	0.3	0.4	0.2
	Occurrence of AE (outcome), N (%)	n<5	17 (0.2)	33 (0.3)	20 (0.2)	6 (0.1)
	Total exposure to AE (outcome), years	n<5	6444	9755	8136	4707
	Annualized rate of AE (outcome)/100 person years	n<5	0.3	0.3	0.2	0.1
	Hazard Ratio (95% CI)	-	-	-	-	-
Patients aged ≥12 and <18 years with asthma (licensed Flutiform 50/5, 125/5)	Number of patients at risk in subgroup, N (%)	77	334	862	614	NA
	Occurrence of AE (baseline), N (%)	n<5	n<5	n<5	n<5	NA
	Total exposure to AE (baseline), years	n<5	n<5	n<5	n<5	NA
	Annualized rate of AE (baseline)/100 person years	n<5	n<5	n<5	n<5	NA
	Occurrence of AE (outcome), N (%)	n<5	n<5	n<5	n<5	NA
	Total exposure to AE (outcome), years	n<5	n<5	n<5	n<5	NA
	Annualized rate of AE (outcome)/100 person years	n<5	n<5	n<5	n<5	NA
	Hazard Ratio (95% CI)	-	-	-	-	NA
Patients aged ≥12 and <18 years with asthma (off-label Flutiform 250/10)	Number of patients at risk in subgroup, N (%)	8	334	862	614	NA
	Occurrence of AE (baseline), N (%)	n<5	n<5	n<5	n<5	NA
	Total exposure to AE (baseline), years	n<5	n<5	n<5	n<5	NA
	Annualized rate of AE (baseline)/100 person years	n<5	n<5	n<5	n<5	NA
	Occurrence of AE (outcome), N (%)	n<5	n<5	n<5	n<5	NA
	Total exposure to AE (outcome), years	n<5	n<5	n<5	n<5	NA

		TOTAL COHORT				
Subgroup	Measure	FP/FOR	FP/SAL DPI	FP/SAL MDI	BUD/FOR	BDP/FOR
	Annualized rate of AE (outcome)/100 person years	n<5	n<5	n<5	n<5	NA
	Hazard Ratio (95% CI)	-	-	-	-	NA
Paediatric asthma patients 4-11 years	Number of patients at risk in subgroup, N (%)	12	150	971	230	NA
	Occurrence of AE (baseline), N (%)	n<5	n<5	n<5	n<5	NA
	Total exposure to AE (baseline), years	n<5	n<5	n<5	n<5	NA
	Annualized rate of AE (baseline)/100 person years	n<5	n<5	n<5	n<5	NA
	Occurrence of AE (outcome), N (%)	n<5	n<5	n<5	n<5	NA
	Total exposure to AE (outcome), years	n<5	n<5	n<5	n<5	NA
	Annualized rate of AE (outcome)/100 person years	n<5	n<5	n<5	n<5	NA
	Hazard Ratio (95% CI)	-	-	-	-	NA
Patients with COPD only, definition 1	Number of patients at risk in subgroup, N (%)	193	5038	NA	2768	535
	Occurrence of AE (baseline), N (%)	n<5	19 (0.4)	NA	12 (0.4)	n<5
	Total exposure to AE (baseline), years	n<5	4465	NA	2387	n<5
	Annualized rate of AE (baseline)/100 person years	n<5	0.4	NA	0.5	n<5
	Occurrence of AE (outcome), N (%)	n<5	25 (0.5)	NA	6 (0.2)	n<5
	Total exposure to AE (outcome), years	n<5	4139	NA	2095	n<5
	Annualized rate of AE (outcome)/100 person years	n<5	0.6	NA	0.3	n<5
	Hazard Ratio (95% CI)	-	-	NA	-	-
Patients with COPD only, definition 2	Number of patients at risk in subgroup, N (%)	143	4085	NA	2185	395
	Occurrence of AE (baseline), N (%)	n<5	12 (0.3)	NA	9 (0.4)	n<5
	Total exposure to AE (baseline), years	n<5	3782	NA	1977	n<5
	Annualized rate of AE (baseline)/100 person years	n<5	0.3	NA	0.5	n<5
	Occurrence of AE (outcome), N (%)	n<5	17 (0.4)	NA	n<5	n<5
	Total exposure to AE (outcome), years	n<5	3433	NA	n<5	n<5
	Annualized rate of AE (outcome)/100 person years	n<5	0.5	NA	n<5	n<5
	Hazard Ratio (95% CI)	-	-	NA	-	-
Patients with COPD only, definition 3	Number of patients at risk in subgroup, N (%)	129	3739	NA	2010	347
	Occurrence of AE (baseline), N (%)	n<5	11 (0.3)	NA	9 (0.4)	n<5
	Total exposure to AE (baseline), years	n<5	3444	NA	1807	n<5
	Annualized rate of AE (baseline)/100 person years	n<5	0.3	NA	0.5	n<5
	Occurrence of AE (outcome), N (%)	n<5	16 (0.4)	NA	n<5	n<5
	Total exposure to AE (outcome), years	n<5	3139	NA	n<5	n<5
	Annualized rate of AE (outcome)/100 person years	n<5	0.5	NA	n<5	n<5
	Hazard Ratio (95% CI)	-	-	NA	-	-
"MART" regimen definition 1	Number of patients at risk in subgroup, N (%)	66	NA	NA	379	308
	Occurrence of AE (baseline), N (%)	n<5	NA	NA	n<5	n<5
	Total exposure to AE (baseline), years	n<5	NA	NA	n<5	n<5
	Annualized rate of AE (baseline)/100 person years	n<5	NA	NA	n<5	n<5

		TOTAL COHORT				
Subgroup	Measure	FP/FOR	FP/SAL DPI	FP/SAL MDI	BUD/FOR	BDP/FOR
	Occurrence of AE (outcome), N (%)	n<5	NA	NA	n<5	n<5
	Total exposure to AE (outcome), years	n<5	NA	NA	n<5	n<5
	Annualized rate of AE (outcome)/100 person years	n<5	NA	NA	n<5	n<5
	Hazard Ratio (95% CI)	-	NA	NA	-	-
"MART" regimen definition 2	Number of patients at risk in subgroup, N (%)	6	NA	NA	102	66
	Occurrence of AE (baseline), N (%)	n<5	NA	NA	n<5	n<5
	Total exposure to AE (baseline), years	n<5	NA	NA	n<5	n<5
	Annualized rate of AE (baseline)/100 person years	n<5	NA	NA	n<5	n<5
	Occurrence of AE (outcome), N (%)	n<5	NA	NA	n<5	n<5
	Total exposure to AE (outcome), years	n<5	NA	NA	n<5	n<5
	Annualized rate of AE (outcome)/100 person years	n<5	NA	NA	n<5	n<5
	Hazard Ratio (95% CI)	-	NA	NA	-	-

Table 48: Pulmonary embolism evaluation by FDC ICS/LABA

5.4.2.5 Tuberculosis

The annualised rate of patients with tuberculosis was low (n<5) or zero for all treatment groups across all subgroups. The hazard ratios were not presented due to <10 events in the FP/FOR group in each of the subgroups.

		TOTAL COHORT				
Subgroup	Measure	FP/FOR	FP/SAL DPI	FP/SAL MDI	BUD/FOR	BDP/FOR
Patients aged ≥18 years with asthma	Number of patients at risk in subgroup, N (%)	2127	8902	12629	10899	7011
	Occurrence of AE (baseline), N (%)	n<5	n<5	n<5	n<5	n<5
	Total exposure to AE (baseline), years	n<5	n<5	n<5	n<5	n<5
	Annualized rate of AE (baseline)/100 person years	n<5	n<5	n<5	n<5	n<5
	Occurrence of AE (outcome), N (%)	n<5	n<5	n<5	n<5	n<5
	Total exposure to AE (outcome), years	n<5	n<5	n<5	n<5	n<5
	Annualized rate of AE (outcome)/100 person years	n<5	n<5	n<5	n<5	n<5
	Hazard Ratio (95% CI)	-	-	-	-	-
Patients aged ≥12 and <18 years with asthma (licensed Flutiform 50/5, 125/5)	Number of patients at risk in subgroup, N (%)	77	334	862	614	NA
	Occurrence of AE (baseline), N (%)	n<5	n<5	n<5	n<5	NA
	Total exposure to AE (baseline), years	n<5	n<5	n<5	n<5	NA
	Annualized rate of AE (baseline)/100 person years	n<5	n<5	n<5	n<5	NA
	Occurrence of AE (outcome), N (%)	n<5	n<5	n<5	n<5	NA
	Total exposure to AE (outcome), years	n<5	n<5	n<5	n<5	NA
	Annualized rate of AE (outcome)/100 person years	n<5	n<5	n<5	n<5	NA
	Hazard Ratio (95% CI)	-	-	-	-	NA

		TOTAL COHORT				
Subgroup	Measure	FP/FOR	FP/SAL DPI	FP/SAL MDI	BUD/FOR	BDP/FOR
Patients aged ≥12 and <18 years with asthma (off-label Flutiform 250/10)	Number of patients at risk in subgroup, N (%)	8	334	862	614	NA
	Occurrence of AE (baseline), N (%)	n<5	n<5	n<5	n<5	NA
	Total exposure to AE (baseline), years	n<5	n<5	n<5	n<5	NA
	Annualized rate of AE (baseline)/100 person years	n<5	n<5	n<5	n<5	NA
	Occurrence of AE (outcome), N (%)	n<5	n<5	n<5	n<5	NA
	Total exposure to AE (outcome), years	n<5	n<5	n<5	n<5	NA
	Annualized rate of AE (outcome)/100 person years	n<5	n<5	n<5	n<5	NA
	Hazard Ratio (95% CI)	-	-	-	-	NA
Paediatric asthma patients 4-11 years	Number of patients at risk in subgroup, N (%)	12	150	971	230	NA
	Occurrence of AE (baseline), N (%)	n<5	n<5	n<5	n<5	NA
	Total exposure to AE (baseline), years	n<5	n<5	n<5	n<5	NA
	Annualized rate of AE (baseline)/100 person years	n<5	n<5	n<5	n<5	NA
	Occurrence of AE (outcome), N (%)	n<5	n<5	n<5	n<5	NA
	Total exposure to AE (outcome), years	n<5	n<5	n<5	n<5	NA
	Annualized rate of AE (outcome)/100 person years	n<5	n<5	n<5	n<5	NA
	Hazard Ratio (95% CI)	-	-	-	-	NA
Patients with COPD only, definition 1	Number of patients at risk in subgroup, N (%)	193	5038	NA	2768	535
	Occurrence of AE (baseline), N (%)	n<5	5 (0.1)	NA	n<5	n<5
	Total exposure to AE (baseline), years	n<5	4465	NA	n<5	n<5
	Annualized rate of AE (baseline)/100 person years	n<5	0.1	NA	n<5	n<5
	Occurrence of AE (outcome), N (%)	n<5	8 (0.2)	NA	n<5	n<5
	Total exposure to AE (outcome), years	n<5	4146	NA	n<5	n<5
	Annualized rate of AE (outcome)/100 person years	n<5	0.2	NA	n<5	n<5
	Hazard Ratio (95% CI)	-	-	NA	-	-
Patients with COPD only, definition 2	Number of patients at risk in subgroup, N (%)	143	4085	NA	2185	395
	Occurrence of AE (baseline), N (%)	n<5	n<5	NA	n<5	n<5
	Total exposure to AE (baseline), years	n<5	n<5	NA	n<5	n<5
	Annualized rate of AE (baseline)/100 person years	n<5	n<5	NA	n<5	n<5
	Occurrence of AE (outcome), N (%)	n<5	7 (0.2)	NA	n<5	n<5
	Total exposure to AE (outcome), years	n<5	3436	NA	n<5	n<5
	Annualized rate of AE (outcome)/100 person years	n<5	0.2	NA	n<5	n<5
	Hazard Ratio (95% CI)	-	-	NA	-	-
Patients with COPD only, definition 3	Number of patients at risk in subgroup, N (%)	129	3739	NA	2010	347
	Occurrence of AE (baseline), N (%)	n<5	n<5	NA	n<5	n<5
	Total exposure to AE (baseline), years	n<5	n<5	NA	n<5	n<5
	Annualized rate of AE (baseline)/100 person years	n<5	n<5	NA	n<5	n<5
	Occurrence of AE (outcome), N (%)	n<5	6 (0.2)	NA	n<5	n<5
	Total exposure to AE (outcome), years	n<5	3141	NA	n<5	n<5

		TOTAL COHORT				
Subgroup	Measure	FP/FOR	FP/SAL DPI	FP/SAL MDI	BUD/FOR	BDP/FOR
	Annualized rate of AE (outcome)/100 person years	n<5	0.2	NA	n<5	n<5
	Hazard Ratio (95% CI)	-	-	NA	-	-
"MART" regimen definition 1	Number of patients at risk in subgroup, N (%)	66	NA	NA	379	308
	Occurrence of AE (baseline), N (%)	n<5	NA	NA	n<5	n<5
	Total exposure to AE (baseline), years	n<5	NA	NA	n<5	n<5
	Annualized rate of AE (baseline)/100 person years	n<5	NA	NA	n<5	n<5
	Occurrence of AE (outcome), N (%)	n<5	NA	NA	n<5	n<5
	Total exposure to AE (outcome), years	n<5	NA	NA	n<5	n<5
	Annualized rate of AE (outcome)/100 person years	n<5	NA	NA	n<5	n<5
	Hazard Ratio (95% CI)	-	NA	NA	-	-
"MART" regimen definition 2	Number of patients at risk in subgroup, N (%)	6	NA	NA	102	66
	Occurrence of AE (baseline), N (%)	n<5	NA	NA	n<5	n<5
	Total exposure to AE (baseline), years	n<5	NA	NA	n<5	n<5
	Annualized rate of AE (baseline)/100 person years	n<5	NA	NA	n<5	n<5
	Occurrence of AE (outcome), N (%)	n<5	NA	NA	n<5	n<5
	Total exposure to AE (outcome), years	n<5	NA	NA	n<5	n<5
	Annualized rate of AE (outcome)/100 person years	n<5	NA	NA	n<5	n<5
	Hazard Ratio (95% CI)	-	NA	NA	-	-

Table 49: Tuberculosis evaluation by FDC ICS/LABA

5.4.2.6 Oral candidiasis

The annualised rate of patients with oral candidiasis was similarly low during the outcome period across all treatment groups in all subgroups for patients without oral candidiasis during the baseline period.

		TOTAL COHORT				
Subgroup	Measure	FP/FOR	FP/SAL DPI	FP/SAL MDI	BUD/FOR	BDP/FOR
Patients aged ≥18 years with asthma	Number of patients at risk in subgroup, N (%)	2100	8775	12434	10773	6922
	Occurrence of AE (outcome), N (%)	7 (0.3)	111 (1.3)	108 (0.9)	74 (0.7)	74 (1.1)
	Total exposure to AE (outcome), years	844	6330	9560	7994	4619
	Annualized rate of AE (outcome)/100 person years	0.8	1.8	1.1	0.9	1.6
Patients aged ≥12 and <18 years with asthma (licensed Flutiform 50/5, 125/5)	Number of patients at risk in subgroup, N (%)	77	332	857	614	NA
	Occurrence of AE (outcome), N (%)	n<5	n<5	n<5	n<5	NA
	Total exposure to AE (outcome), years	n<5	n<5	n<5	n<5	NA
	Annualized rate of AE (outcome)/100 person years	n<5	n<5	n<5	n<5	NA
	Number of patients at risk in subgroup, N (%)	8	332	857	614	NA

		TOTAL COHORT				
Subgroup	Measure	FP/FOR	FP/SAL DPI	FP/SAL MDI	BUD/FOR	BDP/FOR
Patients aged ≥12 and <18 years with asthma (off-label Flutiform 250/10)	Occurrence of AE (outcome), N (%)	n<5	n<5	n<5	n<5	NA
	Total exposure to AE (outcome), years	n<5	n<5	n<5	n<5	NA
	Annualized rate of AE (outcome)/100 person years	n<5	n<5	n<5	n<5	NA
Paediatric asthma patients 4-11 years	Number of patients at risk in subgroup, N (%)	12	148	966	230	NA
	Occurrence of AE (outcome), N (%)	n<5	n<5	n<5	n<5	NA
	Total exposure to AE (outcome), years	n<5	n<5	n<5	n<5	NA
	Annualized rate of AE (outcome)/100 person years	n<5	n<5	n<5	n<5	NA
Patients with COPD only, definition 1	Number of patients at risk in subgroup, N (%)	192	4974	NA	2726	527
	Occurrence of AE (outcome), N (%)	n<5	89 (1.8)	NA	37 (1.4)	8 (1.5)
	Total exposure to AE (outcome), years	n<5	4070	NA	2042	367
	Annualized rate of AE (outcome)/100 person years	n<5	2.2	NA	1.8	2.2
Patients with COPD only, definition 2	Number of patients at risk in subgroup, N (%)	143	4035	NA	2150	391
	Occurrence of AE (outcome), N (%)	n<5	71 (1.8)	NA	29 (1.3)	7 (1.8)
	Total exposure to AE (outcome), years	n<5	3378	NA	1648	290
	Annualized rate of AE (outcome)/100 person years	n<5	2.1	NA	1.8	2.4
Patients with COPD only, definition 3	Number of patients at risk in subgroup, N (%)	129	3696	NA	1975	344
	Occurrence of AE (outcome), N (%)	n<5	63 (1.7)	NA	26 (1.3)	6 (1.7)
	Total exposure to AE (outcome), years	n<5	3093	NA	1516	251
	Annualized rate of AE (outcome)/100 person years	n<5	2.0	NA	1.7	2.4
"MART" regimen definition 1	Number of patients at risk in subgroup, N (%)	64	NA	NA	375	299
	Occurrence of AE (outcome), N (%)	n<5	NA	NA	n<5	n<5
	Total exposure to AE (outcome), years	n<5	NA	NA	n<5	n<5
	Annualized rate of AE (outcome)/100 person years	n<5	NA	NA	n<5	n<5
"MART" regimen definition 2	Number of patients at risk in subgroup, N (%)	6	NA	NA	101	62
	Occurrence of AE (outcome), N (%)	n<5	NA	NA	n<5	n<5
	Total exposure to AE (outcome), years	n<5	NA	NA	n<5	n<5
	Annualized rate of AE (outcome)/100 person years	n<5	NA	NA	n<5	n<5

Table 50: Oral candidiasis evaluation by FDC ICS/LABA

5.4.2.7 Dysphonia / hoarse voice

The annualised rate of patients with dysphonia/hoarse voice was similarly low across all treatment groups in all subgroups for patients without prior events.

		TOTAL COHORT				
Subgroup	Measure	FP/FOR	FP/SAL DPI	FP/SAL MDI	BUD/FOR	BDP/FOR
Patients aged ≥18 years with asthma	Number of patients at risk in subgroup, N (%)	2101	8822	12477	10797	6952
	Occurrence of AE (outcome), N (%)	5 (0.2)	59 (0.7)	119 (1.0)	82 (0.8)	34 (0.5)
	Total exposure to AE (outcome), years	848	6369	9597	8026	4652
	Annualized rate of AE (outcome)/100 person years	0.6	0.9	1.2	1.0	0.7
Patients aged ≥12 and <18 years with asthma (licensed Flutiform 50/5, 125/5)	Number of patients at risk in subgroup, N (%)	77	334	859	613	NA
	Occurrence of AE (outcome), N (%)	n<5	n<5	n<5	n<5	NA
	Total exposure to AE (outcome), years	n<5	n<5	n<5	n<5	NA
	Annualized rate of AE (outcome)/100 person years	n<5	n<5	n<5	n<5	NA
Patients aged ≥12 and <18 years with asthma (off-label Flutiform 250/10)	Number of patients at risk in subgroup, N (%)	8	334	859	613	NA
	Occurrence of AE (outcome), N (%)	n<5	n<5	n<5	n<5	NA
	Total exposure to AE (outcome), years	n<5	n<5	n<5	n<5	NA
	Annualized rate of AE (outcome)/100 person years	n<5	n<5	n<5	n<5	NA
Paediatric asthma patients 4-11 years	Number of patients at risk in subgroup, N (%)	12	150	970	230	NA
	Occurrence of AE (outcome), N (%)	n<5	n<5	n<5	n<5	NA
	Total exposure to AE (outcome), years	n<5	n<5	n<5	n<5	NA
	Annualized rate of AE (outcome)/100 person years	n<5	n<5	n<5	n<5	NA
Patients with COPD only, definition 1	Number of patients at risk in subgroup, N (%)	190	5004	NA	2744	527
	Occurrence of AE (outcome), N (%)	n<5	46 (0.9)	NA	31 (1.1)	5 (0.9)
	Total exposure to AE (outcome), years	n<5	4095	NA	2062	367
	Annualized rate of AE (outcome)/100 person years	n<5	1.1	NA	1.5	1.4
Patients with COPD only, definition 2	Number of patients at risk in subgroup, N (%)	141	4056	NA	2167	389
	Occurrence of AE (outcome), N (%)	n<5	38 (0.9)	NA	25 (1.2)	n<5
	Total exposure to AE (outcome), years	n<5	3393	NA	1669	n<5
	Annualized rate of AE (outcome)/100 person years	n<5	1.1	NA	1.5	n<5
Patients with COPD only, definition 3	Number of patients at risk in subgroup, N (%)	127	3711	NA	1997	341
	Occurrence of AE (outcome), N (%)	n<5	31 (0.8)	NA	22 (1.1)	n<5
	Total exposure to AE (outcome), years	n<5	3106	NA	1542	n<5
	Annualized rate of AE (outcome)/100 person years	n<5	1.0	NA	1.4	n<5
"MART" regimen definition 1	Number of patients at risk in subgroup, N (%)	65	NA	NA	376	307
	Occurrence of AE (outcome), N (%)	n<5	NA	NA	5 (1.3)	n<5
	Total exposure to AE (outcome), years	n<5	NA	NA	323	n<5
	Annualized rate of AE (outcome)/100 person years	n<5	NA	NA	1.5	n<5
"MART" regimen definition 2	Number of patients at risk in subgroup, N (%)	6	NA	NA	102	66
	Occurrence of AE (outcome), N (%)	n<5	NA	NA	n<5	n<5
	Total exposure to AE (outcome), years	n<5	NA	NA	n<5	n<5

		TOTAL COHORT				
Subgroup	Measure	FP/FOR	FP/SAL DPI	FP/SAL MDI	BUD/FOR	BDP/FOR
	Annualized rate of AE (outcome)/100 person years	n<5	NA	NA	n<5	n<5

Table 51: Dysphonia / hoarse voice evaluation by FDC ICS/LABA

5.4.2.8 Local oral adverse events

The annualised rate of patients with other local oral adverse events was similarly low across all treatment groups in all subgroups for patients without prior events.

		TOTAL COHORT				
Subgroup	Measure	FP/FOR	FP/SAL DPI	FP/SAL MDI	BUD/FOR	BDP/FOR
Patients aged ≥18 years with asthma	Number of patients at risk in subgroup, N (%)	2091	8758	12429	10710	6873
	Occurrence of AE (outcome), N (%)	12 (0.6)	111 (1.3)	159 (1.3)	125 (1.2)	81 (1.2)
	Total exposure to AE (outcome), years	840	6292	9514	7925	4577
	Annualized rate of AE (outcome)/100 person years	1.4	1.8	1.7	1.6	1.8
Patients aged ≥12 and <18 years with asthma (licensed Flutiform 50/5, 125/5)	Number of patients at risk in subgroup, N (%)	74	331	839	604	NA
	Occurrence of AE (outcome), N (%)	n<5	n<5	15 (1.8)	10 (1.7)	NA
	Total exposure to AE (outcome), years	n<5	n<5	646	447	NA
	Annualized rate of AE (outcome)/100 person years	n<5	n<5	2.3	2.2	NA
Patients aged ≥12 and <18 years with asthma (off-label Flutiform 250/10)	Number of patients at risk in subgroup, N (%)	8	331	839	604	NA
	Occurrence of AE (outcome), N (%)	n<5	n<5	15 (1.8)	10 (1.7)	NA
	Total exposure to AE (outcome), years	n<5	n<5	646	447	NA
	Annualized rate of AE (outcome)/100 person years	n<5	n<5	2.3	2.2	NA
Paediatric asthma patients 4-11 years	Number of patients at risk in subgroup, N (%)	12	146	951	223	NA
	Occurrence of AE (outcome), N (%)	n<5	n<5	23 (2.4)	n<5	NA
	Total exposure to AE (outcome), years	n<5	n<5	767	n<5	NA
	Annualized rate of AE (outcome)/100 person years	n<5	n<5	3.0	n<5	NA
Patients with COPD only, definition 1	Number of patients at risk in subgroup, N (%)	189	4983	NA	2731	525
	Occurrence of AE (outcome), N (%)	n<5	53 (1.1)	NA	15 (0.5)	5 (1.0)
	Total exposure to AE (outcome), years	n<5	4079	NA	2065	368
	Annualized rate of AE (outcome)/100 person years	n<5	1.3	NA	0.7	1.4
Patients with COPD only, definition 2	Number of patients at risk in subgroup, N (%)	140	4037	NA	2153	387
	Occurrence of AE (outcome), N (%)	n<5	41 (1.0)	NA	8 (0.4)	n<5
	Total exposure to AE (outcome), years	n<5	3382	NA	1668	n<5
	Annualized rate of AE (outcome)/100 person years	n<5	1.2	NA	0.5	n<5
Patients with COPD	Number of patients at risk in subgroup, N (%)	126	3695	NA	1979	339
	Occurrence of AE (outcome), N (%)	n<5	37 (1.0)	NA	7 (0.4)	n<5

		TOTAL COHORT				
Subgroup	Measure	FP/FOR	FP/SAL DPI	FP/SAL MDI	BUD/FOR	BDP/FOR
only, definition 3	Total exposure to AE (outcome), years	n<5	3093	NA	1535	n<5
	Annualized rate of AE (outcome)/100 person years	n<5	1.2	NA	0.5	n<5
"MART" regimen definition 1	Number of patients at risk in subgroup, N (%)	65	NA	NA	378	298
	Occurrence of AE (outcome), N (%)	n<5	NA	NA	n<5	n<5
	Total exposure to AE (outcome), years	n<5	NA	NA	n<5	n<5
	Annualized rate of AE (outcome)/100 person years	n<5	NA	NA	n<5	n<5
"MART" regimen definition 2	Number of patients at risk in subgroup, N (%)	6	NA	NA	101	63
	Occurrence of AE (outcome), N (%)	n<5	NA	NA	n<5	n<5
	Total exposure to AE (outcome), years	n<5	NA	NA	n<5	n<5
	Annualized rate of AE (outcome)/100 person years	n<5	NA	NA	n<5	n<5

Table 52: Local oral adverse events evaluation by FDC ICS/LABA

5.4.2.9 Adrenal failure

The annualised rate of patients with adrenal failure was similarly low across all treatment groups in the patients with asthma age ≥18 for patients without prior events. The number of events was low (n<5) or zero for FP/FOR across the rest of the treatment groups.

		TOTAL COHORT				
Subgroup	Measure	FP/FOR	FP/SAL DPI	FP/SAL MDI	BUD/FOR	BDP/FOR
Patients aged ≥18 years with asthma	Number of patients at risk in subgroup, N (%)	2127	8902	12629	10899	7011
	Occurrence of AE (outcome), N (%)	12 (0.6)	111 (1.2)	159 (1.3)	125 (1.1)	81 (1.2)
	Total exposure to AE (outcome), years	860	6457	9771	8148	4710
	Annualized rate of AE (outcome)/100 person years	1.4	1.7	1.6	1.5	1.7
Patients aged ≥12 and <18 years with asthma (licensed Flutiform 50/5, 125/5)	Number of patients at risk in subgroup, N (%)	77	334	862	614	NA
	Occurrence of AE (outcome), N (%)	n<5	n<5	15 (1.7)	10 (1.6)	NA
	Total exposure to AE (outcome), years	n<5	n<5	676	458	NA
	Annualized rate of AE (outcome)/100 person years	n<5	n<5	2.2	2.2	NA
Patients aged ≥12 and <18 years with asthma (off-label Flutiform 250/10)	Number of patients at risk in subgroup, N (%)	8	334	862	614	NA
	Occurrence of AE (outcome), N (%)	n<5	n<5	15 (1.7)	10 (1.6)	NA
	Total exposure to AE (outcome), years	n<5	n<5	676	458	NA
	Annualized rate of AE (outcome)/100 person years	n<5	n<5	2.2	2.2	NA
Paediatric asthma patients 4-11 years	Number of patients at risk in subgroup, N (%)	12	150	971	230	NA
	Occurrence of AE (outcome), N (%)	n<5	n<5	23 (2.4)	n<5	NA
	Total exposure to AE (outcome), years	n<5	n<5	792	n<5	NA
	Annualized rate of AE (outcome)/100 person years	n<5	n<5	2.9	n<5	NA

		TOTAL COHORT				
Subgroup	Measure	FP/FOR	FP/SAL DPI	FP/SAL MDI	BUD/FOR	BDP/FOR
Patients with COPD only, definition 1	Number of patients at risk in subgroup, N (%)	193	5038	NA	2768	535
	Occurrence of AE (outcome), N (%)	n<5	53 (1.1)	NA	15 (0.5)	5 (0.9)
	Total exposure to AE (outcome), years	n<5	4154	NA	2098	377
	Annualized rate of AE (outcome)/100 person years	n<5	1.3	NA	0.7	1.3
Patients with COPD only, definition 2	Number of patients at risk in subgroup, N (%)	143	4085	NA	2185	395
	Occurrence of AE (outcome), N (%)	n<5	41 (1.0)	NA	8 (0.4)	n<5
	Total exposure to AE (outcome), years	n<5	3444	NA	1695	n<5
	Annualized rate of AE (outcome)/100 person years	n<5	1.2	NA	0.5	n<5
Patients with COPD only, definition 3	Number of patients at risk in subgroup, N (%)	129	3739	NA	2010	347
	Occurrence of AE (outcome), N (%)	n<5	37 (1.0)	NA	7 (0.3)	n<5
	Total exposure to AE (outcome), years	n<5	3148	NA	1562	n<5
	Annualized rate of AE (outcome)/100 person years	n<5	1.2	NA	0.4	n<5
"MART" regimen definition 1	Number of patients at risk in subgroup, N (%)	66	NA	NA	379	308
	Occurrence of AE (outcome), N (%)	n<5	NA	NA	n<5	n<5
	Total exposure to AE (outcome), years	n<5	NA	NA	n<5	n<5
	Annualized rate of AE (outcome)/100 person years	n<5	NA	NA	n<5	n<5
"MART" regimen definition 2	Number of patients at risk in subgroup, N (%)	6	NA	NA	102	66
	Occurrence of AE (outcome), N (%)	n<5	NA	NA	n<5	n<5
	Total exposure to AE (outcome), years	n<5	NA	NA	n<5	n<5
	Annualized rate of AE (outcome)/100 person years	n<5	NA	NA	n<5	n<5

Table 53: Adrenal failure evaluation by FDC ICS/LABA

5.4.2.10 Cardiac arrhythmias and ischemia

The annualised rate of patients with cardiac events was similarly low across all treatment groups in the patients with asthma age ≥18 for patients without prior events. The number of events was too low (n<5) or zero for FP/FOR across the rest of the treatment groups.

		TOTAL COHORT				
Subgroup	Measure	FP/FOR	FP/SAL DPI	FP/SAL MDI	BUD/FOR	BDP/FOR
Patients aged ≥18 years with asthma	Number of patients at risk in subgroup, N (%)	2084	8526	12210	10568	6829
	Occurrence of AE (outcome), N (%)	15 (0.7)	186 (2.2)	204 (1.7)	160 (1.5)	91 (1.3)
	Total exposure to AE (outcome), years	838	6067	9357	7823	4537
	Annualized rate of AE (outcome)/100 person years	1.8	3.1	2.2	2.0	2.0
Patients aged ≥12 and <18 years with	Number of patients at risk in subgroup, N (%)	77	334	862	614	NA
	Occurrence of AE (outcome), N (%)	n<5	n<5	n<5	n<5	NA
	Total exposure to AE (outcome), years	n<5	n<5	n<5	n<5	NA

		TOTAL COHORT				
Subgroup	Measure	FP/FOR	FP/SAL DPI	FP/SAL MDI	BUD/FOR	BDP/FOR
asthma (licensed Flutiform 50/5, 125/5)	Annualized rate of AE (outcome)/100 person years	n<5	n<5	n<5	n<5	NA
Patients aged ≥12 and <18 years with asthma (off-label Flutiform 250/10)	Number of patients at risk in subgroup, N (%)	8	334	862	614	NA
	Occurrence of AE (outcome), N (%)	n<5	n<5	n<5	n<5	NA
	Total exposure to AE (outcome), years	n<5	n<5	n<5	n<5	NA
	Annualized rate of AE (outcome)/100 person years	n<5	n<5	n<5	n<5	NA
Paediatric asthma patients 4-11 years	Number of patients at risk in subgroup, N (%)	12	149	971	229	NA
	Occurrence of AE (outcome), N (%)	n<5	n<5	n<5	n<5	NA
	Total exposure to AE (outcome), years	n<5	n<5	n<5	n<5	NA
	Annualized rate of AE (outcome)/100 person years	n<5	n<5	n<5	n<5	NA
Patients with COPD only, definition 1	Number of patients at risk in subgroup, N (%)	179	4621	NA	2546	506
	Occurrence of AE (outcome), N (%)	n<5	194 (4.2)	NA	115 (4.5)	26 (5.1)
	Total exposure to AE (outcome), years	n<5	3710	NA	1875	342
	Annualized rate of AE (outcome)/100 person years	n<5	5.2	NA	6.1	7.6
Patients with COPD only, definition 2	Number of patients at risk in subgroup, N (%)	131	3764	NA	2008	375
	Occurrence of AE (outcome), N (%)	n<5	154 (4.1)	NA	91 (4.5)	21 (5.6)
	Total exposure to AE (outcome), years	n<5	3086	NA	1512	268
	Annualized rate of AE (outcome)/100 person years	n<5	5.0	NA	6.0	7.8
Patients with COPD only, definition 3	Number of patients at risk in subgroup, N (%)	118	3449	NA	1847	333
	Occurrence of AE (outcome), N (%)	n<5	139 (4.0)	NA	82 (4.4)	18 (5.4)
	Total exposure to AE (outcome), years	n<5	2822	NA	1395	229
	Annualized rate of AE (outcome)/100 person years	n<5	4.9	NA	5.9	7.8
"MART" regimen definition 1	Number of patients at risk in subgroup, N (%)	65	NA	NA	374	302
	Occurrence of AE (outcome), N (%)	n<5	NA	NA	n<5	6 (2.0)
	Total exposure to AE (outcome), years	n<5	NA	NA	n<5	147
	Annualized rate of AE (outcome)/100 person years	n<5	NA	NA	n<5	4.1
"MART" regimen definition 2	Number of patients at risk in subgroup, N (%)	6	NA	NA	101	65
	Occurrence of AE (outcome), N (%)	n<5	NA	NA	n<5	n<5
	Total exposure to AE (outcome), years	n<5	NA	NA	n<5	n<5
	Annualized rate of AE (outcome)/100 person years	n<5	NA	NA	n<5	n<5

Table 54: Cardiac arrhythmias and ischemia evaluation by FDC ICS/LABA

5.4.2.11 Hyperglycaemia*

* Hyperglycaemia diagnosis or indication for hyperglycaemia, such as raised blood glucose

The annualised rate of patients with hyperglycaemia was similarly low across all treatment groups in the patients with asthma age ≥18 and slightly higher for FP/FOR in patients with COPD (definition 1) for patients without prior hyperglycaemia or type 2 diabetes. The number of events was too low (n<5) or zero for FP/FOR across the rest of the treatment groups to make comparisons.

		TOTAL COHORT				
Subgroup	Measure	FP/FOR	FP/SAL DPI	FP/SAL MDI	BUD/FOR	BDP/FOR
Patients aged ≥18 years with asthma	Number of patients at risk in subgroup, N (%)	1997	8174	11830	10297	6613
	Occurrence of AE (outcome), N (%)	14 (0.7)	201 (2.5)	256 (2.2)	193 (1.9)	95 (1.4)
	Total exposure to AE (outcome), years	796	5718	8920	7562	4380
	Annualized rate of AE (outcome)/100 person years	1.8	3.5	2.9	2.6	2.2
Patients aged ≥12 and <18 years with asthma (licensed Flutiform 50/5, 125/5)	Number of patients at risk in subgroup, N (%)	77	334	859	613	NA
	Occurrence of AE (outcome), N (%)	n<5	n<5	n<5	n<5	NA
	Total exposure to AE (outcome), years	n<5	n<5	n<5	n<5	NA
	Annualized rate of AE (outcome)/100 person years	n<5	n<5	n<5	n<5	NA
Patients aged ≥12 and <18 years with asthma (off-label Flutiform 250/10)	Number of patients at risk in subgroup, N (%)	8	334	859	613	NA
	Occurrence of AE (outcome), N (%)	n<5	n<5	n<5	n<5	NA
	Total exposure to AE (outcome), years	n<5	n<5	n<5	n<5	NA
	Annualized rate of AE (outcome)/100 person years	n<5	n<5	n<5	n<5	NA
Paediatric asthma patients 4-11 years	Number of patients at risk in subgroup, N (%)	12	150	970	230	NA
	Occurrence of AE (outcome), N (%)	n<5	n<5	n<5	n<5	NA
	Total exposure to AE (outcome), years	n<5	n<5	n<5	n<5	NA
	Annualized rate of AE (outcome)/100 person years	n<5	n<5	n<5	n<5	NA
Patients with COPD only, definition 1	Number of patients at risk in subgroup, N (%)	169	4570	NA	2509	486
	Occurrence of AE (outcome), N (%)	6 (3.6)	175 (3.8)	NA	84 (3.3)	10 (2.1)
	Total exposure to AE (outcome), years	78	3644	NA	1839	338
	Annualized rate of AE (outcome)/100 person years	7.7	4.8	NA	4.6	3.0
Patients with COPD only, definition 2	Number of patients at risk in subgroup, N (%)	128	3713	NA	1982	359
	Occurrence of AE (outcome), N (%)	n<5	121 (3.3)	NA	70 (3.5)	9 (2.5)
	Total exposure to AE (outcome), years	n<5	3048	NA	1484	269
	Annualized rate of AE (outcome)/100 person years	n<5	4.0	NA	4.7	3.3
Patients with COPD only, definition 3	Number of patients at risk in subgroup, N (%)	115	3400	NA	1833	317
	Occurrence of AE (outcome), N (%)	n<5	110 (3.2)	NA	61 (3.3)	7 (2.2)
	Total exposure to AE (outcome), years	n<5	2788	NA	1380	235
	Annualized rate of AE (outcome)/100 person years	n<5	3.9	NA	4.4	3.0
	Number of patients at risk in subgroup, N (%)	64	NA	NA	363	292

		TOTAL COHORT				
Subgroup	Measure	FP/FOR	FP/SAL DPI	FP/SAL MDI	BUD/FOR	BDP/FOR
"MART" regimen definition 1	Occurrence of AE (outcome), N (%)	n<5	NA	NA	6 (1.7)	n<5
	Total exposure to AE (outcome), years	n<5	NA	NA	315	n<5
	Annualized rate of AE (outcome)/100 person years	n<5	NA	NA	1.9	n<5
"MART" regimen definition 2	Number of patients at risk in subgroup, N (%)	6	NA	NA	98	61
	Occurrence of AE (outcome), N (%)	n<5	NA	NA	n<5	n<5
	Total exposure to AE (outcome), years	n<5	NA	NA	n<5	n<5
	Annualized rate of AE (outcome)/100 person years	n<5	NA	NA	n<5	n<5

Table 55: Hyperglycaemia evaluation by FDC ICS/LABA

5.4.2.12 Diagnosis of type 2 diabetes mellitus

The annualised rate of diagnosis of type 2 diabetes mellitus was similarly low across all treatment groups in the patients with asthma age ≥18 without prior type 2 diabetes. The number of events was too low (n<5) or zero for FP/FOR across the rest of the treatment groups to make comparisons.

		TOTAL COHORT				
Subgroup	Measure	FP/FOR	FP/SAL DPI	FP/SAL MDI	BUD/FOR	BDP/FOR
Patients aged ≥18 years with asthma	Number of patients at risk in subgroup, N (%)	2108	8718	12437	10741	6923
	Occurrence of AE (outcome), N (%)	14 (0.7)	79 (0.9)	130 (1.0)	101 (0.9)	41 (0.6)
	Total exposure to AE (outcome), years	848	6253	9530	7977	4631
	Annualized rate of AE (outcome)/100 person years	1.7	1.3	1.4	1.3	0.9
Patients aged ≥12 and <18 years with asthma (licensed Flutiform 50/5, 125/5)	Number of patients at risk in subgroup, N (%)	77	334	862	614	NA
	Occurrence of AE (outcome), N (%)	n<5	n<5	n<5	n<5	NA
	Total exposure to AE (outcome), years	n<5	n<5	n<5	n<5	NA
	Annualized rate of AE (outcome)/100 person years	n<5	n<5	n<5	n<5	NA
Patients aged ≥12 and <18 years with asthma (off-label Flutiform 250/10)	Number of patients at risk in subgroup, N (%)	8	334	862	614	NA
	Occurrence of AE (outcome), N (%)	n<5	n<5	n<5	n<5	NA
	Total exposure to AE (outcome), years	n<5	n<5	n<5	n<5	NA
	Annualized rate of AE (outcome)/100 person years	n<5	n<5	n<5	n<5	NA
Paediatric asthma patients 4-11 years	Number of patients at risk in subgroup, N (%)	12	150	971	230	NA
	Occurrence of AE (outcome), N (%)	n<5	n<5	n<5	n<5	NA
	Total exposure to AE (outcome), years	n<5	n<5	n<5	n<5	NA
	Annualized rate of AE (outcome)/100 person years	n<5	n<5	n<5	n<5	NA
	Number of patients at risk in subgroup, N (%)	189	4942	NA	2706	519

		TOTAL COHORT				
Subgroup	Measure	FP/FOR	FP/SAL DPI	FP/SAL MDI	BUD/FOR	BDP/FOR
Patients with COPD only, definition 1	Occurrence of AE (outcome), N (%)	n<5	71 (1.4)	NA	34 (1.3)	n<5
	Total exposure to AE (outcome), years	n<5	4024	NA	2025	n<5
	Annualized rate of AE (outcome)/100 person years	n<5	1.8	NA	1.7	n<5
Patients with COPD only, definition 2	Number of patients at risk in subgroup, N (%)	141	4020	NA	2145	384
	Occurrence of AE (outcome), N (%)	n<5	55 (1.4)	NA	27 (1.3)	n<5
	Total exposure to AE (outcome), years	n<5	3345	NA	1639	n<5
	Annualized rate of AE (outcome)/100 person years	n<5	1.6	NA	1.6	n<5
Patients with COPD only, definition 3	Number of patients at risk in subgroup, N (%)	127	3676	NA	1975	337
	Occurrence of AE (outcome), N (%)	n<5	49 (1.3)	NA	23 (1.2)	n<5
	Total exposure to AE (outcome), years	n<5	3055	NA	1513	n<5
	Annualized rate of AE (outcome)/100 person years	n<5	1.6	NA	1.5	n<5
"MART" regimen definition 1	Number of patients at risk in subgroup, N (%)	66	NA	NA	377	307
	Occurrence of AE (outcome), N (%)	n<5	NA	NA	n<5	n<5
	Total exposure to AE (outcome), years	n<5	NA	NA	n<5	n<5
	Annualized rate of AE (outcome)/100 person years	n<5	NA	NA	n<5	n<5
"MART" regimen definition 2	Number of patients at risk in subgroup, N (%)	6	NA	NA	102	66
	Occurrence of AE (outcome), N (%)	n<5	NA	NA	n<5	n<5
	Total exposure to AE (outcome), years	n<5	NA	NA	n<5	n<5
	Annualized rate of AE (outcome)/100 person years	n<5	NA	NA	n<5	n<5

Table 56: Type 2 diabetes mellitus evaluation by FDC ICS/LABA

5.4.2.13 Anaphylactic reactions

There were low (n<5 events) or no occurrences of anaphylactic reactions for FP/FOR in all subgroups.

		TOTAL COHORT				
Subgroup	Measure	FP/FOR	FP/SAL DPI	FP/SAL MDI	BUD/FOR	BDP/FOR
Patients aged ≥18 years with asthma	Number of patients at risk in subgroup, N (%)	2126	8898	12623	10894	7008
	Occurrence of AE (outcome), N (%)	n<5	n<5	n<5	5 (0.0)	n<5
	Total exposure to AE (outcome), years	n<5	n<5	n<5	8143	n<5
	Annualized rate of AE (outcome)/100 person years	n<5	n<5	n<5	0.1	n<5
Patients aged ≥12 and <18 years with asthma (licensed Flutiform 50/5, 125/5)	Number of patients at risk in subgroup, N (%)	77	334	861	614	NA
	Occurrence of AE (outcome), N (%)	n<5	n<5	n<5	n<5	NA
	Total exposure to AE (outcome), years	n<5	n<5	n<5	n<5	NA
	Annualized rate of AE (outcome)/100 person years	n<5	n<5	n<5	n<5	NA
	Number of patients at risk in subgroup, N (%)	8	334	861	614	NA

		TOTAL COHORT				
Subgroup	Measure	FP/FOR	FP/SAL DPI	FP/SAL MDI	BUD/FOR	BDP/FOR
Patients aged ≥12 and <18 years with asthma (off-label Flutiform 250/10)	Occurrence of AE (outcome), N (%)	n<5	n<5	n<5	n<5	NA
	Total exposure to AE (outcome), years	n<5	n<5	n<5	n<5	NA
	Annualized rate of AE (outcome)/100 person years	n<5	n<5	n<5	n<5	NA
Paediatric asthma patients 4-11 years	Number of patients at risk in subgroup, N (%)	12	150	970	230	NA
	Occurrence of AE (outcome), N (%)	n<5	n<5	n<5	n<5	NA
	Total exposure to AE (outcome), years	n<5	n<5	n<5	n<5	NA
	Annualized rate of AE (outcome)/100 person years	n<5	n<5	n<5	n<5	NA
Patients with COPD only, definition 1	Number of patients at risk in subgroup, N (%)	193	5037	NA	2768	535
	Occurrence of AE (outcome), N (%)	n<5	n<5	NA	n<5	n<5
	Total exposure to AE (outcome), years	n<5	n<5	NA	n<5	n<5
	Annualized rate of AE (outcome)/100 person years	n<5	n<5	NA	n<5	n<5
Patients with COPD only, definition 2	Number of patients at risk in subgroup, N (%)	143	4085	NA	2185	395
	Occurrence of AE (outcome), N (%)	n<5	n<5	NA	n<5	n<5
	Total exposure to AE (outcome), years	n<5	n<5	NA	n<5	n<5
	Annualized rate of AE (outcome)/100 person years	n<5	n<5	NA	n<5	n<5
Patients with COPD only, definition 3	Number of patients at risk in subgroup, N (%)	129	3739	NA	2010	347
	Occurrence of AE (outcome), N (%)	n<5	n<5	NA	n<5	n<5
	Total exposure to AE (outcome), years	n<5	n<5	NA	n<5	n<5
	Annualized rate of AE (outcome)/100 person years	n<5	n<5	NA	n<5	n<5
"MART" regimen definition 1	Number of patients at risk in subgroup, N (%)	66	NA	NA	379	308
	Occurrence of AE (outcome), N (%)	n<5	NA	NA	n<5	n<5
	Total exposure to AE (outcome), years	n<5	NA	NA	n<5	n<5
	Annualized rate of AE (outcome)/100 person years	n<5	NA	NA	n<5	n<5
"MART" regimen definition 2	Number of patients at risk in subgroup, N (%)	6	NA	NA	102	66
	Occurrence of AE (outcome), N (%)	n<5	NA	NA	n<5	n<5
	Total exposure to AE (outcome), years	n<5	NA	NA	n<5	n<5
	Annualized rate of AE (outcome)/100 person years	n<5	NA	NA	n<5	n<5

Table 57: Anaphylactic reactions evaluation by FDC ICS/LABA

5.4.2.14 Cataract diagnosis

The annualised rate of patients with cataracts was similarly low across all treatment groups in the patients with asthma age ≥18. The number of events was too low (n<5) or zero for FP/FOR in the rest of the subgroups to make comparisons.

		TOTAL COHORT				
Subgroup	Measure	FP/FOR	FP/SAL DPI	FP/SAL MDI	BUD/FOR	BDP/FOR
Patients aged ≥18 years with asthma	Number of patients at risk in subgroup, N (%)	2107	8757	12464	10796	6949
	Occurrence of AE (outcome), N (%)	11 (0.5)	88 (1.0)	97 (0.8)	60 (0.6)	37 (0.5)
	Total exposure to AE (outcome), years	846	6293	9577	8030	4644
	Annualized rate of AE (outcome)/100 person years	1.3	1.4	1.0	0.7	0.8
Patients aged ≥12 and <18 years with asthma (licensed Flutiform 50/5, 125/5)	Number of patients at risk in subgroup, N (%)	77	334	862	614	NA
	Occurrence of AE (outcome), N (%)	n<5	n<5	n<5	n<5	NA
	Total exposure to AE (outcome), years	n<5	n<5	n<5	n<5	NA
	Annualized rate of AE (outcome)/100 person years	n<5	n<5	n<5	n<5	NA
Patients aged ≥12 and <18 years with asthma (off-label Flutiform 250/10)	Number of patients at risk in subgroup, N (%)	8	334	862	614	NA
	Occurrence of AE (outcome), N (%)	n<5	n<5	n<5	n<5	NA
	Total exposure to AE (outcome), years	n<5	n<5	n<5	n<5	NA
	Annualized rate of AE (outcome)/100 person years	n<5	n<5	n<5	n<5	NA
Paediatric asthma patients 4-11 years	Number of patients at risk in subgroup, N (%)	12	150	971	230	NA
	Occurrence of AE (outcome), N (%)	n<5	n<5	n<5	n<5	NA
	Total exposure to AE (outcome), years	n<5	n<5	n<5	n<5	NA
	Annualized rate of AE (outcome)/100 person years	n<5	n<5	n<5	n<5	NA
Patients with COPD only, definition 1	Number of patients at risk in subgroup, N (%)	185	4907	NA	2707	526
	Occurrence of AE (outcome), N (%)	n<5	76 (1.5)	NA	42 (1.6)	6 (1.1)
	Total exposure to AE (outcome), years	n<5	3993	NA	2028	366
	Annualized rate of AE (outcome)/100 person years	n<5	1.9	NA	2.1	1.6
Patients with COPD only, definition 2	Number of patients at risk in subgroup, N (%)	136	3976	NA	2142	388
	Occurrence of AE (outcome), N (%)	n<5	65 (1.6)	NA	34 (1.6)	n<5
	Total exposure to AE (outcome), years	n<5	3301	NA	1642	n<5
	Annualized rate of AE (outcome)/100 person years	n<5	2.0	NA	2.1	n<5
Patients with COPD only, definition 3	Number of patients at risk in subgroup, N (%)	123	3637	NA	1971	342
	Occurrence of AE (outcome), N (%)	n<5	61 (1.7)	NA	33 (1.7)	n<5
	Total exposure to AE (outcome), years	n<5	3013	NA	1511	n<5
	Annualized rate of AE (outcome)/100 person years	n<5	2.0	NA	2.2	n<5
"MART" regimen definition 1	Number of patients at risk in subgroup, N (%)	66	NA	NA	377	307
	Occurrence of AE (outcome), N (%)	n<5	NA	NA	n<5	n<5
	Total exposure to AE (outcome), years	n<5	NA	NA	n<5	n<5
	Annualized rate of AE (outcome)/100 person years	n<5	NA	NA	n<5	n<5
"MART" regimen definition 2	Number of patients at risk in subgroup, N (%)	6	NA	NA	101	66
	Occurrence of AE (outcome), N (%)	n<5	NA	NA	n<5	n<5
	Total exposure to AE (outcome), years	n<5	NA	NA	n<5	n<5

		TOTAL COHORT				
Subgroup	Measure	FP/FOR	FP/SAL DPI	FP/SAL MDI	BUD/FOR	BDP/FOR
	Annualized rate of AE (outcome)/100 person years	n<5	NA	NA	n<5	n<5

Table 58: Cataract evaluation by FDC ICS/LABA

5.4.2.15 Glaucoma diagnosis

The annualised rate of patients with glaucoma was too low (n<5) or zero for FP/FOR in all subgroups to make comparisons.

		TOTAL COHORT				
Subgroup	Measure	FP/FOR	FP/SAL DPI	FP/SAL MDI	BUD/FOR	BDP/FOR
Patients aged ≥18 years with asthma	Number of patients at risk in subgroup, N (%)	2121	8877	12586	10871	6999
	Occurrence of AE (outcome), N (%)	n<5	23 (0.3)	20 (0.2)	13 (0.1)	8 (0.1)
	Total exposure to AE (outcome), years	n<5	6424	9724	8120	4697
	Annualized rate of AE (outcome)/100 person years	n<5	0.4	0.2	0.2	0.2
Patients aged ≥12 and <18 years with asthma (licensed Flutiform 50/5, 125/5)	Number of patients at risk in subgroup, N (%)	77	334	862	614	NA
	Occurrence of AE (outcome), N (%)	n<5	n<5	n<5	n<5	NA
	Total exposure to AE (outcome), years	n<5	n<5	n<5	n<5	NA
	Annualized rate of AE (outcome)/100 person years	n<5	n<5	n<5	n<5	NA
Patients aged ≥12 and <18 years with asthma (off-label Flutiform 250/10)	Number of patients at risk in subgroup, N (%)	8	334	862	614	NA
	Occurrence of AE (outcome), N (%)	n<5	n<5	n<5	n<5	NA
	Total exposure to AE (outcome), years	n<5	n<5	n<5	n<5	NA
	Annualized rate of AE (outcome)/100 person years	n<5	n<5	n<5	n<5	NA
Paediatric asthma patients 4-11 years	Number of patients at risk in subgroup, N (%)	12	150	971	230	NA
	Occurrence of AE (outcome), N (%)	n<5	n<5	n<5	n<5	NA
	Total exposure to AE (outcome), years	n<5	n<5	n<5	n<5	NA
	Annualized rate of AE (outcome)/100 person years	n<5	n<5	n<5	n<5	NA
Patients with COPD only, definition 1	Number of patients at risk in subgroup, N (%)	192	5023	NA	2753	530
	Occurrence of AE (outcome), N (%)	n<5	10 (0.2)	NA	10 (0.4)	n<5
	Total exposure to AE (outcome), years	n<5	4136	NA	2082	n<5
	Annualized rate of AE (outcome)/100 person years	n<5	0.2	NA	0.5	n<5
Patients with COPD only, definition 2	Number of patients at risk in subgroup, N (%)	142	4073	NA	2176	391
	Occurrence of AE (outcome), N (%)	n<5	9 (0.2)	NA	8 (0.4)	n<5
	Total exposure to AE (outcome), years	n<5	3429	NA	1684	n<5
	Annualized rate of AE (outcome)/100 person years	n<5	0.3	NA	0.5	n<5
Patients with COPD	Number of patients at risk in subgroup, N (%)	128	3728	NA	2002	344
	Occurrence of AE (outcome), N (%)	n<5	8 (0.2)	NA	8 (0.4)	n<5

		TOTAL COHORT				
Subgroup	Measure	FP/FOR	FP/SAL DPI	FP/SAL MDI	BUD/FOR	BDP/FOR
only, definition 3	Total exposure to AE (outcome), years	n<5	3136	NA	1550	n<5
	Annualized rate of AE (outcome)/100 person years	n<5	0.3	NA	0.5	n<5
"MART" regimen definition 1	Number of patients at risk in subgroup, N (%)	66	NA	NA	378	307
	Occurrence of AE (outcome), N (%)	n<5	NA	NA	n<5	n<5
	Total exposure to AE (outcome), years	n<5	NA	NA	n<5	n<5
	Annualized rate of AE (outcome)/100 person years	n<5	NA	NA	n<5	n<5
"MART" regimen definition 2	Number of patients at risk in subgroup, N (%)	6	NA	NA	102	65
	Occurrence of AE (outcome), N (%)	n<5	NA	NA	n<5	n<5
	Total exposure to AE (outcome), years	n<5	NA	NA	n<5	n<5
	Annualized rate of AE (outcome)/100 person years	n<5	NA	NA	n<5	n<5

Table 59: Glaucoma evaluation by FDC ICS/LABA

5.4.2.16 Hypokalaemia diagnosis

The annualised rate of patients with hypokalaemia was zero or too low (n<5) for FP/FOR in all subgroups to make comparisons.

		TOTAL COHORT				
Subgroup	Measure	FP/FOR	FP/SAL DPI	FP/SAL MDI	BUD/FOR	BDP/FOR
Patients aged ≥18 years with asthma	Number of patients at risk in subgroup, N (%)	2127	8890	12620	10891	7005
	Occurrence of AE (outcome), N (%)	n<5	12 (0.1)	8 (0.1)	7 (0.1)	7 (0.1)
	Total exposure to AE (outcome), years	n<5	6441	9761	8140	4700
	Annualized rate of AE (outcome)/100 person years	n<5	0.2	0.1	0.1	0.1
Patients aged ≥12 and <18 years with asthma (licensed Flutiform 50/5, 125/5)	Number of patients at risk in subgroup, N (%)	77	334	862	614	NA
	Occurrence of AE (outcome), N (%)	n<5	n<5	n<5	n<5	NA
	Total exposure to AE (outcome), years	n<5	n<5	n<5	n<5	NA
	Annualized rate of AE (outcome)/100 person years	n<5	n<5	n<5	n<5	NA
Patients aged ≥12 and <18 years with asthma (off-label Flutiform 250/10)	Number of patients at risk in subgroup, N (%)	8	334	862	614	NA
	Occurrence of AE (outcome), N (%)	n<5	n<5	n<5	n<5	NA
	Total exposure to AE (outcome), years	n<5	n<5	n<5	n<5	NA
	Annualized rate of AE (outcome)/100 person years	n<5	n<5	n<5	n<5	NA
Paediatric asthma patients 4-11 years	Number of patients at risk in subgroup, N (%)	12	150	971	230	NA
	Occurrence of AE (outcome), N (%)	n<5	n<5	n<5	n<5	NA
	Total exposure to AE (outcome), years	n<5	n<5	n<5	n<5	NA
	Annualized rate of AE (outcome)/100 person years	n<5	n<5	n<5	n<5	NA
	Number of patients at risk in subgroup, N (%)	193	5029	NA	2761	535

		TOTAL COHORT				
Subgroup	Measure	FP/FOR	FP/SAL DPI	FP/SAL MDI	BUD/FOR	BDP/FOR
Patients with COPD only, definition 1	Occurrence of AE (outcome), N (%)	n<5	8 (0.2)	NA	9 (0.3)	n<5
	Total exposure to AE (outcome), years	n<5	4139	NA	2090	n<5
	Annualized rate of AE (outcome)/100 person years	n<5	0.2	NA	0.4	n<5
Patients with COPD only, definition 2	Number of patients at risk in subgroup, N (%)	143	4080	NA	2180	395
	Occurrence of AE (outcome), N (%)	n<5	n<5	NA	7 (0.3)	n<5
	Total exposure to AE (outcome), years	n<5	n<5	NA	1690	n<5
	Annualized rate of AE (outcome)/100 person years	n<5	n<5	NA	0.4	n<5
Patients with COPD only, definition 3	Number of patients at risk in subgroup, N (%)	129	3736	NA	2005	347
	Occurrence of AE (outcome), N (%)	n<5	n<5	NA	7 (0.3)	n<5
	Total exposure to AE (outcome), years	n<5	n<5	NA	1556	n<5
	Annualized rate of AE (outcome)/100 person years	n<5	n<5	NA	0.4	n<5
"MART" regimen definition 1	Number of patients at risk in subgroup, N (%)	66	NA	NA	379	308
	Occurrence of AE (outcome), N (%)	n<5	NA	NA	n<5	n<5
	Total exposure to AE (outcome), years	n<5	NA	NA	n<5	n<5
	Annualized rate of AE (outcome)/100 person years	n<5	NA	NA	n<5	n<5
"MART" regimen definition 2	Number of patients at risk in subgroup, N (%)	6	NA	NA	102	66
	Occurrence of AE (outcome), N (%)	n<5	NA	NA	n<5	n<5
	Total exposure to AE (outcome), years	n<5	NA	NA	n<5	n<5
	Annualized rate of AE (outcome)/100 person years	n<5	NA	NA	n<5	n<5

Table 60: Hypokalaemia evaluation by FDC ICS/LABA

5.4.2.17 Diagnosis of anxiety or depression

The annualised rates of patients diagnosed with anxiety or depression were similar across all treatment groups in the subgroup of patients with asthma aged ≥18 years and COPD subgroup (definition 1). The annualised rate of patients with diagnosed with anxiety or depression was zero or too low (n<5) for FP/FOR in all other subgroups to make comparisons.

		TOTAL COHORT				
Subgroup	Measure	FP/FOR	FP/SAL DPI	FP/SAL MDI	BUD/FOR	BDP/FOR
Patients aged ≥18 years with asthma	Number of patients at risk in subgroup, N (%)	1906	7977	11280	9787	6247
	Occurrence of AE (outcome), N (%)	62 (3.3)	430 (5.4)	677 (6.0)	524 (5.4)	327 (5.2)
	Total exposure to AE (outcome), years	760	5538	8335	7025	4015
	Annualized rate of AE (outcome)/100 person years	8.2	7.8	8.1	7.5	8.1
Patients aged ≥12 and <18 years with	Number of patients at risk in subgroup, N (%)	75	326	844	597	NA
	Occurrence of AE (outcome), N (%)	n<5	12 (3.7)	17 (2.0)	16 (2.7)	NA
	Total exposure to AE (outcome), years	n<5	230	655	440	NA

		TOTAL COHORT				
Subgroup	Measure	FP/FOR	FP/SAL DPI	FP/SAL MDI	BUD/FOR	BDP/FOR
asthma (licensed Flutiform 50/5, 125/5)	Annualized rate of AE (outcome)/100 person years	n<5	5.2	2.6	3.6	NA
Patients aged ≥12 and <18 years with asthma (off-label Flutiform 250/10)	Number of patients at risk in subgroup, N (%)	7	326	844	597	NA
	Occurrence of AE (outcome), N (%)	n<5	12 (3.7)	17 (2.0)	16 (2.7)	NA
	Total exposure to AE (outcome), years	n<5	230	655	440	NA
	Annualized rate of AE (outcome)/100 person years	n<5	5.2	2.6	3.6	NA
Paediatric asthma patients 4-11 years	Number of patients at risk in subgroup, N (%)	12	150	966	228	NA
	Occurrence of AE (outcome), N (%)	n<5	n<5	n<5	n<5	NA
	Total exposure to AE (outcome), years	n<5	n<5	n<5	n<5	NA
	Annualized rate of AE (outcome)/100 person years	n<5	n<5	n<5	n<5	NA
Patients with COPD only, definition 1	Number of patients at risk in subgroup, N (%)	178	4655	NA	2534	485
	Occurrence of AE (outcome), N (%)	5 (2.8)	194 (4.2)	NA	125 (4.9)	26 (5.4)
	Total exposure to AE (outcome), years	79	3713	NA	1837	322
	Annualized rate of AE (outcome)/100 person years	6.4	5.2	NA	6.8	8.1
Patients with COPD only, definition 2	Number of patients at risk in subgroup, N (%)	135	3788	NA	2002	354
	Occurrence of AE (outcome), N (%)	n<5	141 (3.7)	NA	86 (4.3)	19 (5.4)
	Total exposure to AE (outcome), years	n<5	3101	NA	1489	251
	Annualized rate of AE (outcome)/100 person years	n<5	4.5	NA	5.8	7.6
Patients with COPD only, definition 3	Number of patients at risk in subgroup, N (%)	122	3465	NA	1842	309
	Occurrence of AE (outcome), N (%)	n<5	131 (3.8)	NA	77 (4.2)	18 (5.8)
	Total exposure to AE (outcome), years	n<5	2837	NA	1370	212
	Annualized rate of AE (outcome)/100 person years	n<5	4.6	NA	5.6	8.5
"MART" regimen definition 1	Number of patients at risk in subgroup, N (%)	58	NA	NA	348	268
	Occurrence of AE (outcome), N (%)	n<5	NA	NA	18 (5.2)	15 (5.6)
	Total exposure to AE (outcome), years	n<5	NA	NA	287	127
	Annualized rate of AE (outcome)/100 person years	n<5	NA	NA	6.3	11.8
"MART" regimen definition 2	Number of patients at risk in subgroup, N (%)	5	NA	NA	90	55
	Occurrence of AE (outcome), N (%)	n<5	NA	NA	6 (6.7)	n<5
	Total exposure to AE (outcome), years	n<5	NA	NA	72	n<5
	Annualized rate of AE (outcome)/100 person years	n<5	NA	NA	8.4	n<5

Table 61: Anxiety or depression evaluation by FDC ICS/LABA

5.4.2.18 Growth retardation

The annualised rate of patients with a record for growth retardation was zero for FP/FOR in all subgroups.

		TOTAL COHORT				
Subgroup	Measure	FP/FOR	FP/SAL DPI	FP/SAL MDI	BUD/FOR	BDP/FOR
Patients aged ≥18 years with asthma	Number of patients at risk in subgroup, N (%)	2127	8902	12628	10899	7011
	Occurrence of AE (outcome), N (%)	n<5	n<5	n<5	n<5	n<5
	Total exposure to AE (outcome), years	n<5	n<5	n<5	n<5	n<5
	Annualized rate of AE (outcome)/100 person years	n<5	n<5	n<5	n<5	n<5
Patients aged ≥12 and <18 years with asthma (licensed Flutiform 50/5, 125/5)	Number of patients at risk in subgroup, N (%)	77	334	862	614	NA
	Occurrence of AE (outcome), N (%)	n<5	n<5	n<5	n<5	NA
	Total exposure to AE (outcome), years	n<5	n<5	n<5	n<5	NA
	Annualized rate of AE (outcome)/100 person years	n<5	n<5	n<5	n<5	NA
Patients aged ≥12 and <18 years with asthma (off-label Flutiform 250/10)	Number of patients at risk in subgroup, N (%)	8	334	862	614	NA
	Occurrence of AE (outcome), N (%)	n<5	n<5	n<5	n<5	NA
	Total exposure to AE (outcome), years	n<5	n<5	n<5	n<5	NA
	Annualized rate of AE (outcome)/100 person years	n<5	n<5	n<5	n<5	NA
Paediatric asthma patients 4-11 years	Number of patients at risk in subgroup, N (%)	12	150	971	230	NA
	Occurrence of AE (outcome), N (%)	n<5	n<5	n<5	n<5	NA
	Total exposure to AE (outcome), years	n<5	n<5	n<5	n<5	NA
	Annualized rate of AE (outcome)/100 person years	n<5	n<5	n<5	n<5	NA
Patients with COPD only, definition 1	Number of patients at risk in subgroup, N (%)	193	5038	NA	2768	535
	Occurrence of AE (outcome), N (%)	n<5	n<5	NA	n<5	n<5
	Total exposure to AE (outcome), years	n<5	n<5	NA	n<5	n<5
	Annualized rate of AE (outcome)/100 person years	n<5	n<5	NA	n<5	n<5
Patients with COPD only, definition 2	Number of patients at risk in subgroup, N (%)	143	4085	NA	2185	395
	Occurrence of AE (outcome), N (%)	n<5	n<5	NA	n<5	n<5
	Total exposure to AE (outcome), years	n<5	n<5	NA	n<5	n<5
	Annualized rate of AE (outcome)/100 person years	n<5	n<5	NA	n<5	n<5
Patients with COPD only, definition 3	Number of patients at risk in subgroup, N (%)	129	3739	NA	2010	347
	Occurrence of AE (outcome), N (%)	n<5	n<5	NA	n<5	n<5
	Total exposure to AE (outcome), years	n<5	n<5	NA	n<5	n<5
	Annualized rate of AE (outcome)/100 person years	n<5	n<5	NA	n<5	n<5
"MART" regimen definition 1	Number of patients at risk in subgroup, N (%)	66	NA	NA	379	308
	Occurrence of AE (outcome), N (%)	n<5	NA	NA	n<5	n<5
	Total exposure to AE (outcome), years	n<5	NA	NA	n<5	n<5
	Annualized rate of AE (outcome)/100 person years	n<5	NA	NA	n<5	n<5
"MART" regimen definition 2	Number of patients at risk in subgroup, N (%)	6	NA	NA	102	66
	Occurrence of AE (outcome), N (%)	n<5	NA	NA	n<5	n<5
	Total exposure to AE (outcome), years	n<5	NA	NA	n<5	n<5

		TOTAL COHORT				
Subgroup	Measure	FP/FOR	FP/SAL DPI	FP/SAL MDI	BUD/FOR	BDP/FOR
	Annualized rate of AE (outcome)/100 person years	n<5	NA	NA	n<5	n<5

Table 62: Growth retardation evaluation by FDC ICS/LABA

5.4.2.19 Decrease in bone mineral density*

The annualised rate of patients with a record for decreased bone mineral density was zero or too low (n<5) for FP/FOR in all subgroups to make comparisons.

		TOTAL COHORT				
Subgroup	Measure	FP/FOR	FP/SAL DPI	FP/SAL MDI	BUD/FOR	BDP/FOR
Patients aged ≥18 years with asthma	Number of patients at risk in subgroup, N (%)	2113	8773	12509	10807	6955
	Occurrence of AE (outcome), N (%)	n<5	66 (0.8)	78 (0.6)	64 (0.6)	36 (0.5)
	Total exposure to AE (outcome), years	n<5	6319	9612	8029	4657
	Annualized rate of AE (outcome)/100 person years	n<5	1.0	0.8	0.8	0.8
Patients aged ≥12 and <18 years with asthma (licensed Flutiform 50/5, 125/5)	Number of patients at risk in subgroup, N (%)	77	334	862	614	NA
	Occurrence of AE (outcome), N (%)	n<5	n<5	n<5	n<5	NA
	Total exposure to AE (outcome), years	n<5	n<5	n<5	n<5	NA
	Annualized rate of AE (outcome)/100 person years	n<5	n<5	n<5	n<5	NA
Patients aged ≥12 and <18 years with asthma (off-label Flutiform 250/10)	Number of patients at risk in subgroup, N (%)	8	334	862	614	NA
	Occurrence of AE (outcome), N (%)	n<5	n<5	n<5	n<5	NA
	Total exposure to AE (outcome), years	n<5	n<5	n<5	n<5	NA
	Annualized rate of AE (outcome)/100 person years	n<5	n<5	n<5	n<5	NA
Paediatric asthma patients 4-11 years	Number of patients at risk in subgroup, N (%)	12	150	971	230	NA
	Occurrence of AE (outcome), N (%)	n<5	n<5	n<5	n<5	NA
	Total exposure to AE (outcome), years	n<5	n<5	n<5	n<5	NA
	Annualized rate of AE (outcome)/100 person years	n<5	n<5	n<5	n<5	NA
Patients with COPD only, definition 1	Number of patients at risk in subgroup, N (%)	193	4970	NA	2718	526
	Occurrence of AE (outcome), N (%)	n<5	78 (1.6)	NA	30 (1.1)	5 (1.0)
	Total exposure to AE (outcome), years	n<5	4047	NA	2047	366
	Annualized rate of AE (outcome)/100 person years	n<5	1.9	NA	1.5	1.4
Patients with COPD only, definition 2	Number of patients at risk in subgroup, N (%)	143	4033	NA	2149	390
	Occurrence of AE (outcome), N (%)	n<5	61 (1.5)	NA	22 (1.0)	n<5
	Total exposure to AE (outcome), years	n<5	3360	NA	1657	n<5

* Diagnosis codes for osteoporosis (including reduction in bone mineral density), diagnosis codes for related complications (fragility fractures [typically vertebral, femur, neck and wrist fractures] or hip fractures)

		TOTAL COHORT				
Subgroup	Measure	FP/FOR	FP/SAL DPI	FP/SAL MDI	BUD/FOR	BDP/FOR
	Annualized rate of AE (outcome)/100 person years	n<5	1.8	NA	1.3	n<5
Patients with COPD only, definition 3	Number of patients at risk in subgroup, N (%)	129	3691	NA	1978	343
	Occurrence of AE (outcome), N (%)	n<5	58 (1.6)	NA	21 (1.1)	n<5
	Total exposure to AE (outcome), years	n<5	3070	NA	1527	n<5
	Annualized rate of AE (outcome)/100 person years	n<5	1.9	NA	1.4	n<5
"MART" regimen definition 1	Number of patients at risk in subgroup, N (%)	66	NA	NA	378	306
	Occurrence of AE (outcome), N (%)	n<5	NA	NA	n<5	n<5
	Total exposure to AE (outcome), years	n<5	NA	NA	n<5	n<5
	Annualized rate of AE (outcome)/100 person years	n<5	NA	NA	n<5	n<5
"MART" regimen definition 2	Number of patients at risk in subgroup, N (%)	6	NA	NA	101	65
	Occurrence of AE (outcome), N (%)	n<5	NA	NA	n<5	n<5
	Total exposure to AE (outcome), years	n<5	NA	NA	n<5	n<5
	Annualized rate of AE (outcome)/100 person years	n<5	NA	NA	n<5	n<5

Table 63: Decrease in bone mineral density evaluation by FDC ICS/LABA

5.4.2.20 All new events*

The annualised rate of patients with new events was similar across all treatment groups in patients aged ≥18 with asthma and patients with COPD (definition 1 and 2). Across all other subgroups, rates of events for FP/FOR were zero or too low to be compared. The number of records of all new adverse events was similarly low in all treatment groups across all subgroups, although the duration of exposure was lower for FP/FOR.

		TOTAL COHORT				
Subgroup	Measure	FP/FOR	FP/SAL DPI	FP/SAL MDI	BUD/FOR	BDP/FOR
Patients aged ≥18 years with asthma	Number of patients at risk in subgroup, N (%)	2127	8902	12629	10899	7011
	Occurrence of AE (outcome), N (%)	157 (7.4)	1402 (15.7)	1945 (15.4)	1498 (13.7)	865 (12.3)
	Total exposure to AE (outcome), years	810	5521	8436	7124	4170
	Annualized rate of AE (outcome)/100 person years	19.4	25.4	23.1	21.0	20.7
	Number of times AE occurred per patient, mean (SD)	0.1 (0.3)	0.2 (0.5)	0.2 (0.5)	0.2 (0.5)	0.1 (0.4)
	Number of times AE occurred per patient, median (IQR)	0 (0, 0)	0 (0, 0)	0 (0, 0)	0 (0, 0)	0 (0, 0)
	Number of times AE occurred per patient, (min,max)	(0, 3)	(0, 5)	(0, 4)	(0, 5)	(0, 4)
	Duration of exposure, months, mean (SD)	4.6 (4.0)	7.4 (7.3)	8.0 (7.4)	7.8 (7.3)	7.1 (6.9)
	Duration of exposure, months, median (IQR)	3.2 (1.4, 7.0)	4.5 (1.7, 12.1)	5.3 (2.0, 13.0)	5.1 (2.0, 12.9)	4.5 (1.8, 11.2)

* Count of any adverse event that occurred for the first time ever in the patient's record after initiation of FP/FOR or FDC ICS/LABA

		TOTAL COHORT				
Subgroup	Measure	FP/FOR	FP/SAL DPI	FP/SAL MDI	BUD/FOR	BDP/FOR
	Duration of exposure, months, (min,max)	(0, 19)	(0, 27)	(0, 27)	(0, 27)	(0, 27)
Patients aged ≥12 and <18 years with asthma (licensed Flutiform 50/5, 125/5)	Number of patients at risk in subgroup, N (%)	77	334	862	614	NA
	Occurrence of AE (outcome), N (%)	n<5	23 (6.9)	52 (6.0)	35 (5.7)	NA
	Total exposure to AE (outcome), years	n<5	229	645	441	NA
	Annualized rate of AE (outcome)/100 person years	n<5	10.0	8.1	7.9	NA
	Number of times AE occurred per patient, mean (SD)	0.0 (0.2)	0.1 (0.3)	0.1 (0.3)	0.1 (0.3)	NA
	Number of times AE occurred per patient, median (IQR)	0 (0, 0)	0 (0, 0)	0 (0, 0)	0 (0, 0)	NA
	Number of times AE occurred per patient, (min,max)	(0, 1)	(0, 2)	(0, 2)	(0, 2)	NA
	Duration of exposure, months, mean (SD)	5.3 (4.6)	8.2 (7.8)	9.0 (7.8)	8.6 (7.6)	NA
	Duration of exposure, months, median (IQR)	4.2 (1.7, 8.9)	5.2 (2.0, 13.7)	6.5 (2.0, 15.0)	5.7 (2.0, 14.3)	NA
	Duration of exposure, months, (min,max)	(0, 15)	(0, 27)	(0, 27)	(0, 27)	NA
Patients aged ≥12 and <18 years with asthma (off-label Flutiform 250/10)	Number of patients at risk in subgroup, N (%)	8	334	862	614	NA
	Occurrence of AE (outcome), N (%)	n<5	23 (6.9)	52 (6.0)	35 (5.7)	NA
	Total exposure to AE (outcome), years	n<5	229	645	441	NA
	Annualized rate of AE (outcome)/100 person years	n<5	10.0	8.1	7.9	NA
	Number of times AE occurred per patient, mean (SD)	0.3 (0.5)	0.1 (0.3)	0.1 (0.3)	0.1 (0.3)	NA
	Number of times AE occurred per patient, median (IQR)	0 (0, 1)	0 (0, 0)	0 (0, 0)	0 (0, 0)	NA
	Number of times AE occurred per patient, (min,max)	(0, 1)	(0, 2)	(0, 2)	(0, 2)	NA
	Duration of exposure, months, mean (SD)	5.3 (4.0)	8.2 (7.8)	9.0 (7.8)	8.6 (7.6)	NA
	Duration of exposure, months, median (IQR)	4.2 (2.4, 7.7)	5.2 (2.0, 13.7)	6.5 (2.0, 15.0)	5.7 (2.0, 14.3)	NA
	Duration of exposure, months, (min,max)	(1.1, 12.2)	(0, 27)	(0, 27)	(0, 27)	NA
Paediatric asthma patients 4-11 years	Number of patients at risk in subgroup, N (%)	12	150	971	230	NA
	Occurrence of AE (outcome), N (%)	n<5	10 (6.7)	49 (5.0)	10 (4.3)	NA
	Total exposure to AE (outcome), years	n<5	104	767	173	NA
	Annualized rate of AE (outcome)/100 person years	n<5	9.6	6.4	5.8	NA
	Number of times AE occurred per patient, mean (SD)	0.0 (0.0)	0.1 (0.3)	0.1 (0.2)	0.0 (0.2)	NA
	Number of times AE occurred per patient, median (IQR)	0 (0, 0)	0 (0, 0)	0 (0, 0)	0 (0, 0)	NA
	Number of times AE occurred per patient, (min,max)	(0, 0)	(0, 2)	(0, 2)	(0, 2)	NA
	Duration of exposure, months, mean (SD)	2.1 (2.3)	8.3 (8.0)	9.5 (7.8)	9.0 (7.6)	NA
	Duration of exposure, months, median (IQR)	1.8 (0.2, 3.2)	5.2 (1.3, 14.4)	7.5 (2.3, 15.5)	7.4 (2.0, 14.1)	NA
	Duration of exposure, months, (min,max)	(0, 6)	(0, 26)	(0, 27)	(0, 26)	NA

		TOTAL COHORT				
Subgroup	Measure	FP/FOR	FP/SAL DPI	FP/SAL MDI	BUD/FOR	BDP/FOR
Patients with COPD only, definition 1	Number of patients at risk in subgroup, N (%)	193	5038	NA	2768	535
	Occurrence of AE (outcome), N (%)	25 (13.0)	1040 (20.6)	NA	528 (19.1)	102 (19.1)
	Total exposure to AE (outcome), years	81	3485	NA	1757	317
	Annualized rate of AE (outcome)/100 person years	31.1	29.8	NA	30.1	32.2
	Number of times AE occurred per patient, mean (SD)	0.2 (0.5)	0.3 (0.6)	NA	0.2 (0.6)	0.2 (0.5)
	Number of times AE occurred per patient, median (IQR)	0 (0, 0)	0 (0, 0)	NA	0 (0, 0)	0 (0, 0)
	Number of times AE occurred per patient, (min,max)	(0, 3)	(0, 5)	NA	(0, 4)	(0, 3)
	Duration of exposure, months, mean (SD)	5.0 (4.8)	8.3 (7.5)	NA	7.6 (7.1)	7.1 (6.9)
	Duration of exposure, months, median (IQR)	2.9 (1.3, 7.8)	5.8 (2.0, 13.3)	NA	5.0 (2.0, 12.1)	4.3 (1.8, 11.9)
	Duration of exposure, months, (min,max)	(0, 16)	(0, 27)	NA	(0, 27)	(0, 27)
Patients with COPD only, definition 2	Number of patients at risk in subgroup, N (%)	143	4085	NA	2185	395
	Occurrence of AE (outcome), N (%)	17 (11.9)	783 (19.2)	NA	403 (18.4)	83 (21.0)
	Total exposure to AE (outcome), years	61	2928	NA	1433	245
	Annualized rate of AE (outcome)/100 person years	28.0	26.7	NA	28.1	33.9
	Number of times AE occurred per patient, mean (SD)	0.2 (0.5)	0.2 (0.5)	NA	0.2 (0.5)	0.2 (0.5)
	Number of times AE occurred per patient, median (IQR)	0 (0, 0)	0 (0, 0)	NA	0 (0, 0)	0 (0, 0)
	Number of times AE occurred per patient, (min,max)	(0, 3)	(0, 5)	NA	(0, 4)	(0, 3)
	Duration of exposure, months, mean (SD)	5.1 (4.8)	8.6 (7.6)	NA	7.9 (7.2)	7.4 (7.3)
	Duration of exposure, months, median (IQR)	3.2 (1.3, 8.0)	6.3 (2.0, 13.7)	NA	5.3 (2.0, 12.5)	4.3 (1.9, 12.4)
	Duration of exposure, months, (min,max)	(0, 16)	(0, 27)	NA	(0, 27)	(0, 27)
Patients with COPD only, definition 3	Number of patients at risk in subgroup, N (%)	129	3739	NA	2010	347
	Occurrence of AE (outcome), N (%)	15 (11.6)	717 (19.2)	NA	373 (18.6)	69 (19.9)
	Total exposure to AE (outcome), years	52	2684	NA	1318	211
	Annualized rate of AE (outcome)/100 person years	28.7	26.7	NA	28.3	32.8
	Number of times AE occurred per patient, mean (SD)	0.2 (0.5)	0.2 (0.5)	NA	0.2 (0.5)	0.2 (0.5)
	Number of times AE occurred per patient, median (IQR)	0 (0, 0)	0 (0, 0)	NA	0 (0, 0)	0 (0, 0)
	Number of times AE occurred per patient, (min,max)	(0, 3)	(0, 5)	NA	(0, 4)	(0, 3)
	Duration of exposure, months, mean (SD)	4.9 (4.7)	8.6 (7.6)	NA	7.9 (7.2)	7.3 (7.2)
	Duration of exposure, months, median (IQR)	2.8 (1.3, 7.8)	6.2 (2.0, 13.8)	NA	5.3 (2.0, 12.5)	4.2 (1.8, 12.3)
	Duration of exposure, months, (min,max)	(0, 16)	(0, 27)	NA	(0, 27)	(0, 26)
	Number of patients at risk in subgroup, N (%)	66	NA	NA	379	308

		TOTAL COHORT				
Subgroup	Measure	FP/FOR	FP/SAL DPI	FP/SAL MDI	BUD/FOR	BDP/FOR
"MART" regimen definition 1	Occurrence of AE (outcome), N (%)	n<5	NA	NA	56 (14.8)	32 (10.4)
	Total exposure to AE (outcome), years	n<5	NA	NA	284	138
	Annualized rate of AE (outcome)/100 person years	n<5	NA	NA	19.7	23.2
	Number of times AE occurred per patient, mean (SD)	0.0 (0.1)	NA	NA	0.2 (0.5)	0.1 (0.3)
	Number of times AE occurred per patient, median (IQR)	0 (0, 0)	NA	NA	0 (0, 0)	0 (0, 0)
	Number of times AE occurred per patient, (min,max)	(0, 1)	NA	NA	(0, 3)	(0, 2)
	Duration of exposure, months, mean (SD)	4.2 (3.7)	NA	NA	9.0 (8.1)	5.4 (5.8)
	Duration of exposure, months, median (IQR)	3.1 (1.3, 6.2)	NA	NA	6.1 (2.0, 15.3)	2.8 (1.3, 8.0)
	Duration of exposure, months, (min,max)	(0, 15)	NA	NA	(0, 27)	(0, 26)
"MART" regimen definition 2	Number of patients at risk in subgroup, N (%)	6	NA	NA	102	66
	Occurrence of AE (outcome), N (%)	n<5	NA	NA	12 (11.8)	6 (9.1)
	Total exposure to AE (outcome), years	n<5	NA	NA	74	28
	Annualized rate of AE (outcome)/100 person years	n<5	NA	NA	16.2	21.2
	Number of times AE occurred per patient, mean (SD)	0.0 (0.0)	NA	NA	0.1 (0.5)	0.1 (0.3)
	Number of times AE occurred per patient, median (IQR)	0 (0, 0)	NA	NA	0 (0, 0)	0 (0, 0)
	Number of times AE occurred per patient, (min,max)	(0, 0)	NA	NA	(0, 3)	(0, 1)
	Duration of exposure, months, mean (SD)	3.4 (2.4)	NA	NA	8.7 (8.1)	5.1 (5.7)
	Duration of exposure, months, median (IQR)	2.0 (2.0, 6.4)	NA	NA	5.9 (2.0, 13.2)	2.6 (1.6, 7.3)
	Duration of exposure, months, (min,max)	(1.5, 6.5)	NA	NA	(0, 26)	(0, 22)

Table 64: All new events evaluation by FDC ICS/LABA

5.4.3 Serious adverse events

5.4.3.1 Adverse events which result in hospitalisations

The annualised rate of patients with adverse events that result in hospitalisation were broadly similar across treatment groups in the subgroups of patients with asthma aged ≥18 years and in patients with COPD (definition 1). In other subgroups, the rate of events was zero or too low in the FP/FOR group to be compared to other treatment groups.

Subgroup	Measure	FP/FOR	FP/SAL DPI	FP/SAL MDI	BUD/FOR	BDP/FOR
Patients aged ≥18 years	Number of patients at risk in subgroup, N (%)	1123 (100)	5465 (100)	7480 (100)	6468 (100)	4202 (100)
	Occurrence of AE (outcome), N (%)	37 (3.3)	681 (12.5)	664 (8.9)	441 (6.8)	226 (5.4)

with asthma	Total exposure to AE (outcome), years	411.4	3430.87	5284.08	4422.97	2692.96
	Annualized rate of AE (outcome)/100 person years	9	19.8	12.6	10	8.4
Patients aged ≥12 and <18 years with asthma (licensed Flutiform 50/5, 125/5)	Number of patients at risk in subgroup, N (%)	44 (100)	169 (100)	516 (100)	353 (100)	n<5
	Occurrence of AE (outcome), N (%)	n<5	n<5	n<5	n<5	n<5
	Total exposure to AE (outcome), years	n<5	n<5	n<5	n<5	n<5
	Annualized rate of AE (outcome)/100 person years	n<5	n<5	n<5	n<5	n<5
Patients aged ≥12 and <18 years with asthma (off-label Flutiform 250/10)	Number of patients at risk in subgroup, N (%)	n<5	169 (100)	516 (100)	353 (100)	n<5
	Occurrence of AE (outcome), N (%)	n<5	n<5	n<5	n<5	n<5
	Total exposure to AE (outcome), years	n<5	n<5	n<5	n<5	n<5
	Annualized rate of AE (outcome)/100 person years	n<5	n<5	n<5	n<5	n<5
Paediatric asthma patients 4-11 years	Number of patients at risk in subgroup, N (%)	8 (100)	89 (100)	587 (100)	139 (100)	n<5
	Occurrence of AE (outcome), N (%)	n<5	n<5	10 (1.7)	n<5	n<5
	Total exposure to AE (outcome), years	n<5	n<5	448.89	n<5	n<5
	Annualized rate of AE (outcome)/100 person years	n<5	n<5	2.2	n<5	n<5
Patients with COPD only, definition 1	Number of patients at risk in subgroup, N (%)	89 (100)	3084 (100)	n<5	1670 (100)	299 (100)
	Occurrence of AE (outcome), N (%)	11 (12.4)	718 (23.3)	n<5	354 (21.2)	46 (15.4)
	Total exposure to AE (outcome), years	28.45	2105.51	n<5	1049.65	181.82
	Annualized rate of AE (outcome)/100 person years	38.7	34.1	n<5	33.7	25.3
Patients with COPD only, definition 2	Number of patients at risk in subgroup, N (%)	60 (100)	2490 (100)	n<5	1315 (100)	231 (100)
	Occurrence of AE (outcome), N (%)	8 (13.3)	542 (21.8)	n<5	268 (20.4)	34 (14.7)
	Total exposure to AE (outcome), years	19.79	1742.64	n<5	859.13	151.6
	Annualized rate of AE (outcome)/100 person years	40.4	31.1	n<5	31.2	22.4
Patients with COPD only, definition 3	Number of patients at risk in subgroup, N (%)	56 (100)	2267 (100)	n<5	1201 (100)	201 (100)
	Occurrence of AE (outcome), N (%)	8 (14.3)	483 (21.3)	n<5	247 (20.6)	29 (14.4)
	Total exposure to AE (outcome), years	18.61	1590.17	n<5	786.67	125.91
	Annualized rate of AE (outcome)/100 person years	43	30.4	n<5	31.4	23
"MART" regimen definition 1	Number of patients at risk in subgroup, N (%)	47 (100)	n<5	n<5	253 (100)	199 (100)
	Occurrence of AE (outcome), N (%)	n<5	n<5	n<5	9 (3.6)	5 (2.5)
	Total exposure to AE (outcome), years	n<5	n<5	n<5	197.83	90.37
	Annualized rate of AE (outcome)/100 person years	n<5	n<5	n<5	4.5	5.5
"MART" regimen definition 2	Number of patients at risk in subgroup, N (%)	n<5	n<5	n<5	63 (100)	40 (100)
	Occurrence of AE (outcome), N (%)	n<5	n<5	n<5	n<5	n<5
	Total exposure to AE (outcome), years	n<5	n<5	n<5	n<5	n<5
	Annualized rate of AE (outcome)/100 person years	n<5	n<5	n<5	n<5	n<5

Table 65: Serious adverse events resulting in hospitalizations by FDC ICS/LABA

For the serious adverse events which resulted in inpatient hospitalisation and were analysed separately due to ≥5 events available, hospitalisations relating to COPD were slightly higher

for patients with COPD (definitions 2 and 3). For all other serious adverse events presented, patients prescribed FP/FOR had similar rates of SAEs to FDC ICS/LABA comparators.

Table	Subgroup	Measure	FP/FOR	FP/SAL DPI	FP/SAL MDI	BUD/FOR	BDP/FOR
SAE Hospitalisations - COPD	Patients with COPD only, definition 1	Number of patients at risk in subgroup, N (%)	89 (100)	3084 (100)	n<5	1670 (100)	299 (100)
		Occurrence of AE (baseline), N (%)	8 (9.0)	669 (21.7)	n<5	320 (19.2)	42 (14.0)
		Total exposure to AE (baseline), years	28.56	2145.6	n<5	1068.53	184.27
		Annualized rate of AE (baseline)/100 person years	28	31.2	n<5	29.9	22.8
	Patients with COPD only, definition 2	Number of patients at risk in subgroup, N (%)	60 (100)	2490 (100)	n<5	1315 (100)	231 (100)
		Occurrence of AE (baseline), N (%)	7 (11.7)	507 (20.4)	n<5	242 (18.4)	32 (13.9)
		Total exposure to AE (baseline), years	19.8	1770.49	n<5	871.52	153.62
		Annualized rate of AE (baseline)/100 person years	35.3	28.6	n<5	27.8	20.8
	Patients with COPD only, definition 3	Number of patients at risk in subgroup, N (%)	56 (100)	2267 (100)	n<5	1201 (100)	201 (100)
		Occurrence of AE (baseline), N (%)	7 (12.5)	456 (20.1)	n<5	223 (18.6)	27 (13.4)
		Total exposure to AE (baseline), years	18.63	1612.26	n<5	797.16	127.92
		Annualized rate of AE (baseline)/100 person years	37.6	28.3	n<5	28	21.1
SAE Hospitalisations - Lower respiratory tract infection (including pneumonia)	Patients aged ≥18 years with asthma	Number of patients at risk in subgroup, N (%)	1123 (100)	5465 (100)	7480 (100)	6468 (100)	4202 (100)
		Occurrence of AE (baseline), N (%)	17 (1.5)	317 (5.8)	289 (3.9)	174 (2.7)	69 (1.6)
		Total exposure to AE (baseline), years	415.93	3667.27	5520.47	4593.68	2792.02
		Annualized rate of AE (baseline)/100 person years	4.1	8.6	5.2	3.8	2.5
SAE Hospitalisations - Pneumonia	Patients aged ≥18 years with asthma	Number of patients at risk in subgroup, N (%)	1123 (100)	5465 (100)	7480 (100)	6468 (100)	4202 (100)
		Occurrence of AE (outcome), N (%)	7 (0.6)	139 (2.5)	141 (1.9)	64 (1.0)	25 (0.6)
		Total exposure to AE (outcome), years	418.75	3766.04	5593.67	4664.54	2813.94
		Annualized rate of AE (outcome)/100 person years	1.7	3.7	2.5	1.4	0.9
SAE Hospitalisations - Cardiac arrhythmias and ischemia	Patients aged ≥18 years with asthma	Number of patients at risk in subgroup, N (%)	1123 (100)	5465 (100)	7480 (100)	6468 (100)	4202 (100)
		Occurrence of AE (outcome), N (%)	18 (1.6)	273 (5.0)	310 (4.1)	200 (3.1)	89 (2.1)
		Total exposure to AE (outcome), years	415.85	3673.77	5484.07	4568.12	2776.42
		Annualized rate of AE (outcome)/100 person years	4.3	7.4	5.7	4.4	3.2
SAE Hospitalisations - New onset of diabetes mellitus	Patients aged ≥18 years with asthma	Number of patients at risk in subgroup, N (%)	1123 (100)	5465 (100)	7480 (100)	6468 (100)	4202 (100)
		Occurrence of AE (outcome), N (%)	7 (0.6)	137 (2.5)	147 (2.0)	98 (1.5)	52 (1.2)
		Total exposure to AE (outcome), years	418.59	3750.01	5565.36	4640.02	2786.25
		Annualized rate of AE (outcome)/100 person years	1.7	3.7	2.6	2.1	1.9

Table 66: Serious adverse events resulting in hospitalisations by FDC ICS/LABA for SAE occurrence ≥5

5.4.3.2 Result in death

For all subgroups, SAEs causing death were low (n<5) or zero for FP/FOR.

Subgroup	Measure	FP/FOR	FP/SAL DPI	FP/SAL MDI	BUD/FOR	BDP/FOR
Patients aged ≥18 years with asthma	Number of patients at risk in subgroup, N (%)	1123 (100)	5465 (100)	7480 (100)	6468 (100)	4202 (100)
	Occurrence of AE (outcome), N (%)	n<5	80 (1.5)	82 (1.1)	22 (0.3)	11 (0.3)
	Total exposure to AE (outcome), years	n<5	3835.29	5654.57	4698.77	2822.66
	Annualized rate of AE (outcome)/100 person years	n<5	2.1	1.5	0.5	0.4
Patients aged ≥12 and <18 years with asthma (licensed Flutiform 50/5, 125/5)	Number of patients at risk in subgroup, N (%)	44 (100)	169 (100)	516 (100)	353 (100)	n<5
	Occurrence of AE (outcome), N (%)	n<5	n<5	n<5	n<5	n<5
	Total exposure to AE (outcome), years	n<5	n<5	n<5	n<5	n<5
	Annualized rate of AE (outcome)/100 person years	n<5	n<5	n<5	n<5	n<5
Patients aged ≥12 and <18 years with asthma (off-label Flutiform 250/10)	Number of patients at risk in subgroup, N (%)	n<5	169 (100)	516 (100)	353 (100)	n<5
	Occurrence of AE (outcome), N (%)	n<5	n<5	n<5	n<5	n<5
	Total exposure to AE (outcome), years	n<5	n<5	n<5	n<5	n<5
	Annualized rate of AE (outcome)/100 person years	n<5	n<5	n<5	n<5	n<5
Paediatric asthma patients 4-11 years	Number of patients at risk in subgroup, N (%)	8 (100)	89 (100)	587 (100)	139 (100)	n<5
	Occurrence of AE (outcome), N (%)	n<5	n<5	n<5	n<5	n<5
	Total exposure to AE (outcome), years	n<5	n<5	n<5	n<5	n<5
	Annualized rate of AE (outcome)/100 person years	n<5	n<5	n<5	n<5	n<5
Patients with COPD only, definition 1	Number of patients at risk in subgroup, N (%)	89 (100)	3084 (100)	n<5	1670 (100)	299 (100)
	Occurrence of AE (outcome), N (%)	n<5	117 (3.8)	n<5	53 (3.2)	8 (2.7)
	Total exposure to AE (outcome), years	n<5	2528.69	n<5	1245.28	205.16
	Annualized rate of AE (outcome)/100 person years	n<5	4.6	n<5	4.3	3.9
Patients with COPD only, definition 2	Number of patients at risk in subgroup, N (%)	60 (100)	2490 (100)	n<5	1315 (100)	231 (100)
	Occurrence of AE (outcome), N (%)	n<5	76 (3.1)	n<5	34 (2.6)	n<5
	Total exposure to AE (outcome), years	n<5	2079.58	n<5	1005.99	n<5
	Annualized rate of AE (outcome)/100 person years	n<5	3.7	n<5	3.4	n<5
Patients with COPD only, definition 3	Number of patients at risk in subgroup, N (%)	56 (100)	2267 (100)	n<5	1201 (100)	201 (100)
	Occurrence of AE (outcome), N (%)	n<5	69 (3.0)	n<5	31 (2.6)	n<5
	Total exposure to AE (outcome), years	n<5	1892.22	n<5	922.21	n<5
	Annualized rate of AE (outcome)/100 person years	n<5	3.6	n<5	3.4	n<5
"MART" regimen definition 1	Number of patients at risk in subgroup, N (%)	47 (100)	n<5	n<5	253 (100)	199 (100)
	Occurrence of AE (outcome), N (%)	n<5	n<5	n<5	n<5	n<5
	Total exposure to AE (outcome), years	n<5	n<5	n<5	n<5	n<5
	Annualized rate of AE (outcome)/100 person years	n<5	n<5	n<5	n<5	n<5
"MART" regimen definition 2	Number of patients at risk in subgroup, N (%)	n<5	n<5	n<5	63 (100)	40 (100)
	Occurrence of AE (outcome), N (%)	n<5	n<5	n<5	n<5	n<5
	Total exposure to AE (outcome), years	n<5	n<5	n<5	n<5	n<5
	Annualized rate of AE (outcome)/100 person years	n<5	n<5	n<5	n<5	n<5

Table 67: Serious adverse events resulting in death by FDC ICS/LABA

Number of SAEs relating to death were too low for any of the SAEs to be analysed separately.

5.5 Other analyses

Patient characterisation and adverse events analyses were split by initiators and switchers of FDC ICS/LABA therapy (see Appendix).

We observed a higher rate of patients experiencing LRTIs, in switching patients with asthma aged 12-18 years (28.9 per 100 person years for FP/FOR prescribed on-label versus 5.5-12.0 per 100 person years for licensed comparators) and patients with COPD (57.4 per 100 person years for FP/FOR versus 44.4-54.7 per 100 person years for licensed comparators, for definition 1 of COPD), although numbers in these subgroups were small (n=35 for FP/FOR for patients with asthma aged 12-18 years and n=110 for patients with COPD definition 1). Furthermore, the time to first event was not significantly different between FP/FOR and licensed comparators for patients with COPD and could not be calculated for patients with asthma aged 12-18 due to low numbers of events. For patients with asthma aged ≥18, rates of LRTIs were similar and the time to the first was not significantly different between treatment groups. Rates were low for patients with asthma aged 4-11 and patients in the MART regimen.

Rates of patients experiencing hyperglycaemia for those with no hyperglycaemia or type 2 diabetes in the baseline period were similarly low for FP/FPR compared to other FDC ICS/LABAs for both initiator and switcher patients with asthma aged ≥18 and too low for reporting or zero for all other subgroups. Rates of onset of type 2 diabetes mellitus were low (n<5) or zero for all treatment groups across all subgroups except for switching patients with asthma aged ≥18, where the rate for FP/FOR was slightly higher (1.9 per 100 person years for FP/FOR versus 0.9-1.2 per 100 person years for licensed comparators).

For patients with at least 1 year of baseline and 1 year of outcome period and at least 6 months of baseline and 6 months of outcome period, there were <5 patients in the initiating and switching FP/FOR groups experiencing the event and so annualised rates of COPD exacerbations could not be compared.

Rates of pneumonia were similar for FP/FOR compared to other FDC ICS/LABAs for those aged ≥18 with asthma and were too low for reporting or zero for FP/FOR for all other subgroups. For tuberculosis and pulmonary embolism, the rate of events during the outcome was low (n<5) or zero for all treatment groups across all subgroups and therefore, the hazard ratios were not be presented due to <10 events in the FP/FOR group in each of the subgroups.

For all new adverse events and anxiety and depression, rates were similarly low for patients with asthma aged ≥18 in both initiator and switcher groups and rates were too low for reporting or zero for all other subgroups studied.

For five of the adverse events studied (oral candidiasis, local oral adverse events, adrenal failure, cardiac arrhythmias and ischaemia and cataracts) the rate of adverse events in those without an event of that kind at baseline was similarly low for FP/FOR and other FDC ICS/LABAs for switching patients with asthma aged ≥18 and was too low for reporting or zero for all other switching subgroups studied (for initiators, rates of events was too low for reporting or zero for all subgroups). For six of the adverse events studied (dysphonia/hoarse voice, anaphylactic reactions, glaucoma, hypokalaemia, growth retardation and bone mineral density) the rate of events adverse events in those without an event of that kind at baseline was too low for reporting or zero for all subgroups studied, in both initiators and switchers.

The annualised rate of patients with adverse events that result in hospitalisation were broadly similar to at least one of the comparator FDC ICS/LABAs, too low for reporting (n<5) or zero for FP/FOR compared to other FDC ICS/LABAs in all subgroups. Hospitalisations relating to COPD were higher for switcher patients prescribed FP/FOR compared to other FDC ICS/LABA treatments for all three definitions of COPD (21.0 per 100 person years for FP/FOR versus 7.7-12.5 per 100 person years for comparators for definition 1, 25.2 per 100 person years for FP/FOR versus 7.8-13.3 per 100 person years for comparators for definition 2, 26.8 per 100 person years for FP/FOR versus 7.0-12.8 per 100 person years for comparators for definition 3), although patient numbers were low (n=45, 36 and 34 for FP/FOR for definitions 1, 2 and 3 of COPD respectively). For all other serious adverse events presented, patients prescribed FP/FOR had similar rates of SAEs to FDC ICS/LABA comparators. For all subgroups, SAEs causing death were low (n<5) or zero for FP/FOR.

5.6 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 was only conducted and presented within the context of this study.

6 Discussion

6.1 Key results

The CPRD database contained a large number of patients aged ≥18 years with asthma prescribed FP/FOR (n=2127) and other licensed comparators (n>7000 for all licensed comparators). However, all other subgroups revealed very low numbers of patients prescribed FP/FOR. For patients with asthma aged ≥12 and <18 years, 77 were prescribed FP/FOR on-label and only 8 off-label, compared to at least 334 patients in the licensed comparator groups. Similarly, for patients with asthma aged 4-11 years, only 12 patients were prescribed FP/FOR, compared to between 150 and 971 patients in the licensed comparator groups. For patients with COPD only, there were 193, 143 and 129 patients prescribed FP/FOR for definitions 1, 2 and 3 respectively with comparator groups FP/SAL DPI and BUD/FOR containing at least 2000 patients each. Lastly for "MART" regimen subgroups, 66 and 6 patients were prescribed FP/FOR for definitions 1 and 2 respectively compared to between 66 and 379 patients for the licensed comparators. Overall, 2204 patients were prescribed FP/FOR on-label and 279 patients prescribed FP/FOR off-label (when considering patients with asthma aged ≥12 and <18 years, patients with asthma aged 4-11 years, definition 1 of COPD and definition 1 of MART regimen). There were also 272 patients prescribed FP/FOR who did not have a diagnosis of asthma or COPD and therefore were not considered in the analyses. The duration of exposure for each adverse event was also lower for FP/FOR versus the licensed comparators in the majority of analyses and subgroups.

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 18 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 between half to a third of that of the comparators (4.85 per 1000 person years for FP/FOR compared to 12.10, 16.85, 15.53 and 10.74 per 1000 person years for FP/SAL DPI, FP/SAL MDI, BUD/FOR and BDP/FOR respectively). For patients with COPD, the prescribing rate was less than 10% that of its on-label comparators, with the exception of BDP/FOR (4.66 per 1000 person years for FP/FOR compared to 71.78, 44.08 and 8.27 per 1000 person years for FP/SAL DPI, BUD/FOR and BDP/FOR respectively. The prescribing rate was particularly low for patients with asthma aged 4-11 years and patients with asthma aged 12-17 years who were prescribed FP/FOR off-label (0.33 per 1000 person years and 0.17 per 1000 person years respectively).

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 18 months post FP/FOR launch.

We observed a higher rate of patients experiencing LRTIs, in patients with asthma aged 12-18 years (16.0 per 100 person years for FP/FOR prescribed on-label versus 6.4-8.3 per 100 person years for licensed comparators) and patients with COPD (50.9 per 100 person years for FP/FOR versus 36.3-42.0 per 100 person years for licensed comparators, for definition 1 of COPD), although rates of patients with occurrence of LRTI were less than double that of FP/SAL DPI and MDI for both subgroups. Furthermore, the time to first event was not significantly different between FP/FOR and licensed comparators for patients with COPD and could not be calculated for patients with asthma aged 12-18 due to low numbers of events. For patients with asthma aged ≥18, rates of LRTIs were similar and the time to the first was not significantly different between treatment groups. Rates were low for patients with asthma aged 4-11 and patients in the MART regimen.

Rates of patients experiencing hyperglycaemia for those with no hyperglycaemia or type 2 diabetes in the baseline period were higher for FP/FOR than other FDC ICS/LABAs for patients with COPD definition 1 only, although these rates were less than double the rates for FP/SAL DPI and BUD/FOR (7.7 per 100 person years for FP/FOR versus 4.8, 4.6 and 3.0 per 100 person years for FP/SAL DPI, FP/SAL MDI and BDP/FOR respectively). Rates were similarly low for patients with asthma aged ≥18 and too low for reporting or zero for all other subgroups.

For patients with at least 1 year of baseline and 1 year of outcome period and also for those at least 6 months of baseline and 6 months of outcome period, there were <5 patients in the FP/FOR group and so annualised rates of COPD exacerbations could not be compared.

Rates of pneumonia were lower for FP/FOR than other FDC ICS/LABAs for those aged ≥18 with asthma and were too low for reporting or zero for FP/FOR for all other subgroups. For tuberculosis and pulmonary embolism, the rate of events during the outcome was low (n<5) or zero for all treatment groups across all subgroups and therefore, the hazard ratios were not be presented due to <10 events in the FP/FOR group in each of the subgroups. For all new adverse events and anxiety and depression, rates were similarly low for patients with asthma aged ≥18 and patients with COPD and rates were too low for reporting or zero for all other subgroups studied.

For seven of the adverse events studied (oral candidiasis, dysphonia/hoarse voice, local oral adverse events, adrenal failure, cardiac arrhythmias and ischaemia, type 2 diabetes and

cataracts) the rate of adverse events in those without an event of that kind at baseline was similarly low for FP/FOR and other FDC ICS/LABAs for patients with asthma aged ≥18 and was too low for reporting or zero for all other subgroups studied. For five of the adverse events studied (anaphylactic reactions, glaucoma, hypokalaemia, growth retardation, bone mineral density) the rate of events adverse events in those without an event of that kind at baseline was too low for reporting or zero for all subgroups studied.

The annualised rate of patients with adverse events that result in hospitalisation were broadly similar, too low for reporting (n<5) or zero for FP/FOR compared to other FDC ICS/LABAs in all subgroups. Hospitalisations relating to COPD were slightly higher for patients prescribed FP/FOR compared to other FDC ICS/LABA treatments for definitions 2 and 3 of COPD (35.3 per 100 person years for FP/FOR versus 20.8-28.6 per 100 person years for comparators for definition 2 and 37.6 per 100 person years for FP/FOR versus 21.1-28.3 per 100 person years for comparators for definition 3), although this difference was not observed for COPD definition 1. For all other serious adverse events presented, patients prescribed FP/FOR had similar rates of SAEs to FDC ICS/LABA comparators. For all subgroups, SAEs causing death were low (n<5) or zero for FP/FOR.

Results for adverse events and serious adverse events were broadly similar when split by initiation and switcher status, to the results for the total cohort.

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 except patients with asthma aged 4-11 years. For example, patients with asthma aged ≥18 years, 66.4% of FP/FOR patients had prescription of an FDC ICS/LABA prior to the index date compared to 23.4-49.3% of comparators and for patients with COPD (definition 1), 57% of FP/FOR patients had prescription of an FDC ICS/LABA prior to the index date compared to 22.1-38.1% of comparators. The main differences noted were patients prescribed FP/FOR more likely to have rhinitis and eczema in the asthma 12-18 group and the COPD groups; earlier first diagnosis of asthma for FP/FOR in the MART subgroups and FP/SAL DPI being more severe patients with a greater amount of comorbid COPD than other comparators for asthma 18+. For patients with asthma aged ≥18, 12-18 and COPD patients, the FP/SAL DPI was prescribed at the highest FP dose followed by FP/FOR. For patients with asthma aged 4-

11 and patients on the MART regimen, FP/FOR patients were prescribed the highest FP equivalent dose compared to licensed comparators.

In terms of the doses of FP/FOR prescribed to patients in each of the subgroups, the majority of patients in the asthma group ≥18 years of age were prescribed 200-600 mcg/day (52.5%) or ≥1000 mcg/day (36.4%). In the patients with asthma aged 12-17 years prescribed FP/FOR on-label, the majority of patients (76.1%) were prescribed 200-600 mcg/day. Patients with asthma aged 4-11 years were fairly equally split between being prescribed ≤200 mcg/day and 200-600 mcg/day. The majority of COPD patients were prescribed ≥1000 mcg/day of FP/FOR (61.3% using COPD definition 1). MART patients were either mostly prescribed 200-400 mcg/day (50%) or 600-1000 mcg/day (35.9% using MART definition 1).

A substantial proportion of patients did not have either a COPD or asthma diagnosis by the time of their initiation or switch to FDC ICS/LABA (index date). When investigated further, around 12% had a COPD diagnosis post index date and around 20% had an asthma diagnosis post index date. At least 80% of these patients had at least one year of prior data in order to capture a record of diagnosis of asthma or COPD but it is possible that their diagnosis was only recorded prior to this. A detailed look at a subsection of these patients revealed that there was no record of an asthma or COPD diagnosis so we have not missed any diagnostic codes. Additionally, we include QOF Read codes in our lists to identify asthma and COPD diagnosis, which are part of the UK national quality improvement initiative and pay-for-performance scheme, ensuring good reporting of these diseases. Therefore, we are confident we are capturing the true populations with a diagnosis of asthma and/or COPD. Furthermore, a very small proportion of these patients without a diagnosis were prescribed FP/FOR (2%), with the majority being prescribed FP/SAL or BUD/FOR.

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 different between FP/FOR and other FDC ICS/LABA treatments for patients with

asthma, with the exception of LRTIs for patients ≥12 years. However, when we consider that the number of patients with asthma aged 12-17 prescribed FP/FOR was low (77 were prescribed FP/FOR on-label and 8 off-label), the differences were less than two-fold and confounding was not accounted for, our results may align with these findings.

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, we did not observe any safety concerns for this subgroup, although we were studying a very small group of FP/FOR patients in this subgroup (n=12).

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 cannot assess our results in the context of other studies.

In terms of the impact of these results, this exploratory analysis suggests there are no clear signals observed of increased adverse events or serious adverse events in patients prescribed FP/FOR in the 18 months post launch when compared to other FDC ICS/LABA therapies. Stage 2 will be conducted to confirm these results using a fully adjusted analysis to make direct comparisons between FP/FOR and other FDC ICS/LABA therapies. Additionally, the patient characterisation revealed that there may be differences between the treatment groups at baseline that need to be accounted for in the analysis during stage 2 of the study.

6.2 Limitations

The analyses were limited by low numbers of patients prescribed FP/FOR, particularly in certain subgroups such as children with asthma aged 4-11 years and 12-17 years and patients on the MART regimen. Additionally, the outcome period available for FP/FOR patients was often substantially shorter than that of its comparators, likely due to the period of study being post-launch therefore being limited by the rate of uptake after launch. The limited the study period over which adverse events could be assessed and for the COPD exacerbations analysis limited the number of patients to be included in the analysis. 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.

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. We have reported the percentage of missing data to show the representativeness of the summary statistics.

6.3 Interpretation

Our interpretation of the results is that there are no safety signals of concern observed, within the context of the exploratory nature of the study. In the majority of adverse events studied, rates of events were low and in no instances were the rates of adverse events for FP/FOR more than double those of other FDC ICS/LABA treatments. Stage 2 will be conducted to confirm these results using a fully adjusted analysis to make direct comparisons between FP/FOR and other FDC ICS/LABA therapies and as it will be conducted over the 36 months post launch we envisage a longer observation period. Additionally, the patient characterisation revealed that there may be differences between the treatment groups at baseline that need to be accounted for in the analysis during stage 2 of the study.

6.4 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, as this is an exploratory unadjusted analysis we view the results as preliminary and stage 2 will provide more informative results on greater numbers of patients with longer exposure times.

7 References

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8 Other information

Please see Appendix 1 containing analysis split by patients initiating and switching FDC

ICS/LABA at the index date.