Research in Real Life

Stage 3: Real-life effectiveness and cost impact evaluation of fixed dose combination fluticasone propionate/formoterol (Flutiform®) compare with fluticasone propionate/salmeterol

Version 0.5 Date: 25 February 2016

STATISTICAL REPORT

Stage 3: Real-life effectiveness and cost impact evaluation of fixed dose combination fluticasone propionate/formoterol (Flutiform®) compare with fluticasone propionate/salmeterol

STUDY SPONSOR: Napp Pharmaceuticals,

RESEARCH ORGANISATION: Research in Real-Life Ltd.,
5a Coles Lane, Oakington, Cambridge, CB24 3BA

TABLE OF CONTENTS

Table of Contents 2
List of Tables 2
List of Figures 3
List of Appendices 4
Datasets and Code 4
Synopsis 5
Aims of the Study 5
Summary 5
effectiveness 5
1.1 Study Outcomes 6
1.1.1 Primary outcome 6
1.1.2 Secondary Effectiveness outcomes 6
1.2 Matching Criteria 6
1.3 Effectiveness Analysis 8
1.3.1 General 8
1.3.2 Primary Effectiveness outcome 8
1.3.3 Secondary Effectiveness outcomes 8
1.3.4 Presentation of results 9
1.4 Statistical Tests 10
2 Exploratory Data Analysis 11
2.1 Baseline Data 11
2.1.1 Baseline comparisons 11
2.1.2 Descriptive Summary 20
2.2 Predictive variables 22
2.3 Correlations 24
2.4 Outcome Data 27
2.4.1 Outcome Characteristics (1) 27
3 Effectiveness Analysis 33
3.1 Matched 33
3.1.1 Primary Outcome 33
3.1.2 Secondary Outcomes 34
4 Summary of Results and Conclusions 41
4.1 Summary of Results 41
4.2 Conclusions 42
5 Appendix 1 – Data Dictionary 43
6 Appendix 2 – Consort Diagram 44

LIST OF TABLES

Table 1: Summary of Statistical Tests 10
Table 2: Summary Statistics for demographic variables measured on the interval scale by Treatment Group 11
Table 3: Summary Statistics for categorical demographic variables by Treatment Group 12
Table 4: Summary Statistics for Co-morbidities and Therapies by Treatment Group 13
Table 5: Summary Statistics for Baseline characterisation variables measured on the interval scale(I) by Treatment Group 14

Table 6: Summary Statistics for Baseline characterisation variables measured on the interval scale (II) by Treatment Group 15
Table 7: Summary Statistics for Baseline categorical characterisation variables (I) by Treatment Group 16
Table 8: Summary Statistics for Baseline categorical characterisation variables (II) by Treatment Group 17
Table 9: Summary Statistics for Baseline categorical characterisation variables (III) by Treatment Group 18
Table 10: Summary Statistics for Baseline categorical characterisation variables (IV) by Treatment Group 19
Table 11: Summary Statistics for Baseline categorical characterisation variables (V) by Treatment Group 20
Table 12: Spearman Correlation Coefficients (1) 24
Table 13: Spearman Correlation Coefficients (2) 24
Table 14: Spearman Correlation Coefficients (3) 25
Table 15: Spearman Correlation Coefficients (4) 25
Table 16: Spearman Correlation Coefficients (5) 26
Table 17: Spearman Correlation Coefficients (6) 26
Table 18: Summary Statistics for Outcome characterisation variables measured on the interval scale (matched cohort) (I) by Treatment Group 27
Table 19: Summary Statistics for Outcome characterisation variables measured on the interval scale (matched cohort) (II) by Treatment Group 28
Table 20: Summary Statistics for Outcome categorical characterisation variables (matched cohort) (I) by Treatment Group 29
Table 21: Summary Statistics for Outcome categorical characterisation variables (matched cohort) (III) by Treatment Group 30
Table 22: Summary Statistics for Outcome categorical characterisation variables (matched cohort) (IV) by Treatment Group 31
Table 23: Summary Statistics for Outcome categorical characterisation variables (Matched Cohort) (V) by Treatment Group 32
Table 24: Summary Statistics for Healthcare Costs (matched cohort) by Treatment Group 32
Table 25: Exacerbation (ATS) (matched cohort) 33
Table 26: Exacerbation Rates (ATS Definition) (Matched Cohort) 34
Table 27: Summary Results for Exacerbations (ATS Definition) (Matched Cohort) 35
Table 28: Summary Results for Asthma Control (excl. SABA Usage) (Matched Cohort) 36
Table 29: Acute respiratory event rate (Matched Cohort) 37
Table 30: Overall asthma control (Matched Cohort) 37
Table 31: SABA usage (Matched Cohort) 37
Table 32: Treatment Stability (Matched Cohort) 38
Table 33: Hospitalisation (Matched Cohort) 38
Table 34: Medication Possession category (Matched Cohort) 38
Table 35: Adherence category (Matched Cohort) 39
Table 36: ICS Usage (Matched Cohort) 39
Table 37: Controller/relieved ratio (Matched Cohort) 39
Table 38: Oral Thrush (Matched Cohort) 40
Table 39: Summary of primary outcome results - matched cohort. 41
Table 40: Summary of secondary outcome results – matched cohort. 41

LIST OF FIGURES

No table of figures entries found.

LIST OF APPENDICES

Appendix 1: Data Dictionary

Appendix 2: Consort Diagrams

DATASETS AND CODE

Available on request:

STATA Datasets (Effectiveness Data)

SAS Datasets (Matched Effectiveness Data)

SAS Code (Matched Effectiveness Analyses)

SYNOPSIS

AIMS OF THE STUDY

The aim of this stage 3 study is to examine the real life effectiveness and cost impact outcomes between FP/FOR and FP/SAL.

SUMMARY

EFFECTIVENESS

The probability of having no ATS exacerbations was found to be non-inferior for FP/FOR compared to FP/SAL, using a lower inferiority boundary of -3.5% for difference in proportion. There was no evidence that exacerbation rate was significantly different between the cohorts using the ATS definition, however using the clinical definition the rate of exacerbations was significantly lower the FP/FOR compared to the FP/SAL cohort.

1.1 STUDY OUTCOMES

1.1.1 PRIMARY OUTCOME

To examine non-inferiority of effectiveness (in terms of the proportion with 'no exacerbations' [ATS/ERS Task Force definition]) of fluticasone propionate / formoterol (Flutiform®; FP/FOR) relative to fluticasone propionate / salmeterol (Seretide®; FP/SAL) in matched patients from two cohorts of patients with asthma.

If the non-inferiority criteria is met, this objective will expand to an assessment of the number of exacerbations observed in patients on fluticasone propionate / formoterol (Flutiform®; FP/FOR) compared with fluticasone propionate / salmeterol (Seretide®; FP/SAL).

1.1.2 SECONDARY EFFECTIVENESS OUTCOMES

To evaluate comparative effectiveness and cost impact outcomes of fluticasone propionate / formoterol (Flutiform®; FP/FOR) relative to fluticasone propionate / salmeterol (Seretide®; FP/SAL) in matched patients from two cohorts of patients with asthma.

1.2 MATCHING CRITERIA

Exact matching for categorical variables and coarsened exact matching for numeric variables was used to match patients using 3:1 nearest neighbour matching, without replacement. Matching variables such as demographic data, disease co-morbidity and indicators of disease severity were considered for selection using a combination of baseline data analysis and predictive modelling of the baseline data in relation to the primary outcome variable (independently of treatment group). The final matching criteria for the study were*:*

- Cohort type
  - Initiation Cohort
  - Change Cohort (patients repeating on Seretide Matched to those switching to Flutiform);
- Gender (M/F);
- Number of ATS/ERS exacerbations during the baseline period, categorised as:
  - 0
  - 1
  - 2+;
- SABA daily dosages (in mcg) during the baseline period, categorised as:
  - 0-150
  - 151-300
  - 301-450
  - 451-600
  - 601+;
- ICS daily dosages (in mcg) during the baseline period, categorised as:
  - 0-250
  - 251-500
  - 501+;

- Smoking Status (Smoker/Non-Smoker/Ex-smoker & Missing Status)
- Age ± 5 years (aged > 18);
- Rhinitis Diagnosis (Y/N)

1.3 EFFECTIVENESS ANALYSIS

1.3.1 GENERAL

A comparison of treatment groups using the matched datasets will be carried out making minimal adjustments for other baseline confounders as necessary.

1.3.2 PRIMARY EFFECTIVENESS OUTCOME

The proportion in the FP/FOR groups with no exacerbations in the outcome period, as defined by ATS/ERS Task Force, will be compared to matched FP/SAL patients using conditional logistic regression. To show non-inferiority, the difference (and 95% confidence interval) in the adjusted proportions between the two treatment groups recording no exacerbations will be calculated. Non-inferiority will be achieved if the proportion of FP/FOR patients calculated to have no exacerbations is no more than 3.5% lower than the proportion of FP/SAL patients calculated to have no exacerbations, i.e. the lower CI of the 95% confidence interval of the difference in proportions is -3.5% or greater. This study provides 90% power to reject the null hypothesis that FP/SAL and FP/FOR are not equivalent in terms of 'no exacerbations.'

If non-inferiority is met, the total number of serious exacerbations in the outcome period will be compared between treatment groups using a conditional Poisson regression model to obtain an estimate of relative exacerbation rates. The model will use empirical standard errors with adjustments for potential baseline confounders.

1.3.3 SECONDARY EFFECTIVENESS OUTCOMES

Proportion of patients with frequent exacerbations
The odds ratios between the FP/FOR and FP/SAL patients with ≥2 exacerbations as defined by the ATS/ERS position statement will be compared. Taking the proportion of patients taking FP/SAL as having frequent exacerbations (≥2 exacerbations) as 0.052, the expected difference in proportions of ≥2 exacerbations is 0.033, a two group continuity corrected chi-square test with a 0.05 significance level has an 80% power of rejecting equivalency of the two treatments.

Risk domain asthma control
The adjusted odds of achieving risk domain asthma control will be compared between matched treatment groups using conditional binary logistic regression models. Asthma control status will be used as the dependent variable with treatment and potential confounding factors as explanatory variables.

Acute respiratory event rate
The total number of acute respiratory events in the outcome period will be compared between treatment groups using a conditional Poisson regression model to obtain an estimate of relative respiratory events. The model will use empirical standard errors with adjustments for potential baseline confounders.

Overall asthma control
The adjusted odds of achieving overall asthma control will be compared between matched treatment groups using conditional binary logistic regression models. Asthma control status will be used as the dependent variable with treatment and potential confounding factors as explanatory variables.

SABA usage (≤200mcg, ≤400mcg and >400mcg)
The adjusted odds of being in a higher SABA usage category will be compared between matched treatment groups using conditional ordinal logistic regressional models. The SABA category will be used as the dependent variable with treatment and potential confounding factors as explanatory variables.

Treatment stability
The adjusted odds of achieving treatment stability will be compared between matched treatment groups using conditional binary logistic regression models. Treatment stability will be used as the dependent variable with treatment and potential confounding factors as explanatory variables.

Hospitalisations
Where event numbers are sufficient, the total number of hospitalisations in the outcome period will be compared between treatment groups using a conditional Poisson regression model to obtain an estimate of relative hospitalisation rates. The model will use empirical standard errors and adjustments will be made for potential baseline confounders.

Medication possession category
The proportion of patients in medication possession categories will be compared between matched treatment groups.

Adherence
The proportion of patients in a higher adherence category will be compared between matched treatment groups.

ICS usage
The proportion of patients in a higher ICS usage category will be compared between matched treatment groups.

Controller/reliever ratio
The proportion of patients in a higher controller/reliever ratio usage category will be compared between matched treatment groups.

Oral Thrush incidence
The proportion of patients in oral thrush incidence categories will be compared between matched treatment groups.

1.3.4 PRESENTATION OF RESULTS

All adjusted odds ratios and rate ratios will be presented along with 95% confidence intervals (CIs).

Unadjusted results will be presented for comparison.

1.4 STATISTICAL TESTS

Table 1 summarises the statistical tests used in the analysis.

Test	Use
Conditional Logistic Regression model	Used to examine the impact of predictors on the odds of a certain dichotomous event/outcome in a matched analysis e.g. Is successful asthma control predicted by cohort membership and potential confounders?
Odds ratio (OR)	Measure of effect size when the outcome measure is binary (it is the ratio of 2 odds, for example, the odds of disease in patients exposed and unexposed to a factor). Estimated using (conditional) logistic regression.
Conditional Ordinal logistic Regression Model	Used to examine the impact of predictors on the odds of levels of an ordinal variable having higher / lower ordered values in a matched analysis.
Conditional Poisson Regression model	A form of generalized linear model used to relate one or more predictors to the log of the expected rate of an event in a matched analysis. Used to model count data such as number of exacerbations.
Rate Ratio	A test for the equality of two Poisson means. This is done by investigating procedures for comparing two independent Poisson variates that are observed over unequal sampling frames.

Table 1: Summary of Statistical Tests

2 EXPLORATORY DATA ANALYSIS

2.1 BASELINE DATA

2.1.1 BASELINE COMPARISONS

Table 2 - Table 11 summarise the baseline differences between matched treatment IPDI cohort.

2.1.1.1 DEMOGRAPHICS

		Treatment Group		TOTAL	p-value*
		FP/FOR	FP/SAL		
Age at IPD § - (years)	N (% non-missing) Mean (SD) Median (IQR)	618 (100.0) 50.0 (18.3) 51 (38, 65)	1854 (100.0) 49.9 (18.1) 51 (38, 65)	2472 (100.0) 49.9 (18.1) 51 (38, 65)	0.245
Weight (kg) – closest to IPD	N (% non-missing) Mean (SD) Median (IQR)	609 (98.5) 79.6 (20.4) 78 (65, 90)	1790 (96.5) 78.5 (20.2) 76 (64, 90)	2399 (97.0) 78.8 (20.3) 76.2 (65.0, 90.0)	0.112
Height (m) – closest to IPD	N (% non-missing) Mean (SD) Median (IQR)	613 (99.2) 1.66 (0.10) 1.66 (1.58, 1.73)	1820 (98.2) 1.66 (0.10) 1.65 (1.58, 1.73)	2433 (98.4) 1.66 (0.10) 1.65 (1.58, 1.73)	0.112
BMI (kg/m^2)	N (% non-missing) Mean (SD) Median (IQR)	597 (96.6) 28.6 (6.3) 28.0 (24.2, 32.1)	1758 (94.8) 28.4 (6.4) 27.5 (23.8, 32.0)	2355 (95.3) 28.5 (6.3) 27.7 (23.9, 32.1)	0.323
FVC Ratio	N (% non-missing) Mean (SD) Median (IQR)	156 (25.2) 0.8 (0.1) 0.8 (0.7, 0.8)	427 (23.0) 0.7 (0.1) 0.7 (0.6, 0.8)	583 (23.6) 0.7 (0.1) 0.7 (0.6, 0.8)	0.043
Percent Predicted Peak Flow readings (%)	N (% non-missing) Mean (SD) Median (IQR)	413 (66.8) 76.3 (19.2) 76.8 (63.5, 90.5)	1266 (68.3) 75.5 (19.0) 76.5 (62.9, 88.8)	1679 (67.9) 75.7 (19.0) 76.6 (63.0, 89.0)	0.213
Year of IPD	N (% non-missing) Mean (SD) Median (IQR)	618 (100.0) 2013 (0.5) 2013 (2013, 2013)	1854 (100.0) 2008 (3.1) 2008 (2006, 2011)	2472 (100.0) 2009 (3.4) 2010 (2007, 2013)	<0.001

Table 2: Summary Statistics for demographic variables measured on the interval scale by Treatment Group
*** Conditional Logistic Regression**
§ Matching Variable

		Treatment Group		TOTAL	P value*
		FP/FOR	FP/SAL		
Gender §	Male n (%)	234 (37.9)	702 (37.9)	936 (37.9)	N/A
	Female n (%)	384 (62.1)	1152 (62.1)	1536 (62.1)	
	Total n (%)	618 (100)	1854 (100)	2472 (100.0)	
Age Group §	12-18 years n (%)	47 (7.6)	141 (7.6)	188 (7.6)	0.428
	19-40 years n (%)	137 (22.2)	416 (22.4)	553 (22.4)	
	41-60 years n (%)	217 (35.1)	659 (35.5)	876 (35.4)	
	61+ years n (%)	217 (35.1)	638 (34.4)	855 (34.6)	
	Total n (%)	618 (100)	1854 (100)	2472 (100.0)	
BMI (categorised)	Underweight (n) (%)	17 (2.8)	53 (3.0)	70 (3.0)	0.248
	Normal (n) (%)	168 (28.1)	517 (29.4)	685 (29.1)	
	Overweight (n) (%)	193 (32.3)	571 (32.5)	764 (32.4)	
	Obese (n) (%)	219 (36.7)	617 (35.1)	836 (35.5)	
	Total n (% non missing)	597 (100)	1758 (100)	2355 (100.0)	
Smoking Status §	Non-smoker n (%)	339 (54.9)	1017 (54.9)	1356 (54.9)	N/A
	Current Smoker n (%)	130 (21.0)	390 (21.0)	520 (21.0)	
	Ex-smoker n (%)	149 (24.1)	447 (24.1)	596 (24.1)	
	Total n (% non missing)	618 (100)	1854 (100)	2472 (100.0)	

Table 3: Summary Statistics for categorical demographic variables by Treatment Group
*** Conditional Logistic Regression**
§ Matching Variable

2.1.1.2 CO-MORBIDITIES & THERAPIES

		Treatment Group		TOTAL	P value*
		FP/FOR	FP/SAL		
Rhinitis Diagnosis	Yes n (%)	191 (30.9)	502 (27.1)	693 (28.0)	0.005
	No n (%)	427 (69.1)	1352 (72.9)	1779 (72.0)	
	Total n (%)	618 (100)	1854 (100)	2472 (100.0)	
Rhinitis Diagnosis and Drugs	Yes n (%)	110 (17.8)	330 (17.8)	440 (17.8)	N/A
	No n (%)	508 (82.2)	1524 (82.2)	2032 (82.2)	
	Total n (%)	618 (100)	1854 (100)	2472 (100.0)	
GERD Diagnosis	Yes n (%)	99 (16.0)	155 (8.4)	254 (10.3)	<0.001
	No n (%)	519 (84.0)	1699 (91.6)	2218 (89.7)	
	Total n (%)	618 (100)	1854 (100)	2472 (100.0)	
GERD Diagnosis and Drugs	Yes n (%)	69 (11.2)	109 (5.9)	178 (7.2)	<0.001
	No n (%)	549 (88.8)	1745 (94.1)	2294 (92.8)	
	Total n (%)	618 (100)	1854 (100)	2472 (100.0)	
Cardiac Disease Diagnosis	Yes n (%)	116 (18.8)	259 (14.0)	375 (15.2)	0.003
	No n (%)	502 (81.2)	1595 (86.0)	2097 (84.8)	
	Total n (%)	618 (100)	1854 (100)	2472 (100.0)	
Cardiac Disease Diagnosis and/or Drugs	Yes n (%)	320 (51.8)	861 (46.4)	1181 (47.8)	0.006
	No n (%)	298 (48.2)	993 (53.6)	1291 (52.2)	
	Total n (%)	618 (100)	1854 (100)	2472 (100.0)	
Ischaemic Heart Disease (IHD) Diagnosis**Error! Bookmark not defined.**	Yes n (%)	42 (6.8)	126 (6.8)	168 (6.8)	1.000
	No n (%)	576 (93.2)	1728 (93.2)	2304 (93.2)	
	Total n (%)	618 (100)	1854 (100)	2472 (100.0)	
Beta Blockers	Yes n (%)	20 (3.2)	52 (2.8)	72 (2.9)	0.572
	No n (%)	598 (96.8)	1802 (97.2)	2400 (97.1)	
	Total n (%)	618 (100)	1854 (100)	2472 (100.0)	
NSAIDs	Yes n (%)	171 (27.7)	459 (24.8)	630 (25.5)	0.133
	No n (%)	447 (72.3)	1395 (75.2)	1842 (74.5)	
	Total n (%)	618 (100)	1854 (100)	2472 (100.0)	
Paracetamol prescriptions	Yes n (%)	193 (31.2)	543 (29.3)	736 (29.8)	0.327
	No n (%)	425 (68.8)	1311 (70.7)	1736 (70.2)	
	Total n (%)	618 (100)	1854 (100)	2472 (100.0)	
CCI Score[1]	None n (%)	92 (14.9)	576 (31.1)	668 (27.0)	<0.001
	1-4 n (%)	470 (76.1)	1167 (62.9)	1637 (66.2)	
	5+ n (%)	56 (9.1)	111 (6.0)	167 (6.8)	
	Total n (%)	618 (100)	1854 (100)	2472 (100.0)	

Table 4: Summary Statistics for Co-morbidities and Therapies by Treatment Group
*** Conditional Logistic Regression**

[1] Calculated using the Charlson CoMorbidity Index (ICD-9 code) over the 1 year prior to (& including) IPD

2.1.1.3 BASELINE CHARACTERISTICS (1)

		Treatment Group		TOTAL	P value*
		FP/FOR	FP/SAL		
Exacerbations (ATS definition)[2]	N (% non-missing) Mean (SD) Median (IQR)	618 (100.0) 0.5 (0.8) 0 (0, 1)	1854 (100.0) 0.5 (0.8) 0 (0, 1)	2472 (100.0) 0.5 (0.8) 0 (0, 1)	0.353
Exacerbations (Clinical Definition)[3]	N (% non-missing) Mean (SD) Median (IQR)	618 (100.0) 0.7 (1.1) 0 (0, 1)	1854 (100.0) 0.8 (1.1) 0 (0, 1)	2472 (100.0) 0.8 (1.1) 0 (0, 1)	0.004
Acute Oral Steroid Courses[4]	N (% non-missing) Mean (SD) Median (IQR)	618 (100.0) 0.5 (0.8) 0 (0, 1)	1854 (100.0) 0.5 (0.8) 0 (0, 1)	2472 (100.0) 0.5 (0.8) 0 (0, 1)	0.965
LRTI Consultations resulting in script for Antibiotics	N (% non-missing) Mean (SD) Median (IQR)	618 (100.0) 0.5 (0.8) 0 (0, 1)	1854 (100.0) 0.6 (1.0) 0 (0, 1)	2472 (100.0) 0.6 (1.0) 0 (0, 1)	0.003
Asthma Consultations[5]	N (% non-missing) Mean (SD) Median (IQR)	618 (100.0) 1.8 (1.8) 1 (1, 2)	1854 (100.0) 2.2 (2.7) 1 (1, 3)	2472 (100.0) 2.1 (2.5) 1 (1, 3)	0.002
Asthma-review Consultations	N (% non-missing) Mean (SD) Median (IQR)	618 (100.0) 1.2 (0.9) 1 (1, 1)	1854 (100.0) 0.9 (1.0) 1 (0, 1)	2472 (100.0) 1.0 (1.0) 1 (0, 1)	<0.001
Primary care Consultations	N (% non-missing) Mean (SD) Median (IQR)	618 (100.0) 8.7 (7.0) 7 (4, 11)	1854 (100.0) 8.9 (7.5) 7 (4, 11)	2472 (100.0) 8.9 (7.4) 7 (4, 11)	0.394
SABA scripts	N (% non-missing) Mean (SD) Median (IQR)	618 (100.0) 5.3 (4.5) 4 (2, 7)	1854 (100.0) 5.0 (4.7) 4 (2, 7)	2472 (100.0) 5.0 (4.6) 4 (2, 7)	0.012

Table 5: Summary Statistics for Baseline characterisation variables measured on the interval scale(I) by Treatment Group
*** Conditional Logistic Regression**

[2] Where exacerbations are defined as an occurrence of the following:
- Unscheduled Hospital Admissions / A&E Attendance for Asthma* **OR**
- Use of acute courses of Oral Steroids[4].

[3] Where exacerbations are defined as an occurrence of the following:
- Unscheduled Hospital Admissions / A&E Attendance / Out of Hours attendance for Asthma* **OR**
- Use of acute courses of Oral Steroids[4] **OR**
- GP consultations for lower respiratory tract infection.

** Where asthma-related includes all events with a **lower respiratory code**, i.e. including all asthma codes, and lower respiratory tract infection codes.*

[4] Acute oral steroid use associated with asthma exacerbation treatment will be defined as:
- all courses that are definitely not maintenance therapy, and/or
- all courses where dosing instructions suggest exacerbation treatment (e.g. 6,5,4,3,2,1 reducing, or 30mg as directed), and/or
- all courses with no dosing instructions, but unlikely to be maintenance therapy with a code for asthma or a lower respiratory event, and/or
- No or undefined dosing instructions but definitely not maintenance therapy, where "**maintenance therapy"** is defined as: daily dosing instructions of ≤10mg Prednisolone or prescriptions for 1mg Prednisolone tablets.

[5] Non-specialist Primary Care Consultation where asthma was recorded

		Treatment Group		TOTAL	P value*
		FP/FOR	FP/SAL		
SABA Inhalers	N (% non-missing)	618 (100.0)	1854 (100.0)	2472 (100.0)	
	Mean (SD)	6.0 (5.9)	6.4 (7.1)	6.3 (6.9)	0.040
	Median (IQR)	4 (2, 8)	4 (2, 8)	4 (2, 8)	
SABA Dosage (mcg)	N (% non-missing)	618 (100.0)	1854 (100.0)	2472 (100.0)	
	Mean (SD)	327.1 (319.7)	346.6 (387.1)	341.7 (371.4)	0.040
	Median (IQR)	219.2 (109.6, 438.4)	219.2 (109.6, 438.4)	219.2 (109.6, 438.4)	
Average Daily ICS dose (mcg)	N (% non-missing)	618 (100.0)	1854 (100.0)	2472 (100.0)	
	Mean (SD)	755.6 (663.0)	720.7 (636.0)	729.4 (642.9)	0.068
	Median (IQR)	575.3 (246.6, 1066)	573.8 (246.6, 986.3)	573.8 (246.6, 986.3)	

Table 6: Summary Statistics for Baseline characterisation variables measured on the interval scale (II) by Treatment Group
*** Conditional Logistic Regression**

2.1.1.4 BASELINE CHARACTERISTICS (2)

		Treatment Group		TOTAL	P value*
		FP/FOR	FP/SAL		
Risk Domain Asthma Control	Controlled n (%)	354 (57.3)	978 (52.8)	1332 (53.9)	0.005
	Uncontrolled n (%)	264 (42.7)	876 (47.2)	1140 (46.1)	
	Total n (%)	618 (100)	1854 (100)	2472 (100.0)	
Overall Asthma Control	Controlled n (%)	172 (27.8)	455 (24.5)	627 (25.4)	0.016
	Uncontrolled n (%)	446 (72.2)	1399 (75.5)	1845 (74.6)	
	Total n (%)	618 (100)	1854 (100)	2472 (100.0)	
GINA Control	Unknown n (%)	28 (4.5)	641 (34.6)	669 (27.1)	<0.001
	Controlled n (%)	59 (9.5)	128 (6.9)	187 (7.6)	
	Partially Controlled n (%)	401 (64.9)	853 (46.0)	1254 (50.7)	
	Uncontrolled	130 (21.0)	232 (12.5)	362 (14.6)	
	Total n (%)	618 (100)	1854 (100)	2472 (100.0)	
Exacerbations (ATS Definition) (categorised)	0 n (%)	430 (69.6)	1290 (69.6)	1720 (69.6)	N/A
	1 n (%)	120 (19.4)	360 (19.4)	480 (19.4)	
	2+ n (%)	68 (11.0)	204 (11.0)	272 (11.0)	
	Total n (%)	618 (100)	1854 (100)	2472 (100.0)	
Exacerbations (Clinical Definition) (categorised)	0 n (%)	354 (57.3)	978 (52.8)	1332 (53.9)	0.013
	1 n (%)	148 (23.9)	504 (27.2)	652 (26.4)	
	2+ n (%)	116 (18.8)	372 (20.1)	488 (19.7)	
	Total n (%)	618 (100)	1854 (100)	2472 (100.0)	
Acute Oral Steroid courses (categorised) §	0 n (%)	431 (69.7)	1299 (70.1)	1730 (70.0)	0.090
	1 n (%)	119 (19.3)	360 (19.4)	479 (19.4)	
	2+ n (%)	68 (11.0)	195 (10.5)	263 (10.6)	
	Total n (%)	618 (100)	1854 (100)	2472 (100.0)	
LRTI Consultations resulting in script for Antibiotics (categorised) §	0 n (%)	432 (69.9)	1189 (64.1)	1621 (65.6)	0.008
	1 n (%)	117 (18.9)	420 (22.7)	537 (21.7)	
	2+ n (%)	69 (11.2)	245 (13.2)	314 (12.7)	
	Total n (%)	618 (100)	1854 (100)	2472 (100.0)	

Table 7: Summary Statistics for Baseline categorical characterisation variables (I) by Treatment Group
*** Conditional Logistic Regression**
§ Matching Variable

		Treatment Group		TOTAL	P value*
		FP/FOR	FP/SAL		
Asthma consultations[6] (categorised)	0 n (%)	81 (13.1)	331 (17.9)	412 (16.7)	0.316
	1 n (%)	262 (42.4)	627 (33.8)	889 (36.0)	
	2-3 n (%)	204 (33.0)	590 (31.8)	794 (32.1)	
	4+ n (%)	71 (11.5)	306 (16.5)	377 (15.3)	
	Total n (%)	618 (100)	1854 (100)	2472 (100.0)	
Primary care consultations (categorised)	0-5 n (%)	226 (36.6)	703 (37.9)	929 (37.6)	0.973
	6-10 n (%)	210 (34.0)	607 (32.7)	817 (33.1)	
	11-15 n (%)	100 (16.2)	290 (15.6)	390 (15.8)	
	16-25 n (%)	63 (10.2)	181 (9.8)	244 (9.9)	
	26+ n (%)	19 (3.1)	73 (3.9)	92 (3.7)	
	Total n (%)	618 (100)	1854 (100)	2472 (100.0)	

Table 8: Summary Statistics for Baseline categorical characterisation variables (II) by Treatment Group
*** Conditional Logistic Regression**

[6] Non-specialist Primary Care Consultation where asthma was recorded

		Treatment Group		TOTAL	P value*
		FP/FOR	FP/SAL		
SABA scripts (categorised)	0 n (%)	53 (8.6)	157 (8.5)	210 (8.5)	<0.001
	1-2 n (%)	154 (24.9)	501 (27.0)	655 (26.5)	
	3-5 n (%)	185 (29.9)	583 (31.4)	768 (31.1)	
	6-10 n (%)	128 (20.7)	365 (19.7)	493 (19.9)	
	11+ n (%)	98 (15.9)	248 (13.4)	346 (14.0)	
	Total n (%)	618 (100)	1854 (100)	2472 (100.0)	
SABA Inhalers (categorised)	None n (%)	53 (8.6)	157 (8.5)	210 (8.5)	0.684
	1-2 n (%)	144 (23.3)	430 (23.2)	574 (23.2)	
	3-5 n (%)	176 (28.5)	525 (28.3)	701 (28.4)	
	6-10 n (%)	125 (20.2)	384 (20.7)	509 (20.6)	
	11+ n (%)	120 (19.4)	358 (19.3)	478 (19.3)	
	Total n (%)	618 (100)	1854 (100)	2472 (100.0)	
SABA Dosage (mcg) (categorised) §	0 - 150 n (%)	198 (32.0)	594 (32.0)	792 (32.0)	N/A
	151-300 n (%)	176 (28.5)	528 (28.5)	704 (28.5)	
	301-450 n (%)	95 (15.4)	285 (15.4)	380 (15.4)	
	451-600 n (%)	31 (5.0)	93 (5.0)	124 (5.0)	
	601+ n (%)	118 (19.1)	354 (19.1)	472 (19.1)	
	Total n (%)	618 (100)	1854 (100)	2472 (100.0)	
Baseline ICS dose (mcg) (categorised)	>0-250 n (%)	160 (25.9)	480 (25.9)	640 (25.9)	N/A
	251-500 n (%)	128 (20.7)	384 (20.7)	512 (20.7)	
	501+n (%)	330 (53.4)	990 (53.4)	1320 (53.4)	
	Total n (%)	618 (100)	1854 (100)	2472 (100.0)	
Baseline Asthma Therapy	None	3 (0.5)	21 (1.1)	24 (1.0)	<0.001
	SABA	23 (3.7)	75 (4.0)	98 (4.0)	
	SAAC + SABA	0 (0.0)	3 (0.2)	3 (0.1)	
	LABA +/- SAAC +/- SABA	1 (0.2)	8 (0.4)	9 (0.4)	
	ICS +/- SAAC +/- SABA	122 (19.7)	252 (13.6)	374 (15.1)	
	ICS + LABA +/- SAAC +/- SABA	356 (57.6)	1278 (68.9)	1634 (66.1)	
	ICS + LAMA +/- SAAC +/- SABA	0 (0.0)	1 (0.1)	1 (0.0)	
	ICS + LABA + LAMA +/- SAAC +/-	6 (1.0)	26 (1.4)	32 (1.3)	
	LTRA +/- SAAC +/- SABA	5 (0.8)	5 (0.3)	10 (0.4)	
	ICS + LTRA +/- SAAC +/- SABA	7 (1.1)	6 (0.3)	13 (0.5)	
	ICS + LAMA + LTRA +/- SAAC +/-	0 (0.0)	1 (0.1)	1 (0.0)	
	ICS + LABA + LAMA + LTRA +/-	0 (0.0)	7 (0.4)	7 (0.3)	
	ICS + LABA + LTRA +/- SAAC +/-	95 (15.4)	171 (9.2)	266 (10.8)	
	Total n(%)	618 (100)	1854 (100)	2472 (100.0)	

Table 9: Summary Statistics for Baseline categorical characterisation variables (III) by Treatment Group

*** Conditional Logistic Regression**

§ Matching Variable

		Treatment Group		TOTAL	P value*
		FP/FOR	FP/SAL		
LABA Use	Yes n (%)	19 (3.1)	253 (13.6)	272 (11.0)	<0.001
	No n (%)	599 (96.9)	1601 (86.4)	2200 (89.0)	
	Total n (%)	618 (100)	1854 (100)	2472 (100.0)	
LAMA Use	Yes n (%)	6 (1.0)	35 (1.9)	41 (1.7)	0.117
	No n (%)	612 (99.0)	1819 (98.1)	2431 (98.3)	
	Total n (%)	618 (100)	1854 (100)	2472 (100.0)	
SAMA Use	Yes n (%)	11 (1.8)	103 (5.6)	114 (4.6)	<0.001
	No n (%)	607 (98.2)	1751 (94.4)	2358 (95.4)	
	Total n (%)	618 (100)	1854 (100)	2472 (100.0)	
LTRA Use	Yes n (%)	107 (17.3)	190 (10.2)	297 (12.0)	<0.001
	No n (%)	511 (82.7)	1664 (89.8)	2175 (88.0)	
	Total n (%)	618 (100)	1854 (100)	2472 (100.0)	
Theophyline Use	Yes n (%)	13 (2.1)	71 (3.8)	84 (3.4)	0.042
	No n (%)	605 (97.9)	1783 (96.2)	2388 (96.6)	
	Total n (%)	618 (100)	1854 (100)	2472 (100.0)	
Spacer Device Use	Yes n (%)	73 (11.8)	303 (16.3)	376 (15.2)	0.005
	No n (%)	545 (88.2)	1551 (83.7)	2096 (84.8)	
	Total n (%)	618 (100)	1854 (100)	2472 (100.0)	
Diagnosis of definite Oral Candidiasis (Categorised)	0 n (%)	612 (99.0)	1834 (98.9)	2446 (98.9)	0.821
	1+ n (%)	6 (1.0)	20 (1.1)	26 (1.1)	
	Total n (%)	618 (100)	1854 (100)	2472 (100.0)	
Diagnosis for Candidiasis and/or anti-fungal definitely for oral thrush (Categorised)	0 n (%)	595 (96.3)	1778 (95.9)	2373 (96.0)	0.680
	1+ n (%)	23 (3.7)	76 (4.1)	99 (4.0)	
	Total n (%)	618 (100)	1854 (100)	2472 (100.0)	
Diagnosis for Candidiasis and/or anti-fungal definitely & possibly for oral thrush (Categorised)	0 n (%)	592 (95.8)	1772 (95.6)	2364 (95.6)	0.822
	1+ n (%)	26 (4.2)	82 (4.4)	108 (4.4)	
	Total n (%)	618 (100)	1854 (100)	2472 (100.0)	

Table 10: Summary Statistics for Baseline categorical characterisation variables (IV) by Treatment Group
*** Conditional Logistic Regression**

		Treatment Group		TOTAL	P value*
		FP/FOR	FP/SAL		
Hospital inpatient admissions[7] (categorised)	0 n (%)	617 (99.8)	1838 (99.1)	2455 (99.3)	0.098
	1+ n (%)	1 (0.2)	16 (0.9)	17 (0.7)	
	Total n (%)	618 (100)	1854 (100)	2472 (100.0)	
A&E attendance (categorised)	0 n (%)	617 (99.8)	1836 (99.0)	2453 (99.2)	0.072
	1+ n (%)	1 (0.2)	18 (1.0)	19 (0.8)	
	Total n (%)	618 (100)	1854 (100)	2472 (100.0)	
OPD attendance (categorised)	0 n (%)	617 (99.8)	1824 (98.4)	2441 (98.7)	0.021
	1+ n (%)	1 (0.2)	30 (1.6)	31 (1.3)	
	Total n (%)	618 (100)	1854 (100)	2472 (100.0)	

Table 11: Summary Statistics for Baseline categorical characterisation variables (V) by Treatment Group
*** Conditional Logistic Regression**

2.1.2 DESCRIPTIVE SUMMARY

After matching, baseline differences ($p < 0.10$) remain between treatment groups in:

- FVC Ratio
- Year of IPD
- Exacerbations Clinical definition (actual number and categorised)
- LRTI Consultations resulting in scripts for antibiotics (actual number and categorised)
- Asthma consultations (actual number)
- Asthma-review consultations (actual number)
- SABA scripts (actual and categorised)
- SABA inhalers (actual)
- SABA dosage (actual)
- Average Daily ICS dose (mcg) (actual)
- Rhinitis Diagnosis (not taking into account drugs)
- GERD Diagnosis (taking and not taking into account drugs)
- Cardiovascular disease (taking and not taking into account drugs)
- CCI score (categorised)
- Risk Domain Asthma Control
- Overall Asthma Control
- GINA Control
- Acute Oral Steroid courses
- Baseline Asthma Therapy
- LABA use
- SAMA use
- LTRA use
- Theophyline use
- Spacer device use
- Hospital Inpatient admissions (categorised)
- A&E attendance (categorised)
- OPD attendance (categorised)

[7] All Hospitalisations with a Lower respiratory read code (include LRTI).

The FVC ratio was higher for the FP/FOR group (0.8 (0.1) compared to 0.7 (0.1) p=0.043) and the index date was later (median (IQR) 2013 (2013 to 2013) compared to 2008(2006, 2011) p<0.001).

There were a higher proportion of patients in the FP/FOR group with no baseline exacerbations (clinical definition) (57% compared to 53% p=0.013) and no baseline LRTI consultations resulting in script for antibiotics (70% compared to 64% p=0.008). Patients in the FP/FOR group had on average lower asthma consultations but more asthma review consultations in baseline (mean (SD) 1.8 (1.8) compared to 2.2 (2.7) p=0.002 and 1.2(0.9) compared to 0.9(1.0) p=<0.001 respectively).

A higher proportion of patients in the FP/FOR group had eleven or more SABA scripts in the baseline period (16% compared to 13% p<0.001). Though there was a statistically significant different number of inhalers and dose between the groups(p=0.04), with the means being lower for the FP/FOR group the median and IQRs were the same (4 inhalers (2 to 8) for FP/FOR and FP/SAL and 219.2 mcg (109.6 to 438.4) (see table 6).

The average daily ICS dose was slightly higher for the FP/FOR group (median (IQR) 575.3mcg (246.6 to 1066) compared to (573.8mcg (246.6 to 986.3) p=0.068)

When only taking into account READ codes more patients had a Rhinitis diagnosis recorded in the FP/FOR group compared to the FP/SAL group (31% compared to 27% p=0.005). More patients in the FP/FOR group had active GERD and Cardiovascular disease diagnosis based on READ code and drugs being received (11% compared to 6% p<0.001 for GERD and 52% compared to 46% for Cardiovascular diseases p=0.006). Similarly when only the READ code was used (16% compared to 8% (p<0.001) and 19% compared to 14% (p=0.003)). There were more patients in the FP/FOR group for which the Charleston Co-morbidity Index could be calculated (85% compared to 69% p<0.001).

There were a higher percentage of patients defined as controlled as defined by the Risk Domain Asthma Control (57% compared to 53% p=0.005) and overall asthma control (28% compared to 24% p=0.016). There were less patients for whom GINA control could not be determined in the FP/FOR group 5% compared to 35% p<0.001). Slightly more patients had two or more acute oral steroid courses in the FP/FOR group (11.0% compared to 10.5% p=0.09).

Baseline Asthma Therapies were differently distributed between the groups (p<0.001)

There was less LABA, SAMA, Theophyline and Spacer Device use in the FP/FOR group compared to the FP/SAL , but more LTRA use (3% vs 14% for LABA p<0.001, 2% vs 6% for SAMA p<0.001, 2% vs 4% for Theophyline p=0.042, 12% vs 16% for Spacer Device p=0.005 and 17% vs 10% for LTRA p<0.001).

There were less hospital inpatient admissions, A&E attendance and outpatient attendance in the FP/FOR group compared to the FP/SAL group (0% compared to 1% for inpatient admissions (p=0.098), 0% compared to 1% for A&E (p=0.072) and 0% compared to 2% for outpatient admissions (p=0.021) .

Although many differences between the groups were statistically significant, most of the actual differences between the groups were not large. The large difference in Index Year, reflects the different time cohorts that the samples come from since FP/FOR was only licenced from September 2012. The other larger differences seen (GERD, Charleston Co-morbidity Index, GINA, LABA and LTRA) are potentially as a result of this different timing ie. due to improved data recording or change in policy.

2.2 PREDICTIVE VARIABLES

Multivariate analyses have been carried out using the full study sample to identify baseline variables that are predictive ($p \leq 0.05$) of each outcome variable during the outcome period. These may be included as potential confounders when modelling outcome variables.

Predictive variables for Primary Outcome (number of exacerbations) include:
Age, Year of IPD, Gender, BMI, Smoking Status, CCI Score, Cardiovascular Disease Diagnosis, Hypertension Diagnosis, Rhinitis Diagnosis and receiving treatment, Osteoporosis diagnosis, MI diagnosis, SABA scripts, SABA inhalers, SABA dosage category, ICS daily dose, ICS inhalers, ICS scripts, spacer device, acute oral steroids, beta blockers, NSAIDs, paracetamol, statins, tricyclics, diabetes diagnosis, eosinophil count, asthma related GP appointments, baseline all GP consultations, baseline asthma review consultations, baseline antibiotics, baseline accident and emergency visits, baseline number of inpatient appointments, baseline number of outpatient appointments, baseline exacerbations (ATS definition), baseline exacerbations (clinical definition), baseline definite candidiasis, baseline candidiasis and anti-fungal for oral thrush, baseline candidiasis and/or anti-fungal possibly for oral thrush, adherence (fixed and variable definition), baseline step-up criteria, GINA control code, baseline LAMA. LABA, LTRA, THEO and SAMA use.

Predictive variables for Secondary outcomes:

i) Frequent (2+) exacerbations

Age, Year of IPD, Gender, BMI, Smoking Status, CCI Score, Cardiovascular Disease Diagnosis, Heart Failure diagnosis, Hypertension Diagnosis, Rhinitis Diagnosis and receiving treatment, Osteoporosis diagnosis, MI diagnosis, baseline SABA inhalers, baseline SABA dosage category, baseline ICS daily dose, baseline ICS inhalers, baseline ICS scripts, baseline acute oral steroids, baseline beta blockers, baseline NSAIDs, baseline paracetamol, baseline statins, baseline tricyclics, baseline diabetes diagnosis, baseline eosinophil count, baseline asthma related GP consultations, baseline all GP consultations, baseline asthma review consultations, baseline antibiotics, baseline A&E appointments, baseline number of inpatient appointments, baseline exacerbations (clinical definition, categorised), adherence (fixed and variable definition), baseline step-up criteria, GINA control code, baseline LAMA., LABA, LTRA, THEO and SAMA use

ii) Risk Domain asthma control

Age, Year of IPD, Sex, BMI, Smoking Status, CCI Score, Cardiovascular Disease Diagnosis, Heart Failure diagnosis, Hypertension Diagnosis, Rhinitis diagnosis, Rhinitis Diagnosis and receiving treatment, Eczema diagnosis and receiving treatment, Osteoporosis diagnosis, GERD diagnosis, Anxiety/depression diagnosis, MI diagnosis, baseline SABA inhalers, baseline SABA dosage category, baseline ICS daily dose, baseline spacer device, baseline acute oral steroids, baseline beta blockers, baseline NSAIDs, baseline paracetamol, baseline tricyclics, baseline diabetes diagnosis, baseline pneumonia, baseline asthma related GP consultations, baseline all GP consultations, baseline asthma review consultations, baseline antibiotics, baseline A&E appointments, baseline number of outpatient appointments, baseline exacerbations (ATS and clinical definition, categorised), baseline candidiasis and/or anti-fungal possibly for oral thrush, adherence (fixed and variable definition), baseline step-up criteria, GINA control code, baseline LAMA, LTRA, THEO and SAMA use

iii) Acute respiratory event

Age, Year of IPD, Gender, BMI, Smoking Status, CCI Score, Cardiovascular Disease Diagnosis, Heart Failure diagnosis, Hypertension Diagnosis, Rhinitis diagnosis, Rhinitis Diagnosis and receiving treatment, Eczema diagnosis and receiving treatment, Osteoporosis diagnosis, GERD diagnosis, baseline SABA inhalers, baseline SABA dosage category, baseline ICS daily dose, baseline ICS inhalers, baseline spacer device, baseline acute oral steroids, baseline beta blockers, baseline NSAIDs, baseline paracetamol, baseline tricyclics, baseline diabetes diagnosis, baseline pneumonia, baseline asthma related GP consultations, baseline all GP consultations,

baseline asthma review consultations, baseline antibiotics, baseline A&E appointments, baseline number of outpatient appointments, baseline exacerbations (ATS and clinical definition), baseline antifungal prescription for oral thrush, baseline anti-fungal used or potentially used for oral thrush and diagnosis code, baseline anti-fungal prescription used for oral thrush and diagnosis code, adherence (fixed and variable definition), baseline step-up criteria, GINA control code, baseline LAMA, LTRA, THEO and SAMA use.

iv) Overall asthma control

Age, Year of IPD, Gender, BMI, Smoking Status, Cardiovascular Disease Diagnosis, Heart Failure diagnosis, Hypertension Diagnosis, Rhinitis Diagnosis and receiving treatment, Eczema diagnosis and receiving treatment, Osteoporosis diagnosis, GERD diagnosis, Anxiety/depression diagnosis, MI diagnosis, baseline SABA scripts, SABA inhalers, SABA dosage category, baseline ICS daily dose, baseline ICS inhalers, baseline ICS scripts, baseline spacer device, baseline beta blockers, baseline NSAIDs, baseline paracetamol, baseline tricyclics, baseline pneumonia, baseline asthma related GP consultations, baseline all GP consultations, baseline asthma review consultations, baseline antibiotics, baseline exacerbations (clinical definition), adherence (fixed and variable definition), baseline step-up criteria, GINA control code, baseline LAMA. LABA, LTRA, THEO SAMA use.

v) SABA usage

Age, Year of IPD, Smoking Status, CCI score, Cardiovascular Disease Diagnosis, Hypertension Diagnosis, Rhinitis Diagnosis, Eczema diagnosis and receiving treatment, GERD diagnosis, GERD diagnosis and receiving treatment, Anxiety/depression diagnosis, MI diagnosis, baseline SABA scripts, SABA inhalers, SABA dosage category, baseline ICS daily dose, baseline ICS inhalers, baseline ICS scripts, baseline acute oral steroids, baseline beta blockers, baseline NSAIDs, baseline paracetamol, baseline statins, baseline tricyclics, baseline diabetes diagnosis, baseline pneumonia, baseline asthma related GP consultations, baseline all GP consultations, baseline asthma review consultations, baseline antibiotics, baseline exacerbations (ATS definition), adherence (fixed and variable definition), GINA control code.

vi) Treatment stability

Age, Year of IPD, Gender, BMI, Smoking Status, CCI Score, Cardiovascular Disease Diagnosis, Heart Failure diagnosis, Hypertension Diagnosis, Rhinitis diagnosis, Rhinitis Diagnosis and receiving treatment, Eczema diagnosis and receiving treatment, Osteoporosis diagnosis, GERD diagnosis, baseline SABA scripts, SABA inhalers, baseline ICS daily dose, baseline ICS inhalers, baseline spacer device, baseline acute oral steroids, baseline beta blockers, baseline NSAIDs, baseline paracetamol, baseline tricyclics, baseline diabetes diagnosis, eosinophil count, baseline asthma related GP consultations, baseline all GP consultations, baseline asthma review consultations, baseline antibiotics, baseline A&E appointments, baseline number of outpatient appointments, baseline exacerbations (ATS and clinical definition), count of anti-fungal prescriptions, adherence (fixed and variable definition), baseline step-up criteria, GINA control code, baseline LAMA, LTRA, THEO and SAMA use.

vii) Hospitalisations (categorised)

Smoking Status, Cardiovascular Disease Diagnosis, IHD diagnosis, Rhinitis Diagnosis, Rhinitis Diagnosis and receiving treatment, Eczema diagnosis and receiving treatment, Osteoporosis diagnosis, MI diagnosis, SABA inhalers, baseline SABA dosage (categorised), baseline ICS daily dose, baseline ICS scripts, baseline NSAIDs, baseline paracetamol, baseline tricyclics, baseline pneumonia, baseline all GP consultations, baseline antibiotics, baseline number of inpatient visits, baseline number of outpatient appointments, baseline exacerbations (ATS definition), number of candidiasis diagnosis codes, count of anti-fungal prescriptions used or potentially used for the treatment of oral Thrush with Thrush diagnosis, adherence (fixed definition), baseline step-up criteria, GINA control code, baseline THEO and SAMA use.

2.3 CORRELATIONS

Correlations between potentially confounding baseline variables have been assessed using Spearman correlation coefficients on the full study data. Relationships with rank correlation coefficients greater than 0.30 are detailed in the following tables. These correlation coefficients will be considered – in conjunction with clinical interpretation – *to identify pairings of variables that may present collinearity issues at the modelling stage.*

	Age at IPD (years)	Cardiovascular Disease	Statins	IHD diagnosis	MI diagnosis	Heart failure
Age at IPD (years)						
Cardiovascular Disease	0.32					
Statins	0.38	0.41				
IHD diagnosis		0.67	0.42			
MI diagnosis		0.34		0.51		
Heart failure				0.39		

Table 12: Spearman Correlation Coefficients (1)

	CCI Score	GP related Asthma Consultations	Asthma Review Consultation
CCI Score			
GP related Asthma Consultations	0.53		
Asthma Review Consultation	0.44	0.59	

Table 13: Spearman Correlation Coefficients (2)

	SABA Script	SABA Inhalers	SABA dosage	ICS daily dose	ICS inhalers	ICS scripts	ICS adherence fixed definition	ICS adherence variable	GINA control	Step therapy
SABA Scripts										
SABA Inhalers	0.96									
SABA dosage	0.92	0.96								
ICS daily dose										
ICS inhalers	0.38	0.38	0.38	0.61						
ICS scripts	0.42	0.36	0.36	0.56	0.87					
ICS adherence fixed definition	0.36	0.37	0.36	0.54	0.89	0.78				
ICS adherence variable		0.31	0.30	0.40	0.71	0.53	0.77			
GINA control	0.46	0.48	0.43							
Step therapy				0.56						

Table 14: Spearman Correlation Coefficients (3)

	NSAIDS	Paracetamol	Statins	Primary Care Consultations	Diabetes
NSAIDS					
Paracetamol	0.31				
Statins	0.32				
Primary Care Consultations		0.30			
Diabetes			0.38		

Table 15: Spearman Correlation Coefficients (4)

	Asthma related GP consultation	Acute Oral Steroids	Primary Care Consultations	Antibiotics	Exacerbations ATS definition	Exacerbations clinical definition	Asthma Control Code
Asthma related GP consultation C							
Acute Oral Steroids	0.31						
Primary Care Consultations	0.39						
Antibiotics	0.31	0.43	0.34				
Exacerbations ATS definition	0.31	0.99		0.43			
Exacerbations clinical definition	0.34	0.74	0.34	0.82	0.75		
Asthma Control Code	-0.32	-0.69	-0.31	-0.79	-0.70	-0.96	

Table 16: Spearman Correlation Coefficients (5)

	Anti-fungal prescriptions used for the treatment of oral Candidiasis	Oral Candidiasis diagnosis codes	Anti-fungal prescriptions used or potentially used for the treatment of oral Candidiasis	Distinct dates for anti-fungal prescriptions used or potentially used for the treatment of oral Candidiasis and definite oral Candidiasis diagnosis codes	Dates for anti-fungal prescriptions used for the treatment of oral Candidiasis and definite oral Candidiasis diagnosis codes
Anti-fungal prescriptions used for the treatment of oral Candidiasis					
Oral Candidiasis diagnosis codes	0.45				
Anti-fungal prescriptions used or potentially used for the treatment of oral Candidiasis	0.91	0.45			
Distinct dates for anti-fungal prescriptions used or potentially used for the treatment of oral Candidiasis and definite oral Candidiasis diagnosis codes	0.91	0.48	0.99		
Dates for anti-fungal prescriptions used for the treatment of oral Candidiasis and definite oral Candidiasis diagnosis codes	0.98	0.51	0.92	0.92	

Table 17: Spearman Correlation Coefficients (6)

2.4 OUTCOME DATA

Table 18 - Table 23 summarise the unadjusted outcome variables by treatment group:

2.4.1 OUTCOME CHARACTERISTICS (1)

		Treatment Group		TOTAL	P value*
		FP/FOR	FP/SAL		
Exacerbations (ATS definition)[8]	N (% non-missing) Mean (SD) Median (IQR)	618 (100.0) 0.4 (0.8) 0 (0, 1)	1854 (100.0) 0.4 (0.8) 0 (0, 1)	2472 (100.0) 0.4 (0.8) 0 (0, 1)	0.760
Exacerbations (Clinical Definition)[9]	N (% non-missing) Mean (SD) Median (IQR)	618 (100.0) 0.6 (1.0) 0 (0, 1)	1854 (100.0) 0.7 (1.2) 0 (0, 1)	2472 (100.0) 0.7 (1.1) 0 (0, 1)	0.072
Acute Oral Steroid Courses[10]	N (% non-missing) Mean (SD) Median (IQR)	618 (100.0) 0.4 (0.8) 0 (0, 1)	1854 (100.0) 0.4 (0.8) 0 (0, 1)	2472 (100.0) 0.4 (0.8) 0 (0, 1)	0.676
LRTI Consultations resulting in script for Antibiotics	N (% non-missing) Mean (SD) Median (IQR)	618 (100.0) 0.4 (0.8) 0 (0, 1)	1854 (100.0) 0.6 (1.1) 0 (0, 1)	2472 (100.0) 0.5 (1.1) 0 (0, 1)	0.008
Asthma Consultations[11]	N (% non-missing) Mean (SD) Median (IQR)	618 (100.0) 1.5 (1.4) 1 (1, 2)	1854 (100.0) 1.8 (2.7) 1 (0, 2)	2472 (100.0) 1.7 (2.4) 1 (1, 2)	<0.001

Table 18: Summary Statistics for Outcome characterisation variables measured on the interval scale (matched cohort) (I) by Treatment Group
*** Conditional Logistic Regression**

[8] Where exacerbations are defined as an occurrence of the following:
- Unscheduled Hospital Admissions / A&E Attendance for Asthma* **OR**
- Use of acute courses of Oral Steroids[10].

[9] Where exacerbations are defined as an occurrence of the following:
- Unscheduled Hospital Admissions / A&E Attendance / Out of Hours attendance for Asthma* **OR**
- Use of acute courses of Oral Steroids[10] **OR**
- GP consultations for lower respiratory tract infection.

** Where asthma-related includes all events with a **lower respiratory code**, i.e. including all asthma codes, and lower respiratory tract infection codes.*

[10] Acute oral steroid use associated with asthma exacerbation treatment will be defined as:
- all courses that are definitely not maintenance therapy, and/or
- all courses where dosing instructions suggest exacerbation treatment (e.g. 6,5,4,3,2,1 reducing, or 30mg as directed), and/or
- all courses with no dosing instructions, but unlikely to be maintenance therapy with a code for asthma or a lower respiratory event, and/or
- No or undefined dosing instructions but definitely not maintenance therapy, where "**maintenance therapy"** is defined as: daily dosing instructions of ≤10mg Prednisolone or prescriptions for 1mg Prednisolone tablets.

[11] Non-specialist Primary Care Consultation where asthma was recorded

		Treatment Group		TOTAL	P value*
		FP/FOR	FP/SAL		
Non Asthma related Consultations	N (% non-missing) Mean (SD) Median (IQR)	618 (100.0) 7.1 (7.2) 5 (2, 10)	1854 (100.0) 7.1 (7.1) 5 (2, 9)	2472 (100.0) 7.1 (7.1) 5 (2, 9)	0.931
Primary Care Consultations	N (% non-missing) Mean (SD) Median (IQR)	618 (100.0) 8.5 (7.6) 7 (3, 12)	1854 (100.0) 8.9 (8.2) 7 (4, 12)	2472 (100.0) 8.8 (8.0) 7 (4, 12)	0.246
SABA Scripts	N (% non-missing) Mean (SD) Median (IQR)	618 (100.0) 5.6 (4.9) 4 (2, 8)	1854 (100.0) 5.4 (4.9) 4 (2, 8)	2472 (100.0) 5.4 (4.9) 4 (2, 8)	0.280
SABA Inhalers	N (% non-missing) Mean (SD) Median (IQR)	618 (100.0) 6.3 (5.9) 5 (2, 9)	1854 (100.0) 6.9 (7.3) 5 (2, 10)	2472 (100.0) 6.8 (7.0) 5 (2, 9)	0.005
SABA Dosage (mcg)	N (% non-missing) Mean (SD) Median (IQR)	618 (100.0) 341.6 (324.3) 274.0 (109.6, 493.2)	1854 (100.0) 377.0 (397.0) 274.0 (109.6, 546.5)	2472 (100.0) 368.2 (380.4) 274.0 (109.6, 493.2)	0.006
ICS Scripts	N (% non-missing) Mean (SD) Median (IQR)	618 (100.0) 9.4 (4.3) 9 (6, 13)	1854 (100.0) 7.9 (3.8) 7 (5, 11)	2472 (100.0) 8.3 (4.0) 7 (5, 11)	<0.001
ICS Inhalers	N (% non-missing) Mean (SD) Median (IQR)	618 (100.0) 9.9 (4.3) 10 (6, 13)	1854 (100.0) 9.3 (4.4) 9 (6, 12)	2472 (100.0) 9.4 (4.4) 9 (6, 12)	0.002
Average Daily ICS dose (mcg)	N (% non-missing) Mean (SD) Median (IQR)	618 (100.0) 1045 (713.0) 901.6 (493.2, 1447)	1854 (100.0) 1009 (726.1) 821.9 (491.8, 1315)	2472 (100.0) 1018 (722.9) 821.9 (491.8, 1315)	0.200
Adherence to ICS Therapy	N (% non-missing) Mean (SD) Median (IQR)	618 (100.0) 82.5 (37.5) 82.2 (49.3, 106.8)	1854 (100.0) 82.6 (44.9) 74 (49, 99)	2472 (100.0) 82.6 (43.1) 82 (49, 107)	0.935
Controller-to-Reliever Ratio	N (% non-missing) Mean (SD) Median (IQR)	618 (100.0) 0.7 (0.2) 0.7 (0.5, 0.8)	1854 (100.0) 0.6 (0.2) 0.6 (0.5, 0.8)	2472 (100.0) 0.7 (0.2) 0.6 (0.5, 0.8)	<0.001

Table 19: Summary Statistics for Outcome characterisation variables measured on the interval scale (matched cohort) (II) by Treatment Group

*** Conditional Logistic Regression**

2.4.1.1 OUTCOME CHARACTERISTICS (2)

		Treatment Group		TOTAL	P value*
		FP/FOR	FP/SAL		
Asthma Control Status (excl. SABA usage)[12]	Controlled n(%)	383 (62.0)	1115 (60.1)	1498 (60.6)	0.400
	Uncontrolled n(%)	235 (38.0)	739 (39.9)	974 (39.4)	
	Total n(%)	618 (100)	1854 (100)	2472 (100.0)	
Asthma Control Status (incl. SABA usage)[13]	Controlled n(%)	180 (29.1)	463 (25.0)	643 (26.0)	0.025
	Uncontrolled n(%)	438 (70.9)	1391 (75.0)	1829 (74.0)	
	Total n(%)	618 (100)	1854 (100)	2472 (100.0)	
Treatment Success Status[14] (Secondary Outcome (1))	Successful n(%)	342 (55.3)	990 (53.4)	1332 (53.9)	0.388
	Unsuccessful n(%)	276 (44.7)	864 (46.6)	1140 (46.1)	
	Total n(%)	618 (100)	1854 (100)	2472 (100.0)	
Treatment Success Status[15] (Secondary Outcome (2))	Successful n(%)	342 (55.3)	990 (53.4)	1332 (53.9)	0.388
	Unsuccessful n(%)	276 (44.7)	864 (46.6)	1140 (46.1)	
	Total n(%)	618 (100)	1854 (100)	2472 (100.0)	
Exacerbations (ATS Definition)[8] (categorised)	0 n(%)	458 (74.1)	1372 (74.0)	1830 (74.0)	0.892
	1 n(%)	99 (16.0)	308 (16.6)	407 (16.5)	
	2+ n(%)	61 (9.9)	174 (9.4)	235 (9.5)	
	Total n(%)	618 (100)	1854 (100)	2472 (100.0)	
Exacerbations (Clinical Definition)[9] (categorised)	0 n(%)	383 (62.0)	1115 (60.1)	1498 (60.6)	0.322
	1 n(%)	135 (21.8)	411 (22.2)	546 (22.1)	
	2+ n(%)	100 (16.2)	328 (17.7)	428 (17.3)	
	Total n(%)	618 (100)	1854 (100)	2472 (100.0)	
Acute Oral Steroid courses (categorised)	0 n(%)	461 (74.6)	1380 (74.4)	1841 (74.5)	0.984
	1 n(%)	99 (16.0)	304 (16.4)	403 (16.3)	
	2+ n(%)	58 (9.4)	170 (9.2)	228 (9.2)	
	Total n(%)	618 (100)	1854 (100)	2472 (100.0)	

Table 20: Summary Statistics for Outcome categorical characterisation variables (matched cohort) (I) by Treatment Group
*** Conditional Logistic Regression**

[12] **Sensitivity Asthma Control** is defined as:

- Asthma Control **excluding** Average daily dose of ≤200mcg salbutamol / ≤500mcg terbutaline.

* Where asthma-related includes all events with a **lower respiratory code**, i.e. including all asthma codes, and lower respiratory tract infection codes.

[13] **Asthma Control** is defined as:

- No asthma-related*:
  - Hospital attendance/admission; OR
  - A&E attendance; OR
  - Out-of-hours attendance; OR
  - Out-Patient Department (OPD) attendance; AND
- No GP consultations for lower respiratory tract infections (LRTI); AND
- No prescriptions for acute courses of oral steroids[10].
- Average daily dose of ≤200mcg salbutamol / ≤500mcg terbutaline.

[14] Where Success is defined as

(i) Asthma Control (***excl.*** *SABA usage*) **AND**

(ii) No change in therapeutic regimen:

a. Increased dose of ICS, **and/or**
b. Change in ICS **and/or**
c. Change in delivery device, **and/or**
d. Use of additional therapy as defined by: long-acting bronchodilator (LABA), theophylline, leukotreine receptor antagonists (LTRAs).

[15] Where Success is defined as

(i) Asthma Control (***excl.*** *SABA usage*) **AND**

(ii) No change in therapeutic regimen:

a. Increased dose of ICS, **and/or**
b. Use of additional therapy as defined by: LABA, theophylline, LTRAs.

		Treatment Group		TOTAL	P value*
		FP/FOR	FP/SAL		
LRTI Consultations resulting in script for Antibiotics (categorised)	0 n(%)	439 (71.0)	1279 (69.0)	1718 (69.5)	0.127
	1 n(%)	119 (19.3)	345 (18.6)	464 (18.8)	
	2+ n(%)	60 (9.7)	230 (12.4)	290 (11.7)	
	Total n(%)	618 (100)	1854 (100)	2472 (100.0)	
Asthma consultations[16] (categorised)	0 n(%)	133 (21.5)	470 (25.4)	603 (24.4)	0.374
	1 n(%)	276 (44.7)	674 (36.4)	950 (38.4)	
	2-3 n(%)	157 (25.4)	496 (26.8)	653 (26.4)	
	4+ n(%)	52 (8.4)	214 (11.5)	266 (10.8)	
	Total n(%)	618 (100)	1854 (100)	2472 (100.0)	
Asthma consultations (no oral steroids) (categorised)	<1 n(%)	194 (31.4)	620 (33.4)	814 (32.9)	0.522
	<2 n(%)	265 (42.9)	676 (36.5)	941 (38.1)	
	2+ n(%)	159 (25.7)	558 (30.1)	717 (29.0)	
	Total n (%)	618 (100)	1854 (100)	2472 (100.0)	
Non Asthma-related consultations (categorised)	0-2 n(%)	165 (26.7)	480 (25.9)	645 (26.1)	0.398
	3-5 n(%)	170 (27.5)	455 (24.5)	625 (25.3)	
	6-9 n(%)	126 (20.4)	459 (24.8)	585 (23.7)	
	10+ n(%)	157 (25.4)	460 (24.8)	617 (25.0)	
	Total n(%)	618 (100)	1854 (100)	2472 (100.0)	
Primary care consultations (categorised)	0-5 n(%)	261 (42.2)	725 (39.1)	986 (39.9)	0.315
	6-10 n(%)	181 (29.3)	589 (31.8)	770 (31.1)	
	11-15 n(%)	101 (16.3)	290 (15.6)	391 (15.8)	
	16-25 n(%)	50 (8.1)	180 (9.7)	230 (9.3)	
	26+ n(%)	25 (4.0)	70 (3.8)	95 (3.8)	
	Total n(%)	618 (100)	1854 (100)	2472 (100.0)	
SABA scripts (categorised)	0 n(%)	60 (9.7)	200 (10.8)	260 (10.5)	0.263
	1-2 n(%)	145 (23.5)	406 (21.9)	551 (22.3)	
	3-5 n(%)	167 (27.0)	537 (29.0)	704 (28.5)	
	6-10 n(%)	141 (22.8)	446 (24.1)	587 (23.7)	
	11+ n(%)	105 (17.0)	265 (14.3)	370 (15.0)	
	Total n(%)	618 (100)	1854 (100)	2472 (100.0)	
SABA Dosage (mcg) (categorised)	0 - 150 n(%)	200 (32.4)	550 (29.7)	750 (30.3)	0.139
	151-300 n(%)	144 (23.3)	466 (25.1)	610 (24.7)	
	301-450 n(%)	106 (17.2)	313 (16.9)	419 (16.9)	
	451-600 n(%)	51 (8.3)	130 (7.0)	181 (7.3)	
	601+ n(%)	117 (18.9)	395 (21.3)	512 (20.7)	
	Total n(%)	618 (100)	1854 (100)	2472 (100.0)	
SABA Dosage categorised +/- 200 mcg	<=200mcg n(%)	245 (39.6)	695 (37.5)	940 (38.0)	0.251
	>200 mcg n(%)	373 (60.4)	1159 (62.5)	1532 (62.0)	
	Total n(%)	618 (100)	1854 (100)	2472 (100.0)	
ICS scripts (categorised)	0-3 n(%)	45 (7.3)	162 (8.7)	207 (8.4)	<0.001
	4-6 n(%)	142 (23.0)	642 (34.6)	784 (31.7)	
	7-9 n(%)	139 (22.5)	466 (25.1)	605 (24.5)	
	10-11 n(%)	80 (12.9)	215 (11.6)	295 (11.9)	
	12+ n(%)	212 (34.3)	369 (19.9)	581 (23.5)	
	Total n(%)	618 (100)	1854 (100)	2472 (100.0)	

Table 21: Summary Statistics for Outcome categorical characterisation variables (matched cohort) (III) by Treatment Group
*** Conditional Logistic Regression**

[16] Non-specialist Primary Care Consultation where asthma was recorded

		Treatment Group		TOTAL	P value*
		FP/FOR	FP/SAL		
Average ICS Daily Dose (mcg) (categorised) (FP Equivalent dose)	0-250 n(%)	61 (9.9)	155 (8.4)	216 (8.7)	0.536
	251-500 n(%)	113 (18.3)	423 (22.8)	536 (21.7)	
	501+ n(%)	444 (71.8)	1276 (68.8)	1720 (69.6)	
	Total n(%)	618 (100)	1854 (100)	2472 (100.0)	
Adherence to ICS Therapy (%)	<70 n(%)	250 (40.5)	838 (45.2)	1088 (44.0)	0.132
	70-120 n(%)	287 (46.4)	766 (41.3)	1053 (42.6)	
	>120 n(%)	81 (13.1)	250 (13.5)	331 (13.4)	
	Total n(%)	618 (100)	1854 (100)	2472 (100.0)	
Medication Possession Ratio for ICS	<80% n (%)	284 (46.0)	945 (51.0)	1229 (49.7)	0.017
	≥80% n (%)	334 (54.0)	909 (49.0)	1243 (50.3)	
	Total n (%)	618 (100)	1854 (100)	2472 (100.0)	
Controller-to-Reliever Ratio	< 0.5 n (%)	79 (12.8)	354 (19.1)	433 (17.5)	<0.001
	0.5+ n (%)	539 (87.2)	1500 (80.9)	2039 (82.5)	
	Total n (%)	618 (100)	1854 (100)	2472 (100.0)	
LABA Use	Yes n(%)	618 (100.0)	1854 (100.0)	2472 (100.0)	N/A
	No n(%)	0	0	0	
	Total n(%)	618 (100)	1854 (100)	2472 (100.0)	
Spacer Device Use	Yes n(%)	76 (12.3)	331 (17.9)	407 (16.5)	<0.001
	No n(%)	542 (87.7)	1523 (82.1)	2065 (83.5)	
	Total n(%)	618 (100)	1854 (100)	2472 (100.0)	
Diagnosis of definite Oral Candidiasis (Categorised)	0 n(%)	613 (99.2)	1828 (98.6)	2441 (98.7)	0.260
	1+ n(%)	5 (0.8)	26 (1.4)	31 (1.3)	
	Total n(%)	618 (100)	1854 (100)	2472 (100.0)	
Diagnosis for Candidiasis and/or anti-fungal definitely for oral thrush (Categorised)	0 n(%)	597 (96.6)	1782 (96.1)	2379 (96.2)	0.581
	1+ n(%)	21 (3.4)	72 (3.9)	93 (3.8)	
	Total n(%)	618 (100)	1854 (100)	2472 (100.0)	
Diagnosis for Candidiasis and/or anti-fungal definitely & possibly for oral thrush (Categorised)	0 n(%)	591 (95.6)	1773 (95.6)	2364 (95.6)	1.000
	1+ n(%)	27 (4.4)	81 (4.4)	108 (4.4)	
	Total n(%)	618 (100)	1854 (100)	2472 (100.0)	
Hospital inpatient admissions[17] (categorised)	0 n(%)	610 (98.7)	1840 (99.2)	2450 (99.1)	0.223
	1+ n(%)	8 (1.3)	14 (0.8)	22 (0.9)	
	Total n(%)	618 (100)	1854 (100)	2472 (100.0)	
Hospital inpatient admissions (inc. vague) (categorised)	0 n(%)	604 (97.7)	1823 (98.3)	2427 (98.2)	0.345
	1+ n(%)	14 (2.3)	31 (1.7)	45 (1.8)	
	Total n(%)	618 (100)	1854 (100)	2472 (100.0)	
A&E attendance (categorised)	0 n(%)	617 (99.8)	1846 (99.6)	2463 (99.6)	0.355
	1+ n(%)	1 (0.2)	8 (0.4)	9 (0.4)	
	Total n(%)	618 (100)	1854 (100)	2472 (100.0)	
OPD attendance (categorised)	0 n(%)	615 (99.5)	1818 (98.1)	2433 (98.4)	0.020
	1+ n(%)	3 (0.5)	36 (1.9)	39 (1.6)	
	Total n(%)	618 (100)	1854 (100)	2472 (100.0)	

Table 22: Summary Statistics for Outcome categorical characterisation variables (matched cohort) (IV) by Treatment Group
*** Conditional Logistic Regression**

[17] All Hospitalisations with Lower respiratory read code (include LRTI).

		Treatment Group		TOTAL	P value*
		FP/FOR	FP/SAL		
Change In Therapy (at any time)	Yes n(%)	100 (16.2)	312 (16.8)	412 (16.7)	0.702
	No n(%)	518 (83.8)	1542 (83.2)	2060 (83.3)	
	Total n(%)	618 (100)	1854 (100)	2472 (100.0)	
Increase in ICS (at any time)	Yes n(%)	44 (7.1)	103 (5.6)	147 (5.9)	0.154
	No n(%)	574 (92.9)	1751 (94.4)	2325 (94.1)	
	Total n(%)	618 (100)	1854 (100)	2472 (100.0)	
Change in ICS Drug (at any time)	Yes n(%)	31 (5.0)	148 (8.0)	179 (7.2)	0.013
	No n(%)	587 (95.0)	1706 (92.0)	2293 (92.8)	
	Total n(%)	618 (100)	1854 (100)	2472 (100.0)	
Change in Device (at any time)	Yes n(%)	19 (3.1)	83 (4.5)	102 (4.1)	0.131
	No n(%)	599 (96.9)	1771 (95.5)	2370 (95.9)	
	Total n(%)	618 (100)	1854 (100)	2472 (100.0)	
Additional Therapy (at any time)	Yes n(%)	33 (5.3)	85 (4.6)	118 (4.8)	0.441
	No n(%)	585 (94.7)	1769 (95.4)	2354 (95.2)	
	Total n(%)	618 (100)	1854 (100)	2472 (100.0)	
Add Seretide (at any time)	Yes n(%)				N/A
	No n(%)	618 (100.0)	1854 (100.0)	2472 (100.0)	
	Total n(%)	618 (100)	1854 (100)	2472 (100.0)	
Add Symbicort (at any time)	Yes n(%)				N/A
	No n(%)	618 (100.0)	1854 (100.0)	2472 (100.0)	
	Total n(%)	618 (100)	1854 (100)	2472 (100.0)	
Add LABA (at any time)	Yes n(%)				N/A
	No n(%)	618 (100.0)	1854 (100.0)	2472 (100.0)	
	Total n(%)	618 (100)	1854 (100)	2472 (100.0)	
Add LTRA (at any time)	Yes n(%)	32 (5.2)	81 (4.4)	113 (4.6)	0.399
	No n(%)	586 (94.8)	1773 (95.6)	2359 (95.4)	
	Total n(%)	618 (100)	1854 (100)	2472 (100.0)	
Add Fostair (at any time)	Yes n(%)				N/A
	No n(%)	618 (100.0)	1854 (100.0)	2472 (100.0)	
	Total n(%)	618 (100)	1854 (100)	2472 (100.0)	
Add Theo (at any time)	Yes n(%)	2 (0.3)	8 (0.4)	10 (0.4)	0.716
	No n(%)	616 (99.7)	1846 (99.6)	2462 (99.6)	
	Total n(%)	618 (100)	1854 (100)	2472 (100.0)	

Table 23: Summary Statistics for Outcome categorical characterisation variables (Matched Cohort) (V) by Treatment Group
*** Conditional Logistic Regression**

2.4.1.2 HEALTHCARE COSTS

		Treatment Group		TOTAL	P value*
		FP/FOR	FP/SAL		
Asthma Related Drug Cost (£)	N (% non-missing)	618 (100.0)	1854 (100.0)	2472 (100.0)	<0.001
	Mean (SD)	363 (215)	423 (281)	408 (267)	
	Median (IQR)	316 (198, 493)	360 (219, 557)	352 (215, 544)	
Asthma Related Resource Cost (£)	N (% non-missing)	618 (100.0)	1854 (100.0)	2472 (100.0)	<0.001
	Mean (SD)	43 (88)	64 (131)	59 (122)	
	Median (IQR)	14 (14, 42)	14 (0, 56)	14 (14, 56)	
All Asthma Related Medical Costs (£)	N (% non-missing)	618 (100.0)	1854 (100.0)	2472 (100.0)	<0.001
	Mean (SD)	406 (240)	487 (332)	467 (314)	
	Median (IQR)	351 (228, 557)	399 (248, 637)	385 (242, 613)	

Table 24: Summary Statistics for Healthcare Costs (matched cohort) by Treatment Group
*** Conditional Logistic Regression**

3 EFFECTIVENESS ANALYSIS

3.1 MATCHED

3.1.1 PRIMARY OUTCOME

3.1.1.1 PROPORTION OF 'NO EXACERBATIONS'

The primary outcome is based on the proportions of 'no exacerbations' (as defined by the American Thoracic Society/European Respiratory Society (ATS/ERS) Joint Task Force. Defined as the occurrence of:

- Asthma-related[18]:
  - Hospital attendance / admissions OR
  - A&E attendance
- Use of acute oral steroids[19].

Exacerbations (ATS/ERS)	Treatment Group		Total
	FP/FOR	**FP/SAL**	
No n (%)	458 (74.1)	1372 (74.0)	1830 (74.0)
Yes n (%)	160 (25.9)	482 (26.0)	642 (26.0)
Total n (%)	618 (100.0)	1854 (100.0)	2472 (100.0)
Mean difference in Proportion f 'no exacerbation' adjusted for baseline confounders * (95% CI)	0.008 (-0.032, 0.047)	N/A	
Non inferiority met? (Lower 95% CI >-3.5%)	-3.5% : MET		

Table 25: Exacerbation (ATS) (matched cohort)
Adjusted for: Baseline GERD, baseline ICS Scripts (categorised).

[18] Asthma-related includes all events with a **lower respiratory code**, i.e. including all asthma codes, and lower respiratory tract infection codes

[19] Where:

- ≥1 oral steroid prescription occurs within 2 weeks of another, or
- ≥1 hospitalisation occurs within 2 weeks of another, or
- ≥1 hospitalisation occurs within 2 weeks of an oral steroid prescription

These events will be considered to be the result of the same exacerbation (and will only be counted once)

3.1.2 SECONDARY OUTCOMES

3.1.2.1 TOTAL NUMBER OF SERIOUS EXACERBATIONS

Defined as the occurrence of:

- Asthma-related[20]:
  - Hospital attendance / admissions OR
  - A&E attendance
- Use of acute oral steroids[21].

Exacerbations (ATS Definition)	Treatment Group	
	FP/FOR	**FP/SAL**
Median (IQR)	**0 (0, 1)**	**0 (0, 1)**
Rate Ratio adjusted for baseline confounders* (95% CI)	0.97 (0.82, 1.14)	1.00

Table 26: Exacerbation Rates (ATS Definition) (Matched Cohort)
Adjusted for baseline ICS daily dose, baseline acute Oral Steroid courses (categorised), baseline SAMA usage (categorised) and baseline LTRA usage. Unadjusted result rate ratio 0.97 (95% ci (0.82, 1.15))

[20] Asthma-related includes all events with a **lower respiratory code**, i.e. including all asthma codes, and lower respiratory tract infection codes

[21] Where:

- ≥1 oral steroid prescription occurs within 2 weeks of another, or
- ≥1 hospitalisation occurs within 2 weeks of another, or
- ≥1 hospitalisation occurs within 2 weeks of an oral steroid prescription

These events will be considered to be the result of the same exacerbation (and will only be counted once)

3.1.2.2 PROPORTION OF PATIENTS WITH FREQUENT EXACERBATION

Defined as the occurrence of:

- Asthma-related[26]:
  - Hospital attendance / admissions OR
  - A&E attendance
- Use of acute oral steroids[27].

Frequent exacerbations (ATS Definition) – IPDI	Treatment Group		Total
	FP/FOR	**FP/SAL**	
< 2 n (%)	557 (90%)	1680 (91%)	2237 (90%)
2+ n (%)	61 (10%)	174 (9%)	235 (10%)
Total (n)	618	1854	2472
Odds Ratio for frequent exacerbation adjusted for baseline confounders * (95% CI)	0.99 (0.72, 1.36)	1	

Table 27: Summary Results for Exacerbations (ATS Definition) (Matched Cohort)

***Logistic regression adjusted for GERD diagnosis, baseline acute oral steroid courses (categorised), baseline SAMA usage, gender, baseline ICS daily dose (categorised), NSAID usage and baseline LTRA usage. Unadjusted odds ratio 1.06 (0.79, 1.41).**

3.1.2.3 RISK DOMAIN ASTHMA CONTROL

Controlled: the absence of the following during the one-year outcome period:

- Asthma-related[22]:
  - Hospital attendance or admission
  - A&E attendance, OR
  - Out of hours consultations, OR
  - Out-patient department attendance
- GP consultations for lower respiratory tract infection
- Prescriptions for acute courses of oral steroids[23].

Uncontrolled: all others.

There is no significant difference between treatment groups (at the 5% level) having adjusted for baseline confounders.

Asthma Control (excl. SABA Usage) – IPDI	Treatment Group		Total
	FP/FOR	**FP/SAL**	
Controlled n (%)	383 (62%)	1115 (60%)	1498 (61%)
Uncontrolled n (%)	235 (38%)	739 (40%)	974 (39%)
Total n (%)	618	1854	2472
Odds Ratio for control adjusted for baseline confounders * (95% CI)	1.11 (0.91, 1.37)		

Table 28: Summary Results for Asthma Control (excl. SABA Usage) (Matched Cohort)
***Adjusted for: baseline asthma exacerbations (clinical definition), ICS daily dose, Cardiovascular diagnosis, Smoking status, LTRA usage, Gender, Rhinitis diagnosis and paracetamol use. Unadjusted odds ratio 1.08 (0.90, 1.29).**

[22] Asthma-related includes all events with a **lower respiratory code**, i.e. including all asthma codes, and lower respiratory tract infection codes

[23] Where:

- ≥1 oral steroid prescription occurs within 2 weeks of another, or
- ≥1 hospitalisation occurs within 2 weeks of another, or
- ≥1 hospitalisation occurs within 2 weeks of an oral steroid prescription

These events will be considered to be the result of the same exacerbation (and will only be counted once)

3.1.2.4 ACUTE RESPIRATORY EVENT RATE

The total number of acute respiratory events in the outcome period.

Acute respiratory event rate	Treatment Group	
	FP/FOR	**FP/SAL**
Median (IQR)	**0 (0,1)**	**0 (0,1)**
Rate Ratio adjusted for baseline confounders* (95% CI)	0.82 (0.71, 0.94)	1.00

Table 29: Acute respiratory event rate (Matched Cohort)

***Adjusted for: Gender, Heart failure diagnosis, NSAIDS use, Rhinitis diagnosis, Baseline exacerbations(ATS definition), GINA control code, baseline LTRA usage and baseline SAMA usage . Unadjusted rate ratio 0.88 (0.77 to 1.00.)**

3.1.2.5 OVERALL ASTHMA CONTROL

Overall asthma control	Treatment Group		Total
	FP/FOR	**FP/SAL**	
Controlled n(%)	180 (29%)	463 (25%)	643 (26%)
Uncontrolled n (%)	438 (71%)	1391 (75%)	1829 (74%)
Total (n)	618	1854	2472
Odds Ratio adjusted for baseline confounders * (95% CI)	1.21 (0.97 to 1.52)	1.0	

Table 30: Overall asthma control (Matched Cohort)

***Adjusted for: Baseline exacerbations (clinical definition), baseline SABA dosage, Cardiovascular diagnosis and CCI score (categorised). Unadjusted odds ratio 1.23 (1.04 to 1.47).**

3.1.2.6 SABA USAGE

SABA usage	Treatment Group		Total
	FP/FOR	**FP/SAL**	
≤400mcg n(%)	245 (40%)	695 (37%)	940 (38%)
≤400 mcg n(%)	167 (27%)	522 (28%)	689 (28%)
>400 mcg	206 (33%)	637 (34%)	843 (34%)
Total (n)	618 (100)	1854 (100)	2472
Odds Ratio for higher SABA usage adjusted for baseline confounders * (95% CI)	0.95 (0.78, 1.16)	1.0	

Table 31: SABA usage (Matched Cohort)

***Adjusted for: baseline antibiotics, baseline SABA dosage, CCI score (categorised), age and smoking status. Unadjusted odds ratio 0.93 (0.82 to 1.05).**

3.1.2.7 TREATMENT STABILITY

Treatment stability achieved	Treatment Group		Total
	FP/FOR	**FP/SAL**	
Yes n(%)	342 (55%)	990 (53%)	1332 (54%)
No n (%)	276 (45%)	864 (47%)	1140 (46%)
Total (n)	618 (100)	1854 (100)	2472
Odds Ratio for stability adjusted for baseline confounders * (95% CI)	1.10 (0.89, 1.35)	1	

Table 32: Treatment Stability (Matched Cohort)

***Adjusted for: baseline exacerbations (clinical definition), Rhinitis diagnosis, GINA control code, age, gender, smoking status, number of GP consultations (categorised) and LTRA usage. Unadjusted odds ratio 1.08 (0.90, 1.29)**

3.1.2.8 HOSPITALISATIONS

Hospitalisation	Treatment Group		Total
	FP/FOR	**FP/SAL**	
Yes n(%)	8 (1%)	14 (1%)	22 (1%)
No n (%)	610 (99%)	1840 (99%)	2450 (99%)
Total (n)	618 (100)	1854 (100)	
Odds Ratio for hospitalisation adjusted for baseline confounders * (95% CI)	2.07 (0.83, 5.16)	1.0	

Table 33: Hospitalisation (Matched Cohort)

***Adjusted for: Year of IPD and baseline number of antibiotics. Unadjusted odds ratio 1.72 (0.72, 4.15).**

3.1.2.9 MEDICATION POSSESSION CATEGORY

Medication possession category	Treatment Group		Total
	FP/FOR	**FP/SAL**	
0<80% n(%)	284 (46%)	945 (51%)	1229 (50%)
80+ n (%)	334 (54%)	909 (49%)	1243 (50%)
Total (n)	618 (100)	1854 (100)	2472 (100)
P-value from logistic regression comparison between treatment groups	0.017		

Table 34: Medication Possession category (Matched Cohort)

3.1.2.10 ADHERENCE

Adherence	Treatment Group		Total
	FP/FOR	FP/SAL	
0-70 n(%)	250 (40%)	838 (45%)	1088 (44%)
71-120 n (%)	287 (46%)	766 (41%)	1053 (43%)
121+ n(%)	81 (13%)	250 (14%)	331 (13%)
Total (n)	618 (100)	1854 (100)	2472 (100)
P-value from logistic regression comparison between treatment groups	0.132		

Table 35: Adherence category (Matched Cohort)

3.1.2.11 ICS USAGE

ICS Usage	Treatment Group		Total
	FP/FOR	FP/SAL	
0-250 n(%)	61 (10%)	155 (8%)	216 (9%)
251-500 n (%)	113 (18%)	423 (23%)	536 (22%)
501+ n(%)	444 (72%)	1276 (69%)	1720 (70%)
Total (n)	618 (100)	1854 (100)	2472 (100)
P-value from logistic regression comparison between treatment groups	0.536		

Table 36: ICS Usage (Matched Cohort)

3.1.2.12 CONTROLLER/RELIEVER RATIO

Controller/reliever ratio	Treatment Group		Total
	FP/FOR	FP/SAL	
<0.5 n(%)	79 (13%)	354 (19%)	433 (18%)
≥0.5 n (%)	539 (87%)	1500 (81%)	2039 (83%)
Total (n)	618 (100)	1854 (100)	2472 (100)
P-value from logistic regression comparison between treatment groups	<0.001		

Table 37: Controller/relieved ratio (Matched Cohort)

3.1.2.13 ORAL THRUSH INCIDENCE

Oral Thrush	Treatment Group		Total
	FP/FOR	FP/SAL	
Yes n(%)	5 (1%)	26 (1%)	31 (1%)
No n (%)	613 (99%)	1828 (99%)	2441 (99%)
Total (n)	618 (100)	1854 (100)	2472 (100.0)
P-value from logistic regression comparison between treatment groups	0.260		

Table 38: Oral Thrush (Matched Cohort)

3.1.2.14 FURTHER ANALYSIS

Further sub-group analysis of secondary outcomes was not carried out due to small numbers.

4 SUMMARY OF RESULTS AND CONCLUSIONS

4.1 SUMMARY OF RESULTS

Table 40 and 40 summarise the results of the primary and secondary analysis respectively. Patients in the were matched in a ratio of 1:3.

Matched Cohort	REFERENCE TREATMENT (OR/RR)	TEST TREATMENT OR (95% CI) relative to REFERENCE TREATMENT	
		OR	% Difference in Proportions (Non-inferiority Limit= - 10%)*
No Exacerbations (ATS Definition)	1.00	0.008 (-0.032, 0.047)	--3.5% : MET

Table 39: Summary of primary outcome results - matched cohort.

*Green highlight denotes non-inferiority criteria met. Red Highlight denotes non-inferiority not criteria met.

Matched Cohort	Reference Treatment (OR/RR)	TEST TREATMENT OR/RR (95% CI) relative to REFERENCE TREATMENT
		OR/RR
Exacerbation Rate (ATS Definition)	1.00	0.97 (0.82, 1.14)
Frequent Exacerbation (ATS Definition)	1.00	0.99 (0.72, 1.36)
Risk Domain Asthma Control	1.00	1.11 (0.91, 1.37)
Acute respiratory event rate	1.00	0.82 (0.71, 0.94)
Overall Asthma Control	1.00	1.21 (0.97 to 1.52)
SABA usage	1.00	0.95 (0.78, 1.16)
Treatment Stability	1.00	1.10 (0.89, 1.35)
Hospitalisations	1.00	2.07 (0.83, 5.16)

Table 40: Summary of secondary outcome results – matched cohort.

The probability of having no ATS exacerbations was found to be non-inferior for FP/FOR compared to FP/SAL, difference in proportion 0.008 (-0.032, 0.047) using the non-inferiority boundary of -3.5%, having adjusted for baseline GERD and baseline ICS Scripts (categorised). There was no evidence that exacerbation rate was significantly different between the cohorts using the ATS definition (see table 26), however the rate of exacerbations using the clinical definition was statistically lower for FP/FOR compared to FP/SAL (RR 0.82 and 95% confidence interval 0.71 to 0.94, having adjusted for gender, heart failure diagnosis, rhinitis diagnosis, baseline exacerbation (ATS definition), GINA control code, NSAIDS use, baseline LTRA usage and baseline SAMA usage.

There was evidence of more patients in the FP/FOR cohort being in higher categories of Medication Possession category and Controller to Reliever ratio compared to the FP/SAL group. There was no evidence of significant differences between the cohorts in any of the other outcomes, although, with the exception of hospitalisation estimates, comparisons between groups were in favour of FP/FOR for the other secondary outcomes; rate of exacerbations (ATS definition), frequent exacerbations (ATS definition), risk domain asthma control, overall asthma control, SABA usage and treatment stability.

4.2 CONCLUSIONS

The probability of having no ATS exacerbations was found to be non-inferior for FP/FOR compared to FP/SAL, using a lower inferiority boundary of -3.5% for difference in proportion. There was no evidence that exacerbation rate was significantly different between the cohorts using the ATS definition, however using the clinical definition the rate of exacerbations was significantly lower the FP/FOR compared to the FP/SAL cohort.

5 APPENDIX 1 – DATA DICTIONARY

Flutiform Phase 3 - Data dictionary - V1.

6 APPENDIX 2 – CONSORT DIAGRAM