Clinical trial results:
Investigating the mechanism of inhaled corticosteroids associated pneumonia by longitudinal characterisation of the airway microbiome in patients with severe COPD

Summary

EudraCT number	2016-000734-21
Trial protocol	GB
Global end of trial date	26 March 2019

Results information

Result version number	v1 (current)
This version publication date	28 June 2023
First version publication date	28 June 2023

Trial information

Trial identification

Sponsor protocol code	2014RC07

Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	NCT02972476
WHO universal trial number (UTN)	-

Notes:

Sponsors

Sponsor organisation name	University of Dundee
Sponsor organisation address	Ninewells Hospital and Medical School, Dundee, United Kingdom, DD1 9SY
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Notes:

Paediatric regulatory details

Is trial part of an agreed paediatric investigation plan (PIP)	No
Does article 45 of REGULATION (EC) No 1901/2006 apply to this trial?	No
Does article 46 of REGULATION (EC) No 1901/2006 apply to this trial?	No

Notes:

Results analysis stage

Analysis stage	Final
Date of interim/final analysis	31 January 2023
Is this the analysis of the primary completion data?	No

Global end of trial reached?	Yes
Global end of trial date	26 March 2019
Was the trial ended prematurely?	Yes

Notes:

General information about the trial

Main objective of the trial:

To determine the effects of the inhaled corticosteroids fluticasone propionate/salmeterol 500/50 mcg vs budesonide/formoterol 400/12 mcg on upper airway bacterial load from oropharyngeal swabs.

Protection of trial subjects:

Patients were excluded if they were unable to give informed consent, had a known allergy, intolerance or contraindication to any of the study drugs, or had any unstable co-morbidities (cardiovascular disease, active malignancy) which in the opinion of the investigator would make the patient unsuitable to be enrolled in the study

Background therapy:

During the study it was anticipated that the patient should continue on their usual treatment for COPD, excluding ICS or nasal corticosteroids, LABAs and LAMAs.

Evidence for comparator:

The 4 treatment regime arms are as follows:
1. Budesonide/formoterol 400/12 mcg (Symbicort Turbohaler) 1 inhalation twice daily + Aclidinium Bromide 322 mcg (Eklira Genuair) 1 inhalation twice daily
2. Fluticasone propionate/salmeterol 500/50 mcg (Seretide Accuhaler) 1 inhalation twice daily + Aclidinium Bromide 322 mcg (Eklira Genuair) 1 inhalation twice daily
3. Fluticasone propionate/salmeterol 250/50 mcg (Seretide Accuhaler) 1 inhalation twice daily + Aclidinium Bromide 322 mcg (Eklira Genuair) 1 inhalation twice daily
4. Aclidinium/formoterol combination 340/12 mcg (Duaklir Genuair) 1 inhalation twice daily

The rationale for these doses were that regime 1 and regime 2 are the licensed doses of Symbicort and Seretide in the UK which are commonly used in this patient population. Treatment regime 3 was included as this is commonly used in clinical practice as an equivalent dose to Symbicort and therefore may help to answer whether there is a dose response relationship effecting the airway microbiome. This treatment is licensed in asthma but is not licensed for the treatment of COPD at this lower dose. It is a lower dose of the licensed fluticasone propionate/salmeterol 500/50 which is licensed in COPD and is administered
through the same device. It is equivalent in dose, as measured by BDP, to all other ICS licensed in the treatment of COPD (beclomethasone dipropionate/formoterol fumarate 100/6 2 puff twice daily= 1000BDP, fluticasone furoate + vilanterol trifenatate 92/22 1 puff once daily=1000BDP, and Budesonide/formoterol as described above= 800BDP). Treatment regime 4 is included as LABA/LAMA therapy is considered an appropriate alternative to ICS/LABA therapy in emerging clinical guidelines. This also acts as a control population without ICS treatment, thus demonstrating that any changes during the study period are the results of the effect of ICS.

Actual start date of recruitment	01 June 2016
Long term follow-up planned	No
Independent data monitoring committee (IDMC) involvement?	No

Notes:

Population of trial subjects

Subjects enrolled per country

Country: Number of subjects enrolled	United Kingdom: 61
Worldwide total number of subjects	61
EEA total number of subjects	0

Notes:

Subjects enrolled per age group

In utero	0
Preterm newborn - gestational age < 37 wk	0
Newborns (0-27 days)	0
Infants and toddlers (28 days-23 months)	0
Children (2-11 years)	0
Adolescents (12-17 years)	0
Adults (18-64 years)	23
From 65 to 84 years	37
85 years and over	1

Subject disposition

Recruitment

Recruitment details:

Patients were recruited at 6 NHS sites in the UK (NHS Tayside, NHS Lothian, NHS Lanarkshire, NHS Fife, NHS Blackpool, NHS Greater Glasgow and Clyde)

Pre-assignment

Screening details:

158 patients screened. Screen failures-asthma (1), antibiotics or oral steroids in previous 28 days (2), dental infection (1), <10 pack year history (1), FEV1/FVC >0.7 (8), did not meet GOLD criteria (22), could not perform spirometry (1). 122 patients started 4-week wash-out (withdrawal COPD exacerbations (45), other (16). 61 subjects randomised

Period 1

Period 1 title	Overall trial (overall period)
Is this the baseline period?	Yes
Allocation method	Randomised - controlled
Blinding used	Not blinded

Blinding implementation details:

Open label

Arms

Are arms mutually exclusive?	Yes
Arm title	Symbicort 400/12 & Eklira Genuair

Arm description:

Budesonide 400mcg & formoterol fumarate 12mcg: 1 inhalation twice daily, inhalation powder and Aclidinium
bromide 322mcg: 1 inhalation twice daily, inhalation powder for 3 months
Budesonide & formoterol fumarate and Aclidinium bromide

Arm type	Active comparator
Investigational medicinal product name	Budesonide & formoterol fumarate and Aclidinium bromide
Investigational medicinal product code	
Other name	Symbicort 400/12 & Eklira Genuair
Pharmaceutical forms	Inhalation powder
Routes of administration	Inhalation use

Dosage and administration details:

Budesonide 400mcg & formoterol fumarate 12mcg: 1 inhalation twice daily, inhalation powder and Aclidinium
bromide 322mcg: 1 inhalation twice daily, inhalation powder for 3 months

Arm title	Seretide 500/50 & Eklira Genuair

Arm description:

Fluticasone propionate 500mcg & salmeterol 50mcg: 1 inhalation twice daily, inhalation powder and Aclidinium
bromide 322mcg: 1 inhalation twice daily, inhalation powder for 3 months
Fluticasone 500 & salmeterol and Aclidinium bromide

Arm type	Active comparator
Investigational medicinal product name	Fluticasone 500 & salmeterol and Aclidinium bromide
Investigational medicinal product code	
Other name	Seretide 500/50 & Eklira Genuair
Pharmaceutical forms	Inhalation powder
Routes of administration	Inhalation use

Dosage and administration details:

Fluticasone propionate 500mcg & salmeterol 50mcg: 1 inhalation twice daily, inhalation powder and Aclidinium

bromide 322mcg: 1 inhalation twice daily, inhalation powder for 3 months

Arm title	Seretide 250/50 & Eklira Genuair

Arm description:

Fluticasone propionate 250mcg & salmeterol 50mcg: 1 inhalation twice daily, inhalation powder and Aclidinium
bromide 322mcg: 1 inhalation twice daily, inhalation powder for 3 months
Fluticasone 250 & salmeterol and Aclidinium bromide

Arm type	Active comparator
Investigational medicinal product name	Fluticasone 250 & salmeterol and Aclidinium bromide
Investigational medicinal product code	
Other name	Seretide 250/50 & Eklira Genuair
Pharmaceutical forms	Inhalation powder
Routes of administration	Inhalation use

Dosage and administration details:

1 inhalation twice daily, inhalation powder for 3 months

Arm title	Duaklir Genuair

Arm description:

Aclidinium bromide 340mcg & formoterol fumarate 12mcg: 1 inhalation twice daily, inhalation powder for 3
months
Aclidinium bromide & formoterol fumarate

Arm type	Active comparator
Investigational medicinal product name	Aclidinium bromide & formoterol fumarate
Investigational medicinal product code	
Other name	Duaklir Genuair
Pharmaceutical forms	Inhalation powder
Routes of administration	Inhalation use

Dosage and administration details:

Aclidinium bromide 340mcg & formoterol fumarate 12mcg: 1 inhalation twice daily, inhalation powder for 3
months

Number of subjects in period 1	Symbicort 400/12 & Eklira Genuair	Seretide 500/50 & Eklira Genuair	Seretide 250/50 & Eklira Genuair
Started	18	13	15
Completed	16	13	14
Not completed	2	0	1
Consent withdrawn by subject	1	-	1
Adverse event, non-fatal	1	-	-

Number of subjects in period 1	Duaklir Genuair
Started	15
Completed	14
Not completed	1
Consent withdrawn by subject	1

Adverse event, non-fatal	-

Baseline characteristics

Reporting groups	
Reporting group title	Overall trial

Reporting group description: -

Reporting group values	Overall trial	Total	
Number of subjects	61	61	
Age categorical Units: Subjects			
In utero		0	
Preterm newborn infants (gestational age < 37 wks)		0	
Newborns (0-27 days)		0	
Infants and toddlers (28 days-23 months)		0	
Children (2-11 years)		0	
Adolescents (12-17 years)		0	
Adults (18-64 years)		0	
From 65-84 years		0	
85 years and over		0	
Age continuous			
Age (years)			
Units: years			
arithmetic mean	66.9		
standard deviation	± 7.8	-	
Gender categorical			
Gender			
Units: Subjects			
Female	28	28	
Male	33	33	
Smoking status			
Smoking status at enrolment			
Units: Subjects			
Ex-smoker	37	37	
Current smoker	24	24	
Blood eosinophil count at baseline Units: Subjects			
<150	21	21	
150-299	28	28	
>=300	12	12	
GOLD classification Units: Subjects			
GOLD B	8	8	
GOLD C	1	1	
GOLD D	52	52	
Pack years			
Smoking pack years			
Units: Years			

arithmetic mean	44.4		
standard deviation	± 21.5	-	
BMI			
Units: kg/m2			
arithmetic mean	28.9		
standard deviation	± 6.9	-	
MRC Dyspnoea Score			
Units: MRC Dyspnoea Score			
arithmetic mean	3.3		
standard deviation	± 1.0	-	
CAT Score			
COPD Assessment Test			
Units: CAT Score			
arithmetic mean	21.5		
standard deviation	± 7.2	-	
FEV1 (L)			
Units: litre(s)			
arithmetic mean	1.32		
standard deviation	± 0.61	-	
FEV1 (%)			
Units: percent			
arithmetic mean	53.0		
standard deviation	± 25.5	-	
FVC (L)			
Units: litre(s)			
arithmetic mean	2.74		
standard deviation	± 0.94	-	
FVC (%)			
Units: percent			
arithmetic mean	88.9		
standard deviation	± 28.7	-	
FEV1/FEVC ratio			
Units: percent			
arithmetic mean	46.6		
standard deviation	± 16.1	-	
FEF 25-75%			
Units: percent			
arithmetic mean	20.8		
standard deviation	± 15.3	-	
Oxygen saturation at rest			
Units: percent			
arithmetic mean	95		
standard deviation	± 2.4	-	
Number of exacerbations in the last year			
Units: exacerbations			
arithmetic mean	2.2		
standard deviation	± 1.5	-	

Subject analysis sets	
Subject analysis set title	Arm 1: BF400
Subject analysis set type	Intention-to-treat
Subject analysis set description: Budesonide & formoterol fumarate and Aclidinium bromide	
Subject analysis set title	Arm 2: FS500
Subject analysis set type	Intention-to-treat
Subject analysis set description: Fluticasone 500 & salmeterol and Aclidinium bromide	
Subject analysis set title	Arm 3: FS250
Subject analysis set type	Intention-to-treat
Subject analysis set description: Fluticasone 250 & salmeterol and Aclidinium bromide	
Subject analysis set title	Arm 4: AF
Subject analysis set type	Intention-to-treat
Subject analysis set description: Aclidinium bromide & formoterol fumarate	
Subject analysis set title	Pooled Fluticasone propionate ICS
Subject analysis set type	Intention-to-treat
Subject analysis set description: Pooled Arms 2 and Arm 3 Fluticasone propionate 250mcg & salmeterol 50mcg: 1 inhalation twice daily, inhalation powder and Aclidinium bromide 322mcg: 1 inhalation twice daily, inhalation powder for 3 months Fluticasone 250 & salmeterol and Aclidinium bromide Fluticasone propionate 500mcg & salmeterol 50mcg: 1 inhalation twice daily, inhalation powder and Aclidinium bromide 322mcg: 1 inhalation twice daily, inhalation powder for 3 months Fluticasone 500 & salmeterol and Aclidinium bromide	
Subject analysis set title	Pooled ICS
Subject analysis set type	Intention-to-treat
Subject analysis set description: Pooled ICS treatments: Budesonide 400mcg & formoterol fumarate 12mcg: 1 inhalation twice daily, inhalation powder and Aclidinium bromide 322mcg: 1 inhalation twice daily, inhalation powder for 3 months. Budesonide & formoterol fumarate and Aclidinium bromide Fluticasone propionate 500mcg & salmeterol 50mcg: 1 inhalation twice daily, inhalation powder and Aclidinium bromide 322mcg: 1 inhalation twice daily, inhalation powder for 3 months. Fluticasone 500 & salmeterol and Aclidinium bromide Fluticasone propionate 250mcg & salmeterol 50mcg: 1 inhalation twice daily, inhalation powder and Aclidinium bromide 322mcg: 1 inhalation twice daily, inhalation powder for 3 months. Fluticasone 250 & salmeterol and Aclidinium bromide	

Reporting group values	Arm 1: BF400	Arm 2: FS500	Arm 3: FS250
Number of subjects	18	13	15
Age categorical Units: Subjects			
In utero Preterm newborn infants (gestational age < 37 wks) Newborns (0-27 days) Infants and toddlers (28 days-23 months) Children (2-11 years) Adolescents (12-17 years) Adults (18-64 years)			

From 65-84 years			
85 years and over			

Age continuous			
Age (years)			
Units: years			
arithmetic mean	68.8	67.4	65.1
standard deviation	± 8.4	± 10.2	± 5.3
Gender categorical			
Gender			
Units: Subjects			
Female	6	9	5
Male	12	4	10
Smoking status			
Smoking status at enrolment			
Units: Subjects			
Ex-smoker	10	8	8
Current smoker	8	5	7
Blood eosinophil count at baseline			
Units: Subjects			
<150	4	4	5
150-299	9	7	7
>=300	5	2	3
GOLD classification			
Units: Subjects			
GOLD B	1	1	2
GOLD C	0	1	0
GOLD D	17	11	13
Pack years			
Smoking pack years			
Units: Years			
arithmetic mean	46.1	49.4	39.7
standard deviation	± 20.3	± 26.9	± 12.9
BMI			
Units: kg/m2			
arithmetic mean	26.4	28.5	29.8
standard deviation	± 6.0	± 7.8	± 8.7
MRC Dyspnoea Score			
Units: MRC Dyspnoea Score			
arithmetic mean	.71	3.4	2.9
standard deviation	± 1.0	± 0.8	± 1.0
CAT Score			
COPD Assessment Test			
Units: CAT Score			
arithmetic mean	21.1	21.6	23.0
standard deviation	± 7.2	± 10.1	± 6.5
FEV1 (L)			
Units: litre(s)			
arithmetic mean	1.49	1.21	1.45
standard deviation	± 0.67	± 0.55	± 0.58
FEV1 (%)			

Units: percent			
arithmetic mean	58.9	57.6	54.3
standard deviation	± 24.7	± 33.6	± 20.0
FVC (L)			
Units: litre(s)			
arithmetic mean	2.72	2.68	3.10
standard deviation	± 0.95	± 1.1	± 0.87
FVC (%)			
Units: percent			
arithmetic mean	86.5	98.6	91.9
standard deviation	± 32.2	± 39.3	± 19.2
FEV1/FEVC ratio			
Units: percent			
arithmetic mean	51.5	43.3	46.6
standard deviation	± 18.1	± 20.4	± 10.6
FEF 25-75%			
Units: percent			
arithmetic mean	23.2	17.5	22.6
standard deviation	± 14.3	± 13.7	± 2.08
Oxygen saturation at rest			
Units: percent			
arithmetic mean	94.2	95.8	95.1
standard deviation	± 3.4	± 2.4	± 1.5
Number of exacerbations in the last year			
Units: exacerbations			
arithmetic mean	2.89	2.28	20.8
standard deviation	± 1.8	± 1.3	± 1.3

Reporting group values	Arm 4: AF	Pooled Fluticasone propionate ICS	Pooled ICS
Number of subjects	15	25	40
Age categorical			
Units: Subjects			
In utero			
Preterm newborn infants (gestational age < 37 wks)			
Newborns (0-27 days)			
Infants and toddlers (28 days-23 months)			
Children (2-11 years)			
Adolescents (12-17 years)			
Adults (18-64 years)			
From 65-84 years			
85 years and over			
Age continuous			
Age (years)			
Units: years			
arithmetic mean	66.0		
standard deviation	± 6.8	±	±
Gender categorical			
Gender			
Units: Subjects			

Female	8		
Male	7		

Smoking status			
Smoking status at enrolment			
Units: Subjects			
Ex-smoker	11		
Current smoker	4		
Blood eosinophil count at baseline			
Units: Subjects			
<150	8		
150-299	5		
>=300	2		
GOLD classification			
Units: Subjects			
GOLD B	4		
GOLD C	0		
GOLD D	11		
Pack years			
Smoking pack years			
Units: Years			
arithmetic mean	42.9		
standard deviation	± 25.3	±	±
BMI			
Units: kg/m2			
arithmetic mean	28.7		
standard deviation	± 4.5	±	±
MRC Dyspnoea Score			
Units: MRC Dyspnoea Score			
arithmetic mean	3.1		
standard deviation	± 1.1	±	±
CAT Score			
COPD Assessment Test			
Units: CAT Score			
arithmetic mean	20.3		
standard deviation	± 4.9	±	±
FEV1 (L)			
Units: litre(s)			
arithmetic mean	1.08		
standard deviation	± 0.57	±	±
FEV1 (%)			
Units: percent			
arithmetic mean	40.4		
standard deviation	± 21.0	±	±
FVC (L)			
Units: litre(s)			
arithmetic mean	2.45		
standard deviation	± 0.83	±	±
FVC (%)			
Units: percent			
arithmetic mean	80.5		

standard deviation	± 20.2	±	±
FEV1/FEVC ratio			
Units: percent			
arithmetic mean	43.5		
standard deviation	± 14.1	±	±
FEF 25-75%			
Units: percent			
arithmetic mean	18.9		
standard deviation	± 2.40	±	±
Oxygen saturation at rest			
Units: percent			
arithmetic mean	94.3		
standard deviation	± 2.9	±	±
Number of exacerbations in the last year			
Units: exacerbations			
arithmetic mean	2.40		
standard deviation	± 2.0	±	±

End points

End points reporting groups

Reporting group title	Symbicort 400/12 & Eklira Genuair
Reporting group description:	
Budesonide 400mcg & formoterol fumarate 12mcg: 1 inhalation twice daily, inhalation powder and Aclidinium bromide 322mcg: 1 inhalation twice daily, inhalation powder for 3 months Budesonide & formoterol fumarate and Aclidinium bromide	
Reporting group title	Seretide 500/50 & Eklira Genuair
Reporting group description:	
Fluticasone propionate 500mcg & salmeterol 50mcg: 1 inhalation twice daily, inhalation powder and Aclidinium bromide 322mcg: 1 inhalation twice daily, inhalation powder for 3 months Fluticasone 500 & salmeterol and Aclidinium bromide	
Reporting group title	Seretide 250/50 & Eklira Genuair
Reporting group description:	
Fluticasone propionate 250mcg & salmeterol 50mcg: 1 inhalation twice daily, inhalation powder and Aclidinium bromide 322mcg: 1 inhalation twice daily, inhalation powder for 3 months Fluticasone 250 & salmeterol and Aclidinium bromide	
Reporting group title	Duaklir Genuair
Reporting group description:	
Aclidinium bromide 340mcg & formoterol fumarate 12mcg: 1 inhalation twice daily, inhalation powder for 3 months Aclidinium bromide & formoterol fumarate	
Subject analysis set title	Arm 1: BF400
Subject analysis set type	Intention-to-treat
Subject analysis set description:	
Budesonide & formoterol fumarate and Aclidinium bromide	
Subject analysis set title	Arm 2: FS500
Subject analysis set type	Intention-to-treat
Subject analysis set description:	
Fluticasone 500 & salmeterol and Aclidinium bromide	
Subject analysis set title	Arm 3: FS250
Subject analysis set type	Intention-to-treat
Subject analysis set description:	
Fluticasone 250 & salmeterol and Aclidinium bromide	
Subject analysis set title	Arm 4: AF
Subject analysis set type	Intention-to-treat
Subject analysis set description:	
Aclidinium bromide & formoterol fumarate	
Subject analysis set title	Pooled Fluticasone propionate ICS
Subject analysis set type	Intention-to-treat
Subject analysis set description:	
Pooled Arms 2 and Arm 3 Fluticasone propionate 250mcg & salmeterol 50mcg: 1 inhalation twice daily, inhalation powder and Aclidinium bromide 322mcg: 1 inhalation twice daily, inhalation powder for 3 months Fluticasone 250 & salmeterol and Aclidinium bromide Fluticasone propionate 500mcg & salmeterol 50mcg: 1 inhalation twice daily, inhalation powder and Aclidinium bromide 322mcg: 1 inhalation twice daily, inhalation powder for 3 months Fluticasone 500 & salmeterol and Aclidinium bromide	
Subject analysis set title	Pooled ICS
Subject analysis set type	Intention-to-treat

Subject analysis set description:

Pooled ICS treatments: Budesonide 400mcg & formoterol fumarate 12mcg: 1 inhalation twice daily, inhalation
powder and Aclidinium bromide 322mcg: 1 inhalation twice daily, inhalation powder for 3 months. Budesonide &
formoterol fumarate and Aclidinium bromide Fluticasone propionate 500mcg & salmeterol 50mcg: 1 inhalation
twice daily, inhalation powder and Aclidinium bromide 322mcg: 1 inhalation twice daily, inhalation powder for
3 months. Fluticasone 500 & salmeterol and Aclidinium bromide Fluticasone propionate 250mcg & salmeterol
50mcg: 1 inhalation twice daily, inhalation powder and Aclidinium bromide 322mcg: 1 inhalation twice daily,
inhalation powder for 3 months. Fluticasone 250 & salmeterol and Aclidinium bromide

Primary: Change in Bacterial Load of Total Respiratory Pathogens in Oropharyngeal Samples FS500 vs BF400

End point title	Change in Bacterial Load of Total Respiratory Pathogens in Oropharyngeal Samples FS500 vs BF400

End point description:

To determine the effects of the inhaled corticosteroids fluticasone propionate/salmeterol 500/50 mcg vs budesonide/
formoterol 400/12 mcg on upper airway bacterial load from oropharyngeal swabs.

End point type	Primary

End point timeframe:

Month 1 to month 3

End point values	Arm 1: BF400	Arm 2: FS500		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	16	12		
Units: cfu/g equivalents				
arithmetic mean (confidence interval 95%)	8.88 (8.46 to 9.30)	8.89 (8.34 to 9.44)		

Statistical analyses

Statistical analysis title	Change in Bacterial Load FS500 vs BF400

Statistical analysis description:

Change in Bacterial Load of Total Respiratory Pathogens in Oropharyngeal Samples FS500 vs BF400

Comparison groups	Arm 1: BF400 v Arm 2: FS500
Number of subjects included in analysis	28
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.5666
Method	Mixed models analysis
Parameter estimate	Mean difference (final values)
Point estimate	0.26

Confidence interval	
level	95 %
sides	2-sided
lower limit	-0.648
upper limit	1.176

Secondary: Change in Bacterial Load of Total Respiratory Pathogens in Sputum Samples FS500 vs BF400

End point title	Change in Bacterial Load of Total Respiratory Pathogens in Sputum Samples FS500 vs BF400

End point description:

To determine the effects of the inhaled corticosteroids fluticasone propionate/salmeterol 500/50 mcg vs budesonide/
formoterol 400/12 mcg on lower airway bacterial load from sputum

End point type	Secondary

End point timeframe:

Month 1 to month 3

End point values	Arm 1: BF400	Arm 2: FS500		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	15	11		
Units: cfu/g equivalent units				
arithmetic mean (confidence interval 95%)	9.87 (9.447 to 10.300)	10.44 (10.049 to 10.822)		

Statistical analyses

Statistical analysis title	Change in Sput BL BF400 vs FS500

Statistical analysis description:

Change in Bacterial Load of Total Respiratory Pathogens in Sputum Samples FS500 vs BF400

Comparison groups	Arm 1: BF400 v Arm 2: FS500
Number of subjects included in analysis	26
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.00037
Method	Mixed models analysis
Parameter estimate	Mean difference (final values)
Point estimate	0.867
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.292
upper limit	1.442

Secondary: Change in Bacterial Load of Total Respiratory Pathogens in Nasopharyngeal Samples FS500 vs BF400

End point title	Change in Bacterial Load of Total Respiratory Pathogens in Nasopharyngeal Samples FS500 vs BF400

End point description:

To determine the effects of the inhaled corticosteroids fluticasone propionate/salmeterol 500/50 mcg vs budesonide/
formoterol 400/12 mcg on bacterial load from nasopharyngeal swabs

End point type	Secondary

End point timeframe:

Month 1 to month 3

End point values	Arm 1: BF400	Arm 2: FS500		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	16	13		
Units: CFU/g equivalent units				
arithmetic mean (confidence interval 95%)	6.96 (6.556 to 7.361)	6.9 (6.461 to 7.339)		

Statistical analyses

Statistical analysis title	Change in NP BL BF400 vs FS500

Statistical analysis description:

Change in Bacterial Load of Total Respiratory Pathogens in Nasopharyngeal Samples FS500 vs BF400

Comparison groups	Arm 1: BF400 v Arm 2: FS500
Number of subjects included in analysis	29
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.5793
Method	Mixed models analysis
Parameter estimate	Mean difference (final values)
Point estimate	-0.222
Confidence interval	
level	95 %
sides	2-sided
lower limit	-1.016
upper limit	0.572

Secondary: Change in the Microbiome by Alpha-diversity in Sputum Samples FS500 vs BF400

End point title	Change in the Microbiome by Alpha-diversity in Sputum Samples FS500 vs BF400

End point description: Treatment period, month 1 to month 3	
End point type	Secondary
End point timeframe: To determine the effects of the inhaled corticosteroids fluticasone propionate/salmeterol 500/50 mcg vs budesonide/ formoterol 400/12 mcg on the microbiome by alpha-diversity from sputum	

End point values	Arm 1: BF400	Arm 2: FS500		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	15	11		
Units: Shannon Weiner diversity index				
arithmetic mean (confidence interval 95%)	1.62 (1.288 to 1.954)	1.58 (1.389 to 1.772)		

Statistical analyses

Statistical analysis title	Change in SWDI FS500 vs BF400
Statistical analysis description: Change in the Microbiome by Alpha-diversity in Sputum Samples FS500 vs BF400	
Comparison groups	Arm 2: FS500 v Arm 1: BF400
Number of subjects included in analysis	26
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.7904
Method	Mixed models analysis
Parameter estimate	Mean difference (final values)
Point estimate	-0.055
Confidence interval	
level	95 %
sides	2-sided
lower limit	-0.463
upper limit	0.353

Secondary: Change in the Microbiome by Alpha-diversity in Nasopharyngeal Samples FS500 vs BF400

End point title	Change in the Microbiome by Alpha-diversity in Nasopharyngeal Samples FS500 vs BF400
End point description: To determine the effects of the inhaled corticosteroids fluticasone propionate/salmeterol 500/50 mcg vs budesonide/ formoterol 400/12 mcg on the microbiome by alpha-diversity from nasopharyngeal swabs	
End point type	Secondary
End point timeframe: Treatment period, month 1 to 3	

End point values	Arm 1: BF400	Arm 2: FS500		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	16	13		
Units: Shannon Weiner diversity index				
arithmetic mean (confidence interval 95%)	1.46 (1.166 to 1.751)	1.18 (0.789 to 1.563)		

Statistical analyses

Statistical analysis title	Change in SWDI NP FS500 vs BF400
Statistical analysis description:	
Change in the Microbiome by Alpha-diversity in Nasopharyngeal Samples FS500 vs BF400	
Comparison groups	Arm 1: BF400 v Arm 2: FS500
Number of subjects included in analysis	29
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.324
Method	Mixed models analysis
Parameter estimate	Mean difference (final values)
Point estimate	0.23
Confidence interval	
level	95 %
sides	2-sided
lower limit	-0.231
upper limit	0.692

Secondary: Change in Total Bacterial Load FS250 vs BF400 in Sputum

End point title	Change in Total Bacterial Load FS250 vs BF400 in Sputum
End point description:	
To determine the effects of the inhaled corticosteroids fluticasone propionate/salmeterol 250/50 mcg vs budesonide/ formoterol 400/12 mcg on lower airway bacterial load from sputum	
End point type	Secondary
End point timeframe:	
Treatment period, months 1 to 3	

End point values	Arm 1: BF400	Arm 3: FS250		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	15	14		
Units: CFU/g equivalent units				
arithmetic mean (confidence interval 95%)	9.87 (9.447 to 10.300)	10.35 (9.897 to 10.798)		

Statistical analyses

Statistical analysis title	Change in BL Sput FS250 vs BF400
Statistical analysis description:	
Change in Total Bacterial Load FS250 vs BF400 in Sputum	
Comparison groups	Arm 1: BF400 v Arm 3: FS250
Number of subjects included in analysis	29
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.3635
Method	Mixed models analysis
Parameter estimate	Mean difference (final values)
Point estimate	0.286
Confidence interval	
level	95 %
sides	2-sided
lower limit	-0.337
upper limit	0.909

Secondary: Change in Total Bacterial Load FS250 vs BF400 in Oropharyngeal Samples

End point title	Change in Total Bacterial Load FS250 vs BF400 in Oropharyngeal Samples
End point description:	
To determine the effects of the inhaled corticosteroids fluticasone propionate/salmeterol 250/50 mcg vs budesonide/formoterol 400/12 mcg on lower airway bacterial load from oropharyngeal samples	
End point type	Secondary
End point timeframe:	
Treatment period, months 1 to 3	

End point values	Arm 1: BF400	Arm 3: FS250		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	16	14		
Units: CFU/g equivalent units				
arithmetic mean (confidence interval 95%)	8.88 (8.462 to 9.298)	8.08 (7.529 to 8.636)		

Statistical analyses

Statistical analysis title	Change in BL OP FS250 vs BF400
Statistical analysis description:	
Change in Total Bacterial Load FS250 vs BF400 in Oropharyngeal Samples	
Comparison groups	Arm 1: BF400 v Arm 3: FS250
Number of subjects included in analysis	30
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.1007
Method	Mixed models analysis
Parameter estimate	Mean difference (final values)
Point estimate	-0.863
Confidence interval	
level	95 %
sides	2-sided
lower limit	-1.897
upper limit	0.171

Secondary: Change in Total Bacterial Load FS250 vs BF400 in Nasopharyngeal Samples

End point title	Change in Total Bacterial Load FS250 vs BF400 in Nasopharyngeal Samples
End point description:	
To determine the effects of the inhaled corticosteroids fluticasone propionate/salmeterol 250/50 mcg vs budesonide/formoterol 400/12 mcg on lower airway bacterial load from nasopharyngeal samples	
End point type	Secondary
End point timeframe:	
Treatment period, months 1 to 3	

End point values	Arm 1: BF400	Arm 3: FS250		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	16	14		
Units: CFU/g equivalent units				
arithmetic mean (confidence interval 95%)	6.96 (6.556 to 7.361)	6.89 (6.306 to 7.479)		

Statistical analyses

Statistical analysis title	Change in BL NP FS250 vs BF400
Statistical analysis description:	
Change in Total Bacterial Load FS250 vs BF400 in Nasopharyngeal Samples	
Comparison groups	Arm 1: BF400 v Arm 3: FS250
Number of subjects included in analysis	30
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.8345
Method	Mixed models analysis
Parameter estimate	Mean difference (final values)
Point estimate	0.122
Confidence interval	
level	95 %
sides	2-sided
lower limit	-1.032
upper limit	1.276

Secondary: Change in the Microbiome by Alpha-diversity in Sputum Samples FS250 vs BF400

End point title	Change in the Microbiome by Alpha-diversity in Sputum Samples FS250 vs BF400
End point description:	
To determine the effects of the inhaled corticosteroids fluticasone propionate/salmeterol 250/50 mcg vs budesonide/ formoterol 400/12 mcg on the microbiome by alpha-diversity from sputum	
End point type	Secondary
End point timeframe:	
Treatment period, months 1 to 3	

End point values	Arm 1: BF400	Arm 3: FS250		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	15	14		
Units: Shannon Weiner diversity index				
arithmetic mean (confidence interval 95%)	1.62 (1.288 to 1.954)	1.56 (1.298 to 1.831)		

Statistical analyses

Statistical analysis title	Change in SWD Sputum FS250 vs BF400
Statistical analysis description:	
Change in the Microbiome by Alpha-diversity in Sputum Samples FS250 vs BF400	
Comparison groups	Arm 1: BF400 v Arm 3: FS250

Number of subjects included in analysis	29
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.8015
Method	Mixed models analysis
Parameter estimate	Mean difference (final values)
Point estimate	-0.052
Confidence interval	
level	95 %
sides	2-sided
lower limit	-0.466
upper limit	0.361

Secondary: Change in the Microbiome by Alpha-diversity in Oropharyngeal Samples FS250 vs BF400

End point title	Change in the Microbiome by Alpha-diversity in Oropharyngeal Samples FS250 vs BF400

End point description:

To determine the effects of the inhaled corticosteroids fluticasone propionate/salmeterol 250/50 mcg vs budesonide/
formoterol 400/12 mcg on the microbiome by alpha-diversity from oropharyngeal samples

End point type	Secondary

End point timeframe:

Treatment period, months 1 to 3

End point values	Arm 1: BF400	Arm 3: FS250		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	16	14		
Units: Shannon Weiner Diversity Index				
arithmetic mean (confidence interval 95%)	1.69 (1.413 to 1.975)	1.28 (0.9 to 1.662)		

Statistical analyses

Statistical analysis title	Change in SWDI OP FS250 vs BF400

Statistical analysis description:

Change in the Microbiome by Alpha-diversity in Oropharyngeal Samples FS250 vs BF400

Comparison groups	Arm 1: BF400 v Arm 3: FS250
Number of subjects included in analysis	30
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.015
Method	Mixed models analysis
Parameter estimate	Mean difference (final values)
Point estimate	-0.51

Confidence interval	
level	95 %
sides	2-sided
lower limit	-0.825
upper limit	-0.194

Secondary: Change in the Microbiome by Alpha-diversity in Nasopharyngeal Samples FS250 vs BF400

End point title	Change in the Microbiome by Alpha-diversity in Nasopharyngeal Samples FS250 vs BF400

End point description:

To determine the effects of the inhaled corticosteroids fluticasone propionate/salmeterol 250/50 mcg vs budesonide/
formoterol 400/12 mcg on the microbiome by alpha-diversity from nasopharyngeal samples

End point type	Secondary

End point timeframe:

Treatment period, months 1 to 3

End point values	Arm 1: BF400	Arm 3: FS250		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	16	14		
Units: Shannon Weiner diversity index				
arithmetic mean (confidence interval 95%)	1.46 (1.166 to 1.751)	1.33 (0.962 to 1.701)		

Statistical analyses

Statistical analysis title	Change in SWDI NP FS250 vs BF400

Statistical analysis description:

Change in the Microbiome by Alpha-diversity in Nasopharyngeal Samples FS250 vs BF400

Comparison groups	Arm 1: BF400 v Arm 3: FS250
Number of subjects included in analysis	30
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.913
Method	Mixed models analysis
Parameter estimate	Mean difference (final values)
Point estimate	-0.026
Confidence interval	
level	95 %
sides	2-sided
lower limit	-0.506
upper limit	0.453

Secondary: Change in the Microbiome by Alpha-diversity in Sputum Samples FS ICS vs LABA/LAMA

End point title	Change in the Microbiome by Alpha-diversity in Sputum Samples FS ICS vs LABA/LAMA

End point description:

To compare the effects on the lower airway microbiome in sputum of inhaled corticosteroids fluticasone propionate
compared to a dual bronchodilator-based regime without ICS

End point type	Secondary

End point timeframe:

Treatment period, months 1 to 3

End point values	Arm 4: AF	Pooled Fluticasone propionate ICS		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	14	25		
Units: Shannon Weiner diversity index				
arithmetic mean (confidence interval 95%)	1.27 (0.897 to 1.650)	1.57 (1.412 to 1.731)		

Statistical analyses

Statistical analysis title	Change in alpha-diversity in sput FS ICS vs LB/LM

Statistical analysis description:

Change in the Microbiome by Alpha-diversity in Sputum Samples FS ICS vs LABA/LAMA

Comparison groups	Arm 4: AF v Pooled Fluticasone propionate ICS
Number of subjects included in analysis	39
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.7553
Method	Mixed models analysis
Parameter estimate	Mean difference (final values)
Point estimate	-0.047
Confidence interval	
level	95 %
sides	2-sided
lower limit	-0.342
upper limit	0.249

Secondary: Change in the Microbiome by Alpha-diversity in Oropharyngeal Samples FS ICS vs LABA/LAMA

End point title	Change in the Microbiome by Alpha-diversity in Oropharyngeal Samples FS ICS vs LABA/LAMA

End point description:

To compare the effects on the upper airway microbiome in oropharyngeal samples of inhaled corticosteroids fluticasone
propionate compared to a dual bronchodilator-based regime without ICS

End point type	Secondary

End point timeframe:

Treatment period, months 1-3

End point values	Arm 4: AF	Pooled Fluticasone propionate ICS		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	13	26		
Units: Shannon Weiner diversity index				
arithmetic mean (confidence interval 95%)	1.32 (1.032 to 1.604)	1.43 (1.207 to 1.646)		

Statistical analyses

Statistical analysis title	Change in microbiome OP FS ICS vs LABA/LAMA

Statistical analysis description:

Change in the Microbiome by Alpha-diversity in Oropharyngeal Samples FS ICS vs LABA/LAMA

Comparison groups	Pooled Fluticasone propionate ICS v Arm 4: AF
Number of subjects included in analysis	39
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.5283
Method	Mixed models analysis
Parameter estimate	Mean difference (final values)
Point estimate	-0.109
Confidence interval	
level	95 %
sides	2-sided
lower limit	-0.45
upper limit	0.232

Secondary: Change in the Microbiome by Alpha-diversity in Nasopharyngeal Samples FS ICS vs LABA/LAMA

End point title	Change in the Microbiome by Alpha-diversity in Nasopharyngeal Samples FS ICS vs LABA/LAMA

End point description:

To compare the effects on the upper airway microbiome in nasopharyngeal samples of inhaled corticosteroids
fluticasone propionate compared to a dual bronchodilator-based regime without ICS

End point type	Secondary

End point timeframe:

Treatment period, months 1-3

End point values	Arm 4: AF	Pooled Fluticasone propionate ICS		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	14	27		
Units: Shannon Weiner diversity index				
arithmetic mean (confidence interval 95%)	1.47 (1.174 to 1.766)	1.26 (1.006 to 1.507)		

Statistical analyses

Statistical analysis title	Change in microbiome NP FS ICS vs LABA/LAMA
Comparison groups	Arm 4: AF v Pooled Fluticasone propionate ICS
Number of subjects included in analysis	41
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.8247
Method	Mixed models analysis
Parameter estimate	Mean difference (final values)
Point estimate	0.108
Confidence interval	
level	95 %
sides	2-sided
lower limit	-0.859
upper limit	1.075

Secondary: Change in the Microbiome by Alpha-diversity in Sputum Samples BF ICS vs LABA/LAMA

End point title	Change in the Microbiome by Alpha-diversity in Sputum Samples BF ICS vs LABA/LAMA

End point description:

To compare the effects on the lower airway microbiome in sputum of inhaled corticosteroids budesonide compared to a
dual bronchodilator-based regime without ICS

End point type	Secondary

End point timeframe:

Treatment period, months 1 to 3

End point values	Arm 1: BF400	Arm 4: AF		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	15	14		
Units: Shannon Weiner diversity index				
arithmetic mean (confidence interval 95%)	1.62 (1.288 to 1.954)	1.27 (0.897 to 1.650)		

Statistical analyses

Statistical analysis title	Change in microbiome Sput BF vs LABA/LAMA
Comparison groups	Arm 1: BF400 v Arm 4: AF
Number of subjects included in analysis	29
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.9556
Method	Mixed models analysis
Parameter estimate	Mean difference (final values)
Confidence interval	
level	95 %
sides	2-sided
lower limit	-1.141
upper limit	1.079

Secondary: Change in the Microbiome by Alpha-diversity in Oropharyngeal Samples BF ICS vs LABA/LAMA

End point title	Change in the Microbiome by Alpha-diversity in Oropharyngeal Samples BF ICS vs LABA/LAMA

End point description:

To compare the effects on the upper airway microbiome in oropharyngeal swabs of inhaled corticosteroids budesonide
compared to a dual bronchodilator-based regime without ICS

End point type	Secondary

End point timeframe:

Treatment period, months 1 to 3

End point values	Arm 1: BF400	Arm 4: AF		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	16	13		
Units: Shannon Weiner diversity index				
arithmetic mean (confidence interval 95%)	1.69 (1.413 to 1.975)	1.32 (1.032 to 1.604)		

Statistical analyses

Statistical analysis title	Change in microbiome OP BF vs LABA/LAMA
Comparison groups	Arm 1: BF400 v Arm 4: AF
Number of subjects included in analysis	29
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.1264
Method	Mixed models analysis
Parameter estimate	Mean difference (final values)
Point estimate	-0.257
Confidence interval	
level	95 %
sides	2-sided
lower limit	-0.587
upper limit	0.074

Secondary: Change in the Microbiome by Alpha-diversity in Nasopharyngeal Samples BF ICS vs LABA/LAMA

End point title	Change in the Microbiome by Alpha-diversity in Nasopharyngeal Samples BF ICS vs LABA/LAMA

End point description:

To compare the effects on the upper airway microbiome in nasopharyngeal swabs of inhaled corticosteroids budesonide
compared to a dual bronchodilator-based regime without ICS

End point type	Secondary

End point timeframe:

Treatment period, months 1 to 3

End point values	Arm 1: BF400	Arm 4: AF		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	16	14		
Units: Shannon Weiner diversity index				
arithmetic mean (confidence interval 95%)	1.46 (1.166 to 1.751)	1.47 (1.174 to 1.766)		

Statistical analyses

Statistical analysis title	Change in microbiome NP BF vs LABA/LAMA
Comparison groups	Arm 1: BF400 v Arm 4: AF

Number of subjects included in analysis	30
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.9367
Method	Mixed models analysis
Parameter estimate	Mean difference (final values)
Point estimate	-0.028
Confidence interval	
level	95 %
sides	2-sided
lower limit	-0.724
upper limit	0.668

Secondary: Change in Total Bacterial Load FS500 vs FS250 in Sputum Samples

End point title	Change in Total Bacterial Load FS500 vs FS250 in Sputum Samples

End point description:

To determine the effects of the inhaled corticosteroids fluticasone propionate/salmeterol 500/50 mcg vs fluticasone
propionate/salmeterol 250/50 mcg on lower airway bacterial load in sputum samples

End point type	Secondary

End point timeframe:

Treatment period, months 1 to 3

End point values	Arm 2: FS500	Arm 3: FS250		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	11	14		
Units: CFU/g equivalent units				
arithmetic mean (confidence interval 95%)	10.44 (10.049 to 10.822)	10.35 (9.897 to 10.798)		

Statistical analyses

Statistical analysis title	Change in BL Sput FS500 vs FS250
Comparison groups	Arm 3: FS250 v Arm 2: FS500
Number of subjects included in analysis	25
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.0712
Method	Mixed models analysis
Parameter estimate	Mean difference (final values)
Point estimate	-0.626

Confidence interval	
level	95 %
sides	2-sided
lower limit	-1.307
upper limit	0.055

Secondary: Change in Total Bacterial Load FS500 vs FS250 in Oropharyngeal Swab Samples

End point title	Change in Total Bacterial Load FS500 vs FS250 in Oropharyngeal Swab Samples

End point description:

To determine the effects of the inhaled corticosteroids fluticasone propionate/salmeterol 500/50 mcg vs fluticasone
propionate/salmeterol 250/50 mcg on upper airway in oropharyngeal samples

End point type	Secondary

End point timeframe:

Treatment period, months 1 to 3

End point values	Arm 2: FS500	Arm 3: FS250		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	12	14		
Units: CFU/g equivalent units				
arithmetic mean (confidence interval 95%)	8.89 (8.337 to 9.438)	8.08 (7.529 to 8.636)		

Statistical analyses

Statistical analysis title	Change in BL OP FS500 vs FS250
Comparison groups	Arm 2: FS500 v Arm 3: FS250
Number of subjects included in analysis	26
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.1279
Method	Mixed models analysis
Parameter estimate	Mean difference (final values)
Point estimate	-1.114
Confidence interval	
level	95 %
sides	2-sided
lower limit	-2.556
upper limit	0.328

Secondary: Change in Total Bacterial Load FS500 vs FS250 in Nasopharyngeal Swab Samples

End point title	Change in Total Bacterial Load FS500 vs FS250 in Nasopharyngeal Swab Samples

End point description:

To determine the effects of the inhaled corticosteroids fluticasone propionate/salmeterol 500/50 mcg vs fluticasone
propionate/salmeterol 250/50 mcg on upper airway in nasopharyngeal samples

End point type	Secondary

End point timeframe:

Treatment period, months 1 to 3

End point values	Arm 2: FS500	Arm 3: FS250		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	13	14		
Units: CFU/g equivalent units				
arithmetic mean (confidence interval 95%)	6.9 (6.461 to 7.339)	6.89 (6.306 to 7.479)		

Statistical analyses

Statistical analysis title	Change in BL NP FS250 vs BF400
Comparison groups	Arm 2: FS500 v Arm 3: FS250
Number of subjects included in analysis	27
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.7561
Method	Mixed models analysis
Parameter estimate	Mean difference (final values)
Point estimate	0.335
Confidence interval	
level	95 %
sides	2-sided
lower limit	-1.807
upper limit	2.477

Secondary: Change in the Microbiome by Alpha-diversity in Sputum Samples FS500 vs FS250

End point title	Change in the Microbiome by Alpha-diversity in Sputum Samples FS500 vs FS250

End point description:

To determine the effects of the inhaled corticosteroids fluticasone propionate/salmeterol 500/50 mcg vs fluticasone
propionate/salmeterol 250/50 mcg on the microbiome by alpha-diversity from sputum

End point type	Secondary

End point timeframe:

Treatment period, months 1 to 3

End point values	Arm 2: FS500	Arm 3: FS250		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	11	14		
Units: Shannon Weiner diversity index				
arithmetic mean (confidence interval 95%)	1.58 (1.389 to 1.772)	1.56 (1.298 to 1.831)		

Statistical analyses

Statistical analysis title	Change in microbiome Sput FS500 vs FS250
Comparison groups	Arm 2: FS500 v Arm 3: FS250
Number of subjects included in analysis	25
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.8517
Method	Mixed models analysis
Parameter estimate	Mean difference (final values)
Confidence interval	
level	95 %
sides	2-sided
lower limit	-0.341
upper limit	0.282

Secondary: Change in the Microbiome by Alpha-diversity in Oropharyngeal Samples FS500 vs FS250

End point title	Change in the Microbiome by Alpha-diversity in Oropharyngeal Samples FS500 vs FS250

End point description:

To determine the effects of the inhaled corticosteroids fluticasone propionate/salmeterol 500/50 mcg vs fluticasone
propionate/salmeterol 250/50 mcg on the microbiome by alpha-diversity from oropharyngeal samples

End point type	Secondary

End point timeframe:

Treatment period, months 1 to 3

End point values	Arm 2: FS500	Arm 3: FS250		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	12	14		
Units: Shannon Weiner diversity index				
arithmetic mean (confidence interval 95%)	1.6 (1.398 to 1.794)	1.28 (0.900 to 1.662)		

Statistical analyses

Statistical analysis title	Change in alpha-diversity in OP FS500 vs FS250
Statistical analysis description:	
Change in the Microbiome by Alpha-diversity in Oropharyngeal Samples FS500 vs FS250	
Comparison groups	Arm 2: FS500 v Arm 3: FS250
Number of subjects included in analysis	26
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.0688
Method	Mixed models analysis
Parameter estimate	Mean difference (final values)
Point estimate	-0.333
Confidence interval	
level	95 %
sides	2-sided
lower limit	-0.693
upper limit	0.026

Secondary: Change in the Microbiome by Alpha-diversity in Nasopharyngeal Samples FS500 vs FS250

End point title	Change in the Microbiome by Alpha-diversity in Nasopharyngeal Samples FS500 vs FS250
End point description:	
To determine the effects of the inhaled corticosteroids fluticasone propionate/salmeterol 500/50 mcg vs fluticasone propionate/salmeterol 250/50 mcg on the microbiome by alpha-diversity from nasopharyngeal samples	
End point type	Secondary
End point timeframe:	
Treatment period, months 1 to 3	

End point values	Arm 2: FS500	Arm 3: FS250		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	13	14		
Units: Shannon Weiner diversity index				
arithmetic mean (confidence interval 95%)	1.18 (0.789 to 1.563)	1.33 (0.962 to 1.701)		

Statistical analyses

Statistical analysis title	Change in alpha-diversity in NP FS500 vs FS250
Comparison groups	Arm 2: FS500 v Arm 3: FS250
Number of subjects included in analysis	27
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.3262
Method	Mixed models analysis
Parameter estimate	Mean difference (final values)
Point estimate	-0.25
Confidence interval	
level	95 %
sides	2-sided
lower limit	-0.755
upper limit	0.254

Secondary: Change in Total Bacterial Load in Pooled ICS vs LABA/LAMA in Sputum Samples

End point title	Change in Total Bacterial Load in Pooled ICS vs LABA/LAMA in Sputum Samples

End point description:

To determine the combined impact of inhaled corticosteroids on bacterial load in upper and lower airway using sputum
samples compared to dual bronchodilator regime

End point type	Secondary

End point timeframe:

Treatment period, months 1 to 3

End point values	Arm 4: AF	Pooled ICS		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	14	40		
Units: CFU/g equivalent units				
arithmetic mean (confidence interval 95%)	9.73 (9.352 to 10.116)	10.19 (9.953 to 10.434)		

Statistical analyses

Statistical analysis title	Change in BL Sput All ICS vs LABA/LAMA
Comparison groups	Pooled ICS v Arm 4: AF
Number of subjects included in analysis	54
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.1455
Method	Mixed models analysis
Parameter estimate	Mean difference (final values)
Point estimate	0.424
Confidence interval	
level	95 %
sides	2-sided
lower limit	-0.148
upper limit	0.996

Secondary: Change in Total Bacterial Load in Pooled ICS vs LABA/LAMA in Oropharyngeal Swab Samples

End point title	Change in Total Bacterial Load in Pooled ICS vs LABA/LAMA in Oropharyngeal Swab Samples
End point description:	
To determine the combined impact of inhaled corticosteroids on bacterial load in upper and lower airway using oropharyngeal swab samples compared to dual bronchodilator regime	
End point type	Secondary
End point timeframe:	
Treatment period, months 1 to 3	

End point values	Arm 4: AF	Pooled ICS		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	13	42		
Units: CFU/g equivalent units				
arithmetic mean (confidence interval 95%)	8.53 (7.762 to 9.294)	8.62 (8.327 to 8.906)		

Statistical analyses

Statistical analysis title	Change in BL OP All ICS vs LABA/LAMA
Comparison groups	Arm 4: AF v Pooled ICS
Number of subjects included in analysis	55
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.607
Method	Mixed models analysis
Parameter estimate	Mean difference (final values)
Point estimate	0.205

Confidence interval	
level	95 %
sides	2-sided
lower limit	-0.581
upper limit	0.991

Secondary: Change in Total Bacterial Load in Pooled ICS vs LABA/LAMA in Nasopharyngeal Swab Samples

End point title	Change in Total Bacterial Load in Pooled ICS vs LABA/LAMA in Nasopharyngeal Swab Samples

End point description:

To determine the combined impact of inhaled corticosteroids on bacterial load in upper and lower airway using
nasopharyngeal swab samples compared to dual bronchodilator regime

End point type	Secondary

End point timeframe:

Treatment period, months 1 to 3

End point values	Arm 4: AF	Pooled ICS		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	14	43		
Units: CFU/g equivalent units				
arithmetic mean (confidence interval 95%)	7.27 (6.695 to 7.836)	6.92 (6.667 to 7.172)		

Statistical analyses

Statistical analysis title	Change in BL NP All ICS vs LABA/LAMA
Comparison groups	Arm 4: AF v Pooled ICS
Number of subjects included in analysis	57
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.463
Method	Mixed models analysis
Parameter estimate	Mean difference (final values)
Point estimate	-0.359
Confidence interval	
level	95 %
sides	2-sided
lower limit	-1.322
upper limit	0.605

Secondary: Change in Microbiome by Alpha-diversity in Pooled ICS vs LABA/LAMA in Sputum Samples

End point title	Change in Microbiome by Alpha-diversity in Pooled ICS vs LABA/LAMA in Sputum Samples

End point description:

To determine the effects of inhaled corticosteroids vs LABA/LAMA on the microbiome by alpha-diversity in sputum
samples

End point type	Secondary

End point timeframe:

Treatment period, months 1-3

End point values	Arm 4: AF	Pooled ICS		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	14	40		
Units: Shannon Weiner diversity index				
arithmetic mean (confidence interval 95%)	1.27 (0.897 to 1.650)	1.59 (1.439 to 1.741)		

Statistical analyses

Statistical analysis title	Change in alpha-diversity Sput All ICS vs LB/LM
Comparison groups	Arm 4: AF v Pooled ICS
Number of subjects included in analysis	54
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.8915
Method	Mixed models analysis
Parameter estimate	Mean difference (final values)
Point estimate	-0.022
Confidence interval	
level	95 %
sides	2-sided
lower limit	-0.338
upper limit	0.294

Secondary: Change in Microbiome by Alpha-diversity in Pooled ICS vs LABA/LAMA in Oropharyngeal Swab Samples

End point title	Change in Microbiome by Alpha-diversity in Pooled ICS vs LABA/LAMA in Oropharyngeal Swab Samples

End point description:

To determine the effects of inhaled corticosteroids vs LABA/LAMA on the microbiome by alpha-diversity in
oropharyngeal swab samples

End point type	Secondary

End point timeframe:

Treatment period, months 1 to 3

End point values	Arm 4: AF	Pooled ICS		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	13	42		
Units: Shannon Weiner diversity index				
arithmetic mean (confidence interval 95%)	1.32 (1.032 to 1.604)	1.53 (1.358 to 1.699)		

Statistical analyses

Statistical analysis title	Change in alpha-diversity in OP ICS vs LABA/LAMA
Comparison groups	Arm 4: AF v Pooled ICS
Number of subjects included in analysis	55
Analysis specification	Pre-specified
Analysis type	
P-value	= 0.846
Method	Mixed models analysis
Parameter estimate	Mean difference (final values)
Point estimate	0.03
Confidence interval	
level	95 %
sides	2-sided
lower limit	-0.273
upper limit	0.332

Secondary: Change in Microbiome by Alpha-diversity in Pooled ICS vs LABA/LAMA in Nasopharyngeal Swab Samples

End point title	Change in Microbiome by Alpha-diversity in Pooled ICS vs LABA/LAMA in Nasopharyngeal Swab Samples

End point description:

To determine the effects of inhaled corticosteroids vs LABA/LAMA on the microbiome by alpha-diversity in
nasopharyngeal swab samples

End point type	Secondary

End point timeframe:

Treatment period, months 1 to 3

End point values	Arm 4: AF	Pooled ICS		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	14	43		
Units: Shannon weiner diversity index				
arithmetic mean (confidence interval 95%)	1.47 (1.174 to 1.766)	1.33 (1.146 to 1.518)		

Statistical analyses

Statistical analysis title	Change in alpha-diversity NP All ICS vs LABA/LAMA
Comparison groups	Arm 4: AF v Pooled ICS
Number of subjects included in analysis	57
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.798
Method	Mixed models analysis
Parameter estimate	Mean difference (final values)
Point estimate	0.073
Confidence interval	
level	95 %
sides	2-sided
lower limit	-0.487
upper limit	0.632

Secondary: Change in Airway MPO for ICS vs LABA/LAMA in Sputum Samples	
End point title	Change in Airway MPO for ICS vs LABA/LAMA in Sputum Samples
End point description:	
To evaluate the impact of inhaled corticosteroids on airway myeloperoxidase compared to LABA/LAMA	
End point type	Secondary
End point timeframe:	
Treatment period, months 1 to 3	

End point values	Arm 4: AF	Pooled ICS		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	14	38		
Units: Units/mL				
arithmetic mean (confidence interval 95%)	0.53 (0.078 to 0.988)	0.49 (0.291 to 0.695)		

Statistical analyses

Statistical analysis title	Change in Sput MPO for ICS vs LABA/LAMA
Comparison groups	Arm 4: AF v Pooled ICS
Number of subjects included in analysis	52
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.0376
Method	Mixed models analysis
Parameter estimate	Mean difference (final values)
Point estimate	0.57
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.034
upper limit	1.105

Secondary: Change in Airway Neutrophil Elastase for ICS vs LABA/LAMA in Sputum Samples

End point title	Change in Airway Neutrophil Elastase for ICS vs LABA/LAMA in Sputum Samples
End point description:	
To evaluate the impact of inhaled corticosteroids on airway neutrophil elastase compared to LABA/LAMA	
End point type	Secondary
End point timeframe:	
Treatment period. months 1 to 3	

End point values	Arm 4: AF	Pooled ICS		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	14	38		
Units: Units/mL				
arithmetic mean (confidence interval 95%)	0.03 (-0.017 to 0.081)	0.70 (-0.565 to 1.973)		

Statistical analyses

Statistical analysis title	Change in Sput NE for ICS vs LABA/LAMA
Comparison groups	Arm 4: AF v Pooled ICS
Number of subjects included in analysis	52
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.897
Method	Mixed models analysis
Parameter estimate	Mean difference (final values)
Point estimate	0.307

Confidence interval	
level	95 %
sides	2-sided
lower limit	-2.84
upper limit	3.454

Secondary: Change in Resistin for ICS vs LABA/LAMA in Whole Blood

End point title	Change in Resistin for ICS vs LABA/LAMA in Whole Blood
End point description:	
To evaluate the impact of inhaled corticosteroids on blood resistin compared to LABA/LAMA	
End point type	Secondary
End point timeframe:	
Treatment period, months 1 to 3	

End point values	Arm 4: AF	Pooled ICS		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	14	43		
Units: ng/mL				
arithmetic mean (confidence interval 95%)	15.08 (11.914 to 18.228)	151.07 (-113.935 to 416.074)		

Statistical analyses

Statistical analysis title	Change in blood resistin ICS vs LABA/LAMA
Comparison groups	Arm 4: AF v Pooled ICS
Number of subjects included in analysis	57
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.3686
Method	Mixed models analysis
Parameter estimate	Mean difference (final values)
Point estimate	0.261
Confidence interval	
level	95 %
sides	2-sided
lower limit	-0.316
upper limit	0.837

Secondary: Change in Airway Resistin for ICS vs LABA/LAMA in Sputum Samples

End point title	Change in Airway Resistin for ICS vs LABA/LAMA in Sputum Samples

End point description:	
To evaluate the impact of inhaled corticosteroids on airway resistin compared to LABA/LAMA	
End point type	Secondary
End point timeframe:	
Treatment period, months 1 to 3	

End point values	Arm 4: AF	Pooled ICS		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	14	38		
Units: ng/mL				
arithmetic mean (confidence interval 95%)	132.83 (17.362 to 248.295)	96.53 (30.625 to 162.426)		

Statistical analyses

Statistical analysis title	Change in sput Resistin ICS vs LABA/LAMA
Comparison groups	Arm 4: AF v Pooled ICS
Number of subjects included in analysis	52
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.8979
Method	Mixed models analysis
Parameter estimate	Mean difference (final values)
Point estimate	0.064
Confidence interval	
level	95 %
sides	2-sided
lower limit	-0.941
upper limit	1.07

Secondary: Change in Airway IL-8 for ICS vs LABA/LAMA in Sputum Samples	
End point title	Change in Airway IL-8 for ICS vs LABA/LAMA in Sputum Samples
End point description:	
To evaluate the impact of inhaled corticosteroids on airway IL-8 compared to LABA/LAMA	
End point type	Secondary
End point timeframe:	
Treatment window, months 1 to 3	

End point values	Arm 4: AF	Pooled ICS		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	14	38		
Units: ng/mL				
arithmetic mean (confidence interval 95%)	1.20 (0.227 to 2.170)	1.27 (0.572 to 1.977)		

Statistical analyses

Statistical analysis title	Change in sput IL8 ICS vs LABA/LAMA
Comparison groups	Arm 4: AF v Pooled ICS
Number of subjects included in analysis	52
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.1098
Method	Mixed models analysis
Parameter estimate	Median difference (final values)
Point estimate	-1.024
Confidence interval	
level	95 %
sides	2-sided
lower limit	-2.287
upper limit	0.24

Secondary: Change in Airway IL1-beta for ICS vs LABA/LAMA in Sputum Samples	
End point title	Change in Airway IL1-beta for ICS vs LABA/LAMA in Sputum Samples
End point description: To evaluate the impact of inhaled corticosteroids on airway IL1-beta compared to LABA/LAMA	
End point type	Secondary
End point timeframe: Treatment period, months 1 to 3	

End point values	Arm 4: AF	Pooled ICS		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	14	38		
Units: ug/mL				
arithmetic mean (confidence interval 95%)	9.57 (-8.659 to 27.803)	5.86 (2.641 to 9.072)		

Statistical analyses

Statistical analysis title	Change in sput IL1b ICS vs LABA/LAMA
Comparison groups	Arm 4: AF v Pooled ICS
Number of subjects included in analysis	52
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.3261
Method	Mixed models analysis
Parameter estimate	Mean difference (final values)
Point estimate	0.752
Confidence interval	
level	95 %
sides	2-sided
lower limit	-0.776
upper limit	2.28

Adverse events

Adverse events information	
Timeframe for reporting adverse events:	
Adverse events were collected from screening to end of study	
Adverse event reporting additional description:	
Adverse events were assessed systematically, and defined using MedDRA dictionary	
Assessment type	Systematic

Dictionary used	
Dictionary name	MedDRA
Dictionary version	24

Reporting groups	
Reporting group title	Symbicort 400/12 & Eklira Genuair
Reporting group description:	
Budesonide 400mcg & formoterol fumarate 12mcg: 1 inhalation twice daily, inhalation powder and Aclidinium bromide 322mcg: 1 inhalation twice daily, inhalation powder for 3 months Budesonide & formoterol fumarate and Aclidinium bromide	
Reporting group title	Seretide 500/50 & Eklira Genuair
Reporting group description:	
Fluticasone propionate 500mcg & salmeterol 50mcg: 1 inhalation twice daily, inhalation powder and Aclidinium bromide 322mcg: 1 inhalation twice daily, inhalation powder for 3 months Fluticasone 500 & salmeterol and Aclidinium bromide	
Reporting group title	Seretide 250/50 & Eklira Genuair
Reporting group description:	
Fluticasone propionate 250mcg & salmeterol 50mcg: 1 inhalation twice daily, inhalation powder and Aclidinium bromide 322mcg: 1 inhalation twice daily, inhalation powder for 3 months Fluticasone 250 & salmeterol and Aclidinium bromide	
Reporting group title	Duaklir Genuair
Reporting group description:	
Aclidinium bromide 340mcg & formoterol fumarate 12mcg: 1 inhalation twice daily, inhalation powder for 3 months Aclidinium bromide & formoterol fumarate	

Serious adverse events	Symbicort 400/12 & Eklira Genuair	Seretide 500/50 & Eklira Genuair	Seretide 250/50 & Eklira Genuair
Total subjects affected by serious adverse events			
subjects affected / exposed	3 / 18 (16.67%)	0 / 13 (0.00%)	0 / 15 (0.00%)
number of deaths (all causes)	0	0	0
number of deaths resulting from adverse events	0	0	0
General disorders and administration site conditions			
Facial injury			
subjects affected / exposed	0 / 18 (0.00%)	0 / 13 (0.00%)	0 / 15 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0

Respiratory, thoracic and mediastinal disorders			
Chronic obstructive pulmonary disease			
subjects affected / exposed	1 / 18 (5.56%)	0 / 13 (0.00%)	0 / 15 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Dyspnoea			
subjects affected / exposed	2 / 18 (11.11%)	0 / 13 (0.00%)	0 / 15 (0.00%)
occurrences causally related to treatment / all	0 / 2	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0

Serious adverse events	Duaklir Genuair		
Total subjects affected by serious adverse events			
subjects affected / exposed	1 / 15 (6.67%)		
number of deaths (all causes)	0		
number of deaths resulting from adverse events	0		
General disorders and administration site conditions			
Facial injury			
subjects affected / exposed	1 / 15 (6.67%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Respiratory, thoracic and mediastinal disorders			
Chronic obstructive pulmonary disease			
subjects affected / exposed	0 / 15 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Dyspnoea			
subjects affected / exposed	0 / 15 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		

Frequency threshold for reporting non-serious adverse events: 5 %

Non-serious adverse events	Symbicort 400/12 & Eklira Genuair	Seretide 500/50 & Eklira Genuair	Seretide 250/50 & Eklira Genuair
Total subjects affected by non-serious adverse events			
subjects affected / exposed	13 / 18 (72.22%)	13 / 13 (100.00%)	12 / 15 (80.00%)
Investigations			
Investigations			
subjects affected / exposed	0 / 18 (0.00%)	0 / 13 (0.00%)	0 / 15 (0.00%)
occurrences (all)	0	0	0
Cardiac disorders			
Cardiac disorders			
subjects affected / exposed	0 / 18 (0.00%)	0 / 13 (0.00%)	1 / 15 (6.67%)
occurrences (all)	0	0	1
Nervous system disorders			
Headache			
subjects affected / exposed	1 / 18 (5.56%)	0 / 13 (0.00%)	0 / 15 (0.00%)
occurrences (all)	1	0	0
Neurological symptom			
subjects affected / exposed	0 / 18 (0.00%)	2 / 13 (15.38%)	0 / 15 (0.00%)
occurrences (all)	0	2	0
General disorders and administration site conditions			
Oral and laryngeal symptoms			
subjects affected / exposed	2 / 18 (11.11%)	2 / 13 (15.38%)	4 / 15 (26.67%)
occurrences (all)	2	2	7
Other			
subjects affected / exposed	1 / 18 (5.56%)	2 / 13 (15.38%)	1 / 15 (6.67%)
occurrences (all)	1	2	1
Immune system disorders			
Allergy			
subjects affected / exposed	1 / 18 (5.56%)	1 / 13 (7.69%)	0 / 15 (0.00%)
occurrences (all)	1	1	0
Gastrointestinal disorders			
Gastrointestinal disorder			
subjects affected / exposed	0 / 18 (0.00%)	1 / 13 (7.69%)	0 / 15 (0.00%)
occurrences (all)	0	1	0
Respiratory, thoracic and mediastinal disorders			
Dyspnoea			
subjects affected / exposed	8 / 18 (44.44%)	4 / 13 (30.77%)	4 / 15 (26.67%)
occurrences (all)	9	4	4

Chronic obstructive pulmonary disease			
subjects affected / exposed	3 / 18 (16.67%)	1 / 13 (7.69%)	4 / 15 (26.67%)
occurrences (all)	4	1	5
Cough			
subjects affected / exposed	5 / 18 (27.78%)	0 / 13 (0.00%)	2 / 15 (13.33%)
occurrences (all)	6	0	2
Lower respiratory tract infection			
subjects affected / exposed	2 / 18 (11.11%)	0 / 13 (0.00%)	1 / 15 (6.67%)
occurrences (all)	2	0	1
Sputum increased			
subjects affected / exposed	0 / 18 (0.00%)	0 / 13 (0.00%)	0 / 15 (0.00%)
occurrences (all)	0	0	0
Upper respiratory tract infection			
subjects affected / exposed	4 / 18 (22.22%)	1 / 13 (7.69%)	1 / 15 (6.67%)
occurrences (all)	4	1	1
Skin and subcutaneous tissue disorders			
Skin disorder			
subjects affected / exposed	1 / 18 (5.56%)	1 / 13 (7.69%)	0 / 15 (0.00%)
occurrences (all)	1	1	0
Musculoskeletal and connective tissue disorders			
Musculoskeletal and connective tissue disorders			
subjects affected / exposed	4 / 18 (22.22%)	4 / 13 (30.77%)	3 / 15 (20.00%)
occurrences (all)	4	5	3
Infections and infestations			
General infections			
subjects affected / exposed	1 / 18 (5.56%)	4 / 13 (30.77%)	0 / 15 (0.00%)
occurrences (all)	1	5	0

Non-serious adverse events	Duaklir Genuair		
Total subjects affected by non-serious adverse events			
subjects affected / exposed	14 / 15 (93.33%)		
Investigations			
Investigations			
subjects affected / exposed	2 / 15 (13.33%)		
occurrences (all)	2		
Cardiac disorders			

Cardiac disorders subjects affected / exposed occurrences (all)	0 / 15 (0.00%) 0		
Nervous system disorders Headache subjects affected / exposed occurrences (all) Neurological symptom subjects affected / exposed occurrences (all)	 1 / 15 (6.67%) 1 1 / 15 (6.67%) 1		
General disorders and administration site conditions Oral and laryngeal symptoms subjects affected / exposed occurrences (all) Other subjects affected / exposed occurrences (all)	 0 / 15 (0.00%) 0 0 / 15 (0.00%) 0		
Immune system disorders Allergy subjects affected / exposed occurrences (all)	 0 / 15 (0.00%) 0		
Gastrointestinal disorders Gastrointestinal disorder subjects affected / exposed occurrences (all)	 3 / 15 (20.00%) 3		
Respiratory, thoracic and mediastinal disorders Dyspnoea subjects affected / exposed occurrences (all) Chronic obstructive pulmonary disease subjects affected / exposed occurrences (all) Cough subjects affected / exposed occurrences (all) Lower respiratory tract infection	 7 / 15 (46.67%) 7 5 / 15 (33.33%) 8 1 / 15 (6.67%) 1		

subjects affected / exposed occurrences (all) Sputum increased subjects affected / exposed occurrences (all) Upper respiratory tract infection subjects affected / exposed occurrences (all)	2 / 15 (13.33%) 2 1 / 15 (6.67%) 1 2 / 15 (13.33%) 3		
Skin and subcutaneous tissue disorders Skin disorder subjects affected / exposed occurrences (all)	1 / 15 (6.67%) 1		
Musculoskeletal and connective tissue disorders Musculoskeletal and connective tissue disorders subjects affected / exposed occurrences (all)	2 / 15 (13.33%) 3		
Infections and infestations General infections subjects affected / exposed occurrences (all)	1 / 15 (6.67%) 2		

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? No

Interruptions (globally)

Were there any global interruptions to the trial? No

Limitations and caveats

None reported