Clinical trial results:
INvestigating COPD Outcomes, Genomics and Neutrophilic Inflammation with Tiotropium and Olodaterol (INCOGNITO trial)

Summary

EudraCT number	2016-004473-41
Trial protocol	GB
Global end of trial date	26 November 2019

Results information

Result version number	v1 (current)
This version publication date	12 July 2022
First version publication date	12 July 2022

Trial information

Trial identification

Sponsor protocol code	2016RC22

Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	NCT03152149
WHO universal trial number (UTN)	-

Notes:

Sponsors

Sponsor organisation name	University of Dundee
Sponsor organisation address	University of Dundee, Mailbox 12, Ninewells Hospital, Dundee, United Kingdom, DD1 9SY
Public contact	Chalmers, University of Dundee, 0044 01382 383642, jchalmers@dundee.ac.uk
Scientific contact	Chalmers, University of Dundee, 7435254338 01382 383642, jchalmers@dundee.ac.uk

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	03 December 2021
Is this the analysis of the primary completion data?	Yes
Primary completion date	26 November 2019
Global end of trial reached?	Yes
Global end of trial date	26 November 2019
Was the trial ended prematurely?	No

Notes:

General information about the trial

Main objective of the trial:

To determine the effects of the Tiotropium and olodaterol combination (Spiolto respimat 2.5/2.5ug) 2 puffs once daily vs Relvar Ellipta (fluticasone furoate 92 micrograms, vilaterol 22 micrograms) 1 puff once daily on airway bacterial load (the numbers of bacteria found) from induced sputum

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:

Participants were permitted to continue all other medications during the trial that would not be expected to interfere with the upper airway microbiota (i.e., short acting beta2-adrenoceptor agonists, theophylline and carbocisteine)

Evidence for comparator:

We hypothesised that the combination of tiotropium and olodaterol may be an ideal treatment option for patients with neutrophilic COPD because
- Tiotropium and olodaterol have both been shown to have potentially beneficial effects in suppressing neutrophilic inflammation without impairing bacterial killing
- These effects may reverse the detrimental impact of inhaled corticosteroids on airway neutrophil function and the microbiome.

In particular olodaterol was evaluated in cigarette smoke- and Lipolpolysaccharide - induced- models of neutrophil lung inflammation in mice and guinea pigs. The results showed Olodaterol to suppress neutrophil recruitment to the lung (by up to 90%) while preserving chemotactic function (which is required for effective phagocytosis of pathogens)(1). Tiotropium has also been extensively investigated and is known to suppress neutrophil recruitment and neutrophil dependent remodelling in a number of in-vivo models and may work synergistically with olodaterol in reducing neutrophil retention in the lung. (2-4)
This extensive preclinical work justified a study of olodaterol/tiotropium in human subjects evaluating its impact on neutrophilic inflammation.

1. Wex E, Kollak I, Duechs MJ et al. The long-acting B2-adrenoceptor agonist olodaterol attenuates pulmonary inflammation. Br J Pharmacol 2015;172(14):3537-47.
2. Profita M, Bonanno A, Montalbano AM et al. B2-long acting and anticholinergic drugs control TGF-B1-mediated neutrophilic inflammation in COPD. Biochim Biophys Acta2012;1822(7):1079-89.
3. Arai N, Kondo M, Izumo T et al. Inihibitoon of neutrophil elastase-induced goblet cell metaplasia by tiotropium in mice. Eur Respir J 2010;35(5):1164-71.
4. Pera T, Zuidhof A, Valadas J et al. Tiotropium inhibits pulmonary inflammation and remodelling in a guinea pig model of COPD. Eur Respir J 2011;38(4):789-96.

Actual start date of recruitment	03 April 2017
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: 80
Worldwide total number of subjects	80
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	55
85 years and over	2

Subject disposition

Recruitment

Recruitment details:

Patients were recruited at 4 NHS sites in the UK (Dundee, Glasgow, North Tyneside and Nottingham) between July 2017 until November 2019.

Pre-assignment

Screening details:

133 participants were screened and 80 participants were randomized. There were 53 screen failures for:
Asthma: 2
Antibiotics in the last 28 days: 4
Less than 10 year pack history: 1
No clinical diagnosis of COPD: 1
FEV1/FVC ratio >0.7: 7
FEV1 >80% predicted: 17
No ICS treatment for at least 12 months: 2
Blood eosinophil

Period 1

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

Arms

Are arms mutually exclusive?	Yes
Arm title	Tiotropium olodaterol

Arm description:

Tiotropium 2.5 micrograms and olodaterol 2.5 micrograms 2 puffs once daily soft mist inhaler.

Arm type	Active comparator
Investigational medicinal product name	Tiotropium olodaterol
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Inhalation vapour
Routes of administration	Inhalation use

Dosage and administration details:

Tiotropium 2.5 micrograms and olodaterol 2.5 micrograms 2 puffs once daily soft mist inhaler.

Arm title	Fluticasone furoate vilanterol

Arm description:

fluticasone furoate 92 micrograms, vilanterol 22 micrograms 1 puff once daily

Arm type	Active comparator
Investigational medicinal product name	fluticasone furoate vilanterol
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Inhalation powder
Routes of administration	Inhalation use

Dosage and administration details:

fluticasone furoate 92 micrograms, vilanterol 22 micrograms 1 puff once daily

Number of subjects in period 1	Tiotropium olodaterol	Fluticasone furoate vilanterol
Started	38	42
Completed	33	34
Not completed	5	8
Consent withdrawn by subject	3	5
Physician decision	1	1
Adverse event, non-fatal	1	1
Lost to follow-up	-	1

Baseline characteristics

Reporting groups	
Reporting group title	Overall trial

Reporting group description: -

Reporting group values	Overall trial	Total	
Number of subjects	80	80	
Age categorical Units: Subjects			
In utero	0	0	
Preterm newborn infants (gestational age < 37 wks)	0	0	
Newborns (0-27 days)	0	0	
Infants and toddlers (28 days-23 months)	0	0	
Children (2-11 years)	0	0	
Adolescents (12-17 years)	0	0	
Adults (18-64 years)	23	23	
From 65-84 years	55	55	
85 years and over	2	2	
Age continuous Units: years			
arithmetic mean	69.3		
standard deviation	± 8.0	-	
Gender categorical Units: Subjects			
Female	39	39	
Male	41	41	
Smoking status			
Smoking status at enrolment			
Units: Subjects			
Current smoker	26	26	
Ex-smoker	54	54	
Blood eosinophil count at baseline			
Blood eosinophil count at baseline (cells/mL)			
Units: Subjects			
<150	35	35	
150-299	45	45	
Medication history			
Medication history at enrolment			
Units: Subjects			
ICS/LABA	9	9	
ICS/LABA/LAMA	67	67	
ICS/LAMA	4	4	
Pack-years			
Smoking pack years			
Units: Years			
arithmetic mean	47.3		

standard deviation	± 24.3	-	
BMI			
Body mass index			
Units: kg/m^2			
arithmetic mean	29.4		
standard deviation	± 8.2	-	
CAT Score			
Chronic Obstructive Pulmonary Disease Assessment Test Score			
Units: NA			
arithmetic mean	20.6		
standard deviation	± 8.2	-	
Pre-bronchodilator FEV1 (L)			
Units: litre(s)			
arithmetic mean	1.3		
standard deviation	± 0.5	-	
Pre-bronchodilator FEV1 (%)			
Units: percent			
arithmetic mean	51.5		
standard deviation	± 16.1	-	
Pre-bronchodilator FVC (L)			
Units: litre(s)			
arithmetic mean	2.8		
standard deviation	± 0.8	-	
Pre-bronchodilator FVC (%)			
Units: percent			
arithmetic mean	89.6		
standard deviation	± 18.3	-	
FEV1/FVC ratio			
Units: NA			
arithmetic mean	46.5		
standard deviation	± 12.8	-	
Post-bronchodilator FEV1 (L)			
Units: litre(s)			
arithmetic mean	1.3		
standard deviation	± 0.5	-	
Post-bronchodilator FEV1 (%)			
Units: percent			
arithmetic mean	54.0		
standard deviation	± 15.8	-	
Post-bronchodilator FVC (L)			
Units: litre(s)			
arithmetic mean	2.8		
standard deviation	± 0.8	-	
Post-bronchodilator FVC (%)			
Units: percent			
arithmetic mean	91.1		
standard deviation	± 19.3	-	
Post-bronchodilator FEV1/FVC ratio			
Units: NA			
arithmetic mean	47.4		
standard deviation	± 12.5	-	
Oxygen saturations at rest			

Units: percent			
arithmetic mean	95.4		
standard deviation	± 2.3	-	

Subject analysis sets	
Subject analysis set title	Arm 1 T/O
Subject analysis set type	Sub-group analysis
Subject analysis set description: Arm 1 - Tiotropium and Olodaterol	
Subject analysis set title	Arm 2 FF/VI
Subject analysis set type	Sub-group analysis
Subject analysis set description: Arm 2 - fluticasone furoate/vilanterol	

Reporting group values	Arm 1 T/O	Arm 2 FF/VI	
Number of subjects	38	42	
Age categorical			
Units: Subjects			
In utero	0	0	
Preterm newborn infants (gestational age < 37 wks)	0	0	
Newborns (0-27 days)	0	0	
Infants and toddlers (28 days-23 months)	0	0	
Children (2-11 years)	0	0	
Adolescents (12-17 years)	0	0	
Adults (18-64 years)	12	11	
From 65-84 years	25	30	
85 years and over	1	1	
Age continuous			
Units: years			
arithmetic mean	69.4	69.3	
standard deviation	± 8.1	± 8.0	
Gender categorical			
Units: Subjects			
Female	20	19	
Male	18	23	
Smoking status			
Smoking status at enrolment			
Units: Subjects			
Current smoker	12	14	
Ex-smoker	26	28	
Blood eosinophil count at baseline			
Blood eosinophil count at baseline (cells/mL)			
Units: Subjects			
<150	18	17	
150-299	20	25	
Medication history			
Medication history at enrolment			
Units: Subjects			

ICS/LABA	3	6	
ICS/LABA/LAMA	34	33	
ICS/LAMA	1	3	
Pack-years			
Smoking pack years			
Units: Years			
arithmetic mean	48.1	47.3	
standard deviation	± 24.3	± 24.4	
BMI			
Body mass index			
Units: kg/m^2			
arithmetic mean	29.5	29.5	
standard deviation	± 8.3	± 8.2	
CAT Score			
Chronic Obstructive Pulmonary Disease Assessment Test Score			
Units: NA			
arithmetic mean	20.7	20.6	
standard deviation	± 8.3	± 8.3	
Pre-bronchodilator FEV1 (L)			
Units: litre(s)			
arithmetic mean	1.3	1.3	
standard deviation	± 0.5	± 0.5	
Pre-bronchodilator FEV1 (%)			
Units: percent			
arithmetic mean	51.6	51.4	
standard deviation	± 16.4	± 16.1	
Pre-bronchodilator FVC (L)			
Units: litre(s)			
arithmetic mean	2.8	2.8	
standard deviation	± 0.7	± 0.8	
Pre-bronchodilator FVC (%)			
Units: percent			
arithmetic mean	89.7	89.4	
standard deviation	± 18.6	± 18.3	
FEV1/FVC ratio			
Units: NA			
arithmetic mean	46.6	46.4	
standard deviation	± 13.0	± 12.8	
Post-bronchodilator FEV1 (L)			
Units: litre(s)			
arithmetic mean	1.3	1.3	
standard deviation	± 0.5	± 0.5	
Post-bronchodilator FEV1 (%)			
Units: percent			
arithmetic mean	54.0	53.7	
standard deviation	± 16.1	± 17.8	
Post-bronchodilator FVC (L)			
Units: litre(s)			
arithmetic mean	2.9	2.8	
standard deviation	± 0.8	± 0.8	
Post-bronchodilator FVC (%)			

Units: percent			
arithmetic mean	91.1	90.8	
standard deviation	± 19.2	± 19.2	
Post-bronchodilator FEV1/FVC ratio			
Units: NA			
arithmetic mean	47.4	47.3	
standard deviation	±	± 12.5	
Oxygen saturations at rest			
Units: percent			
arithmetic mean	95.4	95.4	
standard deviation	± 2.3	± 2.3	

End points

End points reporting groups

Reporting group title	Tiotropium olodaterol
Reporting group description:	
Tiotropium 2.5 micrograms and olodaterol 2.5 micrograms 2 puffs once daily soft mist inhaler.	
Reporting group title	Fluticasone furoate vilanterol
Reporting group description:	
fluticasone furoate 92 micrograms, vilanterol 22 micrograms 1 puff once daily	
Subject analysis set title	Arm 1 T/O
Subject analysis set type	Sub-group analysis
Subject analysis set description:	
Arm 1 - Tiotropium and Olodaterol	
Subject analysis set title	Arm 2 FF/VI
Subject analysis set type	Sub-group analysis
Subject analysis set description:	
Arm 2 - fluticasone furoate/vilanterol	

Primary: Difference in sputum bacterial load between the T/O group and the FF/VI group

End point title	Difference in sputum bacterial load between the T/O group and the FF/VI group
End point description:	
To determine the effects of the Tiotropium and olodaterol combination (Spiolto respimat 2.5/2.5ug) 2 puffs once daily vs Relvar Ellipta (fluticasone furoate 92 micrograms, vilanterol 22 micrograms) 1 puff once daily on airway bacterial load in sputum	
End point type	Primary
End point timeframe:	
Treatment period, visit 3 to visit 6	

End point values	Tiotropium olodaterol	Fluticasone furoate vilanterol	Arm 1 T/O	Arm 2 FF/VI
Subject group type	Reporting group	Reporting group	Subject analysis set	Subject analysis set
Number of subjects analysed	38	42	38	42
Units: CFUs				
arithmetic mean (confidence interval 95%)	10.5 (10.3 to 10.7)	10.6 (10.4 to 10.8)	0 (0 to 0)	0 (0 to 0)

Statistical analyses

Statistical analysis title	mean difference
Comparison groups	Arm 1 T/O v Arm 2 FF/VI

Number of subjects included in analysis	80
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.99
Method	Mixed models analysis
Parameter estimate	Mean difference (final values)
Point estimate	0
Confidence interval	
level	95 %
sides	2-sided
lower limit	-0.25
upper limit	0.25
Variability estimate	Standard error of the mean

Secondary: Sputum bacterial community composition as measured by the Shannon Weiner Diversity Index

End point title	Sputum bacterial community composition as measured by the Shannon Weiner Diversity Index

End point description:

To determine the effects of the Tiotropium and olodaterol combination (Spiolto respimat 2.52.5ug) 2 puffs once daily vs Relvar Ellipta (fluticasone furoate 92 micrograms, vilanterol 22 micrograms) 1 puff once daily on the airway sputum microbiota.

End point type	Secondary

End point timeframe:

Treatment period, visit 3 to visit 6

End point values	Tiotropium olodaterol	Fluticasone furoate vilanterol	Arm 1 T/O	Arm 2 FF/VI
Subject group type	Reporting group	Reporting group	Subject analysis set	Subject analysis set
Number of subjects analysed	38	42	38	42
Units: NA				
arithmetic mean (confidence interval 95%)	1.51 (1.37 to 1.66)	1.61 (1.44 to 1.79)	0 (0 to 0)	0 (0 to 0)

Statistical analyses

Statistical analysis title	mean difference
Comparison groups	Arm 1 T/O v Arm 2 FF/VI
Number of subjects included in analysis	80
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.04
Method	Mixed models analysis
Parameter estimate	Mean difference (final values)
Point estimate	0.29

Confidence interval	
level	95 %
sides	2-sided
lower limit	0.17
upper limit	0.54
Variability estimate	Standard error of the mean

Secondary: Oropharyngeal bacterial community composition as measured by the Shannon Weiner Diversity Index

End point title	Oropharyngeal bacterial community composition as measured by the Shannon Weiner Diversity Index

End point description:

To determine the effects of the Tiotropium and olodaterol combination (Spiolto respimat 2.52.5ug) 2 puffs once daily vs Relvar Ellipta (fluticasone furoate 92 micrograms, vilanterol 22 micrograms) 1 puff once daily on the airway oropharyngeal microbiota.

End point type	Secondary

End point timeframe:

Treatment period, visit 3 to visit 6

End point values	Tiotropium olodaterol	Fluticasone furoate vilanterol	Arm 1 T/O	Arm 2 FF/VI
Subject group type	Reporting group	Reporting group	Subject analysis set	Subject analysis set
Number of subjects analysed	38	42	38	42
Units: NA				
arithmetic mean (confidence interval 95%)	1.44 (1.25 to 1.63)	1.72 (1.59 to 1.85)	0 (0 to 0)	0 (0 to 0)

Statistical analyses

Statistical analysis title	mean difference
Comparison groups	Arm 2 FF/VI v Arm 1 T/O
Number of subjects included in analysis	80
Analysis specification	Pre-specified
Analysis type	superiority
Method	Mixed models analysis
Parameter estimate	Mean difference (final values)
Point estimate	0.17
Confidence interval	
level	95 %
sides	2-sided
lower limit	-0.026
upper limit	0.37
Variability estimate	Standard error of the mean

Secondary: Nasopharyngeal bacterial community composition as measured by the Shannon Weiner Diversity Index

End point title	Nasopharyngeal bacterial community composition as measured by the Shannon Weiner Diversity Index

End point description:

To determine the effects of the Tiotropium and olodaterol combination (Spiolto respimat 2.52.5ug) 2 puffs once daily vs Relvar Ellipta (fluticasone furoate 92 micrograms, vilanterol 22 micrograms) 1 puff once daily on the airway nasopharyngeal microbiota by Shannon Weiner Diversity Index

End point type	Secondary

End point timeframe:

Treatment period, visit 3 to 6

End point values	Tiotropium olodaterol	Fluticasone furoate vilanterol	Arm 1 T/O	Arm 2 FF/VI
Subject group type	Reporting group	Reporting group	Subject analysis set	Subject analysis set
Number of subjects analysed	38	42	38	42
Units: NA				
arithmetic mean (confidence interval 95%)	1.23 (1.08 to 1.38)	1.09 (0.92 to 1.26)	0 (0 to 0)	0 (0 to 0)

Statistical analyses

Statistical analysis title	mean difference
Comparison groups	Arm 1 T/O v Arm 2 FF/VI
Number of subjects included in analysis	80
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.44
Method	Mixed models analysis
Parameter estimate	Mean difference (final values)
Point estimate	-0.07
Confidence interval	
level	95 %
sides	2-sided
lower limit	-0.25
upper limit	0.11
Variability estimate	Standard error of the mean

Secondary: Difference in oropharngeal bacterial load between the T/O group and the FF/VI group

End point title	Difference in oropharngeal bacterial load between the T/O group and the FF/VI group

End point description:

To determine the effects of the Tiotropium and olodaterol combination (Spiolto respimat 2.5/2.5ug) 2 puffs once daily vs Relvar Ellipta (fluticasone furoate 92 micrograms, vilanterol 22 micrograms) 1 puff once daily on airway bacterial load in oropharyngeal samples

End point type	Secondary

End point timeframe:

Treatment period, visit 3 to 6

End point values	Tiotropium olodaterol	Fluticasone furoate vilanterol	Arm 1 T/O	Arm 2 FF/VI
Subject group type	Reporting group	Reporting group	Subject analysis set	Subject analysis set
Number of subjects analysed	38	42	38	42
Units: CFUs				
arithmetic mean (confidence interval 95%)	8.55 (8.13 to 8.97)	8.98 (8.65 to 9.30)	0 (0 to 0)	0 (0 to 0)

Statistical analyses

Statistical analysis title	mean difference
Comparison groups	Arm 1 T/O v Arm 2 FF/VI
Number of subjects included in analysis	80
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.09
Method	Mixed models analysis
Parameter estimate	Mean difference (final values)
Point estimate	0.32
Confidence interval	
level	95 %
sides	2-sided
lower limit	-0.05
upper limit	0.68
Variability estimate	Standard error of the mean

Secondary: Difference in nasopharyngeal bacterial load between the T/O group and the FF/VI group

End point title	Difference in nasopharyngeal bacterial load between the T/O group and the FF/VI group

End point description:

To determine the effects of the Tiotropium and olodaterol combination (Spiolto respimat 2.5/2.5ug) 2 puffs once daily vs Relvar Ellipta (fluticasone furoate 92 micrograms, vilanterol 22 micrograms) 1 puff once daily on airway bacterial load in nasopharyngeal samples

End point type	Secondary

End point timeframe:

Treatment period, visit 3 to 6

End point values	Tiotropium olodaterol	Fluticasone furoate vilanterol	Arm 1 T/O	Arm 2 FF/VI
Subject group type	Reporting group	Reporting group	Subject analysis set	Subject analysis set
Number of subjects analysed	38	42	38	42
Units: CFUs				
arithmetic mean (confidence interval 95%)	0 (0 to 0)	0.131 (-0.185 to 0.447)	0 (0 to 0)	0 (0 to 0)

Statistical analyses

Statistical analysis title	mean difference
Comparison groups	Arm 2 FF/VI v Arm 1 T/O
Number of subjects included in analysis	80
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.41
Method	Mixed models analysis
Parameter estimate	Mean difference (final values)
Point estimate	0.13
Confidence interval	
level	95 %
sides	2-sided
lower limit	-0.19
upper limit	0.45
Variability estimate	Standard error of the mean

Secondary: Sputum bacterial community composition as measured by difference in Haemophilus OTUs

End point title	Sputum bacterial community composition as measured by difference in Haemophilus OTUs

End point description:

End point type	Secondary

End point timeframe:

To determine the effects of the T/O combination (Spiolto respimat 2.52.5ug) 2 puffs once daily vs Relvar Ellipta (FF 92 micrograms, VI 22 micrograms) 1 puff once daily on the airway sputum microbiota in difference in Haemophilus OTUs

End point values	Tiotropium olodaterol	Fluticasone furoate vilanterol	Arm 1 T/O	Arm 2 FF/VI
Subject group type	Reporting group	Reporting group	Subject analysis set	Subject analysis set
Number of subjects analysed	38	42	38	42
Units: OTUs				
arithmetic mean (confidence interval 95%)	0.04 (0.001 to 0.08)	0.05 (0.01 to 0.10)	0 (0 to 0)	0 (0 to 0)

Statistical analyses

Statistical analysis title	mean difference
Comparison groups	Arm 1 T/O v Arm 2 FF/VI
Number of subjects included in analysis	80
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.21
Method	Mixed models analysis
Parameter estimate	Mean difference (final values)
Point estimate	0.04
Confidence interval	
level	95 %
sides	2-sided
lower limit	-0.09
upper limit	0.21
Variability estimate	Standard error of the mean

Secondary: Oropharyngeal bacterial community composition as measured by difference in Haemophilus OTUs

End point title	Oropharyngeal bacterial community composition as measured by difference in Haemophilus OTUs

End point description:

To determine the effects of FF/VI compared to T/O on relative abundance of Haemophilus OTUs in oropharyngeal samples

End point type	Secondary

End point timeframe:

Treatment period, visit 3 to 6

End point values	Tiotropium olodaterol	Fluticasone furoate vilanterol	Arm 1 T/O	Arm 2 FF/VI
Subject group type	Reporting group	Reporting group	Subject analysis set	Subject analysis set
Number of subjects analysed	38	42	38	42
Units: OTUs				
arithmetic mean (confidence interval 95%)	0.002 (0 to 0.004)	0.0006 (0.0002 to 0.009)	0 (0 to 0)	0 (0 to 0)

Statistical analyses

Statistical analysis title	mean difference
Comparison groups	Arm 1 T/O v Arm 2 FF/VI
Number of subjects included in analysis	80
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.035
Method	Mixed models analysis
Parameter estimate	Mean difference (final values)
Point estimate	0.011
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.001
upper limit	0.022
Variability estimate	Standard error of the mean

Secondary: Nasopharyngeal bacterial community composition as measured by difference in Haemophilus OTUs

End point title	Nasopharyngeal bacterial community composition as measured by difference in Haemophilus OTUs

End point description:

End point type	Secondary

End point timeframe:

To determine the effects of FF/VI compared to T/O treatment on the relative abundance of Haemophilus OTUs in nasopharyngeal samples

End point values	Tiotropium olodaterol	Fluticasone furoate vilanterol	Arm 1 T/O	Arm 2 FF/VI
Subject group type	Reporting group	Reporting group	Subject analysis set	Subject analysis set
Number of subjects analysed	38	42	38	42
Units: OTUs				
arithmetic mean (confidence interval 95%)	0 (0 to 0)	0 (0 to 0)	0 (0 to 0)	0 (0 to 0)

Statistical analyses

Statistical analysis title	mean difference
Comparison groups	Arm 1 T/O v Arm 2 FF/VI
Number of subjects included in analysis	80
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.52
Method	Mixed models analysis
Parameter estimate	Mean difference (final values)
Point estimate	0.0002
Confidence interval	
level	95 %
sides	2-sided
lower limit	-0.0003
upper limit	0.0007
Variability estimate	Standard error of the mean

Secondary: Sputum bacterial community composition as measured by difference in Streptococcus OTUs

End point title	Sputum bacterial community composition as measured by difference in Streptococcus OTUs
End point description:	
To determine the effect of FF/VI compared to T/O on the relative abundance of Streptococcus OTUs	
End point type	Secondary
End point timeframe:	
Treatment period, visit 3 to 6	

End point values	Tiotropium olodaterol	Fluticasone furoate vilanterol	Arm 1 T/O	Arm 2 FF/VI
Subject group type	Reporting group	Reporting group	Subject analysis set	Subject analysis set
Number of subjects analysed	38	42	38	42
Units: OTUs				
arithmetic mean (confidence interval 95%)	0.55 (0.50 to 0.59)	0.52 (0.47 to 0.57)	0 (0 to 0)	0 (0 to 0)

Statistical analyses

Statistical analysis title	mean difference
Comparison groups	Arm 1 T/O v Arm 2 FF/VI

Number of subjects included in analysis	80
Analysis specification	Pre-specified
Analysis type	superiority
P-value	≥ 0.01
Method	Mixed models analysis
Parameter estimate	Mean difference (final values)
Point estimate	-0.07
Confidence interval	
level	95 %
sides	2-sided
lower limit	-0.13
upper limit	-0.02
Variability estimate	Standard error of the mean

Secondary: Oropharyngeal bacterial community composition as measured by difference in Streptococcus OTUs

End point title	Oropharyngeal bacterial community composition as measured by difference in Streptococcus OTUs
End point description:	
To determine the effect of FF/VI compared to T/O on the relative abundance of Streptococcus OTUs	
End point type	Secondary
End point timeframe:	
Treatment period, visit 3 to 6	

End point values	Tiotropium olodaterol	Fluticasone furoate vilanterol	Arm 1 T/O	Arm 2 FF/VI
Subject group type	Reporting group	Reporting group	Subject analysis set	Subject analysis set
Number of subjects analysed	38	42	38	42
Units: OTUs				
arithmetic mean (confidence interval 95%)	0.56 (0.49 to 0.62)	0.46 (0.41 to 0.51)	0 (0 to 0)	0 (0 to 0)

Statistical analyses

Statistical analysis title	mean difference
Comparison groups	Arm 1 T/O v Arm 2 FF/VI
Number of subjects included in analysis	80
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.1
Method	Mixed models analysis
Parameter estimate	Mean difference (final values)
Point estimate	-0.055

Confidence interval	
level	95 %
sides	2-sided
lower limit	-0.12
upper limit	0.01
Variability estimate	Standard error of the mean

Secondary: Nasopharyngeal bacterial community composition as measured by difference in Streptococcus OTUs

End point title	Nasopharyngeal bacterial community composition as measured by difference in Streptococcus OTUs
End point description:	
To determine the effect of FF/VI compared to T/O on the relative abundance of Streptococcus OTUs	
End point type	Secondary
End point timeframe:	
Treatment period, visit 3 to visit 6	

End point values	Tiotropium olodaterol	Fluticasone furoate vilanterol	Arm 1 T/O	Arm 2 FF/VI
Subject group type	Reporting group	Reporting group	Subject analysis set	Subject analysis set
Number of subjects analysed	38	42	38	42
Units: OTUs				
arithmetic mean (confidence interval 95%)	0.09 (0.03 to 0.16)	0.05 (0.004 to 0.10)	0 (0 to 0)	0 (0 to 0)

Statistical analyses

Statistical analysis title	mean difference
Comparison groups	Arm 1 T/O v Arm 2 FF/VI
Number of subjects included in analysis	80
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.03
Method	Mixed models analysis
Parameter estimate	Mean difference (final values)
Point estimate	-0.02
Confidence interval	
level	95 %
sides	2-sided
lower limit	-0.04
upper limit	-0.003
Variability estimate	Standard error of the mean

Secondary: Difference in sputum neutrophil elastase activity	
End point title	Difference in sputum neutrophil elastase activity
End point description: To determine the effect of FF/VI compared to T/O on sputum neutrophil elastase activity	
End point type	Secondary
End point timeframe: Treatment period, visit 3 to 6	

End point values	Tiotropium olodaterol	Fluticasone furoate vilanterol	Arm 1 T/O	Arm 2 FF/VI
Subject group type	Reporting group	Reporting group	Subject analysis set	Subject analysis set
Number of subjects analysed	38	42	38	42
Units: ng/ml				
arithmetic mean (confidence interval 95%)	230.9 (142.9 to 318.9)	361.4 (171.8 to 550.9)	0 (0 to 0)	0 (0 to 0)

Statistical analyses

Statistical analysis title	mean difference
Comparison groups	Arm 1 T/O v Arm 2 FF/VI
Number of subjects included in analysis	80
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.9
Method	Mixed models analysis
Parameter estimate	Mean difference (final values)
Point estimate	6.51
Confidence interval	
level	95 %
sides	2-sided
lower limit	-148.8
upper limit	161.8
Variability estimate	Standard error of the mean

Secondary: Difference in sputum neutrophil extracellular trap formation	
End point title	Difference in sputum neutrophil extracellular trap formation
End point description: To determine the effect of FF/VI compared to T/O on sputum neutrophil extracellular trap formation	
End point type	Secondary

End point timeframe:
Treatment period, visit 3 to 6

End point values	Tiotropium olodaterol	Fluticasone furoate vilanterol	Arm 1 T/O	Arm 2 FF/VI
Subject group type	Reporting group	Reporting group	Subject analysis set	Subject analysis set
Number of subjects analysed	38	42	38	42
Units: units/ml				
arithmetic mean (confidence interval 95%)	12.7 (4.7 to 20.7)	9.1 (5.5 to 12.7)	0 (0 to 0)	0 (0 to 0)

Statistical analyses

Statistical analysis title	mean difference
Comparison groups	Arm 1 T/O v Arm 2 FF/VI
Number of subjects included in analysis	80
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.52
Method	Mixed models analysis
Parameter estimate	Mean difference (final values)
Point estimate	-1.58
Confidence interval	
level	95 %
sides	2-sided
lower limit	-6.4
upper limit	3.2
Variability estimate	Standard error of the mean

Secondary: Difference in sputum resistin

End point title	Difference in sputum resistin
End point description:	
To determine the effect of FF/VI compared to T/O on sputum resistin	
End point type	Secondary
End point timeframe:	
Treatment period, visit 3 to 6	

End point values	Tiotropium olodaterol	Fluticasone furoate vilanterol	Arm 1 T/O	Arm 2 FF/VI
Subject group type	Reporting group	Reporting group	Subject analysis set	Subject analysis set
Number of subjects analysed	38	42	38	42
Units: ng/ml				
arithmetic mean (confidence interval 95%)	174 (46 to 302)	118 (31 to 204)	0 (0 to 0)	0 (0 to 0)

Statistical analyses

Statistical analysis title	mean difference
Comparison groups	Arm 1 T/O v Arm 2 FF/VI
Number of subjects included in analysis	80
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.97
Method	Mixed models analysis
Parameter estimate	Mean difference (final values)
Point estimate	-1.58
Confidence interval	
level	95 %
sides	2-sided
lower limit	-6.4
upper limit	3.2
Variability estimate	Standard error of the mean

Secondary: Difference in sputum IL1-beta

End point title	Difference in sputum IL1-beta
End point description:	
To determine the effect of FF/VI compared to T/O on sputum IL1-beta	
End point type	Secondary
End point timeframe:	
Treatment period, visit 3 to 6	

End point values	Tiotropium olodaterol	Fluticasone furoate vilanterol	Arm 1 T/O	Arm 2 FF/VI
Subject group type	Reporting group	Reporting group	Subject analysis set	Subject analysis set
Number of subjects analysed	38	42	38	42
Units: pg/mL				
arithmetic mean (confidence interval 95%)	251 (-11.6 to 513)	178 (-48.6 to 403)	0 (0 to 0)	0 (0 to 0)

Statistical analyses

Statistical analysis title	mean difference
Comparison groups	Arm 1 T/O v Arm 2 FF/VI
Number of subjects included in analysis	80
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.53
Method	Mixed models analysis
Parameter estimate	Mean difference (final values)
Point estimate	-45.6
Confidence interval	
level	95 %
sides	2-sided
lower limit	-190
upper limit	98.9
Variability estimate	Standard error of the mean

Secondary: Difference in sputum IL-13

End point title	Difference in sputum IL-13
End point description: To determine the effect of FF/VI compared to T/O on sputum IL-13	
End point type	Secondary
End point timeframe: Treatment period, visit 3 to 6	

End point values	Tiotropium olodaterol	Fluticasone furoate vilanterol	Arm 1 T/O	Arm 2 FF/VI
Subject group type	Reporting group	Reporting group	Subject analysis set	Subject analysis set
Number of subjects analysed	38	42	38	42
Units: pg/ml				
arithmetic mean (confidence interval 95%)	0 (0 to 0)	-0.98 (-2.62 to 0.67)	0 (0 to 0)	0 (0 to 0)

Statistical analyses

Statistical analysis title	mean difference
Comparison groups	Arm 1 T/O v Arm 2 FF/VI
Number of subjects included in analysis	80
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.24
Method	Mixed models analysis
Parameter estimate	Mean difference (final values)
Point estimate	-0.98
Confidence interval	
level	95 %
sides	2-sided
lower limit	-2.6
upper limit	0.67
Variability estimate	Standard error of the mean

Secondary: Difference in sputum IL-17A
End point title: Difference in sputum IL-17A
End point description: To determine the effect of FF/VI compared to T/O on sputum IL-17A
End point type: Secondary
End point timeframe: Treatment period, visit 3 to 6

End point values	Tiotropium olodaterol	Fluticasone furoate vilanterol	Arm 1 T/O	Arm 2 FF/VI
Subject group type	Reporting group	Reporting group	Subject analysis set	Subject analysis set
Number of subjects analysed	38	42	38	42
Units: pg/ml				
arithmetic mean (confidence interval 95%)	1.58 (0.38 to 2.79)	1.94 (0.58 to 3.31)	0 (0 to 0)	0 (0 to 0)

Statistical analyses

Statistical analysis title	mean difference
Comparison groups	Arm 1 T/O v Arm 2 FF/VI
Number of subjects included in analysis	80
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.5
Method	Mixed models analysis
Parameter estimate	Mean difference (final values)
Point estimate	-0.25

Confidence interval	
level	95 %
sides	2-sided
lower limit	-0.98
upper limit	0.48
Variability estimate	Standard error of the mean

Secondary: Difference in sputum CXCL-8

End point title	Difference in sputum CXCL-8
End point description:	
To determine the effect of FF/VI compared to T/O on sputum CXCL-8	
End point type	Secondary
End point timeframe:	
Treatment period, visit 3 to 6	

End point values	Tiotropium olodaterol	Fluticasone furoate vilanterol	Arm 1 T/O	Arm 2 FF/VI
Subject group type	Reporting group	Reporting group	Subject analysis set	Subject analysis set
Number of subjects analysed	38	42	38	42
Units: ng/ml				
arithmetic mean (confidence interval 95%)	0 (0 to 0)	-3.16 (-7.25 to 0.94)	0 (0 to 0)	0 (0 to 0)

Statistical analyses

Statistical analysis title	mean difference
Comparison groups	Arm 1 T/O v Arm 2 FF/VI
Number of subjects included in analysis	80
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.13
Method	Mixed models analysis
Parameter estimate	Mean difference (final values)
Point estimate	-3.2
Confidence interval	
level	95 %
sides	2-sided
lower limit	-7.3
upper limit	0.94
Variability estimate	Standard error of the mean

Adverse events

Adverse events information

Timeframe for reporting adverse events:

Adverse events were recorded from screening to end of study, from July 2017 until November 2019

Assessment type	Systematic

Dictionary used

Dictionary name	MedDRA
Dictionary version	24

Reporting groups

Reporting group title	Tiotropium/Olodaterol
Reporting group description: -	
Reporting group title	Fluticasone furoate/Vilaterol

Reporting group description: -

Serious adverse events	Tiotropium/Olodaterol	Fluticasone furoate/Vilaterol	
Total subjects affected by serious adverse events			
subjects affected / exposed	6 / 38 (15.79%)	1 / 42 (2.38%)	
number of deaths (all causes)	0	0	
number of deaths resulting from adverse events	0	0	
Respiratory, thoracic and mediastinal disorders			
Chronic obstructive pulmonary disease			
subjects affected / exposed	3 / 38 (7.89%)	0 / 42 (0.00%)	
occurrences causally related to treatment / all	0 / 3	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Infections and infestations			
Pneumonia			
subjects affected / exposed	3 / 38 (7.89%)	1 / 42 (2.38%)	
occurrences causally related to treatment / all	0 / 3	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	

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

Non-serious adverse events	Tiotropium/Olodaterol	Fluticasone furoate/Vilaterol	
Total subjects affected by non-serious adverse events			
subjects affected / exposed	28 / 38 (73.68%)	22 / 42 (52.38%)	

General disorders and administration site conditions			
Chest pain			
subjects affected / exposed	4 / 38 (10.53%)	0 / 42 (0.00%)	
occurrences (all)	5	0	
Respiratory, thoracic and mediastinal disorders			
Cough			
subjects affected / exposed	7 / 38 (18.42%)	1 / 42 (2.38%)	
occurrences (all)	7	1	
Dyspnoea			
subjects affected / exposed	16 / 38 (42.11%)	11 / 42 (26.19%)	
occurrences (all)	19	11	
Epistaxis			
subjects affected / exposed	0 / 38 (0.00%)	3 / 42 (7.14%)	
occurrences (all)	0	3	
Lower respiratory tract infection			
subjects affected / exposed	0 / 38 (0.00%)	4 / 42 (9.52%)	
occurrences (all)	0	5	
Oropharyngeal pain			
subjects affected / exposed	1 / 38 (2.63%)	3 / 42 (7.14%)	
occurrences (all)	1	3	

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