Clinical trial results:
A randomised, open label 2-way cross-over study to compare the effects of inhaled Beclometasone/Formoterol/Glycopyrronium (TRIMBOW) pMDI to Beclometasone/Formoterol (FOSTAIR) pMDI on hyperinflation and expiratory flow limitation in moderate to severe chronic obstructive pulmonary disease (COPD).

Summary

EudraCT number	2018-003113-17
Trial protocol	GB
Global end of trial date	06 August 2019

Results information

Result version number	v1 (current)
This version publication date	23 August 2020
First version publication date	23 August 2020

Trial information

Trial identification

Sponsor protocol code	MEU 17/361

Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	NCT03842904
WHO universal trial number (UTN)	-
Other trial identifiers	MEU number: MEU 17/361

Notes:

Sponsors

Sponsor organisation name	Medicines Evaluation Unit (MEU) Ltd.
Sponsor organisation address	The Langley Building, Southmoor Road, Manchester, United Kingdom, M23 9QZ
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Scientific contact	Professor Dave Singh, The Medicines Evaluation Unit (MEU) Ltd., 0044 0161 946 4050, enquiries@meu.org.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	12 December 2019
Is this the analysis of the primary completion data?	Yes
Primary completion date	06 August 2019
Global end of trial reached?	Yes
Global end of trial date	06 August 2019
Was the trial ended prematurely?	No

Notes:

General information about the trial

Main objective of the trial:

1) To compare the effect of Trimbow and Fostair on FEV1 [(forced expiratory volume in 1 second – changes from pre-dose day 1)].
2) To compare the effect of Trimbow and Fostair on RV [(residual volume) – changes from pre-dose day 1)].

Protection of trial subjects:

The study was conducted in accordance with the Declaration of Helsinki, Good Clinical Practice (GCP) guidelines and local law requirements .

Trained medical staff, necessary equipment and appropriate medication were available at the clinic, or at the nearby hospital, in case of any emergencies.

Safety assessments (e.g. vital signs, ECGs, physical examinations and safety laboratory samples) were performed prior to enrolment into the study. Vital signs and physical examinations were performed regularly to ensure the health and safety of trial subjects.

Background therapy:

Salbutamol (metered-dose inhaler pMDI) was provided to all subjects as rescue medication for as-needed use any time during the study. At the investigator's discretion it could be regularly taken during the run-in and washout periods, if for example a subject was withdrawing from a long-acting β2-agonist. However, it could not be used up to 8 hours before each study centre visit or, during study centre visits with lung function procedures unless medically necessary.

Subjects withdrawing from a long-acting muscarinic antagonist could use the provided short-acting anticholinergic ipratropium regularly (40 µg, up to 3 times a day) during the run-in and washout periods, at the discretion of the investigator. However, it could not be used for at least 8 hours before spirometry assessments at Visit 1, Visit 2 and Day 1 of either treatment period or during each treatment period (Day 1 to Day 5).

During the run-in and washout periods and after screening spirometry criteria were met, subjects switched to supplied background corticosteroid monotherapy Clenil
(R) Modulite(R) beclometasone dipropionate (400 µg daily: 2 × 100 µg pMDI doses twice daily [BID]) omitting the morning dose on Visit 2 and Day 1 of each treatment period.

Hormonal contraception or hormone replacement therapy and medications that the investigator considered would not compromise subject safety or affect study data were permitted (unless listed as not permitted below).

Evidence for comparator:

The study drugs called Trimbow and Fostair are licensed medications for the treatment of chronic obstructive pulmonary disease (COPD). The most commonly used treatments for COPD are inhaled bronchodilators (beta agonists and muscarinic antagonists) which open up the airways and inhaled steroids which reduce inflammation of the airways. Trimbow is a triple combination pressurised metered dose inhaler (pMDI) containing a steroid (called beclometasone diproprionate), a long acting beta agonist (called formoterol fumarate) and a long acting antagonist (called glycopyrronium bromide), which has shown to improve lung function and reduce COPD exacerbation (worsening) rates. Fostair is a dual combination pMDI containing the same steroid and long acting beta agonist that are found in Trimbow.

Trimbow is an "extrafine" formulation with increased delivery of small particles to the peripheral airways. This has the advantage of targeted delivery to the anatomical site of pathophysiological

abnormalities.

The study investigated the contributions of extra-fine glycopyrronium and formoterol (within triple therapy) to improvements in small airway function in COPD patients. This was achieved by recruiting patients with hyperinflation, and measuring improvements in hyperinflation and expiratory flow limitation as measurements of small airway disease. The purpose of the study was to help understand the mechanisms of action of the bronchodilators within Trimbow, and potentially encourage treatment of small airway disease in COPD with extra-fine bronchodilator treatments.

Actual start date of recruitment	13 December 2018
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: 23
Worldwide total number of subjects	23
EEA total number of subjects	23

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)	11
From 65 to 84 years	12
85 years and over	0

Subject disposition

Recruitment

Recruitment details:

The first patient was consented on 13 December 2018. 23 subjects were randomised, 22 of which completed the study.

1 subject was withdrawn during treatment period 1 due to non-compliance with the study medication.

Pre-assignment

Screening details:

Overall, 66 subjects were screened for the study. The main reason for screen failure was that subjects didn't meet inclusion criterion 7 i.e. residual volume at screening or baseline was less than or equal to 120% of their predicted value.

Period 1

Period 1 title	Baseline visit
Is this the baseline period?	Yes
Allocation method	Not applicable
Blinding used	Not blinded

Blinding implementation details:

The study was open-label

Arms

Arm title	Baseline (Visit 2)

Arm description:

Participants entered a run-in period after screening and received a supply of Clenil Modulite Beclometasone Diproprionate to administer 2 inhalations, twice daily.

Visit 2 (Baseline) was conducted 10 days after the start of the run-in period. The dose of beclometasone was administered on the morning of Visit 2 at the research unit.

Arm type	Run-in
Investigational medicinal product name	Clenil Modulite 100 micrograms
Investigational medicinal product code	Non-IMP
Other name	
Pharmaceutical forms	Inhalation solution
Routes of administration	Inhalation use

Dosage and administration details:

Twice daily dosing after screening (2 inhalations per dose) until Day -1. 100µg per inhalation, 2 inhalations BID (total daily metered dose: 400µg).

Number of subjects in period 1	Baseline (Visit 2)
Started	23
Completed	23

Period 2

Period 2 title	Overall Trial (overall period)
Is this the baseline period?	No
Allocation method	Randomised - controlled
Blinding used	Not blinded

Blinding implementation details:

The study was open-label

Arms

Are arms mutually exclusive?	No
Arm title	Test Treatment 1

Arm description:

Participants received Trimbow (Beclometasone/Formoterol/Glycopyrronium) twice daily for 4 consecutive days - two inhalations in the morning and two in the evening administered via pressurized metered dose inhaler (pMDI). After the morning dose on Day 1, subjects received a supply of study medication to take home and administer themselves. The last dose administration was on the morning of Day 5 at the research unit.

Arm type	Experimental
Investigational medicinal product name	Trimbow 87 micrograms/5 micrograms/9 micrograms pressurised inhalation, solution
Investigational medicinal product code	
Other name	Beclometasone/Formoterol/Glycopyrronium
Pharmaceutical forms	Pressurised inhalation, solution
Routes of administration	Inhalation use

Dosage and administration details:

Twice daily dosing on Days 1 - 4 (2 inhalations per dose). Last dose taken on the morning of Day 5. Administered via pMDI.
Total daily metered dose: 400 µg (beclometasone)/24 µg (formoterol)/40 µg (glycopyrronium).
Delivered dose: 348/20/36 µg

Arm title	Test Treatment 2

Arm description:

Participants received Fostair (Beclometasone/Formoterol) twice daily for 4 consecutive days - two inhalations in the morning and two in the evening administered via pressurized metered dose inhaler (pMDI). After the morning dose on Day 1, subjects received a supply of study medication to take home and administer themselves. The last dose administration was on the morning of Day 5 at the research unit.

Arm type	Experimental
Investigational medicinal product name	Fostair 100/6 micrograms per actuation pressurised inhalation solution
Investigational medicinal product code	
Other name	Beclometasone/Formoterol
Pharmaceutical forms	Pressurised inhalation, solution
Routes of administration	Inhalation use

Dosage and administration details:

Twice daily dosing on Days 1 - 4 (2 inhalations per dose). Last dose taken on the morning of Day 5. Administered via pMDI.
Total daily metered dose: 400 µg (beclometasone)/24 µg (formoterol).

Number of subjects in period 2	Test Treatment 1	Test Treatment 2
Started	23	22
Completed	22	22
Not completed	1	0
non-compliance	1	-

Baseline characteristics

Reporting groups	
Reporting group title	Baseline visit

Reporting group description: -

Reporting group values	Baseline visit	Total	
Number of subjects	23	23	
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)	11	11	
From 65-84 years	12	12	
85 years and over	0	0	
Age continuous Units: years			
median	66		
full range (min-max)	48 to 75	-	
Gender categorical Units: Subjects			
Female	14	14	
Male	9	9	
Ethnic Origin Units: Subjects			
Caucasian	23	23	
Black	0	0	
North-East Asian	0	0	
South-East Asian	0	0	
Other	0	0	

End points

End points reporting groups

Reporting group title	Baseline (Visit 2)

Reporting group description:

Participants entered a run-in period after screening and received a supply of Clenil Modulite Beclometasone Diproprionate to administer 2 inhalations, twice daily.

Visit 2 (Baseline) was conducted 10 days after the start of the run-in period. The dose of beclometasone was administered on the morning of Visit 2 at the research unit.

Reporting group title	Test Treatment 1

Reporting group description:

Participants received Trimbow (Beclometasone/Formoterol/Glycopyrronium) twice daily for 4 consecutive days - two inhalations in the morning and two in the evening administered via pressurized metered dose inhaler (pMDI). After the morning dose on Day 1, subjects received a supply of study medication to take home and administer themselves. The last dose administration was on the morning of Day 5 at the research unit.

Reporting group title	Test Treatment 2

Reporting group description:

Participants received Fostair (Beclometasone/Formoterol) twice daily for 4 consecutive days - two inhalations in the morning and two in the evening administered via pressurized metered dose inhaler (pMDI). After the morning dose on Day 1, subjects received a supply of study medication to take home and administer themselves. The last dose administration was on the morning of Day 5 at the research unit.

Primary: FEV1 AUC0-12 Response at Day 5

End point title	FEV1 AUC0-12 Response at Day 5

End point description:

To compare the FEV1 area under the curve response at Day 5 between the 2 treatments.

End point type	Primary

End point timeframe:

Over 12 hours after treatment on Day 5 of each treatment period.

End point values	Test Treatment 1	Test Treatment 2		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	22	22		
Units: litre(s)				
least squares mean (standard error)	0.333 (± 0.0372)	0.229 (± 0.0372)		

Statistical analyses

Statistical analysis title	FEV1 AUC0-12 Response at Day 5 (ITT)
Comparison groups	Test Treatment 1 v Test Treatment 2

Number of subjects included in analysis	44
Analysis specification	Pre-specified
Analysis type	other
P-value	= 0.0071
Method	t-test, 2-sided
Parameter estimate	Mean difference (final values)
Point estimate	0.104
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.037
upper limit	0.171
Variability estimate	Standard error of the mean

Primary: Peak FEV1 Response at Day 5

End point title	Peak FEV1 Response at Day 5

End point description:

To compare the peak FEV1 response at Day 5 between the 2 treatments.

End point type	Primary

End point timeframe:

Over 12 hours after treatment on Day 5 of each treatment period.

End point values	Test Treatment 1	Test Treatment 2		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	22	22		
Units: litre(s)				
least squares mean (standard error)	0.503 (± 0.0454)	0.384 (± 0.0454)		

Statistical analyses

Statistical analysis title	Peak FEV1 Response at Day 5 (ITT)
Comparison groups	Test Treatment 1 v Test Treatment 2
Number of subjects included in analysis	44
Analysis specification	Pre-specified
Analysis type	other
P-value	= 0.0016
Method	t-test, 2-sided
Parameter estimate	Mean difference (final values)
Point estimate	0.12

Confidence interval	
level	95 %
sides	2-sided
lower limit	0.055
upper limit	0.184
Variability estimate	Standard error of the mean

Primary: Pre-dose Trough FEV1 Response at Day 5

End point title	Pre-dose Trough FEV1 Response at Day 5
End point description:	
To compare the pre-dose trough FEV1 response at Day 5 between the 2 treatments.	
End point type	Primary
End point timeframe:	
Prior to the subject dosing on Day 5.	

End point values	Test Treatment 1	Test Treatment 2		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	22	22		
Units: litre(s)				
least squares mean (standard error)	0.243 (± 0.0333)	0.134 (± 0.0333)		

Statistical analyses

Statistical analysis title	Pre-dose Trough FEV1 Response at Day 5 (ITT)
Comparison groups	Test Treatment 1 v Test Treatment 2
Number of subjects included in analysis	44
Analysis specification	Pre-specified
Analysis type	other
P-value	= 0.0126
Method	t-test, 2-sided
Parameter estimate	Mean difference (final values)
Point estimate	0.109
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.026
upper limit	0.191
Variability estimate	Standard error of the mean

Primary: Post-dose Trough FEV1 Response at Day 5

End point title	Post-dose Trough FEV1 Response at Day 5
End point description:	
To compare the post-dose trough FEV1 response at Day 5 between the 2 treatments.	
End point type	Primary
End point timeframe:	
12 hours after subject dosing is complete on Day 5.	

End point values	Test Treatment 1	Test Treatment 2		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	22	22		
Units: litre(s)				
least squares mean (standard error)	0.175 (± 0.0291)	0.109 (± 0.0291)		

Statistical analyses

Statistical analysis title	Post-dose Trough FEV1 Response at Day 5 (ITT)
Comparison groups	Test Treatment 1 v Test Treatment 2
Number of subjects included in analysis	44
Analysis specification	Pre-specified
Analysis type	other
P-value	= 0.0797
Method	t-test, 2-sided
Parameter estimate	Mean difference (final values)
Point estimate	0.065
Confidence interval	
level	95 %
sides	2-sided
lower limit	-0.009
upper limit	0.139
Variability estimate	Standard error of the mean

Primary: RV AUC0-12 Response at Day 5

End point title	RV AUC0-12 Response at Day 5
End point description:	
To compare the RV area under the curve response at Day 5 between the 2 treatments.	
End point type	Primary
End point timeframe:	
Over 12 hours after treatment on Day 5 of each treatment period.	

End point values	Test Treatment 1	Test Treatment 2		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	22	22		
Units: litre(s)				
least squares mean (standard error)	-0.696 (± 0.0750)	-0.532 (± 0.0750)		

Statistical analyses

Statistical analysis title	RV AUC0-12 Response at Day 5 (ITT)
Comparison groups	Test Treatment 1 v Test Treatment 2
Number of subjects included in analysis	44
Analysis specification	Pre-specified
Analysis type	other
P-value	= 0.0028
Method	t-test, 2-sided
Parameter estimate	Mean difference (final values)
Point estimate	-0.163
Confidence interval	
level	95 %
sides	2-sided
lower limit	-0.263
upper limit	-0.064
Variability estimate	Standard error of the mean

Primary: Peak RV Response at Day 5

End point title	Peak RV Response at Day 5
End point description:	
To compare the peak RV response at Day 5 between the 2 treatments.	
End point type	Primary
End point timeframe:	
Over 12 hours after treatment on Day 5 of each treatment period.	

End point values	Test Treatment 1	Test Treatment 2		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	22	22		
Units: litre(s)				
least squares mean (standard error)	-0.947 (± 0.0873)	-0.869 (± 0.0873)		

Statistical analyses

Statistical analysis title	Peak RV Response at Day 5 (ITT)
Comparison groups	Test Treatment 1 v Test Treatment 2
Number of subjects included in analysis	44
Analysis specification	Pre-specified
Analysis type	other
P-value	= 0.1092
Method	t-test, 2-sided
Parameter estimate	Mean difference (final values)
Point estimate	-0.079
Confidence interval	
level	95 %
sides	2-sided
lower limit	-0.176
upper limit	0.019
Variability estimate	Standard error of the mean

Primary: Pre-dose Trough RV Response at Day 5

End point title	Pre-dose Trough RV Response at Day 5
End point description:	
To compare the pre-dose trough RV response at Day 5 between the 2 treatments.	
End point type	Primary
End point timeframe:	
Prior to the subject dosing on Day 5.	

End point values	Test Treatment 1	Test Treatment 2		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	22	22		
Units: litre(s)				
least squares mean (standard error)	-0.531 (± 0.0723)	-0.360 (± 0.0723)		

Statistical analyses

Statistical analysis title	Pre-dose Trough RV Response at Day 5 (ITT)
Comparison groups	Test Treatment 1 v Test Treatment 2
Number of subjects included in analysis	44
Analysis specification	Pre-specified
Analysis type	other
P-value	= 0.0331
Method	t-test, 2-sided
Parameter estimate	Mean difference (final values)
Point estimate	-0.171

Confidence interval	
level	95 %
sides	2-sided
lower limit	-0.327
upper limit	-0.015
Variability estimate	Standard error of the mean

Primary: Post-dose Trough RV Response at Day 5

End point title	Post-dose Trough RV Response at Day 5
End point description:	
To compare the post-dose trough RV response at Day 5 between the 2 treatments.	
End point type	Primary
End point timeframe:	
12 hours after subject dosing is complete on Day 5.	

End point values	Test Treatment 1	Test Treatment 2		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	22	22		
Units: litre(s)				
least squares mean (standard error)	-0.446 (± 0.0749)	-0.268 (± 0.0749)		

Statistical analyses

Statistical analysis title	Post-dose Trough RV Response at Day 5 (ITT)
Comparison groups	Test Treatment 1 v Test Treatment 2
Number of subjects included in analysis	44
Analysis specification	Pre-specified
Analysis type	other
P-value	= 0.0097
Method	t-test, 2-sided
Parameter estimate	Mean difference (final values)
Point estimate	-0.179
Confidence interval	
level	95 %
sides	2-sided
lower limit	-0.308
upper limit	-0.049
Variability estimate	Standard error of the mean

Secondary: Spirometry parameters AUC0-12 Response at Day 5 (FEF)

End point title	Spirometry parameters AUC0-12 Response at Day 5 (FEF)

End point description:

To compare the FEF area under the curve response at Day 5 between the 2 treatment groups.

End point type	Secondary

End point timeframe:

Over 12 hours after treatment on Day 5 of each treatment period.

End point values	Test Treatment 1	Test Treatment 2		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	22	22		
Units: L/s				
least squares mean (standard error)	0.110 (± 0.0160)	0.083 (± 0.0160)		

Statistical analyses

Statistical analysis title	Spirometry Parameters AUC0-12 Response at Day 5

Statistical analysis description:

FEF 25-75% (L/s)

Comparison groups	Test Treatment 2 v Test Treatment 1
Number of subjects included in analysis	44
Analysis specification	Pre-specified
Analysis type	other
P-value	= 0.0395
Method	t-test, 2-sided
Parameter estimate	Mean difference (final values)
Point estimate	0.026
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.001
upper limit	0.051
Variability estimate	Standard error of the mean

Secondary: Spirometry parameters AUC0-12 Response at Day 5(FVC)

End point title	Spirometry parameters AUC0-12 Response at Day 5(FVC)

End point description:

To compare the FVC area under the curve response at Day 5 between the 2 treatment groups.

End point type	Secondary

End point timeframe:

Over 12 hours after treatment on Day 5 of each treatment period.

End point values	Test Treatment 1	Test Treatment 2		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	22	22		
Units: litre(s)				
least squares mean (standard error)	0.545 (± 0.0642)	0.339 (± 0.0642)		

Statistical analyses

Statistical analysis title	Spirometry Parameters AUC0-12 Response at Day 5
Statistical analysis description: FVC (L)	
Comparison groups	Test Treatment 2 v Test Treatment 1
Number of subjects included in analysis	44
Analysis specification	Pre-specified
Analysis type	other
P-value	= 0.0116
Method	t-test, 2-sided
Parameter estimate	Mean difference (final values)
Point estimate	0.206
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.054
upper limit	0.359
Variability estimate	Standard error of the mean

Secondary: Spirometry Parameters Peak Response at Day 5 (FEF)

End point title	Spirometry Parameters Peak Response at Day 5 (FEF)
End point description: To compare the peak FEF response at Day 5 between the 2 treatment groups.	
End point type	Secondary
End point timeframe: Over 12 hours after treatment on Day 5 of each treatment period.	

End point values	Test Treatment 1	Test Treatment 2		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	22	22		
Units: L/s				
least squares mean (standard error)	0.210 (± 0.0271)	0.166 (± 0.0271)		

Statistical analyses

Statistical analysis title	Spirometry Parameters Peak Response at Day 5 (ITT)
Statistical analysis description: FEF 25-75% (L/s)	
Comparison groups	Test Treatment 1 v Test Treatment 2
Number of subjects included in analysis	44
Analysis specification	Pre-specified
Analysis type	other
P-value	= 0.0442
Method	t-test, 2-sided
Parameter estimate	Mean difference (final values)
Point estimate	0.044
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.001
upper limit	0.088
Variability estimate	Standard error of the mean

Secondary: Spirometry Parameters Peak Response at Day 5 (FVC)

End point title	Spirometry Parameters Peak Response at Day 5 (FVC)
End point description: To compare the peak FVC response at Day 5 between the 2 treatment groups.	
End point type	Secondary
End point timeframe: Over 12 hours after treatment on Day 5 of each treatment period.	

End point values	Test Treatment 1	Test Treatment 2		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	22	22		
Units: litre(s)				
least squares mean (standard error)	0.850 (± 0.0919)	0.607 (± 0.0919)		

Statistical analyses

Statistical analysis title	Spirometry Parameters Peak Response at Day 5 (ITT)
Statistical analysis description: FVC (L)	
Comparison groups	Test Treatment 1 v Test Treatment 2
Number of subjects included in analysis	44
Analysis specification	Pre-specified
Analysis type	other
P-value	= 0.0106
Method	t-test, 2-sided
Parameter estimate	Mean difference (final values)
Point estimate	0.243
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.068
upper limit	0.419
Variability estimate	Standard error of the mean

Secondary: Impulse Oscillometry Parameters AUC0-12 Response at Day 5 (AX)

End point title	Impulse Oscillometry Parameters AUC0-12 Response at Day 5 (AX)

End point description:

To compare the AX area under the curve response at Day 5 between the 2 treatment groups.

End point type	Secondary

End point timeframe:

Over 12 hours after treatment on Day 5 of each treatment period.

End point values	Test Treatment 1	Test Treatment 2		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	22	22		
Units: kPa/L				
least squares mean (standard error)	-2.911 (± 0.2668)	-2.205 (± 0.2668)		

Statistical analyses

Statistical analysis title	AX AUC0-12 Response at Day 5 (ITT)
Comparison groups	Test Treatment 1 v Test Treatment 2
Number of subjects included in analysis	44
Analysis specification	Pre-specified
Analysis type	other
P-value	= 0.0004
Method	t-test, 2-sided
Parameter estimate	Mean difference (final values)
Point estimate	-0.706
Confidence interval	
level	95 %
sides	2-sided
lower limit	-1.047
upper limit	-0.365
Variability estimate	Standard deviation

Secondary: Impulse Oscillometry Parameters AUC0-12 Response at Day 5 (Delta X5)

End point title	Impulse Oscillometry Parameters AUC0-12 Response at Day 5 (Delta X5)

End point description:

To compare the Delta X5 area under the curve response at Day 5 between the 2 treatment groups.

End point type	Secondary

End point timeframe:

Over 12 hours after treatment on Day 5 of each treatment period.

End point values	Test Treatment 1	Test Treatment 2		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	22	22		
Units: kPa/L/s				
least squares mean (standard error)	-0.137 (± 0.0387)	-0.095 (± 0.0387)		

Statistical analyses

Statistical analysis title	Delta X5 AUC0-12 Response at Day 5 (ITT)
Comparison groups	Test Treatment 1 v Test Treatment 2

Number of subjects included in analysis	44
Analysis specification	Pre-specified
Analysis type	other
P-value	= 0.0575
Method	t-test, 2-sided
Parameter estimate	Mean difference (final values)
Point estimate	-0.042
Confidence interval	
level	95 %
sides	2-sided
lower limit	-0.086
upper limit	0.002
Variability estimate	Standard error of the mean

Secondary: Impulse Oscillometry Parameters AUC0-12 Response at Day 5 (Fres)

End point title	Impulse Oscillometry Parameters AUC0-12 Response at Day 5 (Fres)

End point description:

To compare the Fres area under the curve response at Day 5 between the 2 treatment groups.

End point type	Secondary

End point timeframe:

Over 12 hours after treatment on Day 5 of each treatment period.

End point values	Test Treatment 1	Test Treatment 2		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	22	22		
Units: 1/s				
least squares mean (standard error)	-7.201 (± 0.9146)	-5.005 (± 0.9146)		

Statistical analyses

Statistical analysis title	Fres AUC0-12 Response at Day 5 (ITT)
Comparison groups	Test Treatment 1 v Test Treatment 2
Number of subjects included in analysis	44
Analysis specification	Pre-specified
Analysis type	other
P-value	= 0.0016
Method	t-test, 2-sided
Parameter estimate	Mean difference (final values)
Point estimate	-2.195

Confidence interval	
level	95 %
sides	2-sided
lower limit	-3.451
upper limit	-0.94
Variability estimate	Standard error of the mean

Secondary: Impulse Oscillometry Parameters AUC0-12 Response at Day 5 (R5)

End point title	Impulse Oscillometry Parameters AUC0-12 Response at Day 5 (R5)

End point description:

To compare the R5 area under the curve response at Day 5 between the 2 treatment groups.

End point type	Secondary

End point timeframe:

Over 12 hours after treatment on Day 5 of each treatment period.

End point values	Test Treatment 1	Test Treatment 2		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	22	22		
Units: kPa/L/s				
least squares mean (standard error)	-0.186 (± 0.0179)	-0.131 (± 0.0179)		

Statistical analyses

Statistical analysis title	R5 AUC0-12 Response at Day 5 (ITT)
Comparison groups	Test Treatment 1 v Test Treatment 2
Number of subjects included in analysis	44
Analysis specification	Pre-specified
Analysis type	other
P-value	= 0.0005
Method	t-test, 2-sided
Parameter estimate	Median difference (final values)
Point estimate	-0.055
Confidence interval	
level	95 %
sides	2-sided
lower limit	-0.082
upper limit	-0.028
Variability estimate	Standard error of the mean

Secondary: Impulse Oscillometry Parameters AUC0-12 Response at Day 5 (R5-R20)	
End point title	Impulse Oscillometry Parameters AUC0-12 Response at Day 5 (R5-R20)

End point description:

To compare the R5-R20 area under the curve response at Day 5 between the 2 treatment groups.

End point type	Secondary

End point timeframe:

Over 12 hours after treatment on Day 5 of each treatment period.

End point values	Test Treatment 1	Test Treatment 2		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	22	22		
Units: kPa/L/s				
least squares mean (standard error)	-0.163 (± 0.0154)	-0.118 (± 0.0154)		

Statistical analyses

Statistical analysis title	R5-R20 AUC0-12 Response at Day 5 (ITT)
Comparison groups	Test Treatment 1 v Test Treatment 2
Number of subjects included in analysis	44
Analysis specification	Pre-specified
Analysis type	other
P-value	= 0.0002
Method	t-test, 2-sided
Parameter estimate	Mean difference (final values)
Point estimate	-0.045
Confidence interval	
level	95 %
sides	2-sided
lower limit	-0.065
upper limit	-0.025
Variability estimate	Standard error of the mean

Secondary: Impulse Oscillometry Parameters AUC0-12 Response at Day 5 (X5)	
End point title	Impulse Oscillometry Parameters AUC0-12 Response at Day 5 (X5)

End point description:

To compare the X5 area under the curve response at Day 5 between the 2 treatment groups.

End point type	Secondary

End point timeframe:

Over 12 hours after treatment on Day 5 of each treatment period.

End point values	Test Treatment 1	Test Treatment 2		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	22	22		
Units: kPa/L/s				
least squares mean (standard error)	0.203 (± 0.0231)	0.156 (± 0.0231)		

Statistical analyses

Statistical analysis title	X5 AUC0-12 Response at Day 5 (ITT)
Comparison groups	Test Treatment 1 v Test Treatment 2
Number of subjects included in analysis	44
Analysis specification	Pre-specified
Analysis type	other
P-value	= 0.0003
Method	t-test, 2-sided
Parameter estimate	Mean difference (final values)
Point estimate	0.047
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.025
upper limit	0.069
Variability estimate	Standard error of the mean

Secondary: Impulse Oscillometry Parameters Peak Response at Day 5 (AX)

End point title	Impulse Oscillometry Parameters Peak Response at Day 5 (AX)

End point description:

To compare the peak AX response at Day 5 between the 2 treatment groups.

End point type	Secondary

End point timeframe:

Over 12 hours after treatment on Day 5 of each treatment period.

End point values	Test Treatment 1	Test Treatment 2		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	22	22		
Units: kPa/L				
least squares mean (standard error)	-3.770 (± 0.2403)	-3.228 (± 0.2403)		

Statistical analyses

Statistical analysis title	AX Peak Response at Day 5 (ITT)
Comparison groups	Test Treatment 1 v Test Treatment 2
Number of subjects included in analysis	44
Analysis specification	Pre-specified
Analysis type	other
P-value	= 0.0072
Method	t-test, 2-sided
Parameter estimate	Mean difference (final values)
Point estimate	-0.542
Confidence interval	
level	95 %
sides	2-sided
lower limit	-0.918
upper limit	-0.166
Variability estimate	Standard error of the mean

Secondary: Impulse Oscillometry Parameters Peak Response at Day 5 (Delta X5)

End point title	Impulse Oscillometry Parameters Peak Response at Day 5 (Delta X5)

End point description:

To compare the peak Delta X5 response at Day 5 between the 2 treatment groups.

End point type	Secondary

End point timeframe:

Over 12 hours after treatment on Day 5 of each treatment period.

End point values	Test Treatment 1	Test Treatment 2		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	22	22		
Units: kPa/L/s				
least squares mean (standard error)	-0.240 (± 0.0290)	-0.210 (± 0.0290)		

Statistical analyses

Statistical analysis title	Delta X5 Peak Response at Day 5 (ITT)
Comparison groups	Test Treatment 1 v Test Treatment 2
Number of subjects included in analysis	44
Analysis specification	Pre-specified
Analysis type	other
P-value	= 0.2892
Method	t-test, 2-sided
Parameter estimate	Mean difference (final values)
Point estimate	-0.03
Confidence interval	
level	95 %
sides	2-sided
lower limit	-0.088
upper limit	0.028
Variability estimate	Standard error of the mean

Secondary: Impulse Oscillometry Parameters Peak Response at Day 5 (Fres)	
End point title	Impulse Oscillometry Parameters Peak Response at Day 5 (Fres)

End point description:

To compare the peak Fres response at Day 5 between the 2 treatment groups.

End point type	Secondary

End point timeframe:

Over 12 hours after treatment on Day 5 of each treatment period.

End point values	Test Treatment 1	Test Treatment 2		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	22	22		
Units: 1/s				
least squares mean (standard error)	-11.130 (± 1.0881)	-8.613 (± 1.0881)		

Statistical analyses

Statistical analysis title	Fres Peak Response at Day 5 (ITT)
Comparison groups	Test Treatment 1 v Test Treatment 2
Number of subjects included in analysis	44
Analysis specification	Pre-specified
Analysis type	other
P-value	= 0.0007
Method	t-test, 2-sided
Parameter estimate	Mean difference (final values)
Point estimate	-2.517
Confidence interval	
level	95 %
sides	2-sided
lower limit	-3.83
upper limit	-1.205
Variability estimate	Standard error of the mean

Secondary: Impulse Oscillometry Parameters Peak Response at Day 5 (R5)

End point title	Impulse Oscillometry Parameters Peak Response at Day 5 (R5)

End point description:

To compare the peak R5 response at Day 5 between the 2 treatment groups.

End point type	Secondary

End point timeframe:

Over 12 hours after treatment on Day 5 of each treatment period.

End point values	Test Treatment 1	Test Treatment 2		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	22	22		
Units: kPa/L/s				
least squares mean (standard error)	-0.258 (± 0.0183)	-0.211 (± 0.0183)		

Statistical analyses

Statistical analysis title	R5 Peak Response at Day 5 (ITT)
Comparison groups	Test Treatment 1 v Test Treatment 2
Number of subjects included in analysis	44
Analysis specification	Pre-specified
Analysis type	other
P-value	= 0.0023
Method	t-test, 2-sided
Parameter estimate	Mean difference (final values)
Point estimate	-0.047

Confidence interval	
level	95 %
sides	2-sided
lower limit	-0.075
upper limit	-0.019
Variability estimate	Standard error of the mean

Secondary: Impulse Oscillometry Parameters Peak Response at Day 5 (R5-R20)

End point title	Impulse Oscillometry Parameters Peak Response at Day 5 (R5-R20)

End point description:

To compare the peak R5-R20 response at Day 5 between the 2 treatment groups.

End point type	Secondary

End point timeframe:

Over 12 hours after treatment on Day 5 of each treatment period.

End point values	Test Treatment 1	Test Treatment 2		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	22	22		
Units: kPa/L/s				
least squares mean (standard error)	-0.221 (± 0.0159)	-0.185 (± 0.0159)		

Statistical analyses

Statistical analysis title	R5-R20 Peak Response at Day 5 (ITT)
Comparison groups	Test Treatment 1 v Test Treatment 2
Number of subjects included in analysis	44
Analysis specification	Pre-specified
Analysis type	other
P-value	= 0.0022
Method	t-test, 2-sided
Parameter estimate	Mean difference (final values)
Point estimate	-0.036
Confidence interval	
level	95 %
sides	2-sided
lower limit	-0.057
upper limit	-0.015
Variability estimate	Standard error of the mean

Secondary: Impulse Oscillometry Parameters Peak Response at Day 5 (X5)

End point title	Impulse Oscillometry Parameters Peak Response at Day 5 (X5)

End point description:

To compare the peak X5 response at Day 5 between the 2 treatment groups.

End point type	Secondary

End point timeframe:

Over 12 hours after treatment on Day 5 of each treatment period.

End point values	Test Treatment 1	Test Treatment 2		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	22	22		
Units: kPa/L/s				
least squares mean (standard error)	0.266 (± 0.0197)	0.231 (± 0.0197)		

Statistical analyses

Statistical analysis title	X5 Peak Response at Day 5 (ITT)
Comparison groups	Test Treatment 1 v Test Treatment 2
Number of subjects included in analysis	44
Analysis specification	Pre-specified
Analysis type	other
P-value	= 0.0355
Method	t-test, 2-sided
Parameter estimate	Mean difference (final values)
Point estimate	0.036
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.003
upper limit	0.068
Variability estimate	Standard error of the mean

Secondary: Whole Body Plethysmography Parameters AUC0-12 Response at Day 5 (FRC)

End point title	Whole Body Plethysmography Parameters AUC0-12 Response at Day 5 (FRC)

End point description:

To compare the FRC area under the curve response at Day 5 between the 2 treatment groups.

End point type	Secondary

End point timeframe:

Over 12 hours after treatment on Day 5 of each treatment period.

End point values	Test Treatment 1	Test Treatment 2		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	22	22		
Units: litre(s)				
least squares mean (standard error)	-0.490 (± 0.0688)	-0.387 (± 0.0688)		

Statistical analyses

Statistical analysis title	FRC AUC0-12 Response at Day 5 (ITT)
Comparison groups	Test Treatment 2 v Test Treatment 1
Number of subjects included in analysis	44
Analysis specification	Pre-specified
Analysis type	other
P-value	= 0.073
Method	t-test, 2-sided
Parameter estimate	Mean difference (final values)
Point estimate	-0.103
Confidence interval	
level	95 %
sides	2-sided
lower limit	-0.217
upper limit	0.011
Variability estimate	Standard error of the mean

Secondary: Whole Body Plethysmography Parameters AUC0-12 Response at Day 5 (IC)

End point title	Whole Body Plethysmography Parameters AUC0-12 Response at Day 5 (IC)

End point description:

To compare the IC area under the curve response at Day 5 between the 2 treatment groups.

End point type	Secondary

End point timeframe:

Over 12 hours after treatment on Day 5 of each treatment period.

End point values	Test Treatment 1	Test Treatment 2		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	22	22		
Units: litre(s)				
least squares mean (standard error)	0.257 (± 0.0599)	0.260 (± 0.0599)		

Statistical analyses

Statistical analysis title	IC AUC0-12 Response at Day 5 (ITT)
Comparison groups	Test Treatment 1 v Test Treatment 2
Number of subjects included in analysis	44
Analysis specification	Pre-specified
Analysis type	other
P-value	= 0.9635
Method	t-test, 2-sided
Parameter estimate	Mean difference (final values)
Point estimate	-0.003
Confidence interval	
level	95 %
sides	2-sided
lower limit	-0.146
upper limit	0.139
Variability estimate	Standard error of the mean

Secondary: Whole Body Plethysmography Parameters AUC0-12 Response at Day 5 (Raw)

End point title	Whole Body Plethysmography Parameters AUC0-12 Response at Day 5 (Raw)

End point description:

To compare the Raw area under the curve response at Day 5 between the 2 treatment groups.

End point type	Secondary

End point timeframe:

Over 12 hours after treatment on Day 5 of each treatment period.

End point values	Test Treatment 1	Test Treatment 2		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	22	22		
Units: kPa/L/s				
least squares mean (standard error)	-0.279 (± 0.0204)	-0.222 (± 0.0204)		

Statistical analyses

Statistical analysis title	Raw AUC0-12 Response at Day 5 (ITT)
Comparison groups	Test Treatment 1 v Test Treatment 2
Number of subjects included in analysis	44
Analysis specification	Pre-specified
Analysis type	other
P-value	< 0.0001
Method	t-test, 2-sided
Parameter estimate	Mean difference (final values)
Point estimate	-0.057
Confidence interval	
level	95 %
sides	2-sided
lower limit	-0.077
upper limit	-0.037
Variability estimate	Standard error of the mean

Secondary: Whole Body Plethysmography Parameters AUC0-12 Response at Day 5 (sGaw)

End point title	Whole Body Plethysmography Parameters AUC0-12 Response at Day 5 (sGaw)

End point description:

To compare the sGaw area under the curve response at Day 5 between the 2 treatment groups.

End point type	Secondary

End point timeframe:

Over 12 hours after treatment on Day 5 of each treatment period.

End point values	Test Treatment 1	Test Treatment 2		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	22	22		
Units: kPa/L/s/L				
least squares mean (standard error)	0.311 (± 0.0328)	0.213 (± 0.0328)		

Statistical analyses

Statistical analysis title	sGaw AUC0-12 Response at Day 5 (ITT)
Comparison groups	Test Treatment 1 v Test Treatment 2
Number of subjects included in analysis	44
Analysis specification	Pre-specified
Analysis type	other
P-value	= 0.0101
Method	t-test, 2-sided
Parameter estimate	Mean difference (final values)
Point estimate	0.099
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.031
upper limit	0.167
Variability estimate	Standard error of the mean

Secondary: Whole Body Plethysmography Parameters AUC0-12 Response at Day 5 (TLC)

End point title	Whole Body Plethysmography Parameters AUC0-12 Response at Day 5 (TLC)

End point description:

To compare the TLC area under the curve response at Day 5 between the 2 treatment groups.

End point type	Secondary

End point timeframe:

Over 12 hours after treatment on Day 5 of each treatment period.

End point values	Test Treatment 1	Test Treatment 2		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	22	22		
Units: litre(s)				
least squares mean (standard error)	-0.218 (± 0.0497)	-0.137 (± 0.0497)		

Statistical analyses

Statistical analysis title	TLC AUC0-12 Response at Day 5 (ITT)
Comparison groups	Test Treatment 1 v Test Treatment 2

Number of subjects included in analysis	44
Analysis specification	Pre-specified
Analysis type	other
P-value	= 0.1585
Method	t-test, 2-sided
Parameter estimate	Mean difference (final values)
Point estimate	-0.081
Confidence interval	
level	95 %
sides	2-sided
lower limit	-0.196
upper limit	0.034
Variability estimate	Standard error of the mean

Secondary: Whole Body Plethysmography Parameters Peak Response at Day 5 (FRC)

End point title	Whole Body Plethysmography Parameters Peak Response at Day 5 (FRC)

End point description:

To compare the peak FRC response at Day 5 between the 2 treatment groups.

End point type	Secondary

End point timeframe:

Over 12 hours after treatment on Day 5 of each treatment period.

End point values	Test Treatment 1	Test Treatment 2		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	22	22		
Units: litre(s)				
least squares mean (standard error)	-0.713 (± 0.0855)	-0.660 (± 0.0855)		

Statistical analyses

Statistical analysis title	FRC Peak Response at Day 5 (ITT)
Comparison groups	Test Treatment 1 v Test Treatment 2
Number of subjects included in analysis	44
Analysis specification	Pre-specified
Analysis type	other
P-value	= 0.2934
Method	t-test, 2-sided
Parameter estimate	Mean difference (final values)
Point estimate	-0.053

Confidence interval	
level	95 %
sides	2-sided
lower limit	-0.156
upper limit	0.05
Variability estimate	Standard error of the mean

Secondary: Whole Body Plethysmography Parameters Peak Response at Day 5 (IC)

End point title	Whole Body Plethysmography Parameters Peak Response at Day 5 (IC)

End point description:

To compare the peak IC response at Day 5 between the 2 treatment groups.

End point type	Secondary

End point timeframe:

Over 12 hours after treatment on Day 5 of each treatment period.

End point values	Test Treatment 1	Test Treatment 2		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	22	22		
Units: litre(s)				
least squares mean (standard error)	0.458 (± 0.0795)	0.470 (± 0.0795)		

Statistical analyses

Statistical analysis title	IC Peak Response at Day 5 (ITT)
Comparison groups	Test Treatment 1 v Test Treatment 2
Number of subjects included in analysis	44
Analysis specification	Pre-specified
Analysis type	other
P-value	= 0.8703
Method	t-test, 2-sided
Parameter estimate	Mean difference (final values)
Point estimate	-0.012
Confidence interval	
level	95 %
sides	2-sided
lower limit	-0.169
upper limit	0.145
Variability estimate	Standard error of the mean

Secondary: Whole Body Plethysmography Parameters Peak Response at Day 5 (Raw)

End point title	Whole Body Plethysmography Parameters Peak Response at Day 5 (Raw)

End point description:

To compare the peak Raw response at Day 5 between the 2 treatment groups.

End point type	Secondary

End point timeframe:

Over 12 hours after treatment on Day 5 of each treatment period.

End point values	Test Treatment 1	Test Treatment 2		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	22	22		
Units: kPa/L/s				
least squares mean (standard error)	-0.351 (± 0.0175)	-0.309 (± 0.0175)		

Statistical analyses

Statistical analysis title	Raw Peak Response at Day 5 (ITT)
Comparison groups	Test Treatment 1 v Test Treatment 2
Number of subjects included in analysis	44
Analysis specification	Pre-specified
Analysis type	other
P-value	= 0.0045
Method	t-test, 2-sided
Parameter estimate	Mean difference (final values)
Point estimate	-0.042
Confidence interval	
level	95 %
sides	2-sided
lower limit	-0.069
upper limit	-0.015
Variability estimate	Standard error of the mean

Secondary: Whole Body Plethysmography Parameters Peak Response at Day 5 (sGaw)

End point title	Whole Body Plethysmography Parameters Peak Response at Day 5 (sGaw)

End point description:

To compare the peak sGaw response at Day 5 between the 2 treatment groups.

End point type	Secondary

End point timeframe:

Over 12 hours after treatment on Day 5 of each treatment period.

End point values	Test Treatment 1	Test Treatment 2		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	22	22		
Units: kPa/L/s/L				
least squares mean (standard error)	0.466 (± 0.0477)	0.365 (± 0.0477)		

Statistical analyses

Statistical analysis title	sGaw Peak Response at Day 5 (ITT)
Comparison groups	Test Treatment 1 v Test Treatment 2
Number of subjects included in analysis	44
Analysis specification	Pre-specified
Analysis type	other
P-value	= 0.0335
Method	t-test, 2-sided
Parameter estimate	Mean difference (final values)
Point estimate	0.101
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.009
upper limit	0.193
Variability estimate	Standard error of the mean

Secondary: Whole Body Plethysmography Parameters Peak Response at Day 5 (TLC)

End point title	Whole Body Plethysmography Parameters Peak Response at Day 5 (TLC)

End point description:

To compare the peak TLC response at Day 5 between the 2 treatment groups.

End point type	Secondary

End point timeframe:

Over 12 hours after treatment on Day 5 of each treatment period.

End point values	Test Treatment 1	Test Treatment 2		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	22	22		
Units: litre(s)				
least squares mean (standard error)	-0.391 (± 0.0508)	-0.306 (± 0.0508)		

Statistical analyses

Statistical analysis title	TLC Peak Response at Day 5 (ITT)
Comparison groups	Test Treatment 1 v Test Treatment 2
Number of subjects included in analysis	44
Analysis specification	Pre-specified
Analysis type	other
P-value	= 0.0902
Method	t-test, 2-sided
Parameter estimate	Mean difference (final values)
Point estimate	-0.085
Confidence interval	
level	95 %
sides	2-sided
lower limit	-0.184
upper limit	0.015
Variability estimate	Standard error of the mean

Secondary: FEV1 AUC0-12 Response Compared to Baseline (Trimbow)

End point title	FEV1 AUC0-12 Response Compared to Baseline (Trimbow)

End point description:

To compare the FEV1 area under the curve response between baseline and Day 5.

End point type	Secondary

End point timeframe:

Over 12 hours after treatment at baseline and on Day 5.

End point values	Baseline (Visit 2)	Test Treatment 1		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	22	22		
Units: litre(s)				
least squares mean (standard error)	0.003 (± 0.0320)	0.324 (± 0.0320)		

Statistical analyses

Statistical analysis title	FEV1 AUC0-12 Response Compared to Baseline Trimbow
Comparison groups	Baseline (Visit 2) v Test Treatment 1
Number of subjects included in analysis	44
Analysis specification	Pre-specified
Analysis type	other
P-value	< 0.0001
Method	t-test, 2-sided
Parameter estimate	Mean difference (final values)
Point estimate	0.32
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.257
upper limit	0.384
Variability estimate	Standard error of the mean

Secondary: FEV1 AUC0-12 Response Compared to Baseline (Fostair)

End point title	FEV1 AUC0-12 Response Compared to Baseline (Fostair)

End point description:

To compare the FEV1 area under the curve response between baseline and Day 5.

End point type	Secondary

End point timeframe:

Over 12 hours after treatment at baseline and on Day 5.

End point values	Baseline (Visit 2)	Test Treatment 2		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	22	22		
Units: litre(s)				
least squares mean (standard error)	0.003 (± 0.0320)	0.230 (± 0.0320)		

Statistical analyses

Statistical analysis title	FEV1 AUC0-12 Response Compared to Baseline Fostair
Comparison groups	Baseline (Visit 2) v Test Treatment 2

Number of subjects included in analysis	44
Analysis specification	Pre-specified
Analysis type	other
P-value	< 0.0001
Method	t-test, 2-sided
Parameter estimate	Mean difference (final values)
Point estimate	0.227
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.163
upper limit	0.29
Variability estimate	Standard error of the mean

Secondary: Peak FEV1 Response Compared to Baseline (Trimbow)

End point title	Peak FEV1 Response Compared to Baseline (Trimbow)

End point description:

To compare the peak FEV1 response between Baseline and Day 5.

End point type	Secondary

End point timeframe:

Over 12 hours after treatment at Baseline and on Day 5.

End point values	Baseline (Visit 2)	Test Treatment 1		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	22	22		
Units: litre(s)				
least squares mean (standard error)	0.092 (± 0.0414)	0.494 (± 0.0414)		

Statistical analyses

Statistical analysis title	Peak FEV1 Response Compared to Baseline - Trimbow
Comparison groups	Baseline (Visit 2) v Test Treatment 1
Number of subjects included in analysis	44
Analysis specification	Pre-specified
Analysis type	other
P-value	< 0.0001
Method	t-test, 2-sided
Parameter estimate	Mean difference (final values)
Point estimate	0.402

Confidence interval	
level	95 %
sides	2-sided
lower limit	0.326
upper limit	0.478
Variability estimate	Standard error of the mean

Secondary: Peak FEV1 Response Compared to Baseline (Fostair)

End point title	Peak FEV1 Response Compared to Baseline (Fostair)

End point description:

To compare the peak FEV1 response between Baseline and Day 5.

End point type	Secondary

End point timeframe:

Over 12 hours after treatment at Baseline and on Day 5.

End point values	Baseline (Visit 2)	Test Treatment 2		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	22	22		
Units: litre(s)				
least squares mean (standard error)	0.092 (± 0.0414)	0.385 (± 0.0414)		

Statistical analyses

Statistical analysis title	Peak FEV1 Response Compared to Baseline - Fostair
Comparison groups	Baseline (Visit 2) v Test Treatment 2
Number of subjects included in analysis	44
Analysis specification	Pre-specified
Analysis type	other
P-value	< 0.0001
Method	t-test, 2-sided
Parameter estimate	Mean difference (final values)
Point estimate	0.293
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.217
upper limit	0.369
Variability estimate	Standard error of the mean

Secondary: RV AUC0-12 Response Compared to Baseline (Trimbow)

End point title	RV AUC0-12 Response Compared to Baseline (Trimbow)

End point description:

To compare the RV area under the curve response between baseline and Day 5.

End point type	Secondary

End point timeframe:

Over 12 hours after treatment at baseline and on Day 5 of the Treatment Period.

End point values	Baseline (Visit 2)	Test Treatment 1		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	22	22		
Units: litre(s)				
least squares mean (standard error)	-0.047 (± 0.0689)	-0.725 (± 0.0689)		

Statistical analyses

Statistical analysis title	RV AUC0-12 Response Compared to Baseline (Trimbow)
Comparison groups	Test Treatment 1 v Baseline (Visit 2)
Number of subjects included in analysis	44
Analysis specification	Pre-specified
Analysis type	other
P-value	< 0.0001
Method	t-test, 2-sided
Parameter estimate	Mean difference (final values)
Point estimate	-0.678
Confidence interval	
level	95 %
sides	2-sided
lower limit	-0.847
upper limit	-0.509
Variability estimate	Standard error of the mean

Secondary: RV AUC0-12 Response Compared to Baseline (Fostair)

End point title	RV AUC0-12 Response Compared to Baseline (Fostair)

End point description:

To compare the RV area under the curve response between baseline and Day 5.

End point type	Secondary

End point timeframe:

Over 12 hours after treatment at baseline and on Day 5 of the Treatment Period

End point values	Baseline (Visit 2)	Test Treatment 2		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	22	22		
Units: litre(s)				
least squares mean (standard error)	-0.047 (± 0.0689)	-0.605 (± 0.0689)		

Statistical analyses

Statistical analysis title	RV AUC0-12 Response Compared to Baseline (Fostair)
Comparison groups	Test Treatment 2 v Baseline (Visit 2)
Number of subjects included in analysis	44
Analysis specification	Pre-specified
Analysis type	other
P-value	< 0.0001
Method	t-test, 2-sided
Parameter estimate	Mean difference (final values)
Point estimate	-0.558
Confidence interval	
level	95 %
sides	2-sided
lower limit	-0.727
upper limit	-0.389
Variability estimate	Standard error of the mean

Secondary: Peak RV Response Compared to baseline (Trimbow)

End point title	Peak RV Response Compared to baseline (Trimbow)

End point description:

To compare the peak RV response between Baseline and Day 5.

End point type	Secondary

End point timeframe:

Over 12 hours after treatment at Baseline and on Day 5

End point values	Baseline (Visit 2)	Test Treatment 1		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	22	22		
Units: litre(s)				
least squares mean (standard error)	-0.276 (± 0.0821)	-0.981 (± 0.0821)		

Statistical analyses

Statistical analysis title	Peak RV Response Compared to Baseline - Trimbow
Comparison groups	Baseline (Visit 2) v Test Treatment 1
Number of subjects included in analysis	44
Analysis specification	Pre-specified
Analysis type	other
P-value	< 0.0001
Method	t-test, 2-sided
Parameter estimate	Mean difference (final values)
Point estimate	-0.705
Confidence interval	
level	95 %
sides	2-sided
lower limit	-0.915
upper limit	-0.495
Variability estimate	Standard error of the mean

Secondary: Peak RV Response Compared to Baseline - Fostair

End point title	Peak RV Response Compared to Baseline - Fostair

End point description:

To compare the peak RV response between Baseline and Day 5.

End point type	Secondary

End point timeframe:

Over 12 hours after treatment at Baseline and on Day 5.

End point values	Baseline (Visit 2)	Test Treatment 2		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	22	22		
Units: litre(s)				
least squares mean (standard error)	-0.276 (± 0.0821)	-0.938 (± 0.0821)		

Statistical analyses

Statistical analysis title	Peak RV Response Compared to Baseline - Fostair
Comparison groups	Baseline (Visit 2) v Test Treatment 2
Number of subjects included in analysis	44
Analysis specification	Pre-specified
Analysis type	other
P-value	< 0.0001
Method	t-test, 2-sided
Parameter estimate	Mean difference (final values)
Point estimate	-0.662
Confidence interval	
level	95 %
sides	2-sided
lower limit	-0.873
upper limit	-0.452
Variability estimate	Standard error of the mean

Secondary: FEF Spirometry Parameters AUC0-12 Response Compared to Baseline (Trimbow)

End point title	FEF Spirometry Parameters AUC0-12 Response Compared to Baseline (Trimbow)

End point description:

To compare the FEF area under the curve response between Day 5 and baseline.

End point type	Secondary

End point timeframe:

Over 12 hours after treatment on Day 5 and at baseline.

End point values	Baseline (Visit 2)	Test Treatment 1		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	22	22		
Units: L/s				
least squares mean (standard error)	0.001 (± 0.0156)	0.113 (± 0.0156)		

Statistical analyses

Statistical analysis title	FEF AUC0-12 Response Compared to baseline, Trimbow
Comparison groups	Baseline (Visit 2) v Test Treatment 1

Number of subjects included in analysis	44
Analysis specification	Pre-specified
Analysis type	other
P-value	< 0.0001
Method	t-test, 2-sided
Parameter estimate	Median difference (final values)
Point estimate	0.112
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.08
upper limit	0.144
Variability estimate	Standard error of the mean

Secondary: FEF Spirometry Parameters AUC0-12 Response Compared to Baseline (Fostair)

End point title	FEF Spirometry Parameters AUC0-12 Response Compared to Baseline (Fostair)

End point description:

To compare the FEF area under the curve response between Day 5 and baseline.

End point type	Secondary

End point timeframe:

Over 12 hours after treatment on Day 5 and at baseline.

End point values	Baseline (Visit 2)	Test Treatment 2		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	22	22		
Units: L/s				
least squares mean (standard error)	0.001 (± 0.0156)	0.083 (± 0.0156)		

Statistical analyses

Statistical analysis title	FEF AUC0-12 Response Compared toBaseline (Fostair)
Comparison groups	Baseline (Visit 2) v Test Treatment 2
Number of subjects included in analysis	44
Analysis specification	Pre-specified
Analysis type	other
P-value	< 0.0001
Method	t-test, 2-sided
Parameter estimate	Mean difference (final values)
Point estimate	0.082

Confidence interval	
level	95 %
sides	2-sided
lower limit	0.05
upper limit	0.113
Variability estimate	Standard error of the mean

Secondary: FVC Spirometry Parameters AUC0-12 Response Compared to Baseline (Trimbow)

End point title	FVC Spirometry Parameters AUC0-12 Response Compared to Baseline (Trimbow)

End point description:

To compare the FVC area under the curve response between Day 5 and baseline.

End point type	Secondary

End point timeframe:

Over 12 hours after treatment on Day 5 and at baseline.

End point values	Baseline (Visit 2)	Test Treatment 1		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	22	22		
Units: litre(s)				
least squares mean (standard error)	0.041 (± 0.0562)	0.564 (± 0.0562)		

Statistical analyses

Statistical analysis title	FVC AUC0-12 Response Compared toBaseline, Trimbow
Comparison groups	Baseline (Visit 2) v Test Treatment 1
Number of subjects included in analysis	44
Analysis specification	Pre-specified
Analysis type	other
P-value	< 0.0001
Method	t-test, 2-sided
Parameter estimate	Mean difference (final values)
Point estimate	0.524
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.42
upper limit	0.627
Variability estimate	Standard error of the mean

Secondary: FVC Spirometry Parameters AUC0-12 Response Compared to Baseline (Fostair)

End point title	FVC Spirometry Parameters AUC0-12 Response Compared to Baseline (Fostair)

End point description:

To compare the FVC area under the curve response between Day 5 and baseline.

End point type	Secondary

End point timeframe:

Over 12 hours after treatment on Day 5 and at baseline.

End point values	Baseline (Visit 2)	Test Treatment 2		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	22	22		
Units: litre(s)				
least squares mean (standard error)	0.041 (± 0.0562)	0.392 (± 0.0562)		

Statistical analyses

Statistical analysis title	FVC AUC0-12 Response Compared to Baseline, Fostair
Comparison groups	Test Treatment 2 v Baseline (Visit 2)
Number of subjects included in analysis	44
Analysis specification	Pre-specified
Analysis type	other
P-value	< 0.0001
Method	t-test, 2-sided
Parameter estimate	Mean difference (final values)
Point estimate	0.351
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.248
upper limit	0.455
Variability estimate	Standard error of the mean

Secondary: AX Impulse Oscillometry Parameters AUC0-12 Response Compared to Baseline (Trimbow)

End point title	AX Impulse Oscillometry Parameters AUC0-12 Response Compared to Baseline (Trimbow)

End point description:

To compare the AX area under the curve response between Day 5 and baseline.

End point type	Secondary

End point timeframe:

Over 12 hours after treatment on Day 5 and at baseline.

End point values	Baseline (Visit 2)	Test Treatment 1		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	22	22		
Units: kPa/L				
least squares mean (standard error)	-0.348 (± 0.2831)	-3.339 (± 0.2831)		

Statistical analyses

Statistical analysis title	AX AUC0-12 Response Compared to Baseline (Trimbow)
Comparison groups	Baseline (Visit 2) v Test Treatment 1
Number of subjects included in analysis	44
Analysis specification	Pre-specified
Analysis type	other
P-value	< 0.0001
Method	t-test, 2-sided
Parameter estimate	Mean difference (final values)
Point estimate	-2.991
Confidence interval	
level	95 %
sides	2-sided
lower limit	-3.614
upper limit	-2.368
Variability estimate	Standard error of the mean

Secondary: AX Impulse Oscillometry Parameters AUC0-12 Response Compared to Baseline (Fostair)

End point title	AX Impulse Oscillometry Parameters AUC0-12 Response Compared to Baseline (Fostair)

End point description:

To compare the AX area under the curve response between Day 5 and baseline.

End point type	Secondary

End point timeframe:

Over 12 hours after treatment on Day 5 and at baseline.

End point values	Baseline (Visit 2)	Test Treatment 2		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	22	22		
Units: kPa/L				
least squares mean (standard error)	-0.348 (± 0.2831)	-2.576 (± 0.2831)		

Statistical analyses

Statistical analysis title	AX AUC0-12 Response Compared to Baseline (Fostair)
Comparison groups	Baseline (Visit 2) v Test Treatment 2
Number of subjects included in analysis	44
Analysis specification	Pre-specified
Analysis type	other
P-value	< 0.0001
Method	t-test, 2-sided
Parameter estimate	Mean difference (final values)
Point estimate	-2.228
Confidence interval	
level	95 %
sides	2-sided
lower limit	-2.851
upper limit	-1.604
Variability estimate	Standard error of the mean

Secondary: Delta X5 Impulse Oscillometry Parameters AUC0-12 Response Compared to Baseline (Trimbow)

End point title	Delta X5 Impulse Oscillometry Parameters AUC0-12 Response Compared to Baseline (Trimbow)

End point description:

To compare the Delta X5 area under the curve response between Day 5 and baseline.

End point type	Secondary

End point timeframe:

Over 12 hours after treatment on Day 5 and at baseline.

End point values	Baseline (Visit 2)	Test Treatment 1		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	22	22		
Units: kPa/L/s				
least squares mean (standard error)	-0.032 (± 0.0299)	-0.240 (± 0.0299)		

Statistical analyses

Statistical analysis title	Delta X5 AUC0-12 Response Compared to Baseline
Statistical analysis description: (Trimbow)	
Comparison groups	Baseline (Visit 2) v Test Treatment 1
Number of subjects included in analysis	44
Analysis specification	Pre-specified
Analysis type	other
P-value	< 0.0001
Method	t-test, 2-sided
Parameter estimate	Mean difference (final values)
Point estimate	-0.207
Confidence interval	
level	95 %
sides	2-sided
lower limit	-0.262
upper limit	-0.152
Variability estimate	Standard error of the mean

Secondary: Delta X5 Impulse Oscillometry Parameters AUC0-12 Response Compared to Baseline (Fostair)

End point title	Delta X5 Impulse Oscillometry Parameters AUC0-12 Response Compared to Baseline (Fostair)

End point description:

To compare the Delta X5 area under the curve response between Day 5 and baseline.

End point type	Secondary

End point timeframe:

Over 12 hours after treatment on Day 5 and at baseline.

End point values	Baseline (Visit 2)	Test Treatment 2		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	22	22		
Units: kPa/L/s				
least squares mean (standard error)	-0.032 (± 0.0299)	-0.173 (± 0.0299)		

Statistical analyses

Statistical analysis title	Delta X5 AUC0-12 Response Compared With Baseline
Statistical analysis description: (Fostair)	
Comparison groups	Baseline (Visit 2) v Test Treatment 2
Number of subjects included in analysis	44
Analysis specification	Pre-specified
Analysis type	other
P-value	< 0.0001
Method	t-test, 2-sided
Parameter estimate	Mean difference (final values)
Point estimate	-0.14
Confidence interval	
level	95 %
sides	2-sided
lower limit	-0.195
upper limit	-0.085
Variability estimate	Standard error of the mean

Secondary: Fres Impulse Oscillometry Parameters AUC0-12 Response Compared to Baseline (Trimbow)

End point title	Fres Impulse Oscillometry Parameters AUC0-12 Response Compared to Baseline (Trimbow)

End point description:

To compare the Fres area under the curve response between Day 5 and baseline.

End point type	Secondary

End point timeframe:

Over 12 hours after treatment on Day 5 and at baseline.

End point values	Baseline (Visit 2)	Test Treatment 1		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	22	22		
Units: 1/s				
least squares mean (standard error)	-0.366 (± 0.9547)	-8.602 (± 0.9547)		

Statistical analyses

Statistical analysis title	Fres AUC0-12 Response Compared to Baseline
Statistical analysis description: (Trimbow)	
Comparison groups	Baseline (Visit 2) v Test Treatment 1
Number of subjects included in analysis	44
Analysis specification	Pre-specified
Analysis type	other
P-value	< 0.0001
Method	t-test, 2-sided
Parameter estimate	Mean difference (final values)
Point estimate	-8.235
Confidence interval	
level	95 %
sides	2-sided
lower limit	-10.108
upper limit	-6.363
Variability estimate	Standard error of the mean

Secondary: Fres Impulse Oscillometry Parameters AUC0-12 Response Compared to Baseline (Fostair)

End point title	Fres Impulse Oscillometry Parameters AUC0-12 Response Compared to Baseline (Fostair)
End point description: To compare the Fres area under the curve response between Day 5 and baseline.	
End point type	Secondary
End point timeframe: Over 12 hours after treatment on Day 5 and at baseline.	

End point values	Baseline (Visit 2)	Test Treatment 2		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	22	22		
Units: 1/s				
least squares mean (standard error)	-0.366 (± 0.9547)	-5.966 (± 0.9547)		

Statistical analyses

Statistical analysis title	Fres AUC0-12 Response Compared to Baseline
Statistical analysis description: (Fostair)	
Comparison groups	Baseline (Visit 2) v Test Treatment 2

Number of subjects included in analysis	44
Analysis specification	Pre-specified
Analysis type	other
P-value	< 0.0001
Method	t-test, 2-sided
Parameter estimate	Mean difference (final values)
Point estimate	-5.6
Confidence interval	
level	95 %
sides	2-sided
lower limit	-7.472
upper limit	-3.727
Variability estimate	Standard error of the mean

Secondary: R5 Impulse Oscillometry Parameters AUC0-12 Response Compared to Baseline (Trimbow)

End point title	R5 Impulse Oscillometry Parameters AUC0-12 Response Compared to Baseline (Trimbow)

End point description:

To compare the R5 area under the curve response between Day 5 and baseline.

End point type	Secondary

End point timeframe:

Over 12 hours after treatment on Day 5 and at baseline.

End point values	Baseline (Visit 2)	Test Treatment 1		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	22	22		
Units: kPa/L/s				
least squares mean (standard error)	-0.030 (± 0.0170)	-0.219 (± 0.0170)		

Statistical analyses

Statistical analysis title	R5 AUC0-12 Response Compared to Baseline (Trimbow)
Comparison groups	Baseline (Visit 2) v Test Treatment 1
Number of subjects included in analysis	44
Analysis specification	Pre-specified
Analysis type	other
P-value	< 0.0001
Method	t-test, 2-sided
Parameter estimate	Mean difference (final values)
Point estimate	-0.189

Confidence interval	
level	95 %
sides	2-sided
lower limit	-0.228
upper limit	-0.15
Variability estimate	Standard error of the mean

Secondary: R5 Impulse Oscillometry Parameters AUC0-12 Response Compared to Baseline (Fostair)

End point title	R5 Impulse Oscillometry Parameters AUC0-12 Response Compared to Baseline (Fostair)

End point description:

To compare the R5 area under the curve response between Day 5 and baseline.

End point type	Secondary

End point timeframe:

Over 12 hours after treatment on Day 5 and at baseline.

End point values	Baseline (Visit 2)	Test Treatment 2		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	22	22		
Units: kPa/L/s				
least squares mean (standard error)	-0.030 (± 0.0170)	-0.162 (± 0.0170)		

Statistical analyses

Statistical analysis title	R5 AUC0-12 Response Compared to Baseline (Fostair)
Comparison groups	Baseline (Visit 2) v Test Treatment 2
Number of subjects included in analysis	44
Analysis specification	Pre-specified
Analysis type	other
P-value	< 0.0001
Method	t-test, 2-sided
Parameter estimate	Mean difference (final values)
Point estimate	-0.132
Confidence interval	
level	95 %
sides	2-sided
lower limit	-0.171
upper limit	-0.093
Variability estimate	Standard error of the mean

Secondary: R5-R20 Impulse Oscillometry Parameters AUC0-12 Response Compared to Baseline (Trimbow)

End point title	R5-R20 Impulse Oscillometry Parameters AUC0-12 Response Compared to Baseline (Trimbow)

End point description:

To compare the R5-R20 area under the curve response between Day 5 and baseline.

End point type	Secondary

End point timeframe:

Over 12 hours after treatment on Day 5 and at baseline.

End point values	Baseline (Visit 2)	Test Treatment 1		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	22	22		
Units: kPa/L/s				
least squares mean (standard error)	-0.017 (± 0.0155)	-0.183 (± 0.0155)		

Statistical analyses

Statistical analysis title	R5-R20 AUC0-12 Response Compared to Baseline

Statistical analysis description:

(Trimbow)

Comparison groups	Baseline (Visit 2) v Test Treatment 1
Number of subjects included in analysis	44
Analysis specification	Pre-specified
Analysis type	other
P-value	< 0.0001
Method	t-test, 2-sided
Parameter estimate	Mean difference (final values)
Point estimate	-0.165
Confidence interval	
level	95 %
sides	2-sided
lower limit	-0.198
upper limit	-0.132
Variability estimate	Standard error of the mean

Secondary: R5-R20 Impulse Oscillometry Parameters AUC0-12 Response Compared to Baseline (Fostair)

End point title	R5-R20 Impulse Oscillometry Parameters AUC0-12 Response

	Compared to Baseline (Fostair)

End point description:

To compare the R5-R20 area under the curve response between Day 5 and baseline.

End point type	Secondary

End point timeframe:

Over 12 hours after treatment on Day 5 and at baseline.

End point values	Baseline (Visit 2)	Test Treatment 2		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	22	22		
Units: kPa/L/s				
least squares mean (standard error)	-0.017 (± 0.0155)	-0.135 (± 0.0155)		

Statistical analyses

Statistical analysis title	R5-R20 AUC0-12 Response Compared to Baseline
Statistical analysis description: (Fostair)	
Comparison groups	Baseline (Visit 2) v Test Treatment 2
Number of subjects included in analysis	44
Analysis specification	Pre-specified
Analysis type	other
P-value	< 0.0001
Method	t-test, 2-sided
Parameter estimate	Mean difference (final values)
Point estimate	-0.117
Confidence interval	
level	95 %
sides	2-sided
lower limit	-0.15
upper limit	-0.084
Variability estimate	Standard error of the mean

Secondary: X5 Impulse Oscillometry Parameters AUC0-12 Response Compared to Baseline (Trimbow)

End point title	X5 Impulse Oscillometry Parameters AUC0-12 Response Compared to Baseline (Trimbow)

End point description:

To compare the X5 area under the curve response between Day 5 and baseline.

End point type	Secondary

End point timeframe:

Over 12 hours after treatment on Day 5 and at baseline.

End point values	Baseline (Visit 2)	Test Treatment 1		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	22	22		
Units: kPa/L/s				
least squares mean (standard error)	0.034 (± 0.0210)	0.242 (± 0.0210)		

Statistical analyses

Statistical analysis title	X5 AUC0-12 Response Compared to Baseline (Trimbow)
Comparison groups	Baseline (Visit 2) v Test Treatment 1
Number of subjects included in analysis	44
Analysis specification	Pre-specified
Analysis type	other
P-value	< 0.0001
Method	t-test, 2-sided
Parameter estimate	Mean difference (final values)
Point estimate	0.208
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.169
upper limit	0.248
Variability estimate	Standard error of the mean

Secondary: X5 Impulse Oscillometry Parameters AUC0-12 Response Compared to Baseline (Fostair)

End point title	X5 Impulse Oscillometry Parameters AUC0-12 Response Compared to Baseline (Fostair)

End point description:

To compare the X5 area under the curve response between Day 5 and baseline.

End point type	Secondary

End point timeframe:

Over 12 hours after treatment on Day 5 and at baseline.

End point values	Baseline (Visit 2)	Test Treatment 2		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	22	22		
Units: kPa/L/s				
least squares mean (standard error)	0.034 (± 0.0210)	0.193 (± 0.0210)		

Statistical analyses

Statistical analysis title	X5 AUC0-12 Response Compared to Baseline (Fostair)
Comparison groups	Baseline (Visit 2) v Test Treatment 2
Number of subjects included in analysis	44
Analysis specification	Pre-specified
Analysis type	other
P-value	< 0.0001
Method	t-test, 2-sided
Parameter estimate	Mean difference (final values)
Point estimate	0.159
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.12
upper limit	0.198
Variability estimate	Standard error of the mean

Secondary: FRC Whole Body Plethysmography Parameters AUC0-12 Response Compared to Baseline (Trimbow)

End point title	FRC Whole Body Plethysmography Parameters AUC0-12 Response Compared to Baseline (Trimbow)

End point description:

To compare the FRC area under the curve response between Day 5 and baseline.

End point type	Secondary

End point timeframe:

Over 12 hours after treatment on Day 5 and at baseline.

End point values	Baseline (Visit 2)	Test Treatment 1		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	22	22		
Units: litre(s)				
least squares mean (standard error)	0.001 (± 0.0598)	-0.467 (± 0.0598)		

Statistical analyses

Statistical analysis title	FRC AUC0-12 Response Compared to Baseline, Trimbow
Comparison groups	Baseline (Visit 2) v Test Treatment 1
Number of subjects included in analysis	44
Analysis specification	Pre-specified
Analysis type	other
P-value	< 0.0001
Method	t-test, 2-sided
Parameter estimate	Mean difference (final values)
Point estimate	-0.468
Confidence interval	
level	95 %
sides	2-sided
lower limit	-0.612
upper limit	-0.323
Variability estimate	Standard error of the mean

Secondary: FRC Whole Body Plethysmography Parameters AUC0-12 Response Compared to Baseline (Fostair)

End point title	FRC Whole Body Plethysmography Parameters AUC0-12 Response Compared to Baseline (Fostair)

End point description:

To compare the FRC area under the curve response between Day 5 and baseline.

End point type	Secondary

End point timeframe:

Over 12 hours after treatment on Day 5 and at baseline.

End point values	Baseline (Visit 2)	Test Treatment 2		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	22	22		
Units: litre(s)				
least squares mean (standard error)	0.001 (± 0.0598)	-0.425 (± 0.0598)		

Statistical analyses

Statistical analysis title	FRC AUC0-12 Response Compared to Baseline, Fostair
Comparison groups	Baseline (Visit 2) v Test Treatment 2
Number of subjects included in analysis	44
Analysis specification	Pre-specified
Analysis type	other
P-value	< 0.0001
Method	t-test, 2-sided
Parameter estimate	Mean difference (final values)
Point estimate	-0.426
Confidence interval	
level	95 %
sides	2-sided
lower limit	-0.571
upper limit	-0.282
Variability estimate	Standard error of the mean

Secondary: IC Whole Body Plethysmography Parameters AUC0-12 Response Compared to Baseline (Trimbow)

End point title	IC Whole Body Plethysmography Parameters AUC0-12 Response Compared to Baseline (Trimbow)

End point description:

To compare the IC area under the curve response between Day 5 and baseline.

End point type	Secondary

End point timeframe:

Over 12 hours after treatment on Day 5 and at baseline.

End point values	Baseline (Visit 2)	Test Treatment 1		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	22	22		
Units: litre(s)				
least squares mean (standard error)	-0.071 (± 0.0507)	0.257 (± 0.0507)		

Statistical analyses

Statistical analysis title	IC AUC0-12 Response Compared to Baseline (Trimbow)
Comparison groups	Baseline (Visit 2) v Test Treatment 1

Number of subjects included in analysis	44
Analysis specification	Pre-specified
Analysis type	other
P-value	< 0.0001
Method	t-test, 2-sided
Parameter estimate	Mean difference (final values)
Point estimate	0.328
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.219
upper limit	0.438
Variability estimate	Standard error of the mean

Secondary: IC Whole Body Plethysmography Parameters AUC0-12 Response Compared to Baseline (Fostair)

End point title	IC Whole Body Plethysmography Parameters AUC0-12 Response Compared to Baseline (Fostair)

End point description:

To compare the IC area under the curve response between Day 5 and baseline.

End point type	Secondary

End point timeframe:

Over 12 hours after treatment on Day 5 and at baseline.

End point values	Baseline (Visit 2)	Test Treatment 2		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	22	22		
Units: litre(s)				
least squares mean (standard error)	-0.071 (± 0.0507)	0.218 (± 0.0507)		

Statistical analyses

Statistical analysis title	IC AUC0-12 Response Compared to Baseline (Fostair)
Comparison groups	Baseline (Visit 2) v Test Treatment 2
Number of subjects included in analysis	44
Analysis specification	Pre-specified
Analysis type	other
P-value	< 0.0001
Method	t-test, 2-sided
Parameter estimate	Mean difference (final values)
Point estimate	0.289

Confidence interval	
level	95 %
sides	2-sided
lower limit	0.18
upper limit	0.399
Variability estimate	Standard error of the mean

Secondary: Raw Whole Body Plethysmography Parameters AUC0-12 Response Compared to Baseline (Trimbow)

End point title	Raw Whole Body Plethysmography Parameters AUC0-12 Response Compared to Baseline (Trimbow)

End point description:

To compare the Raw area under the curve response between Day 5 and baseline.

End point type	Secondary

End point timeframe:

Over 12 hours after treatment on Day 5 and at baseline.

End point values	Baseline (Visit 2)	Test Treatment 1		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	22	22		
Units: kPa/L/s				
least squares mean (standard error)	0.017 (± 0.0253)	-0.281 (± 0.0253)		

Statistical analyses

Statistical analysis title	Raw AUC0-12 Response Compared to Baseline, Trimbow
Comparison groups	Baseline (Visit 2) v Test Treatment 1
Number of subjects included in analysis	44
Analysis specification	Pre-specified
Analysis type	other
P-value	< 0.0001
Method	t-test, 2-sided
Parameter estimate	Mean difference (final values)
Point estimate	-0.298
Confidence interval	
level	95 %
sides	2-sided
lower limit	-0.369
upper limit	-0.226
Variability estimate	Standard error of the mean

Secondary: Raw Whole Body Plethysmography Parameters AUC0-12 Response Compared to Baseline (Fostair)

End point title	Raw Whole Body Plethysmography Parameters AUC0-12 Response Compared to Baseline (Fostair)

End point description:

To compare the Raw area under the curve response between Day 5 and baseline.

End point type	Secondary

End point timeframe:

Over 12 hours after treatment on Day 5 and at baseline.

End point values	Baseline (Visit 2)	Test Treatment 2		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	22	22		
Units: kPa/L/s				
least squares mean (standard error)	0.017 (± 0.0253)	-0.225 (± 0.0253)		

Statistical analyses

Statistical analysis title	Raw AUC0-12 Response Compared to Baseline, Fostair
Comparison groups	Baseline (Visit 2) v Test Treatment 2
Number of subjects included in analysis	44
Analysis specification	Pre-specified
Analysis type	other
P-value	< 0.0001
Method	t-test, 2-sided
Parameter estimate	Mean difference (final values)
Point estimate	-0.242
Confidence interval	
level	95 %
sides	2-sided
lower limit	-0.313
upper limit	-0.17
Variability estimate	Standard error of the mean

Secondary: sGaw Whole Body Plethysmography Parameters AUC0-12 Response Compared to Baseline (Trimbow)

End point title	sGaw Whole Body Plethysmography Parameters AUC0-12 Response Compared to Baseline (Trimbow)

End point description:

To compare the sGaw area under the curve response between Day 5 and baseline.

End point type	Secondary

End point timeframe:

Over 12 hours after treatment on Day 5 and at baseline.

End point values	Baseline (Visit 2)	Test Treatment 1		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	22	22		
Units: kPa/L/s/L				
least squares mean (standard error)	-0.003 (± 0.0252)	0.307 (± 0.0252)		

Statistical analyses

Statistical analysis title	sGaw AUC0-12 Response Compared to Baseline
Statistical analysis description: (Trimbow)	
Comparison groups	Baseline (Visit 2) v Test Treatment 1
Number of subjects included in analysis	44
Analysis specification	Pre-specified
Analysis type	other
P-value	< 0.0001
Method	t-test, 2-sided
Parameter estimate	Mean difference (final values)
Point estimate	0.31
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.259
upper limit	0.362
Variability estimate	Standard error of the mean

Secondary: sGaw Whole Body Plethysmography Parameters AUC0-12 Response Compared to Baseline (Fostair)

End point title	sGaw Whole Body Plethysmography Parameters AUC0-12 Response Compared to Baseline (Fostair)

End point description:

To compare the sGaw area under the curve response between Day 5 and baseline.

End point type	Secondary

End point timeframe:

Over 12 hours after treatment on Day 5 and at baseline.

End point values	Baseline (Visit 2)	Test Treatment 2		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	22	22		
Units: kPa/L/s/L				
least squares mean (standard error)	-0.003 (± 0.0252)	0.221 (± 0.0252)		

Statistical analyses

Statistical analysis title	sGaw AUC0-12 Response Compared to Baseline
Statistical analysis description: (Fostair)	
Comparison groups	Baseline (Visit 2) v Test Treatment 2
Number of subjects included in analysis	44
Analysis specification	Pre-specified
Analysis type	other
P-value	< 0.0001
Method	t-test, 2-sided
Parameter estimate	Mean difference (final values)
Point estimate	0.224
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.172
upper limit	0.275
Variability estimate	Standard error of the mean

Secondary: TLC Whole Body Plethysmography Parameters AUC0-12 Response Compared to Baseline (Trimbow)

End point title	TLC Whole Body Plethysmography Parameters AUC0-12 Response Compared to Baseline (Trimbow)

End point description:

To compare the TLC area under the curve response between Day 5 and baseline.

End point type	Secondary

End point timeframe:

Over 12 hours after treatment on Day 5 and at baseline.

End point values	Baseline (Visit 2)	Test Treatment 1		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	22	22		
Units: litre(s)				
least squares mean (standard error)	-0.064 (± 0.0465)	-0.200 (± 0.0465)		

Statistical analyses

Statistical analysis title	TLC AUC0-12 Response Compared to Baseline, Trimbow
Comparison groups	Baseline (Visit 2) v Test Treatment 1
Number of subjects included in analysis	44
Analysis specification	Pre-specified
Analysis type	other
P-value	= 0.0144
Method	t-test, 2-sided
Parameter estimate	Mean difference (final values)
Point estimate	-0.136
Confidence interval	
level	95 %
sides	2-sided
lower limit	-0.243
upper limit	-0.028
Variability estimate	Standard error of the mean

Secondary: TLC Whole Body Plethysmography Parameters AUC0-12 Response Compared to Baseline (Fostair)

End point title	TLC Whole Body Plethysmography Parameters AUC0-12 Response Compared to Baseline (Fostair)

End point description:

To compare the TLC area under the curve response between Day 5 and baseline.

End point type	Secondary

End point timeframe:

Over 12 hours after treatment on Day 5 and at baseline.

End point values	Baseline (Visit 2)	Test Treatment 2		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	22	22		
Units: litre(s)				
least squares mean (standard error)	-0.064 (± 0.0465)	-0.196 (± 0.0465)		

Statistical analyses

Statistical analysis title	TLC AUC0-12 Response Compared to Baseline, Fostair
Comparison groups	Test Treatment 2 v Baseline (Visit 2)
Number of subjects included in analysis	44
Analysis specification	Pre-specified
Analysis type	other
P-value	= 0.0174
Method	t-test, 2-sided
Parameter estimate	Mean difference (final values)
Point estimate	-0.132
Confidence interval	
level	95 %
sides	2-sided
lower limit	-0.239
upper limit	-0.024
Variability estimate	Standard error of the mean

Adverse events

Adverse events information

Timeframe for reporting adverse events:

The recording period for Adverse Events is the period starting from the Informed Consent signature, until last scheduled telephone follow up call.

Assessment type	Systematic

Dictionary used

Dictionary name	MedDRA
Dictionary version	21.1

Reporting groups

Reporting group title	Trimbow 87 micrograms/5 micrograms/9 micrograms
Reporting group description: -	
Reporting group title	Fostair 100/6 micrograms

Reporting group description: -

Serious adverse events	Trimbow 87 micrograms/5 micrograms/9 micrograms	Fostair 100/6 micrograms	
Total subjects affected by serious adverse events			
subjects affected / exposed	0 / 23 (0.00%)	0 / 22 (0.00%)	
number of deaths (all causes)	0	0	
number of deaths resulting from adverse events	0	0	

Frequency threshold for reporting non-serious adverse events: 3 %

Non-serious adverse events	Trimbow 87 micrograms/5 micrograms/9 micrograms	Fostair 100/6 micrograms	
Total subjects affected by non-serious adverse events			
subjects affected / exposed	3 / 23 (13.04%)	7 / 22 (31.82%)	
Surgical and medical procedures			
Papilloma excision			
subjects affected / exposed	1 / 23 (4.35%)	0 / 22 (0.00%)	
occurrences (all)	1	0	
Nervous system disorders			
Dizziness			
subjects affected / exposed	0 / 23 (0.00%)	1 / 22 (4.55%)	
occurrences (all)	0	1	
Tension headache			

subjects affected / exposed	0 / 23 (0.00%)	1 / 22 (4.55%)	
occurrences (all)	0	1	
Ear and labyrinth disorders			
Ear discomfort			
subjects affected / exposed	0 / 23 (0.00%)	1 / 22 (4.55%)	
occurrences (all)	0	1	
Gastrointestinal disorders			
Nausea			
subjects affected / exposed	0 / 23 (0.00%)	1 / 22 (4.55%)	
occurrences (all)	0	1	
Respiratory, thoracic and mediastinal disorders			
Dyspnoea			
subjects affected / exposed	0 / 23 (0.00%)	4 / 22 (18.18%)	
occurrences (all)	0	4	
Chronic obstructive pulmonary disease			
subjects affected / exposed	1 / 23 (4.35%)	0 / 22 (0.00%)	
occurrences (all)	1	0	
Nasal congestion			
subjects affected / exposed	1 / 23 (4.35%)	0 / 22 (0.00%)	
occurrences (all)	1	0	

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
17 April 2019	The protocol was updated with changes to two inclusion criteria relating to BMI (an increase to the upper limit from 33 to 35 kg/m2) and FEV1 (an increase to the upper limit of the range from 70% to 80%). The upper limit of the inclusion criteria for body mass index and post-bronchodilator FEV1 percentage of the predicted normal value was increased to aid recruitment.

Notes:

Interruptions (globally)

Were there any global interruptions to the trial? No

Limitations and caveats

Limitations of the trial such as small numbers of subjects analysed or technical problems leading to unreliable data.

None reported.

Notes: