Clinical trial results:
A Phase III, randomised, double-blind, placebo-controlled, parallel group study to determine the effect of 12 weeks treatment of orally inhaled tiotropium + olodaterol fixed dose combination (2.5/5 µg, 5/5 µg) delivered by the Respimat® Inhaler, on exercise endurance time during constant work rate cycle ergometry in patients with Chronic Obstructive Pulmonary Disease (COPD) (TorractoTM)

Due to a system error, the data reported in v1 is not correct and has been removed from public view.

Summary

EudraCT number	2011-004253-11
Trial protocol	FI DE HU ES IE IT GB
Global end of trial date	26 September 2013

Results information

Result version number	v2 (current)
This version publication date	23 July 2016
First version publication date	26 July 2015
Version creation reason	• Correction of full data set Data correction due to a system error in EudraCT- Results

Trial information

Trial identification

Sponsor protocol code	1237.15

Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	NCT01525615
WHO universal trial number (UTN)	-

Notes:

Sponsors

Sponsor organisation name	Boehringer Ingelheim
Sponsor organisation address	Binger Strasse 173 , Ingelheim am Rhein , Germany, 55216
Public contact	QRPE Processes and Systems Coordination Clinical Trial Information Disclosure, Boehringer Ingelheim, +1 800 243 0127 , clintriage.rdg@boehringer-ingelheim.com
Scientific contact	QRPE Processes and Systems Coordination Clinical Trial Information Disclosure, Boehringer Ingelheim, +1 800 243 0127 , clintriage.rdg@boehringer-ingelheim.com

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	06 November 2013
Is this the analysis of the primary completion data?	Yes
Primary completion date	26 September 2013
Global end of trial reached?	Yes
Global end of trial date	26 September 2013
Was the trial ended prematurely?	No

Notes:

General information about the trial

Main objective of the trial:

The primary objective of this study is to compare the effects of orally inhaled tiotropium + olodaterol fixed dose combination (2.5/5 µg; 5/5 µg) with placebo on exercise tolerance after 12 weeks of treatment in patients with COPD. Exercise tolerance will be assessed by measurement of symptom-limited endurance time during constant work rate cycle ergometry at 75% Wcap (Maximal Work Capacity).

Protection of trial subjects:

Only subjects that met all the study inclusion and none of the exclusion criteria were entered in the study. All subjects were free to withdraw from the clinical trial at any time for any reason given. Close monitoring of all subjects was adhered to throughout the trial conduct. Rescue medication was allowed for all patients as required.

An individual patient could be withdrawn from the clinical trial prior to completion if any of the following criteria apply:
1. The patient was no longer able to participate for medical reasons (e.g. pregnancy, surgery, adverse events, or other diseases).
2. Administrative reasons (protocol violations, persistent non-compliance).
3. Decision by Boehringer Ingelheim to discontinue a specific patient (e.g. in case of SAEs)

Background therapy: -

Evidence for comparator: -

Actual start date of recruitment	12 March 2012
Long term follow-up planned	No
Independent data monitoring committee (IDMC) involvement?	Yes

Notes:

Population of trial subjects

Subjects enrolled per country

Country: Number of subjects enrolled	Spain: 50
Country: Number of subjects enrolled	United Kingdom: 73
Country: Number of subjects enrolled	Finland: 24
Country: Number of subjects enrolled	France: 22
Country: Number of subjects enrolled	Germany: 76
Country: Number of subjects enrolled	Hungary: 76
Country: Number of subjects enrolled	Italy: 43
Country: Number of subjects enrolled	Argentina: 31

Country: Number of subjects enrolled	Canada: 56
Country: Number of subjects enrolled	United States: 93
Worldwide total number of subjects	544
EEA total number of subjects	364

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)	313
From 65 to 84 years	231
85 years and over	0

Subject disposition

Recruitment

Recruitment details: -

Pre-assignment

Screening details:

All subjects were screened for eligibility to participate in the trial. Subjects attended specialist sites which would then ensure that they (the subjects) met all strictly implemented inclusion/exclusion criteria. Subjects were not randomised to trial treatment if any one of the specific entry criteria were violated.

Period 1

Period 1 title	Treatment period (overall period)
Is this the baseline period?	Yes
Allocation method	Randomised - controlled
Blinding used	Double blind
Roles blinded	Subject, Investigator, Monitor, Data analyst

Arms

Are arms mutually exclusive?	Yes
Arm title	Placebo

Arm description:

Once daily 2 puffs, solution for inhalation Respimat placebo to tiotropium+olodaterol during the 12-week treatment period: comparator

Arm type	Placebo
Investigational medicinal product name	placebo
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Inhalation solution
Routes of administration	Inhalation use

Dosage and administration details:

Matching placebo

During the 12-week treatment period, patients were to inhale 2 actuations from the RESPIMAT Inhaler, once a day, in the morning.

Arm title	Tio+Olo 2.5 / 5.0 µg

Arm description:

Oral inhalation of fixed dose combination (FDC) of Tiotropium (Tio) 2.5 µg and Olodaterol (Olo) 5 µg (Tiotropium: 1.25 µg per actuation and Olodaterol: 2.5 µg per actuation), 2 puffs from the RESPIMAT inhaler, once daily, in the morning during the 12-week treatment period.

Arm type	Experimental
Investigational medicinal product name	Tiotropium/Olodaterol FDC
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Inhalation solution
Routes of administration	Inhalation use

Dosage and administration details:

2.5 µg tiotropium / 5 µg olodaterol (1.25 µg + 2.5 µg per actuation, respectively)

During the 12-week treatment period, patients were to inhale 2 actuations from the RESPIMAT Inhaler, once a day, in the morning.

Arm title	Tio+Olo 5.0 / 5.0 µg

Arm description:

Oral inhalation of FDC of Tiotropium (Tio) 5 µg and Olodaterol (Olo) 5 µg (Tiotropium and Olodaterol:

2.5 µg per actuation), 2 puffs from the RESPIMAT inhaler, once daily, in the morning during the 12-week treatment period.

Arm type	Experimental
Investigational medicinal product name	Tiotropium/Olodaterol FDC
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Inhalation solution
Routes of administration	Inhalation use

Dosage and administration details:

5 µg tiotropium / 5 µg olodaterol (2.5 µg each per actuation)

During the 12-week treatment period, patients were to inhale 2 actuations from the RESPIMAT Inhaler, once a day, in the morning.

Number of subjects in period 1[1]	Placebo	Tio+Olo 2.5 / 5.0 µg	Tio+Olo 5.0 / 5.0 µg
Started	132	133	139
Completed	118	126	133
Not completed	14	7	6
Adverse event, serious fatal	-	2	-
Consent withdrawn by subject	1	-	-
Adverse event, non-fatal	11	5	5
Not defined above	1	-	1
Lost to follow-up	1	-	-

Notes:

[1] - The number of subjects reported to be in the baseline period are not the same as the worldwide number enrolled in the trial. It is expected that these numbers will be the same.

Justification: Baseline characteristics are based on patients who were randomised after successfully completing the screening period and received at least one dose of the trial medication.

Baseline characteristics

Reporting groups	
Reporting group title	Placebo
Reporting group description:	
Once daily 2 puffs, solution for inhalation Respimat placebo to tiotropium+olodaterol during the 12-week treatment period: comparator	
Reporting group title	Tio+Olo 2.5 / 5.0 µg
Reporting group description:	
Oral inhalation of fixed dose combination (FDC) of Tiotropium (Tio) 2.5 µg and Olodaterol (Olo) 5 µg (Tiotropium: 1.25 µg per actuation and Olodaterol: 2.5 µg per actuation), 2 puffs from the RESPIMAT inhaler, once daily, in the morning during the 12-week treatment period.	
Reporting group title	Tio+Olo 5.0 / 5.0 µg
Reporting group description:	
Oral inhalation of FDC of Tiotropium (Tio) 5 µg and Olodaterol (Olo) 5 µg (Tiotropium and Olodaterol: 2.5 µg per actuation), 2 puffs from the RESPIMAT inhaler, once daily, in the morning during the 12-week treatment period.	

Reporting group values	Placebo	Tio+Olo 2.5 / 5.0 µg	Tio+Olo 5.0 / 5.0 µg
Number of subjects	132	133	139
Age Categorical			
Units: participants			

Age Continuous |			
Treated set (TS): This analysis set includes all randomised patients who were dispensed study medication and were documented to have taken any dose of study medication.			
Units: years			
arithmetic mean	60.8	61.9	63.1
standard deviation	± 7.6	± 7.3	± 7.5
Gender, Male/Female			
Units: participants			
Female	45	46	44
Male	87	87	95

Reporting group values	Total		
Number of subjects	404		
Age Categorical			
Units: participants			

Age Continuous |			
Treated set (TS): This analysis set includes all randomised patients who were dispensed study medication and were documented to have taken any dose of study medication.			
Units: years			
arithmetic mean			
standard deviation	-		
Gender, Male/Female			
Units: participants			
Female	135		
Male	269		

End points

End points reporting groups

Reporting group title	Placebo
Reporting group description:	
Once daily 2 puffs, solution for inhalation Respimat placebo to tiotropium+olodaterol during the 12-week treatment period: comparator	
Reporting group title	Tio+Olo 2.5 / 5.0 µg
Reporting group description:	
Oral inhalation of fixed dose combination (FDC) of Tiotropium (Tio) 2.5 µg and Olodaterol (Olo) 5 µg (Tiotropium: 1.25 µg per actuation and Olodaterol: 2.5 µg per actuation), 2 puffs from the RESPIMAT inhaler, once daily, in the morning during the 12-week treatment period.	
Reporting group title	Tio+Olo 5.0 / 5.0 µg
Reporting group description:	
Oral inhalation of FDC of Tiotropium (Tio) 5 µg and Olodaterol (Olo) 5 µg (Tiotropium and Olodaterol: 2.5 µg per actuation), 2 puffs from the RESPIMAT inhaler, once daily, in the morning during the 12-week treatment period.	

Primary: Adjusted mean endurance time (sec) during constant work rate cycle ergometry (CWRCE) after 12 weeks

End point title	Adjusted mean endurance time (sec) during constant work rate cycle ergometry (CWRCE) after 12 weeks
End point description:	
Primary endpoint was endurance time during constant work rate cycle ergometry to symptom limitation at 75% of maximal work capacity after 12 weeks of treatment.The endurance time in seconds was transformed using log10 scale to correct skewness in endurance time on original scale and then the MMRM model was fitted to the log10-transformed data and the least square means and SEs were obtained. To present the results in a way easier for interpretation, the least square mean from the MMRM fitted to the log10-transformed data were transformed back taking 10 to the power of the least square estimate for the log10 of geometric mean and the corresponding SE was transformed using delta method to get the corresponding SEs of the geometric mean. Full analysis set (FAS). FAS is defined as all patients that were randomised, received treatment and had baseline and at least one post-baseline measurement before or at Week 12 for the primary endpoint.	
End point type	Primary
End point timeframe:	
12 weeks	

End point values	Placebo	Tio+Olo 2.5 / 5.0 µg	Tio+Olo 5.0 / 5.0 µg	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	121[1]	129[2]	135[3]	
Units: seconds				
least squares mean (standard error)	463.63 (± 18.813)	503.64 (± 19.642)	527.51 (± 20.154)	

Notes:

[1] - Full analysis set (FAS)

[2] - FAS

[3] - FAS

Statistical analyses

Statistical analysis title	Tio+Olo 5.0 / 5.0 µg versus Placebo

Statistical analysis description:

Treatment ratio between Tio+Olo 5.0/5.0 and placebo. This treatment comparison is the first one in the alpha-protected hierarchical testing chain.
Tio+Olo 5.0/5.0 is numerator and placebo is denominator.

Comparison groups	Placebo v Tio+Olo 5.0 / 5.0 µg
Number of subjects included in analysis	256
Analysis specification	Pre-specified
Analysis type	superiority[4]
P-value	= 0.0209 [5]
Method	Mixed models analysis
Parameter estimate	Treatment ratio
Point estimate	1.138
Confidence interval	
level	95 %
sides	2-sided
lower limit	1.02
upper limit	1.269
Variability estimate	Standard error of the mean
Dispersion value	0.063

Notes:

[4] - Mean and 95% confidence limits were transformed from log10 back to the original scale. SE was calculated using the delta method.
[5] - Mixed effects Model Repeated Measures (MMRM) with fixed effects of treatment, test day, treatment by test day interaction, log10 (baseline endurance time), log10 (baseline endurance time) by test day interaction, and patient as a random effect.

Statistical analysis title	Tio+Olo 2.5 / 5.0 µg versus Placebo

Statistical analysis description:

Treatment ratio between Tio+Olo 2.5/5.0 and placebo. This treatment comparison is the second one in the alpha-protected hierarchical testing chain. Since the p-value for this treatment comparison is >0.05, the hierarchical testing chain is broken and all of the following hypothesis tests in this hierarchical chain are considered as descriptive only.
Tio+Olo 2.5/5.0 is numerator and placebo is denominator.

Comparison groups	Placebo v Tio+Olo 2.5 / 5.0 µg
Number of subjects included in analysis	250
Analysis specification	Pre-specified
Analysis type	superiority[6]
P-value	= 0.1419 [7]
Method	Mixed models analysis
Parameter estimate	Treatment ratio
Point estimate	1.086
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.973
upper limit	1.213
Variability estimate	Standard error of the mean
Dispersion value	0.061

Notes:

[6] - Mean and 95% confidence limits were transformed from log10 back to the original scale. SE was calculated using the delta method.
[7] - MMRM for log10 (endurance time [s]) with fixed effects of treatment, test day, treatment by test day interaction, log10 (baseline endurance time [s]), log10 (baseline endurance time [s]) by test day

interaction and patient as a random effect.

Statistical analysis title	Tio+Olo 5.0 / 5.0 µg versus Tio+Olo 2.5 / 5.0 µg

Statistical analysis description:

Treatment ratio between Tio+Olo 5.0/5.0 and Tio+Olo 2.5/5.0. This treatment comparison is not included in the alpha-protected hierarchical testing chain.
Tio+Olo 5.0/5.0 is numerator and Tio+Olo 2.5/5.0 is denominator.

Comparison groups	Tio+Olo 2.5 / 5.0 µg v Tio+Olo 5.0 / 5.0 µg
Number of subjects included in analysis	264
Analysis specification	Pre-specified
Analysis type	superiority[8]
P-value	= 0.397 [9]
Method	Mixed models analysis
Parameter estimate	Treatment ratio
Point estimate	1.047
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.941
upper limit	1.166
Variability estimate	Standard error of the mean
Dispersion value	0.057

Notes:

[8] - Mean and 95% confidence limits were transformed from log10 back to the original scale. SE was calculated using the delta method.
[9] - MMRM for log10 (endurance time [s]) with fixed effects of treatment, test day, treatment by test day interaction, log10 (baseline endurance time [s]), log10 (baseline endurance time [s]) by test day interaction and patient as a random effect.

Secondary: Adjusted mean endurance time (sec) during endurance shuttle walk test (ESWT) after 12 weeks

End point title	Adjusted mean endurance time (sec) during endurance shuttle walk test (ESWT) after 12 weeks

End point description:

Key secondary endpoint was endurance time during endurance shuttle walk test to symptom limitation at 85% of predicted maximum oxygen consumption (VO2) peak after 12 weeks of treatment.The endurance time in seconds was transformed using log10 scale to correct skewness in endurance time on original scale & then MMRM model was fitted to the log10-transformed data &the least square means &SEs were obtained.To present the results in a way easier for interpretation, least square mean from the MMRM fitted to the log10-transformed data were transformed back taking 10 to the power of the least square estimate for the log10 of geometric mean & the corresponding SE was transformed using delta method to get the corresponding SEs of the geometric mean.
Endurance shuttle walk test (ESWT) substudy set: It includes all patients in the TS who had given informed consent for participating in the ESWT substudy &had a baseline and at least one postbaseline measurement during ESWT before or at Week 12.

End point type	Secondary

End point timeframe:

12 weeks

End point values	Placebo	Tio+Olo 2.5 / 5.0 µg	Tio+Olo 5.0 / 5.0 µg	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	50[10]	56[11]	59[12]	
Units: seconds				
least squares mean (standard error)	311.41 (± 22.519)	377.2 (± 25.942)	376.39 (± 25.033)	

Notes:

[10] - ESWT substudy set

[11] - ESWT substudy set

[12] - ESWT substudy set

Statistical analyses

Statistical analysis title	Tio+Olo 5.0 / 5.0 µg versus Placebo

Statistical analysis description:

Treatment ratio between Tio+Olo 5.0/5.0 and placebo. Since the hierarchical testing chain has been broken, even though this treatment comparison is included as the 3rd one in the alpha-protected hierarchical testing chain, this hypothesis test is descriptive only.
Tio+Olo 5.0/5.0 is the numerator and placebo is the denominator.

Comparison groups	Placebo v Tio+Olo 5.0 / 5.0 µg
Number of subjects included in analysis	109
Analysis specification	Pre-specified
Analysis type	superiority[13]
P-value	= 0.0552 [14]
Method	Mixed models analysis
Parameter estimate	Treatment ratio
Point estimate	1.209
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.996
upper limit	1.467
Variability estimate	Standard error of the mean
Dispersion value	0.119

Notes:

[13] - Mean and 95% confidence limits were transformed from log10 back to the original scale. SE was calculated using the delta method.
[14] - MMRM for log10 (endurance time [s]) with fixed effects of treatment, test day, treatment by test day interaction, log10 (baseline endurance time [s]), log10 (baseline endurance time [s]) by test day interaction and patient as a random effect.

Statistical analysis title	Tio+Olo 2.5 / 5.0 µg versus Placebo

Statistical analysis description:

Treatment ratio between Tio+Olo 2.5/5.0 and placebo.
Tio+Olo 2.5/5.0 is the numerator and placebo is the denominator. The hypothesis test is descriptive only.

Comparison groups	Placebo v Tio+Olo 2.5 / 5.0 µg
Number of subjects included in analysis	106
Analysis specification	Pre-specified
Analysis type	superiority[15]
P-value	= 0.0562 [16]
Method	Mixed models analysis
Parameter estimate	Treatment ratio
Point estimate	1.211

Confidence interval	
level	95 %
sides	2-sided
lower limit	0.995
upper limit	1.475
Variability estimate	Standard error of the mean
Dispersion value	0.121

Notes:

[15] - Mean and 95% confidence limits were transformed from log10 back to the original scale. SE was calculated using the delta method.
[16] - MMRM for log10 (endurance time [s]) with fixed effects of treatment, test day, treatment by test day interaction, log10 (baseline endurance time [s]), log10 (baseline endurance time [s]) by test day interaction and patient as a random effect.

Statistical analysis title	Tio+Olo 5.0 / 5.0 µg versus Tio+Olo 2.5 / 5.0 µg

Statistical analysis description:

Treatment ratio between Tio+Olo 5.0/5.0 and Tio+Olo 2.5/5.0. This treatment comparison is not included in the alpha-protected hierarchical testing chain. The hypothesis test is descriptive only. Tio+Olo 5.0/5.0 is the numerator and Tio+Olo 2.5/5.0 is the denominator.

Comparison groups	Tio+Olo 2.5 / 5.0 µg v Tio+Olo 5.0 / 5.0 µg
Number of subjects included in analysis	115
Analysis specification	Pre-specified
Analysis type	superiority[17]
P-value	= 0.9822 [18]
Method	Mixed models analysis
Parameter estimate	Treatment ratio
Point estimate	0.998
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.826
upper limit	1.205
Variability estimate	Standard error of the mean
Dispersion value	0.095

Notes:

[17] - Mean and 95% confidence limits were transformed from log10 back to the original scale. SE was calculated using the delta method.
[18] - MMRM for log10 (endurance time [s]) with fixed effects of treatment, test day, treatment by test day interaction, log10 (baseline endurance time [s]), log10 (baseline endurance time [s]) by test day interaction andpatient as a random effect.

Secondary: Adjusted mean inspiratory capacity (L) at pre-exercise after 12 weeks

End point title	Adjusted mean inspiratory capacity (L) at pre-exercise after 12 weeks

End point description:

Secondary endpoint was inspiratory capacity (IC) before constant work rate cycle ergometry to symptom limitation at 75% maximal work capacity (Wcap) after 12 weeks of treatment.
Full analysis set (FAS): This patient set included all patients in the TS who had a baseline and at least one post-baseline measurement before or at Week 12 for the primary endpoint.

End point type	Secondary

End point timeframe:

12 weeks

End point values	Placebo	Tio+Olo 2.5 / 5.0 µg	Tio+Olo 5.0 / 5.0 µg	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	119[19]	128[20]	133[21]	
Units: liters				
least squares mean (standard error)	2.39 (± 0.038)	2.597 (± 0.036)	2.624 (± 0.035)	

Notes:

[19] - FAS

[20] - FAS

[21] - FAS

Statistical analyses

Statistical analysis title	Tio+Olo 5.0 / 5.0 µg versus Placebo

Statistical analysis description:

Difference calculated as Tio+Olo 5.0 / 5.0 minus Placebo.
The hypothesis test is descriptive only.

Comparison groups	Placebo v Tio+Olo 5.0 / 5.0 µg
Number of subjects included in analysis	252
Analysis specification	Pre-specified
Analysis type	superiority
P-value	< 0.0001 [22]
Method	Mixed models analysis
Parameter estimate	LSMean Difference-Final Values
Point estimate	0.234
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.133
upper limit	0.336
Variability estimate	Standard error of the mean
Dispersion value	0.052

Notes:

[22] - MMRM for inspiratory capacity with fixed effects of treatment, test day, treatment by test day interaction, baseline inspiratory capacity, baseline inspiratory capacity by test day interaction and patient as a random effect.

Statistical analysis title	Tio+Olo 2.5 / 5.0 µg versus Placebo

Statistical analysis description:

Difference calculated as Tio+Olo 2.5 / 5.0 minus Placebo.
The hypothesis test is descriptive only.

Comparison groups	Placebo v Tio+Olo 2.5 / 5.0 µg
Number of subjects included in analysis	247
Analysis specification	Pre-specified
Analysis type	superiority
P-value	< 0.0001 [23]
Method	Mixed models analysis
Parameter estimate	LSMean Difference-Final Values
Point estimate	0.207

Confidence interval	
level	95 %
sides	2-sided
lower limit	0.105
upper limit	0.309
Variability estimate	Standard error of the mean
Dispersion value	0.052

Notes:

[23] - MMRM for inspiratory capacity with fixed effects of treatment, test day, treatment by test day interaction, baseline inspiratory capacity, baseline inspiratory capacity by test day interaction and patient as a random effect.

Statistical analysis title	Tio+Olo 5.0 / 5.0 µg versus Tio+Olo 2.5 / 5.0 µg

Statistical analysis description:

Difference calculated as Tio+Olo 5.0 / 5.0 minus Tio+Olo 2.5 / 5.0.
The hypothesis test is descriptive only.

Comparison groups	Tio+Olo 5.0 / 5.0 µg v Tio+Olo 2.5 / 5.0 µg
Number of subjects included in analysis	261
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.5892 [24]
Method	Mixed models analysis
Parameter estimate	LSMean Difference-Final Values
Point estimate	0.027
Confidence interval	
level	95 %
sides	2-sided
lower limit	-0.072
upper limit	0.126
Variability estimate	Standard error of the mean
Dispersion value	0.05

Notes:

[24] - MMRM for inspiratory capacity with fixed effects of treatment, test day, treatment by test day interaction, baseline inspiratory capacity, baseline inspiratory capacity by test day interaction and patient as a random effect.

Secondary: Adjusted mean endurance time (sec) during constant work rate cycle ergometry (CWRCE) on Day 1

End point title	Adjusted mean endurance time (sec) during constant work rate cycle ergometry (CWRCE) on Day 1

End point description:

Secondary endpoint was endurance time during constant work rate cycle ergometry to symptom limitation at 75% of maximal work capacity on Day 1. Analysis of covariance model on log10 transformed data. Adjusted means are back transformed to report in original units as geometric mean. Standard errors (SEs) are calculated using the delta method.
The V4 set included all patients in the TS who had evaluable measurements of endurance time at Baseline (Visit 3) and at Visit 4 (Day 1) during CWRCE. Patients were assigned to the Visit 4 set after implementation of data handling rules that set measurements to missing.

End point type	Secondary

End point timeframe:

Day 1

End point values	Placebo	Tio+Olo 2.5 / 5.0 µg	Tio+Olo 5.0 / 5.0 µg	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	77[25]	77[26]	80[27]	
Units: seconds				
least squares mean (standard error)	478.59 (± 17.861)	527.69 (± 19.67)	538.76 (± 19.715)	

Notes:

[25] - Visit 4 (V4) set

[26] - V4 set

[27] - V4 set

Statistical analyses

Statistical analysis title	Tio+Olo 5.0 / 5.0 µg versus Placebo

Statistical analysis description:

Treatment ratio between Tio+Olo 5.0/5.0 and placebo.
Tio+Olo 5.0/5.0 is numerator and placebo is denominator.
The hypothesis test is descriptive only.

Comparison groups	Placebo v Tio+Olo 5.0 / 5.0 µg
Number of subjects included in analysis	157
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.0245 [28]
Method	ANCOVA
Parameter estimate	Treatment ratio
Point estimate	1.126
Confidence interval	
level	95 %
sides	2-sided
lower limit	1.015
upper limit	1.248
Variability estimate	Standard error of the mean
Dispersion value	0.059

Notes:

[28] - ANCOVA model for log10 (endurance time [s]) with categorical effects of treatment and (log10-transformed) baseline as continuous covariate.

Statistical analysis title	Tio+Olo 2.5 / 5.0 µg versus Placebo

Statistical analysis description:

Treatment ratio between Tio+Olo 2.5/5.0 and placebo.
Tio+Olo 2.5/5.0 is numerator and placebo is denominator.
The hypothesis test is descriptive only.

Comparison groups	Placebo v Tio+Olo 2.5 / 5.0 µg
Number of subjects included in analysis	154
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.0655 [29]
Method	ANCOVA
Parameter estimate	Treatment ratio
Point estimate	1.103

Confidence interval	
level	95 %
sides	2-sided
lower limit	0.994
upper limit	1.223
Variability estimate	Standard error of the mean
Dispersion value	0.058

Notes:

[29] - ANCOVA model for log10 (endurance time [s]) with categorical effects of treatment and (log10-transformed) baseline as continuous covariate.

Statistical analysis title	Tio+Olo 5.0 / 5.0 µg versus Tio+Olo 2.5 / 5.0 µg

Statistical analysis description:

Treatment ratio between Tio+Olo 5.0/5.0 and Tio+Olo 2.5/5.0.
Tio+Olo 5.0/5.0 is numerator and Tio+Olo 2.5/5.0 is denominator.
The hypothesis test is descriptive only.

Comparison groups	Tio+Olo 5.0 / 5.0 µg v Tio+Olo 2.5 / 5.0 µg
Number of subjects included in analysis	157
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.6912 [30]
Method	ANCOVA
Parameter estimate	Treatment ratio
Point estimate	1.021
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.921
upper limit	1.132
Variability estimate	Standard error of the mean
Dispersion value	0.053

Notes:

[30] - ANCOVA model for log10 (endurance time [s]) with categorical effects of treatment and (log10-transformed) baseline as continuous covariate.

Secondary: Adjusted mean endurance time (sec) during constant work rate cycle ergometry (CWRCE) after 6 weeks treatment

End point title	Adjusted mean endurance time (sec) during constant work rate cycle ergometry (CWRCE) after 6 weeks treatment

End point description:

Secondary endpoint was endurance time during constant work rate cycle ergometry to symptom limitation at 75% of maximal work capacity after 6 weeks of treatment. The endurance time in seconds was transformed using log10 scale to correct skewness in endurance time on original scale and then the MMRM model was fitted to the log10-transformed data and the least square means and SEs were obtained. To present the results in a way easier for interpretation, the least square mean from the MMRM fitted to the log10-transformed data were transformed back taking 10 to the power of the least square estimate for the log10 of geometric mean and the corresponding SE was transformed using delta method to get the corresponding SEs of the geometric mean.
Full analysis set (FAS). FAS is defined as all patients that were randomised, received treatment and had baseline and at least one post-baseline measurement before or at Week 12 for the primary endpoint.

End point type	Secondary

End point timeframe:

6 weeks

End point values	Placebo	Tio+Olo 2.5 / 5.0 µg	Tio+Olo 5.0 / 5.0 µg	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	121[31]	129[32]	135[33]	
Units: seconds				
least squares mean (standard error)	427.74 (± 17.093)	522.26 (± 20.232)	525.62 (± 19.99)	

Notes:

[31] - FAS

[32] - FAS

[33] - FAS

Statistical analyses

Statistical analysis title	Tio+Olo 5.0 / 5.0 µg versus Placebo

Statistical analysis description:

Treatment ratio between Tio+Olo 5.0/5.0 and placebo. Hypothesis test is descriptive.
Tio+Olo 5.0/5.0 is numerator and placebo is denominator.

Comparison groups	Placebo v Tio+Olo 5.0 / 5.0 µg
Number of subjects included in analysis	256
Analysis specification	Pre-specified
Analysis type	superiority[34]
P-value	= 0.0002 [35]
Method	Mixed models analysis
Parameter estimate	Treatment ratio
Point estimate	1.229
Confidence interval	
level	95 %
sides	2-sided
lower limit	1.103
upper limit	1.37
Variability estimate	Standard error of the mean
Dispersion value	0.068

Notes:

[34] - Mean and 95% confidence limits were transformed from log10 back to the original scale. SE was calculated using the delta method.

[35] - MMRM for log10 (endurance time [s]) with fixed effects of treatment, test day, treatment by test day interaction, log10 (baseline endurance time [s]), log10 (baseline endurance time [s]) by test day interaction and patient as a random effect.

Statistical analysis title	Tio+Olo 2.5 / 5.0 µg versus Placebo

Statistical analysis description:

Treatment ratio between Tio+Olo 2.5/5.0 and placebo. Hypothesis test is descriptive.
Tio+Olo 2.5/5.0 is numerator and placebo is denominator.

Comparison groups	Placebo v Tio+Olo 2.5 / 5.0 µg

Number of subjects included in analysis	250
Analysis specification	Pre-specified
Analysis type	superiority[36]
P-value	= 0.0004 [37]
Method	Mixed models analysis
Parameter estimate	Treatment ratio
Point estimate	1.221
Confidence interval	
level	95 %
sides	2-sided
lower limit	1.095
upper limit	1.362
Variability estimate	Standard error of the mean
Dispersion value	0.068

Notes:

[36] - Mean and 95% confidence limits were transformed from log10 back to the original scale. SE was calculated using the delta method.
[37] - MMRM for log10 (endurance time [s]) with fixed effects of treatment, test day, treatment by test day interaction, log10 (baseline endurance time [s]), log10 (baseline endurance time [s]) by test day interaction and patient as a random effect.

Statistical analysis title	Tio+Olo 5.0 / 5.0 µg versus Tio+Olo 2.5 / 5.0 µg

Statistical analysis description:

Treatment ratio between Tio+Olo 5.0/5.0 and Tio+Olo 2.5/5.0. Hypothesis test is descriptive. Tio+Olo 5.0/5.0 is numerator and Tio+Olo 2.5/5.0 is denominator.

Comparison groups	Tio+Olo 5.0 / 5.0 µg v Tio+Olo 2.5 / 5.0 µg
Number of subjects included in analysis	264
Analysis specification	Pre-specified
Analysis type	superiority[38]
P-value	= 0.9062 [39]
Method	Mixed models analysis
Parameter estimate	Treatment ratio
Point estimate	1.006
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.905
upper limit	1.12
Variability estimate	Standard error of the mean
Dispersion value	0.055

Notes:

[38] - Mean and 95% confidence limits were transformed from log10 back to the original scale. SE was calculated using the delta method.
[39] - MMRM for log10 (endurance time [s]) with fixed effects of treatment, test day, treatment by test day interaction, log10 (baseline endurance time [s]), log10 (baseline endurance time [s]) by test day interaction and patient as a random effect.

Secondary: Adjusted mean inspiratory capacity (L) at pre-exercise on Day 1

End point title	Adjusted mean inspiratory capacity (L) at pre-exercise on Day 1

End point description:

Secondary endpoint was pre-exercise inspiratory capacity (IC) on Day 1.
The V4 set included all patients in the TS who had evaluable measurements of endurance time at Baseline (Visit 3) and at Visit 4 (Day 1) during CWRCE. Patients were assigned to the Visit 4 set after implementation of data handling rules that set measurements to missing.

End point type	Secondary

End point timeframe:

Day 1

End point values	Placebo	Tio+Olo 2.5 / 5.0 µg	Tio+Olo 5.0 / 5.0 µg	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	75[40]	77[41]	76[42]	
Units: liters				
least squares mean (standard error)	2.44 (± 0.041)	2.642 (± 0.041)	2.605 (± 0.041)	

Notes:

[40] - V4 set

[41] - V4 set

[42] - V4 set

Statistical analyses

Statistical analysis title	Tio+Olo 5.0 / 5.0 µg versus Placebo

Statistical analysis description:

Difference calculated as Tio+Olo 5.0 / 5.0 minus Placebo.
The hypothesis test is descriptive only.

Comparison groups	Placebo v Tio+Olo 5.0 / 5.0 µg
Number of subjects included in analysis	151
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.0049 [43]
Method	ANCOVA
Parameter estimate	LSMean Difference-Final Values
Point estimate	0.165
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.051
upper limit	0.279
Variability estimate	Standard error of the mean
Dispersion value	0.058

Notes:

[43] - ANCOVA model for inspiratory capacity (liters) with categorical effect of treatment and baseline as continuous covariate.

Statistical analysis title	Tio+Olo 2.5 / 5.0 µg versus Placebo

Statistical analysis description:

Difference calculated as Tio+Olo 2.5 / 5.0 minus Placebo.
The hypothesis test is descriptive only.

Comparison groups	Tio+Olo 2.5 / 5.0 µg v Placebo

Number of subjects included in analysis	152
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.0006 [44]
Method	ANCOVA
Parameter estimate	LSMean Difference-Final Values
Point estimate	0.202
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.088
upper limit	0.316
Variability estimate	Standard error of the mean
Dispersion value	0.058

Notes:

[44] - ANCOVA model for inspiratory capacity (liters) with categorical effect of treatment and baseline as continuous covariate.

Statistical analysis title	Tio+Olo 5.0 / 5.0 µg versus Tio+Olo 2.5 / 5.0 µg

Statistical analysis description:

Difference calculated as Tio+Olo 5.0 / 5.0 minus Tio+Olo 2.5 / 5.0.
The hypothesis test is descriptive only.

Comparison groups	Tio+Olo 2.5 / 5.0 µg v Tio+Olo 5.0 / 5.0 µg
Number of subjects included in analysis	153
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.5162 [45]
Method	ANCOVA
Parameter estimate	LSMean Difference-Final Values
Point estimate	-0.037
Confidence interval	
level	95 %
sides	2-sided
lower limit	-0.151
upper limit	0.076
Variability estimate	Standard error of the mean
Dispersion value	0.058

Notes:

[45] - ANCOVA model for inspiratory capacity (liters) with categorical effect of treatment and baseline as continuous covariate.

Secondary: Adjusted mean inspiratory capacity (L) at pre-exercise after 6 weeks

End point title	Adjusted mean inspiratory capacity (L) at pre-exercise after 6 weeks

End point description:

Secondary endpoint was pre-exercise inspiratory capacity (IC) after 6 weeks of treatment.
Full analysis set (FAS): This patient set included all patients in the TS who had a baseline and at least one post-baseline measurement before or at Week 12 for the primary endpoint.

End point type	Secondary

End point timeframe:

6 weeks

End point values	Placebo	Tio+Olo 2.5 / 5.0 µg	Tio+Olo 5.0 / 5.0 µg	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	119[46]	128[47]	133[48]	
Units: liters				
least squares mean (standard error)	2.402 (± 0.037)	2.589 (± 0.036)	2.627 (± 0.035)	

Notes:

[46] - FAS

[47] - FAS

[48] - FAS

Statistical analyses

Statistical analysis title	Tio+Olo 5.0 / 5.0 µg versus Placebo

Statistical analysis description:

Difference calculated as Tio+Olo 5.0 / 5.0 minus Placebo.
The hypothesis test is descriptive only.

Comparison groups	Placebo v Tio+Olo 5.0 / 5.0 µg
Number of subjects included in analysis	252
Analysis specification	Pre-specified
Analysis type	superiority
P-value	< 0.0001 [49]
Method	Mixed models analysis
Parameter estimate	LSMean Difference-Final Values
Point estimate	0.225
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.124
upper limit	0.326
Variability estimate	Standard error of the mean
Dispersion value	0.051

Notes:

[49] - MMRM for inspiratory capacity with fixed effects of treatment, test day, treatment by test day interaction, baseline inspiratory capacity, baseline inspiratory capacity by test day interaction and patient as a random effect.

Statistical analysis title	Tio+Olo 2.5 / 5.0 µg versus Placebo

Statistical analysis description:

Difference calculated as Tio+Olo 2.5 / 5.0 minus Placebo.
The hypothesis test is descriptive only.

Comparison groups	Placebo v Tio+Olo 2.5 / 5.0 µg
Number of subjects included in analysis	247
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.0003 [50]
Method	Mixed models analysis
Parameter estimate	LSMean Difference-Final Values
Point estimate	0.187

Confidence interval	
level	95 %
sides	2-sided
lower limit	0.086
upper limit	0.288
Variability estimate	Standard error of the mean
Dispersion value	0.052

Notes:

[50] - MMRM for inspiratory capacity with fixed effects of treatment, test day, treatment by test day interaction, baseline inspiratory capacity, baseline inspiratory capacity by test day interaction and patient as a random effect.

Statistical analysis title	Tio+Olo 5.0 / 5.0 µg versus Tio+Olo 2.5 / 5.0 µg

Statistical analysis description:

Difference calculated as Tio+Olo 5.0 / 5.0 minus Tio+Olo 2.5 / 5.0.
The hypothesis test is descriptive only.

Comparison groups	Tio+Olo 2.5 / 5.0 µg v Tio+Olo 5.0 / 5.0 µg
Number of subjects included in analysis	261
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.4541 [51]
Method	Mixed models analysis
Parameter estimate	LSMean Difference-Final Values
Point estimate	0.038
Confidence interval	
level	95 %
sides	2-sided
lower limit	-0.061
upper limit	0.137
Variability estimate	Standard error of the mean
Dispersion value	0.05

Notes:

[51] - MMRM for inspiratory capacity with fixed effects of treatment, test day, treatment by test day interaction, baseline inspiratory capacity, baseline inspiratory capacity by test day interaction and patient as a random effect.

Secondary: Adjusted mean slope of the intensity of breathing discomfort on Day 1

End point title	Adjusted mean slope of the intensity of breathing discomfort on Day 1

End point description:

Secondary endpoint was the slope of the intensity of breathing discomfort during constant work rate cycle ergometry to symptom limitation at 75% of maximal work capacity after 1 day of treatment. The intensity of breathing discomfort was rated on the Borg Scale with categories from 0 (nothing at all) to 10 (maximal). The slope of the intensity of breathing discomfort was defined as the Borg scale value of breathing discomfort at the end of exercise minus the Borg scale value of breathing discomfort at pre-exercise divided by the endurance time. A decrease in slope indicates slowing down in decline in breathing, i.e., favorable results.
The V4 set included all patients in the TS who had evaluable measurements of endurance time at Baseline (Visit 3) and at Visit 4 (Day 1) during CWRCE. Patients were assigned to the Visit 4 set after implementation of data handling rules that set measurements to missing.

End point type	Secondary

End point timeframe:

Day 1

End point values	Placebo	Tio+Olo 2.5 / 5.0 µg	Tio+Olo 5.0 / 5.0 µg	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	76[52]	77[53]	80[54]	
Units: units / seconds				
least squares mean (standard error)	0.014 (± 0.001)	0.012 (± 0.001)	0.012 (± 0.001)	

Notes:

[52] - V4 set

[53] - V4 set

[54] - V4 set

Statistical analyses

Statistical analysis title	Tio+Olo 5.0 / 5.0 µg versus Placebo

Statistical analysis description:

Difference calculated as Tio+Olo 5.0 / 5.0 minus Placebo.
The hypothesis test is descriptive only.

Comparison groups	Placebo v Tio+Olo 5.0 / 5.0 µg
Number of subjects included in analysis	156
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.0468 [55]
Method	ANCOVA
Parameter estimate	LSMean Difference-Final Values
Point estimate	-0.002
Confidence interval	
level	95 %
sides	2-sided
lower limit	-0.004
upper limit	0
Variability estimate	Standard error of the mean
Dispersion value	0.001

Notes:

[55] - ANCOVA model for mean slope of the intensity of breathing discomfort with categorical effect of treatment and baseline as continuous covariate.

Statistical analysis title	Tio+Olo 2.5 / 5.0 µg versus Placebo

Statistical analysis description:

Difference calculated as Tio+Olo 2.5 / 5.0 minus Placebo.
The hypothesis test is descriptive only.

Comparison groups	Placebo v Tio+Olo 2.5 / 5.0 µg
Number of subjects included in analysis	153
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.018 [56]
Method	ANCOVA
Parameter estimate	LSMean Difference-Final Values
Point estimate	-0.002
Confidence interval	
level	95 %
sides	2-sided
lower limit	-0.005
upper limit	0

Variability estimate	Standard error of the mean
Dispersion value	0.001

Notes:

[56] - ANCOVA model for mean slope of the intensity of breathing discomfort with categorical effect of treatment and baseline as continuous covariate.

Statistical analysis title	Tio+Olo 5.0 / 5.0 µg versus Tio+Olo 2.5 / 5.0 µg

Statistical analysis description:

Difference calculated as Tio+Olo 5.0 / 5.0 minus Tio+Olo 2.5 / 5.0.
The hypothesis test is descriptive only.

Comparison groups	Tio+Olo 5.0 / 5.0 µg v Tio+Olo 2.5 / 5.0 µg
Number of subjects included in analysis	157
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.6856 [57]
Method	ANCOVA
Parameter estimate	LSMean Difference-Final Values
Point estimate	0
Confidence interval	
level	95 %
sides	2-sided
lower limit	-0.002
upper limit	0.002
Variability estimate	Standard error of the mean
Dispersion value	0.001

Notes:

[57] - ANCOVA model for mean slope of the intensity of breathing discomfort with categorical effect of treatment and baseline as continuous covariate.

Secondary: Adjusted mean slope of the intensity of breathing discomfort after week 6

End point title	Adjusted mean slope of the intensity of breathing discomfort after week 6

End point description:

Secondary endpoint was the slope of the intensity of breathing discomfort during constant work rate cycle ergometry to symptom limitation at 75% of maximal work capacity after 6 weeks of treatment. The intensity of breathing discomfort was rated on the Borg Scale with categories from 0 (nothing at all) to 10 (maximal). The slope of the intensity of breathing discomfort was defined as the Borg scale value of breathing discomfort at the end of exercise minus the Borg scale value of breathing discomfort at pre-exercise divided by the endurance time. A decrease in slope indicates favorable results.
Full analysis set (FAS): This patient set included all patients in the TS who had a baseline and at least one post-baseline measurement before or at Week 12 for the primary endpoint.

End point type	Secondary

End point timeframe:

6 weeks

End point values	Placebo	Tio+Olo 2.5 / 5.0 µg	Tio+Olo 5.0 / 5.0 µg	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	120[58]	129[59]	135[60]	
Units: units / seconds				
least squares mean (standard error)	0.016 (± 0.001)	0.013 (± 0.001)	0.013 (± 0.001)	

Notes:
[58] - FAS
[59] - FAS
[60] - FAS

Statistical analyses

Statistical analysis title	Tio+Olo 5.0 / 5.0 µg versus Placebo

Statistical analysis description:

Difference calculated as Tio+Olo 5.0 / 5.0 minus Placebo.
The hypothesis test is descriptive only.

Comparison groups	Placebo v Tio+Olo 5.0 / 5.0 µg
Number of subjects included in analysis	255
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.0081 [61]
Method	Mixed models analysis
Parameter estimate	LSMean Difference-Final Values
Point estimate	-0.003
Confidence interval	
level	95 %
sides	2-sided
lower limit	-0.005
upper limit	-0.001
Variability estimate	Standard error of the mean
Dispersion value	0.001

Notes:

[61] - MMRM with fixed effects of treatment, test day, treatment by test day interaction, baseline, baseline by test day interaction and patient as a random effect.

Statistical analysis title	Tio+Olo 2.5 / 5.0 µg versus Placebo

Statistical analysis description:

Difference calculated as Tio+Olo 2.5 / 5.0 minus Placebo.
The hypothesis test is descriptive only.

Comparison groups	Placebo v Tio+Olo 2.5 / 5.0 µg
Number of subjects included in analysis	249
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.0099 [62]
Method	Mixed models analysis
Parameter estimate	LSMean Difference-Final Values
Point estimate	-0.003
Confidence interval	
level	95 %
sides	2-sided
lower limit	-0.005
upper limit	-0.001
Variability estimate	Standard error of the mean
Dispersion value	0.001

Notes:

[62] - MMRM with fixed effects of treatment, test day, treatment by test day interaction, baseline, baseline by test day interaction and patient as a random effect.

Statistical analysis title	Tio+Olo 5.0 / 5.0 µg versus Tio+Olo 2.5 / 5.0 µg

Statistical analysis description:

Difference calculated as Tio+Olo 5.0 / 5.0 minus Tio+Olo 2.5 / 5.0.
The hypothesis test is descriptive only.

Comparison groups	Tio+Olo 5.0 / 5.0 µg v Tio+Olo 2.5 / 5.0 µg
Number of subjects included in analysis	264
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.9626 [63]
Method	Mixed models analysis
Parameter estimate	LSMean Difference-Final Values
Point estimate	0
Confidence interval	
level	95 %
sides	2-sided
lower limit	-0.002
upper limit	0.002
Variability estimate	Standard error of the mean
Dispersion value	0.001

Notes:

[63] - MMRM with fixed effects of treatment, test day, treatment by test day interaction, baseline, baseline by test day interaction and patient as a random effect.

Secondary: Adjusted mean slope of the intensity of breathing discomfort after week 12

End point title	Adjusted mean slope of the intensity of breathing discomfort after week 12

End point description:

Secondary endpoint was the slope of the intensity of breathing discomfort during constant work rate cycle ergometry to symptom limitation at 75% of maximal work capacity after 12 weeks of treatment. The intensity of breathing discomfort was rated on the Borg Scale with categories from 0 (nothing at all) to 10 (maximal). The slope of the intensity of breathing discomfort was defined as the Borg scale value of breathing discomfort at the end of exercise minus the Borg scale value of breathing discomfort at pre-exercise divided by the endurance time. A decrease in slope indicates favorable results.
Full analysis set (FAS): This patient set included all patients in the TS who had a baseline and at least one post-baseline measurement before or at Week 12 for the primary endpoint.

End point type	Secondary

End point timeframe:

12 weeks

End point values	Placebo	Tio+Olo 2.5 / 5.0 µg	Tio+Olo 5.0 / 5.0 µg	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	120[64]	129[65]	135[66]	
Units: units / seconds				
least squares mean (standard error)	0.015 (± 0.001)	0.013 (± 0.001)	0.013 (± 0.001)	

Notes:
[64] - FAS
[65] - FAS
[66] - FAS

Statistical analyses

Statistical analysis title	Tio+Olo 5.0 / 5.0 µg versus Placebo

Statistical analysis description:

Difference calculated as Tio+Olo 5.0 / 5.0 minus Placebo.
The hypothesis test is descriptive only.

Comparison groups	Placebo v Tio+Olo 5.0 / 5.0 µg
Number of subjects included in analysis	255
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.0598 [67]
Method	Mixed models analysis
Parameter estimate	LSMean Difference-Final Values
Point estimate	-0.002
Confidence interval	
level	95 %
sides	2-sided
lower limit	-0.004
upper limit	0
Variability estimate	Standard error of the mean
Dispersion value	0.001

Notes:

[67] - MMRM with fixed effects of treatment, test day, treatment by test day interaction, baseline, baseline by test day interaction and patient as a random effect.

Statistical analysis title	Tio+Olo 2.5 / 5.0 µg versus Placebo

Statistical analysis description:

Difference calculated as Tio+Olo 2.5 / 5.0 minus Placebo.
The hypothesis test is descriptive only.

Comparison groups	Placebo v Tio+Olo 2.5 / 5.0 µg
Number of subjects included in analysis	249
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.0218 [68]
Method	Mixed models analysis
Parameter estimate	LSMean Difference-Final Values
Point estimate	-0.003
Confidence interval	
level	95 %
sides	2-sided
lower limit	-0.005
upper limit	0
Variability estimate	Standard error of the mean
Dispersion value	0.001

Notes:

[68] - MMRM with fixed effects of treatment, test day, treatment by test day interaction, baseline, baseline by test day interaction and patient as a random effect.

Statistical analysis title	Tio+Olo 5.0 / 5.0 µg versus Tio+Olo 2.5 / 5.0 µg

Statistical analysis description:

Difference calculated as Tio+Olo 5.0 / 5.0 minus Tio+Olo 2.5 / 5.0.
The hypothesis test is descriptive only.

Comparison groups	Tio+Olo 5.0 / 5.0 µg v Tio+Olo 2.5 / 5.0 µg
Number of subjects included in analysis	264
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.6549 [69]
Method	Mixed models analysis
Parameter estimate	LSMean Difference-Final Values
Point estimate	0
Confidence interval	
level	95 %
sides	2-sided
lower limit	-0.002
upper limit	0.003
Variability estimate	Standard error of the mean
Dispersion value	0.001

Notes:

[69] - MMRM with fixed effects of treatment, test day, treatment by test day interaction, baseline, baseline by test day interaction and patient as a random effect.

Secondary: Adjusted mean 1-hour post-dose Forced Expiratory Volume in one second (FEV1) (L) on Day 1

End point title	Adjusted mean 1-hour post-dose Forced Expiratory Volume in one second (FEV1) (L) on Day 1

End point description:

Secondary endpoint was adjusted mean 1-hour post-dose Forced Expiratory Volume in one second (FEV1) observed on Day 1.
Full analysis set (FAS): This patient set included all patients in the TS who had a baseline and at least one post-baseline measurement before or at Week 12 for the primary endpoint.

End point type	Secondary

End point timeframe:

Day 1

End point values	Placebo	Tio+Olo 2.5 / 5.0 µg	Tio+Olo 5.0 / 5.0 µg	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	121[70]	129[71]	135[72]	
Units: liters				
least squares mean (standard error)	1.509 (± 0.02)	1.693 (± 0.019)	1.679 (± 0.019)	

Notes:

[70] - FAS

[71] - FAS

[72] - FAS

Statistical analyses

Statistical analysis title	Tio+Olo 5.0 / 5.0 µg versus Placebo

Statistical analysis description:

Difference calculated as Tio+Olo 5.0 / 5.0 minus Placebo.
The hypothesis test is descriptive only.

Comparison groups	Placebo v Tio+Olo 5.0 / 5.0 µg
Number of subjects included in analysis	256
Analysis specification	Pre-specified
Analysis type	superiority
P-value	< 0.0001 [73]
Method	Mixed models analysis
Parameter estimate	LSMean Difference-Final Values
Point estimate	0.17
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.116
upper limit	0.224
Variability estimate	Standard error of the mean
Dispersion value	0.028

Notes:

[73] - MMRM with fixed effects of treatment, test day, treatment by test day interaction, baseline, baseline by test day interaction and patient as a random effect.

Statistical analysis title	Tio+Olo 2.5 / 5.0 µg versus Placebo

Statistical analysis description:

Difference calculated as Tio+Olo 2.5 / 5.0 minus Placebo.
The hypothesis test is descriptive only.

Comparison groups	Placebo v Tio+Olo 2.5 / 5.0 µg
Number of subjects included in analysis	250
Analysis specification	Pre-specified
Analysis type	superiority
P-value	< 0.0001 [74]
Method	Mixed models analysis
Parameter estimate	LSMean Difference-Final Values
Point estimate	0.184
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.129
upper limit	0.239
Variability estimate	Standard error of the mean
Dispersion value	0.028

Notes:

[74] - MMRM with fixed effects of treatment, test day, treatment by test day interaction, baseline, baseline by test day interaction and patient as a random effect.

Statistical analysis title	Tio+Olo 5.0 / 5.0 µg versus Tio+Olo 2.5 / 5.0 µg

Statistical analysis description:

Difference calculated as Tio+Olo 5.0 / 5.0 minus Tio+Olo 2.5 / 5.0.
The hypothesis test is descriptive only.

Comparison groups	Tio+Olo 5.0 / 5.0 µg v Tio+Olo 2.5 / 5.0 µg

Number of subjects included in analysis	264
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.6105 [75]
Method	Mixed models analysis
Parameter estimate	LSMean Difference-Final Values
Point estimate	-0.014
Confidence interval	
level	95 %
sides	2-sided
lower limit	-0.067
upper limit	0.04
Variability estimate	Standard error of the mean
Dispersion value	0.027

Notes:

[75] - MMRM with fixed effects of treatment, test day, treatment by test day interaction, baseline, baseline by test day interaction and patient as a random effect.

Secondary: Adjusted mean 1-hour post-dose Forced Expiratory Volume in one second (FEV1) (L) after 6 weeks

End point title	Adjusted mean 1-hour post-dose Forced Expiratory Volume in one second (FEV1) (L) after 6 weeks

End point description:

Secondary endpoint was adjusted mean 1-hour post-dose Forced Expiratory Volume in one second (FEV1) observed after 6 weeks of treatment.
Full analysis set (FAS): This patient set included all patients in the TS who had a baseline and at least one post-baseline measurement before or at Week 12 for the primary endpoint.

End point type	Secondary

End point timeframe:

6 weeks

End point values	Placebo	Tio+Olo 2.5 / 5.0 µg	Tio+Olo 5.0 / 5.0 µg	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	121[76]	129[77]	135[78]	
Units: liters				
least squares mean (standard error)	1.517 (± 0.02)	1.79 (± 0.019)	1.763 (± 0.019)	

Notes:

[76] - FAS

[77] - FAS

[78] - FAS

Statistical analyses

Statistical analysis title	Tio+Olo 5.0 / 5.0 µg versus Placebo

Statistical analysis description:

Difference calculated as Tio+Olo 5.0 / 5.0 minus Placebo.
The hypothesis test is descriptive only.

Comparison groups	Placebo v Tio+Olo 5.0 / 5.0 µg

Number of subjects included in analysis	256
Analysis specification	Pre-specified
Analysis type	superiority
P-value	< 0.0001 [79]
Method	Mixed models analysis
Parameter estimate	LSMean Difference-Final Values
Point estimate	0.246
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.192
upper limit	0.3
Variability estimate	Standard error of the mean
Dispersion value	0.028

Notes:

[79] - MMRM with fixed effects of treatment, test day, treatment by test day interaction, baseline, baseline by test day interaction and patient as a random effect.

Statistical analysis title	Tio+Olo 2.5 / 5.0 µg versus Placebo

Statistical analysis description:

Difference calculated as Tio+Olo 2.5 / 5.0 minus Placebo.
The hypothesis test is descriptive only.

Comparison groups	Placebo v Tio+Olo 2.5 / 5.0 µg
Number of subjects included in analysis	250
Analysis specification	Pre-specified
Analysis type	superiority
P-value	< 0.0001 [80]
Method	Mixed models analysis
Parameter estimate	LSMean Difference-Final Values
Point estimate	0.273
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.218
upper limit	0.328
Variability estimate	Standard error of the mean
Dispersion value	0.028

Notes:

[80] - MMRM with fixed effects of treatment, test day, treatment by test day interaction, baseline, baseline by test day interaction and patient as a random effect.

Statistical analysis title	Tio+Olo 5.0 / 5.0 µg versus Tio+Olo 2.5 / 5.0 µg

Statistical analysis description:

Difference calculated as Tio+Olo 5.0 / 5.0 minus Tio+Olo 2.5 / 5.0.
The hypothesis test is descriptive only.

Comparison groups	Tio+Olo 5.0 / 5.0 µg v Tio+Olo 2.5 / 5.0 µg
Number of subjects included in analysis	264
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.3236 [81]
Method	Mixed models analysis
Parameter estimate	LSMean Difference-Final Values
Point estimate	-0.027

Confidence interval	
level	95 %
sides	2-sided
lower limit	-0.08
upper limit	0.027
Variability estimate	Standard error of the mean
Dispersion value	0.027

Notes:

[81] - MMRM with fixed effects of treatment, test day, treatment by test day interaction, baseline, baseline by test day interaction and patient as a random effect.

Secondary: Adjusted mean 1-hour post-dose Forced Expiratory Volume in one second (FEV1) (L) after 12 weeks

End point title	Adjusted mean 1-hour post-dose Forced Expiratory Volume in one second (FEV1) (L) after 12 weeks

End point description:

Secondary endpoint was adjusted mean 1-hour post-dose Forced Expiratory Volume in one second (FEV1) observed after 12 weeks of treatment.
Full analysis set (FAS): This patient set included all patients in the TS who had a baseline and at least one post-baseline measurement before or at Week 12 for the primary endpoint.

End point type	Secondary

End point timeframe:

12 weeks

End point values	Placebo	Tio+Olo 2.5 / 5.0 µg	Tio+Olo 5.0 / 5.0 µg	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	121[82]	129[83]	135[84]	
Units: liters				
least squares mean (standard error)	1.527 (± 0.02)	1.784 (± 0.019)	1.778 (± 0.019)	

Notes:

[82] - FAS

[83] - FAS

[84] - FAS

Statistical analyses

Statistical analysis title	Tio+Olo 5.0 / 5.0 µg versus Placebo

Statistical analysis description:

Difference calculated as Tio+Olo 5.0 / 5.0 minus Placebo.
The hypothesis test is descriptive only.

Comparison groups	Placebo v Tio+Olo 5.0 / 5.0 µg
Number of subjects included in analysis	256
Analysis specification	Pre-specified
Analysis type	superiority
P-value	< 0.0001 [85]
Method	Mixed models analysis
Parameter estimate	LSMean Difference-Final Values
Point estimate	0.251

Confidence interval	
level	95 %
sides	2-sided
lower limit	0.196
upper limit	0.305
Variability estimate	Standard error of the mean
Dispersion value	0.028

Notes:

[85] - MMRM with fixed effects of treatment, test day, treatment by test day interaction, baseline, baseline by test day interaction and patient as a random effect.

Statistical analysis title	Tio+Olo 2.5 / 5.0 µg versus Placebo

Statistical analysis description:

Difference calculated as Tio+Olo 2.5/ 5.0 minus Placebo.
The hypothesis test is descriptive only.

Comparison groups	Placebo v Tio+Olo 2.5 / 5.0 µg
Number of subjects included in analysis	250
Analysis specification	Pre-specified
Analysis type	superiority
P-value	< 0.0001 [86]
Method	Mixed models analysis
Parameter estimate	LSMean Difference-Final Values
Point estimate	0.257
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.202
upper limit	0.312
Variability estimate	Standard error of the mean
Dispersion value	0.028

Notes:

[86] - MMRM with fixed effects of treatment, test day, treatment by test day interaction, baseline, baseline by test day interaction and patient as a random effect.

Statistical analysis title	Tio+Olo 5.0 / 5.0 µg versus Tio+Olo 2.5 / 5.0 µg

Statistical analysis description:

Difference calculated as Tio+Olo 5.0 / 5.0 minus Tio+Olo 2.5 / 5.0.
The hypothesis test is descriptive only.

Comparison groups	Tio+Olo 5.0 / 5.0 µg v Tio+Olo 2.5 / 5.0 µg
Number of subjects included in analysis	264
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.8156 [87]
Method	Mixed models analysis
Parameter estimate	LSMean Difference-Final Values
Point estimate	-0.006
Confidence interval	
level	95 %
sides	2-sided
lower limit	-0.06
upper limit	0.047
Variability estimate	Standard error of the mean
Dispersion value	0.027

Notes:

[87] - MMRM with fixed effects of treatment, test day, treatment by test day interaction, baseline, baseline by test day interaction and patient as a random effect.

Adverse events

Adverse events information

Timeframe for reporting adverse events:

142 days

Adverse event reporting additional description:

All adverse events, occurring during the course of the clinical trial (i.e. from signing the informed consent onwards throughout the 12 week treatment period and the 21-day follow up period) were to be collected, documented, and reported to the sponsor on the appropriate electronic case report form / serious adverse event reporting forms.

Assessment type	Systematic

Dictionary used

Dictionary name	MedDRA
Dictionary version	16.1

Reporting groups

Reporting group title	Placebo

Reporting group description:

Once daily 2 puffs, solution for inhalation Respimat placebo to tiotropium+olodaterol during the 12-week treatment period: comparator

Reporting group title	Tio+Olo 5.0 / 5.0 µg

Reporting group description:

Oral inhalation of FDC of Tiotropium (Tio) 5 µg and Olodaterol (Olo) 5 µg (Tiotropium and Olodaterol: 2.5 µg per actuation), 2 puffs from the RESPIMAT inhaler, once daily, in the morning during the 12-week treatment period.

Reporting group title	Tio+Olo 2.5 / 5.0 µg

Reporting group description:

Oral inhalation of fixed dose combination (FDC) of Tiotropium (Tio) 2.5 µg and Olodaterol (Olo) 5 µg (Tiotropium: 1.25 µg per actuation and Olodaterol: 2.5 µg per actuation), 2 puffs from the RESPIMAT inhaler, once daily, in the morning during the 12-week treatment period.

Serious adverse events	Placebo	Tio+Olo 5.0 / 5.0 µg	Tio+Olo 2.5 / 5.0 µg
Total subjects affected by serious adverse events			
subjects affected / exposed	5 / 132 (3.79%)	4 / 139 (2.88%)	9 / 133 (6.77%)
number of deaths (all causes)	0	0	2
number of deaths resulting from adverse events	0	0	0
Neoplasms benign, malignant and unspecified (incl cysts and polyps)			
Invasive ductal breast carcinoma			
subjects affected / exposed	1 / 132 (0.76%)	0 / 139 (0.00%)	0 / 133 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Lung neoplasm malignant			
subjects affected / exposed	0 / 132 (0.00%)	0 / 139 (0.00%)	1 / 133 (0.75%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 1

Malignant neoplasm of unknown primary site			
subjects affected / exposed	0 / 132 (0.00%)	0 / 139 (0.00%)	1 / 133 (0.75%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Metastases to adrenals			
subjects affected / exposed	0 / 132 (0.00%)	0 / 139 (0.00%)	1 / 133 (0.75%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Metastases to bone			
subjects affected / exposed	0 / 132 (0.00%)	0 / 139 (0.00%)	1 / 133 (0.75%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Metastases to liver			
subjects affected / exposed	0 / 132 (0.00%)	0 / 139 (0.00%)	1 / 133 (0.75%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Metastases to lung			
subjects affected / exposed	0 / 132 (0.00%)	0 / 139 (0.00%)	1 / 133 (0.75%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Metastases to lymph nodes			
subjects affected / exposed	0 / 132 (0.00%)	0 / 139 (0.00%)	1 / 133 (0.75%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Paraneoplastic syndrome			
subjects affected / exposed	0 / 132 (0.00%)	0 / 139 (0.00%)	1 / 133 (0.75%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Injury, poisoning and procedural complications			
Toxicity to various agents			
subjects affected / exposed	0 / 132 (0.00%)	0 / 139 (0.00%)	1 / 133 (0.75%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0

Cardiac disorders			
Angina pectoris			
subjects affected / exposed	0 / 132 (0.00%)	1 / 139 (0.72%)	0 / 133 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Cardiac failure			
subjects affected / exposed	0 / 132 (0.00%)	1 / 139 (0.72%)	0 / 133 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Cardio-respiratory arrest			
subjects affected / exposed	0 / 132 (0.00%)	0 / 139 (0.00%)	1 / 133 (0.75%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 1
Nervous system disorders			
Epilepsy			
subjects affected / exposed	1 / 132 (0.76%)	0 / 139 (0.00%)	0 / 133 (0.00%)
occurrences causally related to treatment / all	1 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Gastrointestinal disorders			
Duodenal ulcer haemorrhage			
subjects affected / exposed	0 / 132 (0.00%)	1 / 139 (0.72%)	0 / 133 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Inguinal hernia			
subjects affected / exposed	0 / 132 (0.00%)	0 / 139 (0.00%)	1 / 133 (0.75%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Hepatobiliary disorders			
Biliary colic			
subjects affected / exposed	0 / 132 (0.00%)	1 / 139 (0.72%)	0 / 133 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Cholelithiasis			

subjects affected / exposed	0 / 132 (0.00%)	1 / 139 (0.72%)	0 / 133 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Respiratory, thoracic and mediastinal disorders			
Chronic obstructive pulmonary disease			
subjects affected / exposed	2 / 132 (1.52%)	0 / 139 (0.00%)	5 / 133 (3.76%)
occurrences causally related to treatment / all	0 / 2	0 / 0	0 / 5
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Psychiatric disorders			
Depression			
subjects affected / exposed	1 / 132 (0.76%)	0 / 139 (0.00%)	0 / 133 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Suicide attempt			
subjects affected / exposed	0 / 132 (0.00%)	0 / 139 (0.00%)	1 / 133 (0.75%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Infections and infestations			
Pneumonia			
subjects affected / exposed	1 / 132 (0.76%)	0 / 139 (0.00%)	1 / 133 (0.75%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Urosepsis			
subjects affected / exposed	0 / 132 (0.00%)	1 / 139 (0.72%)	0 / 133 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0

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

Non-serious adverse events	Placebo	Tio+Olo 5.0 / 5.0 µg	Tio+Olo 2.5 / 5.0 µg
Total subjects affected by non-serious adverse events			
subjects affected / exposed	25 / 132 (18.94%)	16 / 139 (11.51%)	25 / 133 (18.80%)
Respiratory, thoracic and mediastinal disorders			

Cough			
subjects affected / exposed	8 / 132 (6.06%)	2 / 139 (1.44%)	9 / 133 (6.77%)
occurrences (all)	8	2	9
Chronic obstructive pulmonary disease			
subjects affected / exposed	15 / 132 (11.36%)	10 / 139 (7.19%)	10 / 133 (7.52%)
occurrences (all)	16	10	11
Infections and infestations			
Nasopharyngitis			
subjects affected / exposed	6 / 132 (4.55%)	4 / 139 (2.88%)	9 / 133 (6.77%)
occurrences (all)	6	4	9

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
15 March 2012	Additional guidance was provided for premature withdrawal, if the patient forgot to take study medication within the specified time window, regarding concomitant medications, and regarding the rescheduling of visits. As a recommendation of local authorities to restrict the trial population to Gold Stage II and III, the inclusion criteria were restricted to patients with a post-bronchodilator 30% ≤FEV1 <80% of predicted normal. A clarification was added that patients had to remain clinically stable for 3 weeks prior to the randomisation visit. For safety reasons, patients with chronic respiratory failure were excluded from the trial. Individual withdrawal criteria were defined. In alignment with the statistical section the list of 'other endpoints' was changed to refer to 'secondary endpoints'. A specification that SAEs needed to be reported until 21 days after the last administration of study medication was added and a list of 'always serious' AEs was included to comply with a new BI internal procedure. For consistency with the recovery phase after cycle ergometry, the IC-maneuver was included in the recovery phase after shuttle walking at sites using the Oxycon Mobile. The procedure of measuring IC was clarified. Administrative changes, minor corrections and further clarifications were introduced.
22 October 2012	The procedure for clinical evaluation of drug-induced liver injury was specified to implement a new BI guideline to comply with the FDA guidance for industry 'Drug-Induced Liver Injury: Premarketing Clinical Evaluation'. As part of the reporting procedure of drug-induced liver injury, protocol-specific significant events were introduced. The period during which a pregnancy test after end of treatment was to be performed was specified. It was specified that mortality adjudication and SAE adjudication was to be performed separately and that vital signs were to be taken prior to each PFT. Clarifications regarding the use of PDE4-inhibitors and on medication restrictions prior to exercise testing were added. The definition of moderate COPD exacerbations was corrected. A clarification was added that more detailed information on exercise testing, equipment and calibration requirements was available in a Manual of Procedures. Administrative changes, minor corrections and further clarifications were introduced.
25 June 2013	The description and categorisation of secondary and other endpoints was changed for the following reasons: Since this was a parallel-group trial, isotime was based on only one treatment. This change resulted in treatment comparisons at isotime to be based on different time points. Therefore, endpoints defined at isotime were regarded as less precise and important for treatment comparisons than planned in the original protocol and were relegated to other endpoints. In addition, slope of the intensity of breathing discomfort was used as a measure of the improvement of breathing discomfort during exercise and was added as one of the secondary efficacy endpoints. To be consistent with other exercise trials in the 1237.P1 project, the list of secondary efficacy endpoints was shortened.

Notes:

Interruptions (globally)

Were there any global interruptions to the trial? No

Limitations and caveats

None reported