Clinical trial results:
A 4-week, randomised, double-blind, parallel group study to evaluate the efficacy and safety of Tiotropium+Olodaterol fixeddose combination [5/5 g] delivered by the RESPIMAT® inhaler versus the free combination of tiotropium 5 g and olodaterol 5 g delivered by separate RESPIMAT® inhalers in patients with Chronic Obstructive Pulmonary Disease [COPD]

Summary

EudraCT number	2015-003879-29
Trial protocol	FI AT SI DK FR
Global end of trial date	30 January 2017

Results information

Result version number	v1 (current)
This version publication date	27 December 2017
First version publication date	27 December 2017

Trial information

Trial identification

Sponsor protocol code	1237.49

Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	NCT02683109
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 8002430127, clintriage.rdg@boehringer-ingelheim.com
Scientific contact	QRPE Processes and Systems Coordination, Clinical Trial Information Disclosure, Boehringer Ingelheim, +1 8002430127, 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	13 March 2017
Is this the analysis of the primary completion data?	Yes
Primary completion date	09 January 2017
Global end of trial reached?	Yes
Global end of trial date	30 January 2017
Was the trial ended prematurely?	No

Notes:

General information about the trial

Main objective of the trial:

The objective of this study was to show that the fixed-dose combination of Tiotropium+Olodaterol [5/5 µg] [Tio+Olo Fixed Dose Combination (FDC)] is non-inferior to the free combination of its individual components Tiotropium 5µg and Olodaterol 5 µg [Tio/Olo free combination], all delivered by the RESPIMAT® inhaler, in patients with moderate to severe COPD.

Protection of trial subjects:

Only subjects that met all the study inclusion and none of the exclusion criteria were to be 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.

Background therapy: -

Evidence for comparator:

Tiotropium/Olodaterol free combination solution for inhalation was the comparator in this study.

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

Notes:

Population of trial subjects

Subjects enrolled per country

Country: Number of subjects enrolled	Austria: 30
Country: Number of subjects enrolled	Denmark: 39
Country: Number of subjects enrolled	France: 48
Country: Number of subjects enrolled	Finland: 46
Country: Number of subjects enrolled	Slovenia: 58
Worldwide total number of subjects	221
EEA total number of subjects	221

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)	75
From 65 to 84 years	146
85 years and over	0

Subject disposition

Recruitment

Recruitment details:

Definition: Open-Label Treated Set [OLTS]: This patient set includes all patients who signed the informed consent and were dispensed open-label study medication during the run-in period prior to randomisation and were documented to have taken any dose of this medication.

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 to be randomised to trial treatment if any one of the specific entry criteria was violated.

Period 1

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

Arms

Are arms mutually exclusive?	Yes
Arm title	T+O 5/5

Arm description:

The subjects were administered Tiotropium [T] + Olodaterol [O] Fixed Dose Combination [FDC] solution for inhalation 2.5 µg/2.5 µg per actuation, 2 inhalations orally once daily via RESPIMAT® inhaler. Placebo matching Tiotropium solution was administered 2 inhalations once daily via RESPIMAT® inhaler.

Arm type	Experimental
Investigational medicinal product name	T+O [FDC]
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Inhalation solution
Routes of administration	Oral use

Dosage and administration details:

Tiotropium+Olodaterol FDC was administered 2.5 µg/2.5 µg per actuation, 2 inhalations once daily via RESPIMAT® inhaler.

Investigational medicinal product name	Placebo
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Inhalation solution
Routes of administration	Oral use

Dosage and administration details:

Placebo was administered 2 inhalations once daily.

Arm title	T 5/O 5

Arm description:

The subjects were administered Tiotropium solution for inhalation, 2.5 µg per actuation + Olodaterol solution for inhalation, 2.5 µg per actuation as a free combination. Two inhalations were administered once daily [a.m. dosing] via RESPIMAT® inhaler for both Tiotropium and Olodaterol.

Arm type	Active comparator

Investigational medicinal product name	Tiotropium
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Inhalation solution
Routes of administration	Oral use

Dosage and administration details:

Tiotropium was administered 2.5 µg per actuation, 2 inhalations once daily via RESPIMAT® inhaler.

Investigational medicinal product name	Olodaterol
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Inhalation solution
Routes of administration	Oral use

Dosage and administration details:

Olodaterol was administered 2.5 µg per actuation, 2 inhalations once daily via RESPIMAT® inhaler.

Number of subjects in period 1	T+O 5/5	T 5/O 5
Started	110	111
Completed	109	111
Not completed	1	0
Adverse event, non-fatal	1	-

Baseline characteristics

Reporting groups	
Reporting group title	T+O 5/5
Reporting group description:	
The subjects were administered Tiotropium [T] + Olodaterol [O] Fixed Dose Combination [FDC] solution for inhalation 2.5 µg/2.5 µg per actuation, 2 inhalations orally once daily via RESPIMAT® inhaler. Placebo matching Tiotropium solution was administered 2 inhalations once daily via RESPIMAT® inhaler.	
Reporting group title	T 5/O 5
Reporting group description:	
The subjects were administered Tiotropium solution for inhalation, 2.5 µg per actuation + Olodaterol solution for inhalation, 2.5 µg per actuation as a free combination. Two inhalations were administered once daily [a.m. dosing] via RESPIMAT® inhaler for both Tiotropium and Olodaterol.	

Reporting group values	T+O 5/5	T 5/O 5	Total
Number of subjects	110	111	221
Age categorical Units: Subjects			
Age Continuous			
Treated set [TS]: This patient set is nested within the RS and includes all patients who were dispensed study medication and were documented to have taken any dose of study medication. Definition: [RS]: This patient set is nested within the OLTS and includes all patients who signed the informed consent form and were also randomised, regardless of whether the patient was treated with study medication or not.			
Units: years			
arithmetic mean	66.5	66.5	
standard deviation	± 7.1	± 6.4	-
Gender, Male/Female			
TS.			
Units: Subjects			
Female	33	30	63
Male	77	81	158

End points

End points reporting groups

Reporting group title	T+O 5/5

Reporting group description:

The subjects were administered Tiotropium [T] + Olodaterol [O] Fixed Dose Combination [FDC] solution for inhalation 2.5 µg/2.5 µg per actuation, 2 inhalations orally once daily via RESPIMAT® inhaler. Placebo matching Tiotropium solution was administered 2 inhalations once daily via RESPIMAT® inhaler.

Reporting group title	T 5/O 5

Reporting group description:

The subjects were administered Tiotropium solution for inhalation, 2.5 µg per actuation + Olodaterol solution for inhalation, 2.5 µg per actuation as a free combination. Two inhalations were administered once daily [a.m. dosing] via RESPIMAT® inhaler for both Tiotropium and Olodaterol.

Primary: Trough Forced Expiratory Volume in 1 second [FEV1][in Liter] after 28 days of treatment

End point title	Trough Forced Expiratory Volume in 1 second [FEV1][in Liter] after 28 days of treatment

End point description:

This outcome measure presents FEV1 after 28 days of treatment [measurement on Day 29]. Trough FEV1 was defined as the FEV1 value at the end of the dosing interval [24 hours], and was measured at 24 hours [+/- 10 minutes] after trial medication administration at Visit 5.
Full Analysis Set [FAS]: This patient set is nested within the TS and includes patients who had a baseline measurement and at least one post-baseline measurement for the primary endpoint.
The FEV1 measurement at Visit 4, which was 24 hours after the last open-label run-in treatment intake and 15 minutes before the first double-blind study drug intake was the baseline measurement.

End point type	Primary

End point timeframe:

Day 29

End point values	T+O 5/5	T 5/O 5		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	108[1]	108[2]		
Units: Liter				
arithmetic mean (standard error)	1.422 (± 0.016)	1.399 (± 0.016)		

Notes:

[1] - FAS.

[2] - FAS.

Statistical analyses

Statistical analysis title	Statistical analysis 1

Statistical analysis description:

The primary analysis was conducted using an Analysis of Covariance [ANCOVA] model including treatment as fixed categorical effect and baseline as continuous covariate.

Comparison groups	T+O 5/5 v T 5/O 5

Number of subjects included in analysis	216
Analysis specification	Pre-specified
Analysis type	non-inferiority[3]
P-value	< 0.0001
Method	ANCOVA
Parameter estimate	Adjusted mean
Point estimate	0.024
Confidence interval	
level	95 %
sides	2-sided
lower limit	-0.02
upper limit	0.067
Variability estimate	Standard error of the mean
Dispersion value	0.022

Notes:

[3] - Non-inferiority of the Tio+Olo FDC versus the Tio/Olo free combination was tested at the one-sided α-level of 0.025 using a non-inferiority margin of 0.1 L.

Secondary: Trough Forced Vital Capacity [FVC] [in Liter] after 28 days of treatment

End point title	Trough Forced Vital Capacity [FVC] [in Liter] after 28 days of treatment

End point description:

This outcome measure presents trough FVC after 28 days of treatment [measurement on Day 29]. The FVC measurement at Visit 4, which was 24 hours after the last open-label run-in treatment intake and 15 minutes before the first double-blind study drug intake was the baseline measurement for FVC.

End point type	Secondary

End point timeframe:

Day 29

End point values	T+O 5/5	T 5/O 5		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	108[4]	108[5]		
Units: Liter				
arithmetic mean (standard error)	3.126 (± 0.024)	3.121 (± 0.024)		

Notes:

[4] - FAS.

[5] - FAS.

Statistical analyses

Statistical analysis title	Statistical analysis 1

Statistical analysis description:

The secondary analysis was conducted using an ANCOVA model including treatment as fixed categorical effect and baseline as continuous covariate.

Comparison groups	T+O 5/5 v T 5/O 5

Number of subjects included in analysis	216
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.8648
Method	ANCOVA
Parameter estimate	Adjusted mean
Point estimate	0.006
Confidence interval	
level	95 %
sides	2-sided
lower limit	-0.061
upper limit	0.073
Variability estimate	Standard error of the mean
Dispersion value	0.034

Secondary: Chronic Obstructive Pulmonary Disease [COPD] Assessment Test™ [CAT] score on Day 28

End point title	Chronic Obstructive Pulmonary Disease [COPD] Assessment Test™ [CAT] score on Day 28

End point description:

This outcome measure presents COPD assessment test score on Day 28.
The COPD Assessment Test™ is a short 8-item questionnaire for assessment and monitoring of COPD health status in routine practice. Its scale is 0-40 [high score = poor health].
The CAT measurement on Visit 4 prior to the first dose of double-blind study drug was the baseline for CAT.

End point type	Secondary

End point timeframe:

Day 28

End point values	T+O 5/5	T 5/O 5		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	108[6]	107[7]		
Units: Score on scale				
arithmetic mean (standard error)	15.423 (± 0.377)	15.750 (± 0.379)		

Notes:

[6] - FAS.

[7] - FAS. One patient in the T 5/O 5 free combination group had missing data for the CAT questionnaire.

Statistical analyses

Statistical analysis title	Statistical analysis 1

Statistical analysis description:

The secondary analysis was conducted using an ANCOVA model including treatment as fixed categorical effect and baseline as continuous covariate.

Comparison groups	T+O 5/5 v T 5/O 5

Number of subjects included in analysis	215
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.542
Method	ANCOVA
Parameter estimate	Adjusted mean
Point estimate	-0.327
Confidence interval	
level	95 %
sides	2-sided
lower limit	-1.384
upper limit	0.729
Variability estimate	Standard error of the mean
Dispersion value	0.536

Adverse events

Adverse events information	
Timeframe for reporting adverse events:	
From first drug administration until 28 days after last drug administration, up to 49 days.	
Assessment type	Systematic

Dictionary used	
Dictionary name	MedDRA
Dictionary version	19.1

Reporting groups	
Reporting group title	T+O 5/5
Reporting group description:	
The subjects were administered Tiotropium [T] + Olodaterol [O] Fixed Dose Combination [FDC] solution for inhalation 2.5 µg/2.5 µg per actuation, 2 inhalations orally once daily via RESPIMAT® inhaler. Placebo matching Tiotropium solution was administered 2 inhalations once daily via RESPIMAT® inhaler.	
Reporting group title	Total
Reporting group description:	
The total number of subjects who were administered T+O 5/5 or T 5/O 5.	
Reporting group title	T 5/O 5
Reporting group description:	
The subjects were administered Tiotropium solution for inhalation, 2.5 µg per actuation + Olodaterol solution for inhalation, 2.5 µg per actuation as a free combination. Two inhalations were administered once daily [a.m. dosing] via RESPIMAT® inhaler for both Tiotropium and Olodaterol.	

Serious adverse events	T+O 5/5	Total	T 5/O 5
Total subjects affected by serious adverse events			
subjects affected / exposed	1 / 110 (0.91%)	3 / 221 (1.36%)	2 / 111 (1.80%)
number of deaths (all causes)	0	0	0
number of deaths resulting from adverse events	0	0	0
Vascular disorders			
Deep vein thrombosis			
subjects affected / exposed	0 / 110 (0.00%)	1 / 221 (0.45%)	1 / 111 (0.90%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Cardiac disorders			
Cardiac failure			
subjects affected / exposed	1 / 110 (0.91%)	1 / 221 (0.45%)	0 / 111 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Left ventricular failure			

subjects affected / exposed	0 / 110 (0.00%)	1 / 221 (0.45%)	1 / 111 (0.90%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 1
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	T+O 5/5	Total	T 5/O 5
Total subjects affected by non-serious adverse events			
subjects affected / exposed	9 / 110 (8.18%)	18 / 221 (8.14%)	9 / 111 (8.11%)
Respiratory, thoracic and mediastinal disorders			
Chronic obstructive pulmonary disease			
subjects affected / exposed	9 / 110 (8.18%)	18 / 221 (8.14%)	9 / 111 (8.11%)
occurrences (all)	10	19	9

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
02 May 2016	The amendment changed the exclusion criterion 5 to exclude patients with a current diagnosis of asthma, not with a history of asthma, as the original Clinical Trial Protocol [CTP] stated. Clarifications concerning the Interactive Response Technology [IRT] call, dispensation of study medications, and collection of vital signs, COPD Assessment TestTM [CAT], and compliance data were added.

Notes:

Interruptions (globally)

Were there any global interruptions to the trial? No

Limitations and caveats

None reported