



Clinical trial results:

A randomised, placebo-controlled, double-blind, single dose, cross-over study to evaluate the efficacy and safety of orally inhaled tiotropium + olodaterol as both a fixed dose combination and a free combination (both delivered by the Respimat® inhaler) in patients with Chronic Obstructive Pulmonary Disease (COPD)

Summary

EudraCT number	2013-002652-32
Trial protocol	DE
Global end of trial date	06 June 2014

Results information

Result version number	v1 (current)
This version publication date	20 June 2016
First version publication date	26 July 2015

Trial information

Trial identification

Sponsor protocol code	1237.7
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Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	NCT02030535
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 2430127, clintrriage.rdg@boehringer-ingelheim.com
Scientific contact	QRPE Processes and Systems Coordination Clinical Trial Information Disclosure, Boehringer Ingelheim, +1 800 2430127, clintrriage.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?	
Does article 46 of REGULATION (EC) No 1901/2006 apply to this trial?	

Notes:

Results analysis stage

Analysis stage	Final
Date of interim/final analysis	21 July 2014
Is this the analysis of the primary completion data?	Yes
Primary completion date	16 May 2014
Global end of trial reached?	Yes
Global end of trial date	06 June 2014
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 evaluate the efficacy and safety of orally inhaled tiotropium and olodaterol as both a fixed dose combination and a free combination with respect to lung function and Electrocardiogram (ECG) parameters

Protection of trial subjects:

Only stable COPD patients 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.

Background therapy: -

Evidence for comparator:

Tiotropium inhalation solution, Olodaterol inhalation solution and Placebo inhalation solution

Actual start date of recruitment	09 January 2014
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	Germany: 60
Worldwide total number of subjects	60
EEA total number of subjects	60

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)	27
From 65 to 84 years	33
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 one specialist site which would then ensure that they (the subjects) met all inclusion/exclusion criteria. Subjects were not to be randomised to trial treatment if any one of the specific entry criteria were violated.

Period 1

Period 1 title	Overall trial
Is this the baseline period?	No
Allocation method	Randomised - controlled
Blinding used	Double blind
Roles blinded	Subject, Investigator

Arms

Arm title	Overall Study
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Arm description:

Total number of patients randomised and treated in the study.

(This is a cross-over trial consisting of a minimum two-week screening period. After screening, eligible patients were randomly assigned to one of 12 treatment sequences. Each patient received all three treatments as single doses on the three test days. Between test days with single dose administration there are 3-week washout periods.)

Arm type	Overall trial by periods
Investigational medicinal product name	Placebo
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Oral solution
Routes of administration	Inhalation use

Dosage and administration details:

2 inhalations ante meridiem (a.m.) dosing.

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

Dosage and administration details:

2 inhalations a.m. dosing via RESPIMAT® inhaler

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

Dosage and administration details:

2 inhalations a.m. dosing via RESPIMAT® inhaler

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

Dosage and administration details:

2 inhalations a.m. dosing via RESPIMAT® inhaler

Number of subjects in period 1	Overall Study
Started	53
Treatment Period 1 (1 Day)	53
Washout Period 1 (21 Days)	53
Treatment Period 2 (1 Day)	52
Washout Period 2 (21 Days)	52
Treatment Period 3 (1 Day)	52
Completed	52
Not completed	1
Adverse event, non-fatal	1

Period 2

Period 2 title	Treatment period
Is this the baseline period?	Yes ^[1]
Allocation method	Randomised - controlled
Blinding used	Double blind
Roles blinded	Subject, Investigator

Arms

Are arms mutually exclusive?	No
Arm title	Placebo

Arm description:

Single test dose of oral inhalation of Placebo via RESPIMAT® inhaler.
2 inhalations ante meridiem (a.m.) dosing.

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

Dosage and administration details:

2 inhalations (a.m.) dosing.

Arm title	Tio+Olo 5/5µg FDC
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Arm description:

Single test dose of oral inhalation of Tio+Olo FDC (fixed dose combination) (5/5 µg) inhalation solution as fixed dose inhalation solution (Tio+Olo FDC) 2.5 µg each per actuation.

2 inhalations a.m. dosing via RESPIMAT® inhaler

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

Dosage and administration details:

2 inhalations a.m. dosing via RESPIMAT® inhaler

Arm title	Tiotropium 5µg + Olodaterol 5µg FC
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Arm description:

Single test dose of oral inhalation of tiotropium (5 µg) and olodaterol (5 µg) free combination (FC) (Tio/Olo free combination);

Olodaterol: 5 µg (2.5 µg per actuation)

Tiotropium: 5 µg (2.5 µg per actuation)

2 inhalations a.m. dosing via RESPIMAT® inhaler.

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

Dosage and administration details:

2 inhalations a.m. dosing via RESPIMAT® inhaler

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

Dosage and administration details:

2 inhalations a.m. dosing via RESPIMAT® inhaler

Notes:

[1] - Period 1 is not the baseline period. It is expected that period 1 will be the baseline period.

Justification: Period 1 evaluates the overall trial by periods, while period 2 reflects the treatment arms, hence period 2 was selected as baseline.

Number of subjects in period 2	Placebo	Tio+Olo 5/5µg FDC	Tiotropium 5µg + Olodaterol 5µg FC
Started	53	52	52
Completed	52	52	52
Not completed	1	0	0
Adverse event, non-fatal	1	-	-

Baseline characteristics

Reporting groups^[1]

Reporting group title	Treatment period
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Reporting group description: -

Notes:

[1] - The number of subjects reported to be in the baseline period is not equal to the worldwide number of subjects 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 of the study medication.

Reporting group values	Treatment period	Total	
Number of subjects	53	53	
Age categorical			
Units: Subjects			

Age Continuous			
Treated set (TS): This patient set included all randomised patients who were administered study medication.			
Units: years			
arithmetic mean	64.4		
standard deviation	± 6.8	-	
Gender, Male/Female			
Treated set (TS): This patient set included all randomised patients who were administered study medication.			
Units: participants			
Female	22	22	
Male	31	31	

End points

End points reporting groups

Reporting group title	Overall Study
Reporting group description: Total number of patients randomised and treated in the study. (This is a cross-over trial consisting of a minimum two-week screening period. After screening, eligible patients were randomly assigned to one of 12 treatment sequences. Each patient received all three treatments as single doses on the three test days. Between test days with single dose administration there are 3-week washout periods.)	
Reporting group title	Placebo
Reporting group description: Single test dose of oral inhalation of Placebo via RESPIMAT® inhaler. 2 inhalations ante meridiem (a.m.) dosing.	
Reporting group title	Tio+Olo 5/5µg FDC
Reporting group description: Single test dose of oral inhalation of Tio+Olo FDC (fixed dose combination) (5/5 µg) inhalation solution as fixed dose inhalation solution (Tio+Olo FDC) 2.5 µg each per actuation. 2 inhalations a.m. dosing via RESPIMAT® inhaler	
Reporting group title	Tiotropium 5µg + Olodaterol 5µg FC
Reporting group description: Single test dose of oral inhalation of tiotropium (5 µg) and olodaterol (5 µg) free combination (FC) (Tio/Olo free combination); Olodaterol: 5 µg (2.5 µg per actuation) Tiotropium: 5 µg (2.5 µg per actuation) 2 inhalations a.m. dosing via RESPIMAT® inhaler.	

Primary: Forced Expiratory Volume in One Second (FEV1) Area Under the Curve (AUC) (0-3hours) Response after single-dose administration

End point title	Forced Expiratory Volume in One Second (FEV1) Area Under the Curve (AUC) (0-3hours) Response after single-dose administration
End point description: The response was defined as the change from patient baseline. Patient baseline was the average of the mean pre-dose values (period baseline) on each test day (Visit 2 (Day 1), Visit 3 (Day 3 (±7days)), and Visit 4 (Day 43±7days)). For patients who did not complete all periods, patient baseline was the average of the available period baselines. The means presented are the adjusted means. Full Analysis Set (FAS): This patient set included all patients in the TS who had at least 1 visit (Visit 2 (Day1), Visit 3 (Day6), or Visit 4(Day43)) with both the period baseline value plus any evaluable post-dose spirometry measurement from the same visit.	
End point type	Primary
End point timeframe: 1 hour (h) and 10 min pre-dose and at 15 min, 30 min, 1 h, 2 h and 3 h post-dose	

End point values	Placebo	Tio+Olo 5/5µg FDC	Tiotropium 5µg + Olodaterol 5µg FC	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	53 ^[1]	52 ^[2]	52 ^[3]	
Units: Litres				
arithmetic mean (standard error)	0.014 (± 0.016)	0.233 (± 0.016)	0.266 (± 0.016)	

Notes:

[1] - FAS

[2] - FAS

[3] - FAS

Statistical analyses

Statistical analysis title	Statistical Analysis 1
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Statistical analysis description:

Mixed effect model repeated measures (MMRM) including fixed effects of treatment and period; patient baseline and period baseline as covariates; patient as a random effect.

Tio+Olo 5/5µg minus Placebo.

Comparison groups	Placebo v Tio+Olo 5/5µg FDC
Number of subjects included in analysis	105
Analysis specification	Pre-specified
Analysis type	other ^[4]
P-value	< 0.0001 ^[5]
Method	Mixed models analysis
Parameter estimate	Adjusted mean difference
Point estimate	0.219
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.187
upper limit	0.252
Variability estimate	Standard error of the mean
Dispersion value	0.016

Notes:

[4] - The actual number of subjects analyzed is 53. As this is a cross over study and arms are not mutually exclusive, the pre-specified, automatically calculated number that is provided in the statistical analysis (105) does not reflect the actual number.

[5] - Kenward–Roger approximation of denominator degrees of freedom. Compound symmetry covariance structure for within–patient variation

Statistical analysis title	Statistical Analysis 2
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Statistical analysis description:

Mixed effect model repeated measures (MMRM) including fixed effects of treatment and period; patient baseline and period baseline as covariates; patient as a random effect.

Tiotropium 5µg + Olodaterol 5µg minus Placebo.

Comparison groups	Placebo v Tiotropium 5µg + Olodaterol 5µg FC
Number of subjects included in analysis	105
Analysis specification	Pre-specified
Analysis type	other ^[6]
P-value	< 0.0001 ^[7]
Method	Mixed models analysis
Parameter estimate	Adjusted mean difference
Point estimate	0.252

Confidence interval	
level	95 %
sides	2-sided
lower limit	0.22
upper limit	0.284
Variability estimate	Standard error of the mean
Dispersion value	0.016

Notes:

[6] - The actual number of subjects analyzed is 53. As this is a cross over study and arms are not mutually exclusive, the pre-specified, automatically calculated number that is provided in the statistical analysis (105) does not reflect the actual number.

[7] - Kenward–Roger approximation of denominator degrees of freedom. Compound symmetry covariance structure for within–patient variation

Statistical analysis title	Statistical Analysis 3
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Statistical analysis description:

Descriptive comparison.

This analysis was not pre-specified in the Clinical trial protocol, but specified in the trial statistical analysis plan.

Comparison groups	Tio+Olo 5/5µg FDC v Tiotropium 5µg + Olodaterol 5µg FC
Number of subjects included in analysis	104
Analysis specification	Pre-specified
Analysis type	other ^[8]
Parameter estimate	Adjusted mean difference
Point estimate	-0.033

Confidence interval

level	95 %
sides	2-sided
lower limit	-0.065
upper limit	-0.001
Variability estimate	Standard error of the mean
Dispersion value	0.016

Notes:

[8] - The actual number of subjects analyzed is 53. As this is a cross over study and arms are not mutually exclusive, the pre-specified, automatically calculated number that is provided in the statistical analysis (104) does not reflect the actual number.

Secondary: Mean Heart Rate Corrected QT Interval (Using Fredericia Adjustment) (QTcF) interval change from patient baseline over all post-dose time points

End point title	Mean Heart Rate Corrected QT Interval (Using Fredericia Adjustment) (QTcF) interval change from patient baseline over all post-dose time points
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End point description:

Mean QTcF interval change from patient baseline over all post-dose time points (5min, 10min, 25min and 50min)

End point type	Secondary
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End point timeframe:

40 min pre-dose and at 5 min, 10 min, 25 min and 50 min post-dose

End point values	Placebo	Tio+Olo 5/5µg FDC	Tiotropium 5µg + Olodaterol 5µg FC	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	52 ^[9]	52 ^[10]	52 ^[11]	
Units: ms				
arithmetic mean (standard deviation)	1.3 (± 7.1)	2.2 (± 6.9)	1.9 (± 6.9)	

Notes:

[9] - Treated set (observed cases)

[10] - Treated set (observed cases)

[11] - Treated set (observed cases)

Statistical analyses

No statistical analyses for this end point

Secondary: Peak QTcF interval change from patient baseline over all post-dose time points

End point title	Peak QTcF interval change from patient baseline over all post-dose time points
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End point description:

Peak QTcF interval change from patient baseline over all post-dose time points (5min, 10min, 25min and 50min)

End point type	Secondary
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End point timeframe:

40 min pre-dose and at 5 min, 10 min, 25 min and 50 min post-dose

End point values	Placebo	Tio+Olo 5/5µg FDC	Tiotropium 5µg + Olodaterol 5µg FC	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	52 ^[12]	52 ^[13]	52 ^[14]	
Units: ms				
arithmetic mean (standard deviation)	5.2 (± 8.3)	5.7 (± 7.6)	5.7 (± 7.3)	

Notes:

[12] - Treated set (observed cases)

[13] - Treated set (observed cases)

[14] - Treated set (observed cases)

Statistical analyses

No statistical analyses for this end point

Secondary: Mean heart rate change from patient baseline over all post-dose time points

End point title	Mean heart rate change from patient baseline over all post-dose time points
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End point description:

Mean heart rate change from patient baseline over all post-dose time points (5min, 10min, 25min and 50min)

End point type	Secondary
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End point timeframe:

40 min pre-dose and at 5 min, 10 min, 25 min and 50 min post-dose

End point values	Placebo	Tio+Olo 5/5µg FDC	Tiotropium 5µg + Olodaterol 5µg FC	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	52 ^[15]	52 ^[16]	52 ^[17]	
Units: bpm				
arithmetic mean (standard deviation)	-3 (± 5.2)	-2.5 (± 5.5)	-3.6 (± 4.3)	

Notes:

[15] - Treated set (observed cases)

[16] - Treated set (observed cases)

[17] - Treated set (observed cases)

Statistical analyses

No statistical analyses for this end point

Secondary: Peak heart rate change from patient baseline over all post-dose time points

End point title	Peak heart rate change from patient baseline over all post-dose time points
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End point description:

Peak heart rate change from patient baseline over all post-dose time points (5min, 10min, 25min and 50min)

End point type	Secondary
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End point timeframe:

40 min pre-dose and at 5 min, 10 min, 25 min and 50 min post-dose

End point values	Placebo	Tio+Olo 5/5µg FDC	Tiotropium 5µg + Olodaterol 5µg FC	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	52 ^[18]	52 ^[19]	52 ^[20]	
Units: bpm				
arithmetic mean (standard deviation)	-0.7 (± 5.5)	-0.3 (± 5.7)	-1.2 (± 4.4)	

Notes:

[18] - Treated set (observed cases)

[19] - Treated set (observed cases)

[20] - Treated set (observed cases)

Statistical analyses

No statistical analyses for this end point

Secondary: Mean RR (Time Interval of ECG) change from patient baseline over all post-dose time points

End point title	Mean RR (Time Interval of ECG) change from patient baseline
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over all post-dose time points

End point description:

Mean RR change from patient baseline over all post-dose time points (5min, 10min, 25min and 50min)

End point type Secondary

End point timeframe:

40 min pre-dose and at 5 min, 10 min, 25 min and 50 min post-dose

End point values	Placebo	Tio+Olo 5/5µg FDC	Tiotropium 5µg + Olodaterol 5µg FC	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	52 ^[21]	52 ^[22]	52 ^[23]	
Units: ms				
arithmetic mean (standard deviation)	40.4 (± 57.7)	29.3 (± 57.1)	39.5 (± 51.5)	

Notes:

[21] - Treated set (observed cases)

[22] - Treated set (observed cases)

[23] - Treated set (observed cases)

Statistical analyses

No statistical analyses for this end point

Secondary: Peak RR change from patient baseline over all post-dose time points

End point title Peak RR change from patient baseline over all post-dose time points

End point description:

Peak RR change from patient baseline over all post-dose time points (5min, 10min, 25min and 50min)

End point type Secondary

End point timeframe:

40 min pre-dose and at 5 min, 10 min, 25 min and 50 min post-dose

End point values	Placebo	Tio+Olo 5/5µg FDC	Tiotropium 5µg + Olodaterol 5µg FC	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	52 ^[24]	52 ^[25]	52 ^[26]	
Units: ms				
arithmetic mean (standard deviation)	68.8 (± 64.3)	55.5 (± 59.5)	68 (± 52.7)	

Notes:

[24] - Treated set (observed cases)

[25] - Treated set (observed cases)

[26] - Treated set (observed cases)

Statistical analyses

No statistical analyses for this end point

Secondary: RR Change From Patient Baseline at Individual Post-dose Time Points

End point title	RR Change From Patient Baseline at Individual Post-dose Time Points
End point description: RR Change From Patient Baseline at Individual Post-dose Time Points	
End point type	Secondary
End point timeframe: 40 min pre-dose and at 5 min, 10 min, 25 min and 50 min post-dose	

End point values	Placebo	Tio+Olo 5/5µg FDC	Tiotropium 5µg + Olodaterol 5µg FC	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	52 ^[27]	52 ^[28]	52 ^[29]	
Units: ms				
arithmetic mean (standard deviation)				
5 min	29.9 (± 62.5)	29.7 (± 58.5)	31.9 (± 55.5)	
10 min	38.8 (± 68.9)	28.1 (± 57.4)	33.5 (± 56.1)	
25 min	40.4 (± 59.4)	33 (± 65.7)	50 (± 59.9)	
50 min	52.3 (± 62.7)	25.2 (± 64.9)	44 (± 57)	

Notes:

[27] - Treated set (observed cases)

[28] - Treated set (observed cases)

[29] - Treated set (observed cases)

Statistical analyses

No statistical analyses for this end point

Secondary: Mean QT (Time Interval of ECG) change from patient baseline over all post-dose time points

End point title	Mean QT (Time Interval of ECG) change from patient baseline over all post-dose time points
End point description: Mean QT change from patient baseline over all post-dose time points (5min, 10min, 25min and 50min)	
End point type	Secondary
End point timeframe: 40 min pre-dose and at 5 min, 10 min, 25 min and 50 min post-dose	

End point values	Placebo	Tio+Olo 5/5µg FDC	Tiotropium 5µg + Olodaterol 5µg FC	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	52 ^[30]	52 ^[31]	52 ^[32]	
Units: ms				
arithmetic mean (standard deviation)	7.2 (± 10.7)	6.5 (± 11.1)	7.9 (± 9.9)	

Notes:

[30] - Treated set (observed cases)

[31] - Treated set (observed cases)

[32] - Treated set (observed cases)

Statistical analyses

No statistical analyses for this end point

Secondary: Peak QT (Time Interval of ECG) change from patient baseline over all post-dose time points

End point title	Peak QT (Time Interval of ECG) change from patient baseline over all post-dose time points
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End point description:

Peak QT change from patient baseline over all post-dose time points (5min, 10min, 25min and 50min)

End point type	Secondary
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End point timeframe:

40 min pre-dose and at 5 min, 10 min, 25 min and 50 min post-dose

End point values	Placebo	Tio+Olo 5/5µg FDC	Tiotropium 5µg + Olodaterol 5µg FC	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	52 ^[33]	52 ^[34]	52 ^[35]	
Units: ms				
arithmetic mean (standard deviation)	12.4 (± 11.5)	11.5 (± 11.1)	13.4 (± 10.6)	

Notes:

[33] - Treated set (observed cases)

[34] - Treated set (observed cases)

[35] - Treated set (observed cases)

Statistical analyses

No statistical analyses for this end point

Secondary: QT(c) Change From Patient Baseline at Individual Post-dose Time Points

End point title	QT(c) Change From Patient Baseline at Individual Post-dose Time Points
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End point description:

QT(c) Change From Patient Baseline at Individual Post-dose Time Points

End point type	Secondary
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End point timeframe:

40 min pre-dose and at 5 min, 10 min, 25 min and 50 min post-dose

End point values	Placebo	Tio+Olo 5/5µg FDC	Tiotropium 5µg + Olodaterol 5µg FC	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	52 ^[36]	52 ^[37]	52 ^[38]	
Units: ms				
arithmetic mean (standard deviation)				
5 min	4.3 (± 10.7)	5.5 (± 11.2)	4.9 (± 10.4)	
10 min	7.1 (± 12.6)	6.3 (± 11.8)	7.9 (± 11.3)	
25 min	7.9 (± 11.4)	7.4 (± 12)	9.6 (± 11.1)	
50 min	9.4 (± 12.1)	6.7 (± 12.6)	9.4 (± 10.9)	

Notes:

[36] - Treated set (observed cases)

[37] - Treated set (observed cases)

[38] - Treated set (observed cases)

Statistical analyses

No statistical analyses for this end point

Secondary: Mean Heart Rate Corrected QT Interval (Using Bazett Adjustment) (QTcB) change from patient baseline over all post-dose time points

End point title	Mean Heart Rate Corrected QT Interval (Using Bazett Adjustment) (QTcB) change from patient baseline over all post-dose time points
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End point description:

Mean QTcB (Heart Rate Corrected QT Interval (Using Bazett Adjustment))change from patient baseline over all post-dose time points (5min, 10min, 25min and 50min)

End point type	Secondary
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End point timeframe:

40 min pre-dose and at 5 min, 10 min, 25 min and 50 min post-dose

End point values	Placebo	Tio+Olo 5/5µg FDC	Tiotropium 5µg + Olodaterol 5µg FC	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	52 ^[39]	52 ^[40]	52 ^[41]	
Units: ms				
arithmetic mean (standard deviation)	-1.9 (± 9)	-0.2 (± 8.6)	-1.4 (± 8.1)	

Notes:

[39] - Treated set (observed cases)

[40] - Treated set (observed cases)

[41] - Treated set (observed cases)

Statistical analyses

No statistical analyses for this end point

Secondary: Peak QTcB change from patient baseline over all post-dose time points

End point title	Peak QTcB change from patient baseline over all post-dose time points
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End point description:

Peak QTcB (Heart Rate Corrected QT Interval (Using Bazett Adjustment))change from patient baseline over all post-dose time points (5min, 10min, 25min and 50min)

End point type	Secondary
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End point timeframe:

40 min pre-dose and at 5 min, 10 min, 25 min and 50 min post-dose

End point values	Placebo	Tio+Olo 5/5µg FDC	Tiotropium 5µg + Olodaterol 5µg FC	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	52 ^[42]	52 ^[43]	52 ^[44]	
Units: ms				
arithmetic mean (standard deviation)	3 (± 10.7)	4.2 (± 9.7)	3.5 (± 8.5)	

Notes:

[42] - Treated set (observed cases)

[43] - Treated set (observed cases)

[44] - Treated set (observed cases)

Statistical analyses

No statistical analyses for this end point

Secondary: Mean PR (Time Interval of ECG) change from patient baseline over all post-dose time points

End point title	Mean PR (Time Interval of ECG) change from patient baseline over all post-dose time points
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End point description:

Mean PR change from patient baseline over all post-dose time points (5min, 10min, 25min and 50min)

End point type	Secondary
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End point timeframe:

40 min pre-dose and at 5 min, 10 min, 25 min and 50 min post-dose

End point values	Placebo	Tio+Olo 5/5µg FDC	Tiotropium 5µg + Olodaterol 5µg FC	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	52 ^[45]	52 ^[46]	52 ^[47]	
Units: ms				
arithmetic mean (standard deviation)	0.6 (± 4.9)	1.6 (± 6.3)	1.4 (± 6.4)	

Notes:

[45] - Treated set (observed cases)

[46] - Treated set (observed cases)

[47] - Treated set (observed cases)

Statistical analyses

No statistical analyses for this end point

Secondary: Peak PR (Time Interval of ECG) change from patient baseline over all post-dose time points

End point title	Peak PR (Time Interval of ECG) change from patient baseline over all post-dose time points
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End point description:

Peak PR change from patient baseline over all post-dose time points (5min, 10min, 25min and 50min)

End point type	Secondary
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End point timeframe:

40 min pre-dose and at 5 min, 10 min, 25 min and 50 min post-dose

End point values	Placebo	Tio+Olo 5/5µg FDC	Tiotropium 5µg + Olodaterol 5µg FC	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	52 ^[48]	52 ^[49]	52 ^[50]	
Units: ms				
arithmetic mean (standard deviation)	3.9 (± 4.8)	4.6 (± 5.9)	4.7 (± 7.2)	

Notes:

[48] - Treated set (observed cases)

[49] - Treated set (observed cases)

[50] - Treated set (observed cases)

Statistical analyses

No statistical analyses for this end point

Secondary: PR Change From Patient Baseline at Individual Post-dose Time Points

End point title	PR Change From Patient Baseline at Individual Post-dose Time Points
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End point description:

PR Change From Patient Baseline at Individual Post-dose Time Points

End point type	Secondary
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End point timeframe:

40 min pre-dose and at 5 min, 10 min, 25 min and 50 min post-dose

End point values	Placebo	Tio+Olo 5/5µg FDC	Tiotropium 5µg + Olodaterol 5µg FC	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	52 ^[51]	52 ^[52]	52 ^[53]	
Units: ms				
arithmetic mean (standard deviation)				
5 min	0.1 (± 5.9)	1.2 (± 7.3)	-0.2 (± 6.6)	
10 min	0.1 (± 6)	2.5 (± 8.4)	1.4 (± 7.1)	
25 min	0.1 (± 6.5)	0.8 (± 6.3)	1.9 (± 7.8)	
50 min	2.2 (± 5.4)	1.9 (± 5.4)	2.7 (± 7.7)	

Notes:

[51] - Treated set (observed cases)

[52] - Treated set (observed cases)

[53] - Treated set (observed cases)

Statistical analyses

No statistical analyses for this end point

Secondary: Mean QRS (Time Interval of ECG) change from patient baseline over all post-dose time points

End point title	Mean QRS (Time Interval of ECG) change from patient baseline over all post-dose time points
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End point description:

Mean QRS change from patient baseline over all post-dose time points (5min, 10min, 25min and 50min)

End point type	Secondary
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End point timeframe:

40 min pre-dose and at 5 min, 10 min, 25 min and 50 min post-dose

End point values	Placebo	Tio+Olo 5/5µg FDC	Tiotropium 5µg + Olodaterol 5µg FC	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	52 ^[54]	52 ^[55]	52 ^[56]	
Units: ms				
arithmetic mean (standard deviation)	-0.3 (± 1.3)	0.1 (± 1.5)	0.1 (± 1.3)	

Notes:

[54] - Treated set (observed cases)

[55] - Treated set (observed cases)

[56] - Treated set (observed cases)

Statistical analyses

No statistical analyses for this end point

Secondary: Peak QRS (Time Interval of ECG) change from patient baseline over all post-dose time points

End point title	Peak QRS (Time Interval of ECG) change from patient baseline over all post-dose time points
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End point description:

Peak QRS change from patient baseline over all post-dose time points (5min, 10min, 25min and 50min)

End point type	Secondary
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End point timeframe:

40 min pre-dose and at 5 min, 10 min, 25 min and 50 min post-dose

End point values	Placebo	Tio+Olo 5/5µg FDC	Tiotropium 5µg + Olodaterol 5µg FC	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	52 ^[57]	52 ^[58]	52 ^[59]	
Units: ms				
arithmetic mean (standard deviation)	0.6 (± 1.5)	0.9 (± 1.5)	1 (± 1.3)	

Notes:

[57] - Treated set (observed cases)

[58] - Treated set (observed cases)

[59] - Treated set (observed cases)

Statistical analyses

No statistical analyses for this end point

Secondary: QRS at individual post-dose time pointsQRS change from patient baseline at individual post-dose time points

End point title	QRS at individual post-dose time pointsQRS change from patient baseline at individual post-dose time points
End point description:	
QRS change from patient baseline at individual post-dose time points	
End point type	Secondary
End point timeframe:	
40 min pre-dose and at 5 min, 10 min, 25 min and 50 min post-dose	

End point values	Placebo	Tio+Olo 5/5µg FDC	Tiotropium 5µg + Olodaterol 5µg FC	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	52 ^[60]	52 ^[61]	52 ^[62]	
Units: ms				
arithmetic mean (standard deviation)				
5 min	-0.3 (± 1.5)	-0.2 (± 1.8)	0 (± 1.6)	
10 min	-0.3 (± 1.6)	0.1 (± 1.6)	0.1 (± 1.6)	
25 min	-0.3 (± 1.4)	0.1 (± 1.6)	0 (± 1.4)	
50 min	-0.4 (± 1.7)	0.2 (± 1.7)	0.2 (± 1.6)	

Notes:

[60] - Treated set (observed cases)

[61] - Treated set (observed cases)

[62] - Treated set (observed cases)

Statistical analyses

No statistical analyses for this end point

Secondary: Heart Rate Change From Patient Baseline at Individual Postdose Time Points

End point title	Heart Rate Change From Patient Baseline at Individual Postdose Time Points
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End point description:

Heart rate change from patient baseline at individual postdose time points

End point type	Secondary
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End point timeframe:

40 min pre-dose and at 5 min, 10 min, 25 min and 50 min post-dose

End point values	Placebo	Tio+Olo 5/5µg FDC	Tiotropium 5µg + Olodaterol 5µg FC	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	52 ^[63]	52 ^[64]	52 ^[65]	
Units: bpm				
arithmetic mean (standard deviation)				
5 min	-2.3 (± 5.2)	-2.5 (± 5.5)	-2.9 (± 4.6)	
10 min	-2.7 (± 5.9)	-2.4 (± 5.5)	-3.1 (± 4.6)	
25 min	-3.1 (± 5.5)	-2.6 (± 6)	-4.5 (± 5)	
50 min	-4.1 (± 5.6)	-2.4 (± 6)	-3.9 (± 4.7)	

Notes:

[63] - Treated set (observed cases)

[64] - Treated set (observed cases)

[65] - Treated set (observed cases)

Statistical analyses

No statistical analyses for this end point

Adverse events

Adverse events information

Timeframe for reporting adverse events:

Adverse events (AEs) occurring up to the minimum of 21 days after drug stop date or the start of the next treatment period were considered on treatment; Up to 64 days.

Assessment type	Systematic
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Dictionary used

Dictionary name	MedDRA
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Dictionary version	17.0
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Reporting groups

Reporting group title	Placebo
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Reporting group description:

Single test dose of oral inhalation of Placebo via RESPIMAT inhaler.

2 inhalations a.m. dosing.

Reporting group title	Tiotropium 5µg + Olodaterol 5µg FC
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Reporting group description:

Single test dose of oral inhalation of tiotropium (5 µg) and olodaterol (5 µg) free combination (FC)

(Tio/Olo free combination) Olodaterol: 5 µg

(2.5 µg per actuation) Tiotropium: 5 µg (2.5 µg per actuation)

2 inhalations a.m. dosing via RESPIMAT® inhaler

Reporting group title	Tio+Olo 5/5µg FDC
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Reporting group description:

Single test dose of oral inhalation of Tio+Olo FDC (fixed dose combination) (5/5 µg) inhalation solution as fixed dose inhalation solution

(Tio+Olo FDC) 2.5 µg each per actuation via RESPIMAT® inhaler.

2 inhalations a.m. dosing.

Serious adverse events	Placebo	Tiotropium 5µg + Olodaterol 5µg FC	Tio+Olo 5/5µg FDC
Total subjects affected by serious adverse events			
subjects affected / exposed	0 / 53 (0.00%)	2 / 52 (3.85%)	0 / 52 (0.00%)
number of deaths (all causes)	0	0	0
number of deaths resulting from adverse events	0	0	0
Cardiac disorders			
Prinzmetal angina			
subjects affected / exposed	0 / 53 (0.00%)	1 / 52 (1.92%)	0 / 52 (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
Reproductive system and breast disorders			
Cystocele			
subjects affected / exposed	0 / 53 (0.00%)	1 / 52 (1.92%)	0 / 52 (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	Tiotropium 5µg + Olodaterol 5µg FC	Tio+Olo 5/5µg FDC
Total subjects affected by non-serious adverse events			
subjects affected / exposed	3 / 53 (5.66%)	2 / 52 (3.85%)	1 / 52 (1.92%)
Infections and infestations			
Nasopharyngitis			
subjects affected / exposed	3 / 53 (5.66%)	2 / 52 (3.85%)	1 / 52 (1.92%)
occurrences (all)	3	2	1

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? No

Interruptions (globally)

Were there any global interruptions to the trial? No

Limitations and caveats

None reported