Clinical trial results:
Efficacy and safety of 2 doses of tiotropium via respimat in adult patients with mild persistent asthma

Summary

EudraCT number	2010-023112-14
Trial protocol	LV HU EE SK AT IT PL
Global end of trial date	19 April 2012

Results information

Result version number	v1 (current)
This version publication date	20 June 2016
First version publication date	17 April 2015

Trial information

Trial identification

Sponsor protocol code	205.442

Additional study identifiers

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

Notes:

Sponsors

Sponsor organisation name	Boehringer Ingelheim Pharma GmbH & Co. KG
Sponsor organisation address	Binger Strasse 173 , Ingelheim am Rhein , Germany, 55216
Public contact	QRPE Processes and Systems Coordination Clinical Trial Information Disclosure , Boehringer Ingelheim Pharma GmbH & Co. KG, +1 800 243 0127, clintriage.rdg@boehringer-ingelheim.com
Scientific contact	QRPE Processes and Systems Coordination Clinical Trial Information Disclosure , Boehringer Ingelheim Pharma GmbH & Co. KG, +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	05 May 2012
Is this the analysis of the primary completion data?	Yes
Primary completion date	19 April 2012
Global end of trial reached?	Yes
Global end of trial date	19 April 2012
Was the trial ended prematurely?	No

Notes:

General information about the trial

Main objective of the trial:

To investigate the efficacy and safety of 2 doses pf tiotropium inhalation solution in comparison to placebo delivered by respimat inhaler in adult patients with uncontrolled, mild, persistent asthma.

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.

Background therapy:

Low-dose inhaled corticosteroid

Evidence for comparator: -

Actual start date of recruitment	31 March 2011
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	Argentina: 22
Country: Number of subjects enrolled	Austria: 40
Country: Number of subjects enrolled	Croatia: 37
Country: Number of subjects enrolled	Estonia: 21
Country: Number of subjects enrolled	Guatemala: 66
Country: Number of subjects enrolled	Hungary: 120
Country: Number of subjects enrolled	India: 95
Country: Number of subjects enrolled	Italy: 16
Country: Number of subjects enrolled	Korea, Democratic People's Republic of: 57
Country: Number of subjects enrolled	Latvia: 58
Country: Number of subjects enrolled	Poland: 50
Country: Number of subjects enrolled	Slovakia: 104
Worldwide total number of subjects	686
EEA total number of subjects	446

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)	653
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 had to meet all inclusion/exclusion criteria. Subjects were not randomised to trial treatment if any one of the specific entry criteria were violated. Rescue medication, open-label salbutamol/albuterol was administered as needed.

Period 1

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

Arms

Are arms mutually exclusive?	Yes
Arm title	Placebo

Arm description:

Patients treated with matching placebo. One patient was randomised to placebo but not treated.

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:

Oral inhalation via the Respimat inhaler once daily in the evening

Arm title	Tio R2.5

Arm description:

Patients treated with tiotropium inhalation solution 2.5 micrograms qd.

Arm type	Experimental
Investigational medicinal product name	Tiotropium 2.5 micrograms
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Inhalation solution
Routes of administration	Inhalation use

Dosage and administration details:

Patients treated with tiotropium inhalation solution 2.5 microgram once daily in the evening

Arm title	Tio R5

Arm description:

Patients treated with tiotropium inhalation solution 5 micrograms qd.

Arm type	Experimental
Investigational medicinal product name	Tiotropium 5 micrograms
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Inhalation solution
Routes of administration	Inhalation use

Dosage and administration details:

Patients treated with tiotropium inhalation solution 5 microgram once daily in the evening

Number of subjects in period 1[1]	Placebo	Tio R2.5	Tio R5
Started	155	154	155
Completed	154	149	152
Not completed	1	5	3
Consent withdrawn by subject	1	2	-
Adverse event, non-fatal	-	2	1
Reasons other than listed above	-	1	1
Protocol deviation	-	-	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 of the trial medication.

Baseline characteristics

Reporting groups	
Reporting group title	Placebo
Reporting group description:	
Patients treated with matching placebo. One patient was randomised to placebo but not treated.	
Reporting group title	Tio R2.5
Reporting group description:	
Patients treated with tiotropium inhalation solution 2.5 micrograms qd.	
Reporting group title	Tio R5
Reporting group description:	
Patients treated with tiotropium inhalation solution 5 micrograms qd.	

Reporting group values	Placebo	Tio R2.5	Tio R5
Number of subjects	155	154	155
Age categorical Units: Subjects			
Age Continuous | Units: Years arithmetic mean standard deviation	 42.8 ± 12.1	 43.8 ± 14	 41.9 ± 13
Gender, Male/Female Units: Participants			
Female	103	82	96
Male	52	72	59

Reporting group values	Total		
Number of subjects	464		
Age categorical Units: Subjects			
Age Continuous | Units: Years arithmetic mean standard deviation	 -		
Gender, Male/Female Units: Participants			
Female	281		
Male	183		

End points

End points reporting groups

Reporting group title	Placebo
Reporting group description:	
Patients treated with matching placebo. One patient was randomised to placebo but not treated.	
Reporting group title	Tio R2.5
Reporting group description:	
Patients treated with tiotropium inhalation solution 2.5 micrograms qd.	
Reporting group title	Tio R5
Reporting group description:	
Patients treated with tiotropium inhalation solution 5 micrograms qd.	

Primary: Peak Forced Expiratory Volume in 1 second (FEV1) response within 3 hours post dosing (0-3h) after a treatment period of 12 weeks.

End point title	Peak Forced Expiratory Volume in 1 second (FEV1) response within 3 hours post dosing (0-3h) after a treatment period of 12 weeks.

End point description:

Peak FEV1 0-3h response was defined as the difference between the maximum FEV1 measured within the first 3 hours post dosing after a treatment period of 12 weeks and the FEV1 baseline measurement (10 minutes before the first dose of trial medication). Mixed Model Repeated Measure (MMRM) results. Means are adjusted for treatment, pooled centre, visit, baseline, treatment*visit and baseline*visit.

FAS= Full analysis set that is defined as all patients in the treated set who received at least one dose of randomised trial medication.

End point type	Primary

End point timeframe:

Baseline and 12 weeks

End point values	Placebo	Tio R2.5	Tio R5	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	154[1]	151[2]	152[3]	
Units: Liter				
least squares mean (standard error)	0.134 (± 0.026)	0.293 (± 0.026)	0.262 (± 0.026)	

Notes:

[1] - FAS- only patients with endpoint values at week 12 were analysed

[2] - FAS- only patients with endpoint values at week 12 were analysed

[3] - FAS- only patients with endpoint values at week 12 were analysed

Statistical analyses

Statistical analysis title	Statistical Analysis 1

Statistical analysis description:

Restricted maximum likelihood (REML)- based repeated measures model was used. Means are adjusted for treatment, pooled centre, visit, baseline, treatment*visit and baseline*visit.

Differences calculated as Tio R5- Placebo

Comparison groups	Placebo v Tio R5
Number of subjects included in analysis	306
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.0005 [4]
Method	Mixed models analysis
Parameter estimate	Mean difference (net)
Point estimate	0.128
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.057
upper limit	0.199
Variability estimate	Standard error of the mean
Dispersion value	0.036

Notes:

[4] - Step-wise testing for the two treatment groups for the primary endpoint, confirmatory only if previous hypotheses had been successful, significance level of alpha=0.025 (one-sided) for primary endpoint.

Statistical analysis title	Statistical Analysis 2

Statistical analysis description:

Restricted maximum likelihood (REML)- based repeated measures model was used. Means are adjusted for treatment, pooled centre, visit, baseline, treatment*visit and baseline*visit.

Differences calculated as Tio R2.5- Placebo

Comparison groups	Placebo v Tio R2.5
Number of subjects included in analysis	305
Analysis specification	Pre-specified
Analysis type	superiority
P-value	< 0.0001 [5]
Method	Mixed models analysis
Parameter estimate	Mean difference (net)
Point estimate	0.159
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.088
upper limit	0.23
Variability estimate	Standard error of the mean
Dispersion value	0.036

Notes:

[5] - Step-wise testing for the two treatment groups for the primary endpoint, confirmatory only if previous hypotheses had been successful, significance level of alpha=0.025 (one-sided) for the primary endpoint.

Secondary: Trough FEV1 response determined after a treatment period of 12 weeks.

End point title	Trough FEV1 response determined after a treatment period of 12 weeks.

End point description:

The trough FEV1 is defined as the pre-dose FEV1 measured 10 minutes before the last administration of randomised treatment. Trough FEV1 response was defined as the difference between the trough FEV1 measured after a treatment period of 12 weeks and the trough FEV1 baseline measurement. MMRM results. Means are adjusted for treatment, pooled centre, visit, baseline, treatment*visit and baseline*visit.

End point type	Secondary

End point timeframe:

Baseline and 12 weeks

End point values	Placebo	Tio R2.5	Tio R5	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	154[6]	151[7]	152[8]	
Units: Liter				
least squares mean (standard error)	0.015 (± 0.026)	0.125 (± 0.026)	0.137 (± 0.027)	

Notes:

[6] - FAS- only patients with endpoint values at week 12 were analysed

[7] - FAS- only patients with endpoint values at week 12 were analysed

[8] - FAS- only patients with endpoint values at week 12 were analysed

Statistical analyses

Statistical analysis title	Statistical Analysis 1

Statistical analysis description:

Restricted maximum likelihood (REML)- based repeated measures model was used. Means are adjusted for treatment, pooled centre, visit, baseline, treatment*visit and baseline*visit.

Differences calculated as Tio R5- Placebo

Comparison groups	Placebo v Tio R5
Number of subjects included in analysis	306
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.001 [9]
Method	Mixed models analysis
Parameter estimate	Mean difference (net)
Point estimate	0.122
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.049
upper limit	0.194
Variability estimate	Standard error of the mean
Dispersion value	0.037

Notes:

[9] - p-values serve an exploratory function only

Statistical analysis title	Statistical Analysis 2

Statistical analysis description:

Restricted maximum likelihood (REML)- based repeated measures model was used. Means are adjusted for treatment, pooled centre, visit, baseline, treatment*visit and baseline*visit.

Differences calculated as Tio R2.5- Placebo

Comparison groups	Placebo v Tio R2.5

Number of subjects included in analysis	305
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.0028 [10]
Method	Mixed models analysis
Parameter estimate	Mean difference (net)
Point estimate	0.11
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.038
upper limit	0.182
Variability estimate	Standard error of the mean
Dispersion value	0.037

Notes:

[10] - p-values serve an exploratory function only

Secondary: Peak (within 3 hours post-dosing) Forced Vital Capacity (FVC) response at the end of the 12-week treatment period.

End point title	Peak (within 3 hours post-dosing) Forced Vital Capacity (FVC) response at the end of the 12-week treatment period.

End point description:

Peak FVC 0-3h response was defined as the difference between the maximum FVC measured within the first 3 hours post dosing after a treatment period of 12 weeks and the FVC baseline measurement (10 minutes before the first dose of trial medication). Mixed Model Repeated Measure (MMRM) results. Means are adjusted for treatment, pooled centre, visit, baseline, treatment*visit and baseline*visit.

End point type	Secondary

End point timeframe:

Baseline and 12 weeks

End point values	Placebo	Tio R2.5	Tio R5	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	154[11]	151[12]	152[13]	
Units: Liter				
least squares mean (standard error)	0.126 (± 0.03)	0.231 (± 0.03)	0.183 (± 0.03)	

Notes:

[11] - FAS- only patients with endpoint values at week 12 were analysed

[12] - FAS- only patients with endpoint values at week 12 were analysed

[13] - FAS- only patients with endpoint values at week 12 were analysed

Statistical analyses

Statistical analysis title	Statistical Analysis 1

Statistical analysis description:

Restricted maximum likelihood (REML)- based repeated measures model was used. Means are adjusted for treatment, pooled centre, visit, baseline, treatment*visit and baseline*visit.

Differences calculated as Tio R5- Placebo

Comparison groups	Placebo v Tio R5

Number of subjects included in analysis	306
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.1714 [14]
Method	Mixed models analysis
Parameter estimate	Mean difference (net)
Point estimate	0.057
Confidence interval	
level	95 %
sides	2-sided
lower limit	-0.025
upper limit	0.14
Variability estimate	Standard error of the mean
Dispersion value	0.042

Notes:

[14] - p-values serve an exploratory function only

Statistical analysis title	Statistical Analysis 2

Statistical analysis description:

Restricted maximum likelihood (REML)- based repeated measures model was used. Means are adjusted for treatment, pooled centre, visit, baseline, treatment*visit and baseline*visit.

Differences calculated as Tio R2.5- Placebo

Comparison groups	Placebo v Tio R2.5
Number of subjects included in analysis	305
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.0119 [15]
Method	Mixed models analysis
Parameter estimate	Mean difference (net)
Point estimate	0.106
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.023
upper limit	0.188
Variability estimate	Standard error of the mean
Dispersion value	0.042

Notes:

[15] - p-values serve an exploratory function only

Secondary: FEV1 Area Under the Curve (AUC0-3h) response at the end of the 12-week treatment period.

End point title	FEV1 Area Under the Curve (AUC0-3h) response at the end of the 12-week treatment period.

End point description:

The AUC0-3h was calculated as area under the curve from zero to 3 hours using the trapezoidal rule divided by the observation time (3 hours) to report in litres. The trough value was assigned to zero time. Response was defined as change from baseline in FEV1 AUC0-3h after a treatment period of 12 weeks. MMRM results. Means are adjusted for treatment, pooled centre, visit, baseline, treatment*visit baseline*visit.

End point type	Secondary

End point timeframe:

Baseline and 12 weeks

End point values	Placebo	Tio R2.5	Tio R5	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	154[16]	151[17]	152[18]	
Units: Liter				
least squares mean (standard error)	0.048 (± 0.024)	0.198 (± 0.024)	0.174 (± 0.025)	

Notes:

[16] - FAS- only patients with endpoint values at week 12 were analysed

[17] - FAS-only patients with endpoint values at week 12 were analysed

[18] - FAS- only patients with endpoint values at week 12 were analysed

Statistical analyses

Statistical analysis title	Statistical Analysis 1

Statistical analysis description:

Restricted maximum likelihood (REML)- based repeated measures model was used. Means are adjusted for treatment, pooled centre, visit, baseline, treatment*visit and baseline*visit.

Differences calculated as Tio R5- Placebo

Comparison groups	Placebo v Tio R5
Number of subjects included in analysis	306
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.0003 [19]
Method	Mixed models analysis
Parameter estimate	Mean difference (net)
Point estimate	0.125
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.058
upper limit	0.192
Variability estimate	Standard error of the mean
Dispersion value	0.034

Notes:

[19] - p-values serve an exploratory function only

Statistical analysis title	Statistical Analysis 2

Statistical analysis description:

Restricted maximum likelihood (REML)- based repeated measures model was used. Means are adjusted for treatment, pooled centre, visit, baseline, treatment*visit and baseline*visit.

Differences calculated as Tio R2.5- Placebo

Comparison groups	Placebo v Tio R2.5

Number of subjects included in analysis	305
Analysis specification	Pre-specified
Analysis type	superiority
P-value	< 0.0001 [20]
Method	Mixed models analysis
Parameter estimate	Median difference (net)
Point estimate	0.149
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.082
upper limit	0.216
Variability estimate	Standard error of the mean
Dispersion value	0.034

Notes:

[20] - p-values serve an exploratory function only

Secondary: FVC (AUC0-3h) response at the end of the 12-week treatment period.

End point title	FVC (AUC0-3h) response at the end of the 12-week treatment period.

End point description:

The AUC0-3h was calculated as area under the curve from zero to 3 hours using the trapezoidal rule divided by the observation time (3 hours) to report in litres. The trough value was assigned to zero time. Response was defined as change from baseline in FVC AUC0-3h after a treatment period of 12 weeks. MMRM results. Means are adjusted for treatment, pooled centre, visit, baseline, treatment*visit baseline*visit.

End point type	Secondary

End point timeframe:

Baseline and 12 weeks

End point values	Placebo	Tio R2.5	Tio R5	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	154[21]	151[22]	152[23]	
Units: Liter				
least squares mean (standard error)	0 (± 0.028)	0.101 (± 0.028)	0.061 (± 0.028)	

Notes:

[21] - FAS-only patients with endpoint values at week 12 were analysed

[22] - FAS-only patients with endpoint values at week 12 were analysed

[23] - FAS- only patients with endpoint values at week 12 were analysed

Statistical analyses

Statistical analysis title	Statistical Analysis 1

Statistical analysis description:

Restricted maximum likelihood (REML)- based repeated measures model was used. Means are adjusted for treatment, pooled centre, visit, baseline, treatment*visit and baseline*visit.

Differences calculated as Tio R5- Placebo

Comparison groups	Placebo v Tio R5

Number of subjects included in analysis	306
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.1182 [24]
Method	Mixed models analysis
Parameter estimate	Mean difference (net)
Point estimate	0.061
Confidence interval	
level	95 %
sides	2-sided
lower limit	-0.016
upper limit	0.138
Variability estimate	Standard error of the mean
Dispersion value	0.039

Notes:

[24] - p-values serve an exploratory function only

Statistical analysis title	Statistical Analysis 2

Statistical analysis description:

Restricted maximum likelihood (REML)- based repeated measures model was used. Means are adjusted for treatment, pooled centre, visit, baseline, treatment*visit and baseline*visit.

Differences calculated as Tio R2.5- Placebo

Comparison groups	Placebo v Tio R2.5
Number of subjects included in analysis	305
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.0102 [25]
Method	Mixed models analysis
Parameter estimate	Mean difference (net)
Point estimate	0.101
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.024
upper limit	0.178
Variability estimate	Standard error of the mean
Dispersion value	0.039

Notes:

[25] - p-values serve an exploratory function only

Secondary: Asthma Control Questionnaire (ACQ) responder after 12 weeks of treatment

End point title	Asthma Control Questionnaire (ACQ) responder after 12 weeks of treatment

End point description:

For the ACQ, the total score was calculated as the mean of the responses to 6 self administered questions and one question which was completed by clinical staff based upon pre-bronchodilator FEV1. The score ranges from 0 (no impairment) to 6 (maximum impairment). Response was categorised as: responder (change from baseline <= -0.5), no change (-0.5 <change from baseline < 0.5) and worsening (change from baseline >= 0.5).

End point type	Secondary

End point timeframe:

12 weeks

End point values	Placebo	Tio R2.5	Tio R5	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	154[26]	149[27]	152[28]	
Units: Number of patients				
Responder	91	91	90	
No change	61	48	57	
Worsening	2	10	5	

Notes:

[26] - FAS- only patients with endpoint values at week 12 were analysed

[27] - FAS-only patients with endpoint values at week 12 were analysed

[28] - FAS- only patients with endpoint values at week 12 were analysed

Statistical analyses

No statistical analyses for this end point

Secondary: Time to first severe asthma exacerbation during the 12-week treatment.

End point title	Time to first severe asthma exacerbation during the 12-week treatment.

End point description:

Severe asthma exacerbations are defined as all asthma exacerbations that required treatment with systemic (including oral) corticosteroids for at least 3 days.

Since only 4 of the 155 patients in the placebo group, 6 of the 154 patients in the Tio R2.5 group and 1 in the Tio R5 group had severe exacerbations, the median times were not calculable (99999)

End point type	Secondary

End point timeframe:

12 weeks

End point values	Placebo	Tio R2.5	Tio R5	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	155[29]	154[30]	155[31]	
Units: Days				
median (inter-quartile range (Q1-Q3))	99999 (99999 to 99999)	99999 (99999 to 99999)	99999 (99999 to 99999)	

Notes:

[29] - FAS-only patients with endpoint values at week 12 were analysed

[30] - FAS-only patients with endpoint values at week 12 were analysed

[31] - FAS- only patients with endpoint values at week 12 were analysed

Statistical analyses

Statistical analysis title	Statistical Analysis 1

Statistical analysis description:

Since the percent patients with event is less than 50% the median is not calculable, but Hazard Ratio is

still estimable from the Cox model. Parameter estimates of Cox proportional hazard model with only treatment fitted as an effect in the model.

Hazard Ratio (HR) below 1 favors tiotropium.

Comparison groups	Placebo v Tio R5
Number of subjects included in analysis	310
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.2155 [32]
Method	Regression, Cox
Parameter estimate	Hazard ratio (HR)
Point estimate	0.25
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.03
upper limit	2.24

Notes:

[32] - Significance level of alpha=0.05 (two-sided). P-values serve an exploratory function only.

Statistical analysis title	Statistical Analysis 2

Statistical analysis description:

Since the percent patients with event is less than 50% the median is not calculable, but Hazard Ratio is still estimable from the Cox model. Parameter estimates of Cox proportional hazard model with only treatment fitted as an effect in the model.

Hazard Ratio (HR) below 1 favors tiotropium.

Comparison groups	Placebo v Tio R2.5
Number of subjects included in analysis	309
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.5071 [33]
Method	Regression, Cox
Parameter estimate	Hazard ratio (HR)
Point estimate	1.53
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.43
upper limit	5.44

Notes:

[33] - Significance level of alpha=0.05 (two-sided). P-values serve an exploratory function only.

Secondary: Time to first asthma exacerbation during the 12-week treatment.

End point title	Time to first asthma exacerbation during the 12-week treatment.

End point description:

An asthma exacerbation was defined as an episode of progressive increase in 1 or more asthma symptom that were outside the patient's usual range of day-to-day asthma symptoms and lasted for at least 2 consecutive days or as a decrease in a patient's best morning PEF of 30% or more from a patient's mean morning PEF for at least 2 consecutive days that may or may not have been accompanied by symptoms.

Since 22 of the 155 patients in the placebo group, 21 of the 154 patients in Toio R2.5 group and 13 of the 155 patients in the Tio R5 group reported at least one asthma exacerbation, the median times were

not calculable (99999)

End point type	Secondary

End point timeframe:

12 weeks

End point values	Placebo	Tio R2.5	Tio R5	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	155[34]	154[35]	155[36]	
Units: Days				
median (inter-quartile range (Q1-Q3))	99999 (87 to 99999)	99999 (99999 to 99999)	99999 (99999 to 99999)	

Notes:

[34] - FAS-only patients with endpoint values at week 12 were analysed

[35] - FAS-only patients with endpoint values at week 12 were analysed

[36] - FAS-only patients with endpoint values at week 12 were analysed

Statistical analyses

Statistical analysis title	Statistical Analysis 1

Statistical analysis description:

Since only 22 of the 155 patients in the placebo group, 21 of the 154 patients in the Tio R2.5 group and 13 of the 155 patients in the Tio R5 group had asthma exacerbations, the median times were not calculable (99999). The Hazard Ratio is still estimable from the Cox model.

Hazard Ratio (HR) below 1 favors tiotropium.

Comparison groups	Placebo v Tio R2.5
Number of subjects included in analysis	309
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.8974 [37]
Method	Regression, Cox
Parameter estimate	Hazard ratio (HR)
Point estimate	0.96
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.53
upper limit	1.75

Notes:

[37] - Significance level of alpha=0.05 (two-sided). P-values serve an exploratory function only.

Statistical analysis title	Statistical Analysis 2

Statistical analysis description:

Since only 22 of the 155 patients in the placebo group, 21 of the 154 patients in the Tio R2.5 group and 13 of the 155 patients in the Tio R5 group had asthma exacerbations, the median times were not calculable (99999)

Hazard Ratio (HR) below 1 favors tiotropium.

Comparison groups	Placebo v Tio R5

Number of subjects included in analysis	310
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.1217 [38]
Method	Regression, Cox
Parameter estimate	Hazard ratio (HR)
Point estimate	0.58
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.29
upper limit	1.16

Notes:

[38] - Significance level of alpha=0.05 (two-sided). P-values serve an exploratory function only.

Secondary: Use of rescue medication during 24h period

End point title	Use of rescue medication during 24h period

End point description:

Use of PRN (pro re nata, or as necessary) salbutamol/albuterol rescue medication (puffs during 24 h period), determined as a weekly mean response from baseline for each week during the treatment period as well as for the last 7 days before treatment stop/Visit 5.

The mean was adjusted for treatment, centre, week, baseline, treatment*week and baseline*week.

End point type	Secondary

End point timeframe:

baseline and 12 weeks

End point values	Placebo	Tio R2.5	Tio R5	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	153[39]	150[40]	152[41]	
Units: puffs of rescue medication				
arithmetic mean (standard error)	-0.815 (± 0.093)	-0.594 (± 0.093)	-0.848 (± 0.093)	

Notes:

[39] - FAS-only patients with endpoint values at week 12 were analysed

[40] - FAS-only patients with endpoint values at week 12 were analysed

[41] - FAS-only patients with endpoint values at week 12 were analysed

Statistical analyses

Statistical analysis title	Statistical Analysis 1

Statistical analysis description:

Restricted maximum likelihood (REML)- based repeated measures model was used. Means are adjusted for treatment, centre, week, baseline, treatment*week and baseline*week.

Differences calculated as Tio R2.5- Placebo

Comparison groups	Tio R2.5 v Placebo

Number of subjects included in analysis	303
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.0872 [42]
Method	Mixed models analysis
Parameter estimate	Mean difference (net)
Point estimate	0.222
Confidence interval	
level	95 %
sides	2-sided
lower limit	-0.032
upper limit	0.476
Variability estimate	Standard error of the mean
Dispersion value	0.129

Notes:

[42] - p-values serve an exploratory function only

Statistical analysis title	Statistical Analysis 2

Statistical analysis description:

Restricted maximum likelihood (REML)- based repeated measures model was used. Means are adjusted for treatment, centre, week, baseline, treatment*week and baseline*week.

Differences calculated as Tio R5- Placebo

Comparison groups	Tio R5 v Placebo
Number of subjects included in analysis	305
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.7995 [43]
Method	Mixed models analysis
Parameter estimate	Mean difference (net)
Point estimate	-0.033
Confidence interval	
level	95 %
sides	2-sided
lower limit	-0.287
upper limit	0.221
Variability estimate	Standard error of the mean
Dispersion value	0.129

Notes:

[43] - p-values serve an exploratory function only

Secondary: Use of rescue medication during daytime

End point title	Use of rescue medication during daytime

End point description:

Use of PRN (pro re nata, or as necessary) salbutamol/albuterol rescue medication (puffs during daytime), determined as a weekly mean response from baseline for each week during the treatment period as well as for the last 7 days before treatment stop/Visit 5.

The mean was adjusted for treatment, centre, week, baseline, treatment*week and baseline*week.

End point type	Secondary

End point timeframe:

baseline and 12 weeks

End point values	Placebo	Tio R2.5	Tio R5	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	153[44]	149[45]	152[46]	
Units: puffs of rescue medication				
arithmetic mean (standard error)	-0.428 (± 0.055)	-0.331 (± 0.055)	-0.436 (± 0.055)	

Notes:

[44] - FAS-only patients with endpoint values at week 12 were analysed

[45] - FAS-only patients with endpoint values at week 12 were analysed

[46] - FAS-only patients with endpoint values at week 12 were analysed

Statistical analyses

Statistical analysis title	Statistical Analysis 1

Statistical analysis description:

Restricted maximum likelihood (REML)- based repeated measures model was used. Means are adjusted for treatment, centre, week, baseline, treatment*week and baseline*week.

Differences calculated as Tio R2.5- Placebo

Comparison groups	Tio R2.5 v Placebo
Number of subjects included in analysis	302
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.2038 [47]
Method	Mixed models analysis
Parameter estimate	Mean difference (net)
Point estimate	0.097
Confidence interval	
level	95 %
sides	2-sided
lower limit	-0.053
upper limit	0.247
Variability estimate	Standard error of the mean
Dispersion value	0.076

Notes:

[47] - p-values serve an exploratory function only

Statistical analysis title	Statistical Analysis 2

Statistical analysis description:

Restricted maximum likelihood (REML)- based repeated measures model was used. Means are adjusted for treatment, centre, week, baseline, treatment*week and baseline*week.

Differences calculated as Tio R5- Placebo

Comparison groups	Tio R5 v Placebo

Number of subjects included in analysis	305
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.9104 [48]
Method	Mixed models analysis
Parameter estimate	Mean difference (net)
Point estimate	-0.009
Confidence interval	
level	95 %
sides	2-sided
lower limit	-0.158
upper limit	0.141
Variability estimate	Standard error of the mean
Dispersion value	0.076

Notes:

[48] - p-values serve an exploratory function only

Secondary: Use of rescue medication during nighttime

End point title	Use of rescue medication during nighttime

End point description:

Use of PRN (pro re nata, or as necessary) salbutamol/albuterol rescue medication (puffs during nighttime), determined as a weekly mean response from baseline for each week during the treatment period as well as for the last 7 days before treatment stop/Visit 5.

The mean was adjusted for treatment, centre, week, baseline, treatment*week and baseline*week.

End point type	Secondary

End point timeframe:

baseline and 12 weeks

End point values	Placebo	Tio R2.5	Tio R5	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	152[49]	150[50]	152[51]	
Units: puffs of rescue medication				
arithmetic mean (standard error)	-0.376 (± 0.049)	-0.245 (± 0.049)	-0.386 (± 0.049)	

Notes:

[49] - FAS-only patients with endpoint values at week 12 were analysed

[50] - FAS-only patients with endpoint values at week 12 were analysed

[51] - FAS-only patients with endpoint values at week 12 were analysed

Statistical analyses

Statistical analysis title	Statistical Analysis 1

Statistical analysis description:

Restricted maximum likelihood (REML)- based repeated measures model was used. Means are adjusted for treatment, centre, week, baseline, treatment*week and baseline*week.

Differences calculated as Tio R2.5- Placebo

Comparison groups	Tio R2.5 v Placebo

Number of subjects included in analysis	302
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.0559 [52]
Method	Mixed models analysis
Parameter estimate	Mean difference (net)
Point estimate	0.131
Confidence interval	
level	95 %
sides	2-sided
lower limit	-0.003
upper limit	0.265
Variability estimate	Standard error of the mean
Dispersion value	0.068

Notes:

[52] - p-values serve an exploratory function only

Statistical analysis title	Statistical Analysis 2

Statistical analysis description:

Restricted maximum likelihood (REML)- based repeated measures model was used. Means are adjusted for treatment, centre, week, baseline, treatment*week and baseline*week.

Differences calculated as Tio R5- Placebo

Comparison groups	Tio R5 v Placebo
Number of subjects included in analysis	304
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.8795 [53]
Method	Mixed models analysis
Parameter estimate	Mean difference (net)
Point estimate	-0.01
Confidence interval	
level	95 %
sides	2-sided
lower limit	-0.144
upper limit	0.123
Variability estimate	Standard error of the mean
Dispersion value	0.068

Notes:

[53] - p-values serve an exploratory function only

Adverse events

Adverse events information	
Timeframe for reporting adverse events: From the first drug administration until 30 days after the last drug administration, up to 157 days	
Assessment type	Systematic

Dictionary used	
Dictionary name	MedDRA
Dictionary version	15.0

Reporting groups	
Reporting group title	Placebo
Reporting group description: Patients treated with matching placebo.	
Reporting group title	Tio R2.5
Reporting group description: Patients treated with tiotropium inhalation solution 2.5 micrograms qd.	
Reporting group title	Tio R5
Reporting group description: Patients treated with tiotropium inhalation solution 5 micrograms qd.	

Serious adverse events	Placebo	Tio R2.5	Tio R5
Total subjects affected by serious adverse events			
subjects affected / exposed	1 / 155 (0.65%)	0 / 154 (0.00%)	1 / 155 (0.65%)
number of deaths (all causes)	0	0	0
number of deaths resulting from adverse events	0	0	0
Neoplasms benign, malignant and unspecified (incl cysts and polyps)			
Breast cancer in situ			
subjects affected / exposed	0 / 155 (0.00%)	0 / 154 (0.00%)	1 / 155 (0.65%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Respiratory, thoracic and mediastinal disorders			
Asthma			
subjects affected / exposed	1 / 155 (0.65%)	0 / 154 (0.00%)	0 / 155 (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

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

Non-serious adverse events	Placebo	Tio R2.5	Tio R5
Total subjects affected by non-serious adverse events			
subjects affected / exposed	25 / 155 (16.13%)	30 / 154 (19.48%)	21 / 155 (13.55%)
Investigations			
Peak expiratory flow rate decreased			
subjects affected / exposed	6 / 155 (3.87%)	9 / 154 (5.84%)	6 / 155 (3.87%)
occurrences (all)	10	14	16
Respiratory, thoracic and mediastinal disorders			
Asthma			
subjects affected / exposed	19 / 155 (12.26%)	24 / 154 (15.58%)	17 / 155 (10.97%)
occurrences (all)	36	30	26

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