Boehringer Ingelheim

Clinical Study Synopsis for Public Disclosure

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Title of trial:	A randomised, active-controlled, double-blind, double-dummy, parallel group design, multi-center trial to compare the efficacy and safety of 2.5 µg and 5 µg Tiotropium Inhalation Solution delivered by the Respimat® Inhaler with Tiotropium inhalation capsules 18 µg delivered by the HandiHaler®
Principal/Coordinating Investigator:	[redacted]
Trial sites:	Multicenter study (1280 sites initiated in 50 countries)
Publication (reference):	1. Wise RA, Anzueto A, Calverley P, Dahl R, Dusser D, Pledger G, et al. The tiotropium safety and performance in Respimat® Trial (TIOSPIR®), a large scale, randomized, controlled, parallel-group trial-design and rationale. Respiratory Research 2013,14:40 (P13-04263). 2. Wise RA, Anzueto A, Cotton D, Dahl R, Devins T, Disse B, et al. Tiotropium Respimat inhaler and the risk of death in COPD. N Engl J Med. Epub 2013 Aug 30 (P13-11053). 3. Wise RA, Anzueto A, Calverley P, Dahl R, Dusser D, Pledger G, et al. Tiospir™: Large-scale trial of tiotropium Respimat® versus HandiHaler® in patients with COPD. 23rd Ann Cong of the European Respiratory Society (ERS), Barcelona, 7-11 Sep 2013 (Poster P-752) (P13-11326). 4. Wise RA, Anzueto A, Calverley P, Dahl R, Dusser D, Pledger G, et al. Tiospir™: Large scale trial of tiotropium Respimat® vs HandiHaler® (HH) in patients (pts) with COPD. 23rd Ann Cong of the European Respiratory Society (ERS), Barcelona, 7-11 Sep 2013 (abstract P752) (P13-11325).
Clinical phase:	IIIb
Objectives:	To compare the efficacy and safety of 2.5 µg and 5 µg tiotropium inhalation solution delivered by the Respimat® inhaler with tiotropium inhalation capsules 18 µg delivered by the HandiHaler®.
Methodology:	Randomized, active-controlled, double-blind, double-dummy, parallel group design, multi-center study.

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No. of subjects:	
planned:	entered: Approximately 16800 randomized (5600 per treatment group)
actual:	enrolled: 20313; entered/randomized: 17183; DAS: 17135; treated: 17116 Tiotropium Respimat® 2.5 µg (Tio R 2.5): entered: 5741 DAS: 5730 treated: 5724 Tiotropium Respimat® 5 µg (Tio R 5): entered: 5729 DAS: 5711 treated: 5705 Tiotropium HandiHaler® 18 µg (Tio HH 18): entered: 5713 DAS: 5694 treated: 5687 The primary analysis of time to death from any cause was based on all subjects included in the death analysis set (DAS). The primary analysis of time to first COPD exacerbation was based on all subjects included in the treated set (TS). A total of 1370 randomized subjects participated in the pulmonary function testing (PFT) substudy.
Diagnosis and main criteria for inclusion:	Chronic Obstructive Pulmonary Disease (COPD) Male and female outpatients with a diagnosis of COPD (post-bronchodilator forced expiratory volume in 1 second [FEV_1] ≤ 70%, predicted FEV_1/ forced vital capacity [FVC] ≤ 70%) aged 40 years or older and a smoking history of ≥ 10 pack years.
Test product:	Tiotropium inhalation solution, Respimat® inhaler
dose:	- 0 µg (two actuations of placebo) once daily for double-dummy design - 2.5 µg (two actuations of 1.25 µg) once daily - 5 µg (two actuations of 2.5 µg) once daily
mode of admin.:	Oral inhalation via the Respimat® inhaler
batch no.:	Refer to Appendix 16.1.6

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Reference therapy:	Tiotropium inhalation capsule, HandiHaler®
dose:	- 0 µg (two inhalations per capsule of placebo) once daily for double-dummy design - 18 µg (two inhalations per capsule) once daily
mode of admin.:	Oral inhalation via the HandiHaler®
batch no.:	Refer to Appendix 16.1.6
Duration of treatment:	The event-driven trial had a recruitment period of 11 months and was to end when approximately 1,266 fatal adverse events were reported. All subjects were to be followed for vital status, regardless of premature discontinuation of study medication, until study closeout. The actual number of deaths was 1302 and the actual duration of the trial was approximately 3 years. Vital status was confirmed for 99.7% of all eligible randomized subjects at the end of the trial.
Criteria for evaluation:	
Efficacy / clinical pharmacology:	Primary endpoints: The primary safety endpoint was time to death (all-cause mortality). The primary efficacy endpoint was time to first COPD exacerbation. Secondary efficacy endpoints: number of COPD exacerbations, time to first COPD exacerbation associated with hospitalization, number of COPD exacerbations associated with hospitalization, time to first moderate to severe COPD exacerbation. Further endpoint: number of moderate to severe COPD exacerbations. PFT sub-study: Spirometry endpoints were evaluated in a subset of 1370 subjects. Trough FEV_1 was defined as a key secondary endpoint within the sub-study (see Statistical Methods section of this synopsis).

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Safety:	The following AEs were collected: all fatal adverse events (FAEs), all serious adverse events (SAEs), all AEs leading to discontinuation of study medication, and all AEs considered by the investigator to be drug-related. The following other AEs were assessed as protocol-defined outcome events: all COPD exacerbations, all pneumonias, all myocardial infarctions (MIs), all strokes, and all transient ischemic attacks (TIAs). Other non-serious, non-related AEs were not routinely collected. Safety endpoints also included time to onset of first major adverse cardiovascular event (MACE), time to death from MACE, time to onset of first stroke, and time to onset of first MI. All deaths reported during the trial were adjudicated to one primary cause of death by an independent Mortality Adjudication Committee (MAC).
Statistical methods:	General: Cox proportional hazards regression model was used to analyze time-to-event endpoints. Analyses of numbers of events were performed using the negative binomial model using the natural log of treatment exposure as offset. A mixed model repeated measures (MMRM) analysis was used to analyze the spirometry endpoints within the sub-study. Kaplan-Meier plot estimation of the survival function and descriptive statistics were also used. Primary analyses: Three tests were conducted in hierarchical order. Non-inferiority of time to death from any cause was tested on the two Respimat doses (Tio R 5 first, followed by Tio R 2.5 if non-inferiority was achieved with Tio R 5) versus Tio HH 18. Additionally, if non-inferiority was also shown with Tio R 2.5, the Respimat dose of 5 µg (Tio R 5) was to be tested for superiority over Tio HH 18 for time to first COPD exacerbation. The non-inferiority delta for time to death was 1.25. Non-inferiority tests were performed at the one-sided $\alpha = 0.025$ level. Superiority tests were performed at the two-sided $\alpha = 0.05$ level.

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Statistical methods (continued):

PFT sub-study analyses: Trough FEV_1 was defined as a key secondary endpoint within the PFT sub-study. The sub-study had its own type I error, so the testing algorithm was performed independent of the hierarchical inferential strategy defined for the primary endpoints in the overall trial. The first test evaluated the main effect for treatment in the MMRM model, specifically the 95% CI for the contrast between Tio R 5 and Tio HH 18 was to be compared to the non-inferiority delta of 50 ml (0.050 L). If that test was successful, the second test evaluated the main effect for treatment in the MMRM model, specifically the 95% CI for the contrast between Tio R 2.5 and Tio HH 18 was compared to the non-inferiority delta of 50 ml.

Safety monitoring: An independent Data Monitoring Committee (DMC) regularly reviewed safety data to detect any relevant imbalance in safety endpoints, with the focus on all-cause mortality. Interim analyses generated for DMC review were partially unblinded with the option to completely unblind if needed. If at any time during the trial, the test for greater mortality of either Respimat dose relative to Tio HH 18 for the time to death endpoint reached $p < 0.01$, the DMC was to have considered modification of the study design.

SUMMARY – CONCLUSIONS:

Efficacy / clinical pharmacology results:

The efficacy results of this trial conclude that Tio R 5 and Tio R 2.5 have similar exacerbation efficacy as compared to Tio HH 18. In the spirometry substudy, Tio R 5 but not Tio R 2.5 demonstrated non-inferiority to Tio HH 18 for the endpoint trough FEV_1. These conclusions are supported by the following:

Second primary endpoint: Time to first COPD exacerbation (see Safety section for results of the first primary endpoint of time to death from any cause)

- The incidence of COPD exacerbations was 49.4% in the Tio R 2.5 group, 47.9% in the Tio R 5 group, and 48.9% in the Tio HH 18 group. The hazard ratio (HR) for time to first COPD exacerbation was 0.978 [95% CI: (0.928, 1.032); p=0.4194] for Tio R 5 versus Tio HH 18, i.e., at any point during the trial a subject in the Tio R 5 group had a 2.2% lower chance of experiencing a COPD exacerbation while on treatment compared to subjects in the Tio HH 18 group. The statistical

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comparison for superiority of Tio R 5 over Tio HH 18 was not achieved.

- The median time to first COPD exacerbation was longer in the Tio R 5 group compared to the Tio HH 18 group (756 days and 719 days, respectively). The Tio R 2.5 group had the shortest median time to first COPD exacerbation with 707 days.
- There were no meaningful differences between either Tio R 5 or Tio R 2.5 compared to Tio HH 18 in predefined subgroup analyses for time to first COPD exacerbation.

Secondary efficacy endpoints:

- The total number of COPD exacerbations was similar between treatment groups (Tio R 2.5: 6565; Tio R 5: 6425; and Tio HH 18: 6504). There were no significant differences between treatment groups in the rate ratios for either Tio R 5 versus Tio HH 18 [rate ratio = 0.99, 95% CI: (0.94, 1.05); p=0.8047] or Tio R 2.5 versus Tio HH 18 [rate ratio = 1.01, 95% CI: (0.95, 1.06); p=0.8330].
- The incidence of COPD exacerbations associated with hospitalization was 15.2% in the Tio R 2.5 group, 14.5% in the Tio R 5 group, and 14.3% in the Tio HH 18 group. There were no significant differences between treatment groups for either Tio R 5 versus Tio HH 18 [HR 1.024, 95% CI: (0.929, 1.128); p =0.6384] or Tio R 2.5 versus Tio HH 18 [HR 1.068, 95% CI: (0.971, 1.176); p=0.1762].
- The total number of COPD exacerbations associated with hospitalization was 1316 for Tio R 2.5, 1284 for Tio R 5, and 1216 for Tio HH 18. There were no significant differences between treatment groups in the rate ratios for either Tio R 5 versus Tio HH 18 [rate ratio = 1.06, 95% CI: (0.94, 1.18); p=0.3441] or Tio R 2.5 versus Tio HH 18 [rate ratio = 1.09, 95% CI: (0.98, 1.22); p=0.1255].
- Nearly all subjects (approximately 98%) who experienced at least one COPD exacerbation during the trial had an exacerbation defined as moderate to severe. Consistent with the primary analysis of time to first

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COPD exacerbation, there were no significant differences between treatment groups for either Tio R 5 versus Tio HH 18 [HR 0.983, 95% CI: (0.932, 1.037); p =0.5377] or Tio R 2.5 versus Tio HH 18 [HR 1.011, 95% CI: (0.959, 1.066); p =0.6823].

Among further comparisons between the two Respimat doses, Tio R 2.5 had a higher incidence of COPD exacerbations compared to Tio R 5. This observation also extends to the incidence of COPD exacerbations associated with hospitalization.

PFT sub-study (1370 subjects)

Key secondary endpoint within sub-study: Trough FEV_1

Pre-defined tests for non-inferiority (the sub-study had its own type I error) demonstrated that Tio R 5 is non-inferior to Tio HH 18 for average trough FEV_1 from Week 24 to 120. The test for non-inferiority for Tio R 2.5 vs. Tio HH 18 was not achieved:

- Adjusted mean trough FEV_1 over 120 weeks was 1.285 L for the Tio R 5 group and 1.295 L for the Tio HH 18 group. The adjusted difference between Tio R 5 and Tio HH 18 was -0.010 L (95% CI: -0.038 to 0.018). Because the lower bound of the CI was greater than the pre-defined non-inferiority delta of -50 mL (-0.050 L), it was demonstrated that Tio R 5 is non-inferior to Tio HH 18 for FEV_1.
- The Tio R 2.5 group also demonstrated improved FEV_1 (1.258 L). The adjusted difference between Tio R 2.5 and Tio HH 18 was -0.037 L (95% CI: -0.065 to -0.009). Because the lower bound of the CI was less than the pre-defined non-inferiority delta of -50 mL (-0.050 L), non-inferiority was not achieved. Further, the upper bound of the CI was less than 0, therefore it can be concluded that Tio R 2.5 is inferior to Tio HH 18 for FEV_1.

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Safety results:

The results of this trial demonstrate similar effects on mortality and safety of Tio R 2.5 and Tio R 5 compared with Tio HH 18 as supported by the following:

First primary endpoint: Time to death from any cause

For the first primary endpoint of time to death from any cause, the two tests for non-inferiority of Tio R 5 versus Tio HH 18 and Tio R 2.5 versus Tio HH 18 were successful.

- The incidence of death from any cause (i.e., total number of deaths during the observation period, regardless of treatment discontinuation) was 7.7% in the Tio R 2.5 group, 7.4% in the Tio R 5 group, and 7.7% in the Tio HH 18 group. The HR for Tio R 5 versus Tio HH 18 was 0.957 [95% CI: (0.837, 1.094)], i.e., at any time during the trial a subject in the Tio R 5 group had a 4.3% lower chance of death from any cause than a subject in the Tio HH 18 group; non-inferiority was achieved for the pre-specified delta of 1.25.
- The HR for Tio R 2.5 versus Tio HH 18 was 0.996 [95% CI: (0.872, 1.136)], i.e., at any time during the trial the chance of death from any cause was nearly identical for Tio R 2.5 compared to Tio HH 18; non-inferiority was achieved for the pre-specified delta of 1.25.
- Similar results were observed in the on-treatment sensitivity analysis. The incidence of fatal adverse events on treatment was 6.3%, 5.7%, and 6.3% in the Tio R 2.5, Tio R 5, and Tio HH 18 treatment groups, respectively. The HR for Tio R 5 versus Tio HH 18 was 0.913 [95% CI: (0.785, 1.060)], i.e., at any time during the trial a subject in the Tio R 5 group had an 8.7% lower chance of experiencing a fatal adverse event on treatment than a subject in the Tio HH 18 group.
- There were no meaningful differences in predefined subgroup analyses for time to death from any cause (based on treated set including vital status follow up), including baseline cardiac arrhythmia and/or cardiac history. For subjects with cardiac arrhythmia at baseline in the Tio R 5 group ([N=1221]: Tio R 5, 10.6%; Tio HH 18, 12.9% [HR 0.81; 95% CI: 0.58, 1.12]) versus those without ([N=10167]: Tio R 5, 7.0%; Tio HH 18, 7.1% [HR 0.99; 95% CI: 0.85, 1.14]). For subjects with

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cardiac arrhythmia at baseline in the Tio R 2.5 group (N=1211): Tio R 2.5, 13.1%; Tio HH 18, 12.9% [HR = 1.02, 95% CI: (0.74, 1.39)] versus those without (N=10194): Tio R 2.5, 7.0%; Tio HH 18, 7.1% [HR = 0.99, 95% CI: (0.86, 1.15)].

Summary of protocol-defined AEs, SAEs, and deaths:

Categories of protocol-specified AEs collected for this trial included protocol-defined outcome events (all COPD exacerbations, all pneumonias, and all serious and non-serious MIs, strokes, and TIAs), FAEs, SAEs, AEs leading to discontinuation of trial medication, and AEs considered drug-related by the investigator. During the trial, 65.5% of subjects (N = 17116) reported at least one of these during treatment (on treatment up to 30 days following last dose). Additionally, 32.9% of subjects experienced at least one SAE and 8.3% of subjects experienced at least one AE that led to discontinuation of trial medication while on treatment. The frequencies of SAEs, AEs leading to discontinuation, and investigator-determined drug-related adverse events were comparable across treatment groups and no substantial imbalance was identified.

Consistent with the primary analysis of time to death from any cause, the percentage of deaths was similar across the three treatment groups. The most common system organ classes (SOCs) in which the primary causes of death were reported (based on adjudication) were respiratory, thoracic and mediastinal disorders (2.2%); general disorders and administration site conditions (1.9%); and neoplasms benign, malignant and unspecified (including cysts and polyps) (1.8%). By preferred term, the most frequently reported adjudicated causes of death were COPD, sudden death, lung neoplasm malignant, death, and sudden cardiac death. The incidence was similar between the three treatment groups at the SOC level and for each of these respective event terms.

The highest incidence of SAEs was observed in the SOC of respiratory, thoracic and mediastinal disorders (17.2%) followed by infections and infestations (8.7%), cardiac disorders (4.9%), and neoplasms benign, malignant and unspecified (including cysts and polyps) (4.7%). By preferred term, the five most frequently reported SAEs were COPD, pneumonia, lung neoplasm malignant, myocardial infarction, and respiratory failure. The incidence was similar between

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the treatment groups at the SOC level and for each of these event terms.

Deaths and SAEs were further evaluated by condensed pharmacovigilance (PV) endpoints and standardized MedDRA queries (SMQs) to assess the incidence rates of medically similar respiratory (including pneumonia and COPD) and cardiac (including cardiac arrhythmias, ischaemic heart disease, cardiac failure) events of special interest. Within the PV endpoint COPD exacerbation (broad) with pneumonia, the incidence was balanced between the three treatment groups for both deaths and SAEs, which also applied to the two most frequently reported preferred terms within this PV endpoint, COPD and pneumonia. For cardiac events, no imbalance was identified between the three treatment groups following assessment of relevant collapsed cardiac SAEs at the SMQ level, including terms for cardiac arrhythmia (SMQ cardiac arrhythmia), ischemic heart disease (SMQ ischemic heart disease), and SMQ cardiac failure (narrow). No imbalance was identified for the stroke PV endpoint.

Secondary endpoints: Time to onset of first MACE and time to death from MACE

The composite endpoint of MACE was a predefined secondary endpoint to further evaluate cardiovascular safety. The overall incidence of MACE (on treatment) was 3.9%, 3.9%, and 3.6% in the Tio R 2.5, Tio R 5, and Tio HH 18 groups, respectively. No statistically significant differences were observed for either treatment comparison [Tio R 5 versus Tio HH 18, HR = 1.100, 95% CI: (0.909, 1.331) and Tio R 2.5 versus Tio HH 18, HR = 1.105, 95% CI: (0.913, 1.336)].

The overall incidence of death from MACE was 2.1%, 2.0%, and 1.8% in the Tio R 2.5, Tio R 5, and Tio HH 18 groups, respectively. The HRs were 1.111 [95% CI: (0.850, 1.453)] for Tio R 5 versus Tio HH 18 and 1.171 [95% CI: (0.898, 1.526)] for Tio R 2.5 versus Tio HH 18. No statistically significant differences were observed for either treatment comparison (Tio R 2.5 or Tio R 5 compared to Tio HH 18).

Evaluation of the individual components of MACE showed no statistically significant differences across treatment groups for all components with the exception of fatal events of MI, summarized in context as follows:

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- Outcome events of MI: Small differences in incidence of the outcome event of (serious and non-serious) MI were observed in the Tio R 2.5 (70 subjects, 1.2%), Tio R 5 (73 subjects, 1.3%), and Tio HH 18 (52 subjects, 0.9%) groups. Analyses of time to onset of first MI (a component of MACE) demonstrated no statistical difference between Tio R 5 versus Tio HH 18 [HR = 1.405, 95% CI: (0.984, 2.004)] or Tio R 2.5 versus Tio HH 18 [HR = 1.339, 95% CI: (0.935, 1.917)].
- SAEs of MI by sub-SMQ: The incidence rate ratios (IRRs) for SAEs reported within the SMQ ischemic heart disease sub-SMQ myocardial infarction (broad) were 1.09 (95% CI: 0.78, 1.53) for Tio R 5 versus Tio HH 18 and 1.23 (95% CI: 0.88, 1.71) for Tio R 2.5 versus Tio HH 18. No statistical differences were observed.
- Deaths due to MI by sub-SMQ: Death events categorized within the SMQ ischemic heart disease sub-SMQ myocardial infarction (broad) were reported for 24 subjects: Tio R 2.5 (10 subjects, 0.2%), Tio R 5 (11 subjects, 0.2%), and Tio HH 18 group (3 subjects, 0.1%). In contrast to the IRR values for SAEs within this sub-SMQ, the 95% CI for one treatment comparison did not include 1 [for Tio R 5 compared to Tio HH 18, IRR = 3.64, 95% CI: (1.02, 13.06); for Tio R 2.5 compared to Tio HH 18, IRR = 3.31, 95% CI: (0.91, 12.03)].
- Outcome events of stroke and TIA: No statistically significant differences were observed for either treatment comparison (Tio R 5 or Tio R 2.5 compared to Tio HH 18) for the time to event analyses for onset of first stroke and onset of first TIA.

Among the components of fatal MACE, an imbalance in fatal MI was observed between the two Respimat [Tio R 2.5 (10 subjects, 0.2%) and Tio R 5 (11 subjects, 0.2%)] and Handihaler doses [Tio HH 18 (3 subjects, 0.1%)] during the trial observation period. The incidence of fatal events within the cardiac disorders and vascular disorders SOC however was balanced in the three treatment groups, and the collective incidence of the preferred terms sudden death, cardiac death, and sudden cardiac death was also similar. The incidence rate of fatal MI associated with Tio HH 18 was low when compared to a large database like UPLIFT.

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Conclusions:

Tio R 5 and Tio R 2.5 achieved non-inferiority to the active comparator Tio HH 18 for the primary safety endpoint of time to death from any cause, demonstrating that both Tio R 5 and Tio R 2.5 are not associated with a higher mortality than Tio HH 18. This conclusion extends to the predefined subgroup of subjects with cardiac arrhythmia at baseline. For the primary efficacy endpoint time to first COPD exacerbation, Tio R 5 was not superior to Tio HH 18.

Trough FEV_1 was defined as the key secondary endpoint within the spirometry sub-study conducted in 1370 subjects (8% of all randomized subjects). The sub-study had its own type I error. Tio R 5 was shown to be non-inferior to Tio HH 18 for adjusted mean trough FEV_1 over 120 weeks, whereas treatment with Tio R 2.5 was shown to be inferior to Tio HH 18.

All three treatments showed comparable safety also for the other safety endpoints. No overall safety advantage was observed for the lower dose of Tio R 2.5 compared to the two approved dose strengths of Tio R 5 and Tio HH 18.

In conclusion, all three tiotropium treatment arms showed similar safety. Tio R 5 and Tio R 2.5 have similar exacerbation efficacy as Tio HH 18. In the spirometry substudy, Tio R 5, but not Tio R 2.5, demonstrated non-inferiority to Tio HH 18 for the endpoint trough FEV_1.