Boehringer Ingelheim

Clinical Study Synopsis for Public Disclosure

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Name of company: Boehringer Ingelheim		**Tabulated Trial Report**	Boehringer Ingelheim
Name of finished product: Spiriva® HandiHaler®		**EudraCT No.:** 2006-004610-41	
Name of active ingredient: Tiotropium bromide		**Page:** 1 of 7	**Synopsis No.:**
Module:		**Volume:**	
Report date: 31 Mar 2011	**Trial No. / U No.:** 205.368 / U11-3094-01	**Date of trial:** 30 Aug 2007 – 30 June 2010	**Date of revision:** Not applicable

Title of trial:	A randomized, double-blind, placebo-controlled two-year trial to examine the changes in Exercise Endurance and COPD Patients Treated with Tiotropium (Spiriva® HandiHaler®) 18 µg once daily (EXACTT trial)
Coordinating Investigator:	[redacted]
Trial sites:	Multicentre Study, cf. Appendix 16.1.4
Publication (reference):	Cooper CB, Abrazado M, Legg D, Kesten S. Development and implementation of treadmill exercise testing protocols in COPD. Int J COPD. 2010: 5: 1-11. R10-1565
Clinical phase:	IV
Objectives:	To determine the effect of long-term treatment with tiotropium on treadmill endurance time (ET) compared with placebo on top of usual care in patients with COPD
Methodology:	96 weeks, randomized, parallel group, double-blind, placebo-controlled, followed by 4 weeks open-label tiotropium in all patients; 100 weeks in total
No. of subjects:	
planned:	entered: 460
actual:	enrolled: 713 Treatment Tiotropium: entered: 260; treated: 260; analysed (for primary endpoint): 239 Treatment Placebo: entered: 259; treated: 259; analysed (for primary endpoint): 225
Diagnosis and main criteria for inclusion:	Male or female, ≥ 40 years old, with a diagnosis of COPD (pre-bronchodilator FEV_1 ≤60% predicted, post bronchodilator FEV_1 ≤65% predicted, FEV_1/FVC <70%), smoking history ≥10 pack-years, no history of asthma

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Test product:	Tiotropium bromide (Spiriva® HandiHaler®)
dose:	18 µg
mode of admin.:	Oral inhalation with the HandiHaler®
batch no.:	707429, 904179, 807157, 804675, 704401, 607875
Reference therapy:	Placebo (HandiHaler®)
dose:	N/A
mode of admin.:	Oral inhalation with the HandiHaler®
batch no.:	607416, 701980, 704110, 810611
Duration of treatment:	96 weeks double-blind phase, 4 weeks open-label follow-up
Criteria for evaluation:	
Efficacy / clinical pharmacology:	Constant work rate (CWR) 90% of maximum work rate exercise duration, pulmonary function tests (PFTs), (FEV_1, FVC), St. George's Respiratory Questionnaire (SGRQ), Modified Borg scale, Exacerbations of COPD, Physician's & Patient's Global Evaluation
Safety:	Adverse events (AEs), vital signs, physical examination, vital status information
Statistical methods:	Mixed effect model with terms for centre, treatment, visit, baseline values and interactions for the primary and secondary endpoints. ET was log-transformed. ANCOVA for Week 100 ET and PFT. The model produced the difference of log-transformed endurance time because the statistical model required a log-transformation of endurance time data. When transformed back to the original scale, the difference became a ratio. Cox regression, Kaplan-Meier estimates, and negative binomial model for exacerbation. Stratified Wilcoxon-Mann-Whitney test and descriptive statistics for safety.

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SUMMARY – CONCLUSIONS:

Efficacy / clinical pharmacology results:

Primary Endpoint: Endurance Time (ET), including secondary endpoint ET at visits 4-9 and post-hoc analysis

The primary endpoint of EXACTT was the 90% of maximum work rate treadmill ET at 96 weeks. Adjusted mean ET was 297.1 seconds (sec) in the placebo and 336.6 sec in the tiotropium group with the adjusted mean ET ratio (95% CI) of tiotropium(tio)/placebo of 1.13 (0.97, 1.32); p=0.106. A statistically significant difference at 96 weeks, was not achieved.

The average difference in ET between treatment groups was 39.6 sec throughout the trial with the relative improvements with tiotropium compared to placebo ranging from 30.0 to 55.9 sec.

In a post-hoc analysis, the average mean adjusted ratio (95% CI) was 1.13 over the duration of the trial of tiotropium compared to placebo (1.03, 1.24); p=0.009.

Adjusted mean ETs in the tiotropium group were always higher than adjusted mean ETs in the placebo group and largely significant during the first year. The effect increased from Baseline to a peak at Week 48 (55.9 sec) with an adjusted mean ratio (95% CI) of 1.18 (1.05, 1.32; p=0.0041). At subsequent visits ET ranged from 35.6 sec and 37.3 sec at Weeks 64 and 80 to 39.5 sec at Week 96.

The ET improvement with tiotropium was more prominent in patients with GOLD Stages II+III (n=398, ratio (95%CI) = 1.16 (0.99, 1.36); p=0.0722) compared to GOLD Stage IV (n=66, ratio (95%CI) = 1.00 (0.65, 1.54); p=0.9976). Additionally, in a post-hoc analysis larger differences were observed in patients with baseline ET between 2 and 10 minutes (n=404, ratio (95%CI) = 1.20 (1.01, 1.43); p=0.0425) as compared to the primary analysis. A significant difference was not observed in the subgroups with a baseline ET < 2 min (n=7, ratio (95% CI) = 0.71 (0.13, 3.90); p=0.6953) or >10 min (n=53, ratio (95% CI) = 0.79 (0.49, 1.26); p=0.3195).

Secondary endpoints: ET at 100 weeks, Lung function, Quality of life, Borg, COPD exacerbations

At 100 weeks, the adjusted mean ET during the open-label period where all patients received open-label tiotropium for 4 weeks remained numerically higher in the previous tiotropium group compared to placebo switched to tiotropium

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(358.8 sec vs. 337.3 sec, respectively) with an adjusted mean ratio (95%CI) for tio/placebo of 1.06 (0.91, 1.25); p=0.44.

Lower ETs at Baseline in the placebo group were associated with an increased rate of withdrawal from study treatment (post-hoc analysis). At Baseline the mean ET of placebo patients who completed treatment was 80.6 sec higher than that of those who withdrew (mean ET 374.1 sec and 293.5 sec, respectively). In contrast, only a -17.4 sec difference was observed between the Baseline ET of completers and non-completers in the tiotropium group.

Lung function was consistently improved with tiotropium. Significant differences in trough and post-treatment pulmonary function tests (FEV_1 and FVC) in favor of tiotropium were seen at all time points ($p<0.01$ for all differences). The mean pre-treatment (trough) difference in FEV_1 ranged from 75 to 116mL with the difference being 75mL in favor of tiotropium at Week 96 (p=0.0059).

Self-reported quality of life was improved with tiotropium as measured by the SGRQ total score with an adjusted mean difference (95% CI) of -4.03 (-6.97, -1.10); p=0.0072. A reduction in score indicates improvement and a change of more than 4 units (as observed on EXACTT) suggests a clinically meaningful change. This 4 unit improvement was achieved in 32.5% of placebo patients and 41.5% of tiotropium patients, odds ratio 1.51 (tio/placebo) 95%CI, (0.91, 2.50).

Analysis of Borg scale dyspnea rating showed no significant difference between treatment groups at Week 96 for peak of dyspnoea or for leg discomfort. For peak of dyspnoea and leg discomfort the adjusted mean difference (SE) was -0.02 (0.18) and 0.09 (0.23), respectively. As a patient's maximum tolerable intensity of dyspnea and leg discomfort is generally consistent over time (the time to arrive at the threshold changes, not the threshold itself) changes in the peak values would not be expected. To address this, an isotime analysis of dyspnea (lowest post-randomisation ET) in patients who completed 96 weeks was conducted. A reduction in the intensity of dyspnea at isotime was observed when tiotropium was compared to placebo. The adjusted mean difference in the intensity of dyspnea at isotime was -0.32 with 95% CI of (-0.72. 0.08); however, this difference was not statistically significant (p=0.1131).

With respect to the Patient and Physician Global Evaluations, no significant change was seen post-randomisation between the groups at 96 weeks. The mean difference between the two groups peaked at Week 8 (patient global = 0.37 units

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	and physician global = 0.36 units), declined over the trial to the nadir at 96 weeks (patient global = 0.07 units and physician global = 0.17 units) and were in favour of tiotropium. The mean rate of exacerbations per patient-year (pt-yr) was similar in both treatment groups (0.54 placebo, 0.51 tiotropium). A significant difference was not seen in time to first exacerbation (hazard ratio (HR)=0.94, 95% CI (0.72, 1.23)). Withdrawal due to exacerbations was more common in the first 6 months of blinded therapy than at future visits. Exacerbation rate during the first 6 months was 0.63 per year in the placebo group, a rate almost double the tiotropium group (0.39 per year). At 96 weeks, however, annualized exacerbation rate between the groups was roughly equivalent.
Safety results:	A total of 519 patients were randomised and received at least one dose of study medication (259 placebo, 260 tiotropium). At completion of the double-blind phase, 162 patients (31.2%) had withdrawn from the trial. Placebo patients were more likely to discontinue the trial than tiotropium patients (HR 0.61, 95%CI, 0.44, 0.83; p=0.0018). Subsequently, exposure between the two groups at 96 weeks was different with 47.8 fewer pt-yr in the placebo group (359.1 pt-yr) compared to the tiotropium group (406.9 pt-yr). A total of 347 of the 519 patients entered the 4-week open-label phase (158 placebo, 189 tiotropium). At 100 weeks, 11 (3.1%) additional patients had withdrawn from the trial, roughly equal numbers between both treatment groups. A total of 4,919 treadmill exercise tests were performed across 60 centres. AEs were reported in 127 (2.6%) exercise tests with only one serious adverse event (SAE) reported (hypotension which recovered promptly). The most common AEs associated with treadmill testing were dizziness and musculoskeletal discomfort. AEs were experienced by 74.5% of placebo patients and 75.0% of tiotropium patients during the double-blind treatment period. The most frequently reported AEs included dry mouth, constipation, dizziness, sinusitis, nasopharyngitis, cough, and arthralgia. Nasopharyngitis was reported more frequently in the placebo group (tio/placebo Rate Ratio=0.50, 95%CI, (0.23, 0.95)). Tiotropium patients reported constipation, dyspepsia, diarrhoea and dizziness (tio/placebo Rate Ratio (95%CI) =5.4 (1.21, 24.20), 8.1 (1.03, 64.00), 2.7 (0.87, 8.36) and 3.9 (1.11, 13.63), respectively) at a higher frequency. Except for diarrhoea, these events are listed in the Investigators Brochure as expected events for tiotropium.

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	SAEs were reported by 22.8% of placebo patients and 24.2% of tiotropium patients during the double-blind treatment period. The most frequently reported (>3%) SAEs were exacerbation of COPD and pneumonia. The total number of deaths during the blinded phase was 12 (6 placebo, 6 tiotropium). The most common cause of death was malignant neoplasms, cardiac and lower respiratory disorders. The HR (95% CI) for death from any cause (tio/placebo) was 1.041 (0.317, 3.411). A total of 19 deaths were reported for the full 100 week study period, including vital status (11, 4.2% in the placebo group and 8, 3.1% in the tiotropium group). The HR (95% CI) was 0.72 (0.29, 1.79).
Conclusions:	This was a 2-year study of CWR treadmill ET in patients with moderate to very severe COPD in which treatment with tiotropium resulted in consistently longer, but not statistically significant, ETs (approximately 40 sec) at approximately 90% of maximum work rate (90% of speed, 100% of grade) compared with placebo (on-top of usual care). The difference in ET between treatment groups at 96 weeks did not achieve statistical significance; although it was in favour of tiotropium and nominally significant at earlier time points. The magnitude of effect was consistent at approximately 40 sec for the duration of the study. A significant difference in favour of tiotropium was seen in lung function (peak and trough FEV_1, FVC) at each visit and at 96 weeks, and in the SGRQ impact, symptom and total score, with total score meeting the criteria to demonstrate a clinically meaningful difference at 96 weeks. Significantly more withdrawals occurred in the placebo group (37.1%) than the tiotropium group (25.4%). Withdrawals from the placebo group were associated with lower baseline ETs and greater risk of exacerbation in the first 6 months of double-blind therapy. This lead to selection of a population in better health and fitness than at randomisation (e.g., 'healthy survivor' bias). Therefore, the differential withdrawal rate impacted the primary and secondary endpoints potentially resulting in a narrowing of treatment effect. This study employed a novel CWR treadmill protocol, which presented a challenge generating an accurate estimation of the effect size or likely difference in ET between the tiotropium and placebo patients. The actual effect size of this CWR treadmill test at 90% of maximum work rate was less than half of the

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estimated effect determined by previous tiotropium exercise studies using 75% maximum work cycle ergometry. As indicated by the work rate-duration relationship in exercise testing, there is a non-linear association between intensity of a task and the duration it can be performed. In retrospect, it may not be surprising that a smaller difference in ET was found than originally estimated.

The incorrect estimation of the effect size and higher withdrawal rate due to the extended duration led to an underestimation of sample size, which reduced the power of the study to demonstrate statistical significance. Nevertheless, at time points during the first 12 months of the study, significant differences were seen in ET with tiotropium compared with placebo. Only in later stages of the study, when more patients withdrew, was statistical significance lost. Thus, the compromised statistical power rendered the study more susceptible to the influence of withdrawals.

There were no statistically significant differences for the Global Evaluations or in the risk for an exacerbation during the trial. The Borg dyspnoea at isotime did demonstrate a numerical reduction in dyspnoea with tiotropium compared to placebo.

The safety assessment from this trial was consistent with the overall safety database from previous tiotropium clinical trials. The trial did not identify any previously unsuspected important adverse reaction to tiotropium. There was no disparity between treatment groups with respect to fatal events during the double-blind phase of the trial. Over the entire course of the trial (100 weeks, including deaths reported from vital status collection) the number of fatal events was numerically lower in the tiotropium group than placebo.

The EXACTT study demonstrated that when compared to placebo (on top of usual care) in patients with moderate to very severe COPD, treatment with tiotropium resulted in consistently longer endurance times (approximately 40 seconds) at greater than 90% of maximum work rate over two years. Due to the differential withdrawal rate and methodological challenges estimating sample size, this difference was not statistically significant. Secondary endpoints showed statistically significant improvements in lung function each time point as well as statistically significant and clinically meaningful change in health status as measured by the SGRQ.