Boehringer Ingelheim

Clinical Study Synopsis for Public Disclosure

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The synopsis - which is part of the clinical study report - had been prepared in accordance with best practice and applicable legal and regulatory requirements at the time of study completion.

The synopsis may include approved and non-approved uses, doses, formulations, treatment regimens and/or age groups; it has not necessarily been submitted to regulatory authorities.

A synopsis is not intended to provide a comprehensive analysis of all data currently available regarding a particular drug. More current information regarding a drug is available in the approved labeling information which may vary from country to country..

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Name of company: Boehringer Ingelheim		Tabulated Trial Report	Boehringer Ingelheim
Name of finished product: Not applicable		**EudraCT No.:** 2009-014417-27 and 2009-014418-86	**Synopsis No.:**
Name of active ingredient: Olodaterol, BI 1744		**Page:** 1 of 5	
Module:		**Volume:** {hyperlink }	
Report date: 04 JAN 2012	**Trial No. / U No.:** 1222.9994 / U10-3301-01	**Date of trial:** 08 JAN 2010 -12 JAN 2011	**Date of revision:** Not applicable

Title of trial:	Combined analysis of efficacy data obtained in Studies 1222.39 and 1222.40 - Randomised, double-blind, double-dummy, placebo-controlled, 4-way cross-over study to characterise the 24-hour FEV_1-time profiles of BI 1744 CL 5 µg and 10 µg (oral inhalation, delivered by the Respimat® Inhaler) and tiotropium bromide 18 µg (oral inhalation, delivered by the HandiHaler®) after 6 weeks of treatment in patients with chronic obstructive pulmonary disease (COPD)
Coordinating Investigator:	[redacted]
Trial sites:	Multicenter studies (15 sites in Germany, Belgium, Denmark and Hungary in Study 1222.39 and 12 sites in Germany, the Netherlands, Norway and the United States in Study 1222.40)
Publication (reference):	Data of this study have not yet been published.
Clinical phase:	III
Objectives:	The primary objective of the replicate Studies 1222.39 and 1222.40 was to compare the 24-hour forced expiratory volume in one second (FEV_1) time profile of olodaterol (5 µg, 10 µg) with the 24-hour FEV_1 time profile of placebo following six weeks of once daily (qd) treatment in patients with COPD. A secondary objective was to compare the 24-hour FEV_1 time profile of olodaterol (5 µg, 10 µg) administered once daily with the 24-hour FEV_1 time profile of Spiriva® HandiHaler® (18 µg) administered according to its registered dosing regimen in patients with COPD. This combined CTR focuses on the comparison of olodaterol (5 µg, 10 µg) vs. Spiriva® HandiHaler®, which was pre-specified as a pooled analysis, based on the combined data from Studies 1222.39 and 1222.40, for increased sensitivity.
Methodology:	Randomised, double-blind, double-dummy, placebo-controlled, four-way cross-over design comparing two active treatment groups with active control for six weeks.

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No. of subjects:	
planned:	200 (100 per study)
actual:	Olodaterol 5 µg: treated: 217 analyzed (for primary endpoint): 215 Olodaterol 10 µg: treated: 214; analyzed (for primary endpoint): 205 Tiotropium bromide18 µg: treated: 214; analyzed (for primary endpoint): 211 Placebo: treated: 212; analyzed (for primary endpoint): 204
Diagnosis and main criteria for inclusion:	Outpatients of either sex, aged ≥40 years with a diagnosis of COPD; smoking history >10 pack years, post-bronchodilator FEV_1 < 80% predicted; post-bronchodilator FEV_1/forced vital capacity (FVC) <70%.
Test product (1):	Olodaterol inhalation solution – RESPIMAT
dose:	5 µg (ex mouthpiece [2 actuations of 2.5 µg]) qd (calculated as free base)
mode of admin.:	Oral inhalation
batch no.:	B072000346, B082000026, B082000007 in Study 1222.39 (U10-3198-01); B082000026 and B072000346 in Study 1222.40 (U10-3199-01)
Test Product (2):	Olodaterol inhalation solution – RESPIMAT
dose:	10 µg (ex mouthpiece [2 actuations of 5 µg]) qd (calculated as free base)
mode of admin.:	Oral inhalation
batch no.:	B072000356, B082000029, B072000354 in Study 1222.39 (U10-3198-01); B082000029 and B072000356 in Study 1222.40 (U10-3199-01)

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Reference therapy (1):	Tiotropium bromide powder capsules – HandiHaler®
dose:	18 µg qd (nominal dose, calculated as free base)
mode of admin.:	Oral inhalation
batch no.:	B102000006 in Study 1222.39 (U10-3198-01) and B072000252, B092000098 in Study 1222.40 (U10-3199-01).
Reference therapy (2):	Placebo – RESPIMAT and Placebo – HandiHaler®
dose:	N/A
mode of admin.:	Oral inhalation
batch no.:	B092000133 in Study 1222.39 (U10-3198-01) and B082000136, B082000022 for placebo RESPIMAT and B092000010 for placebo HandiHaler® in Study 1222.40 (U10-3199-01).
Duration of treatment:	Four six-week treatment periods with a 3 week wash-out between each treatment period (total treatment duration 24 weeks)
Criteria for evaluation:	
Efficacy/Clinical Pharmacology:	The following endpoints were evaluated for the combined data: • Area under the FEV_1 curve calculated from time zero to 12 hours (FEV_1 AUC_{0-12}) response, area under the FEV_1 curve calculated from 12 to 24 hours (FEV_1 AUC_{12-24}) response, area under the FEV_1 curve calculated from time zero to 24 hours (FEV_1 AUC_{0-24}) response in patients treated with olodaterol 10 µg, olodaterol 5 µg and tiotropium 18 µg compared with those treated with placebo, after six weeks • FEV_1 AUC_{0-12} response, FEV_1 AUC_{12-}24 response, and FEV_1 AUC_{0-24} response in patients treated with olodaterol 10 µg and olodaterol 5 µg compared with those treated with tiotropium, after six weeks • FEV_1 AUC_{0-12} response, FEV_1 AUC_{12-}24 response, and FEV_1 AUC_{0-24} response in patients treated with olodaterol 10 µg compared with those treated with olodaterol 5 µg, after six weeks

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Safety:	Adverse events (including physical examination), vital signs, laboratory evaluations, 12-lead electrocardiogram were evaluated in the individual reports (Study 1222.39 [U10-3198-01] and Study 1222.40 [U10-3199-01]).
Statistical methods:	Both comparisons to placebo and comparisons among active treatment groups are presented. Analysis of the co-primary endpoints used a mixed effects model with repeated measures (MMRM) that included treatment and period as fixed effects, patient as a random effect and study baseline as a continuous covariate.

SUMMARY – CONCLUSIONS:

Efficacy/Clinical Pharmacology:

For FEV_1 AUC_{0-12} response after six weeks of treatment, both doses of olodaterol and tiotropium 18 µg showed statistically significant increases compared with placebo ($p<0.0001$), with differences of 216 mL (184 vs. -31 mL) for olodaterol 10 µg, 193 mL (162 vs. -31 mL) for olodaterol 5 µg, and 200 mL (168 vs. -31 mL) for tiotropium 18 µg.

For FEV_1 AUC_{12-24} response after six weeks of treatment, both olodaterol doses and tiotropium 18 µg showed statistically significant increases compared with placebo ($p<0.0001$), with differences of 175 mL (98 vs. -77 mL) for olodaterol 10 µg, 143 mL (66 vs. -77 mL) for olodaterol 5 µg, and 145 mL (68 vs. -77 mL) for tiotropium 18 µg.

For FEV_1 AUC_{0-24} response after six weeks of treatment, both doses of olodaterol and tiotropium 18 µg showed statistically significant increases compared with placebo ($p<0.0001$) with differences compared with placebo of 193 mL (139 vs. -54 mL) for olodaterol 10 µg, 168 mL (114 vs. -54 mL) for olodaterol 5 µg, and 172 mL (118 vs. -77 mL) for tiotropium 18 µg.

There were no statistically significant differences between the three active treatment groups for FEV_1 AUC_{0-12} response after six weeks of treatment. The difference in FEV_1 AUC_{0-12} response was 16 mL (184 vs. 168 mL; $p=0.2372$) between olodaterol 10 µg qd and tiotropium, -7 mL (162 vs. 168 mL; $p=0.5900$) between olodaterol 5 µg qd and tiotropium 18 µg, and 23 mL (184 vs. 162 mL; $p=0.0855$) between olodaterol 10 µg qd and olodaterol 5 µg qd.

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Efficacy/Clinical Pharmacology (continued):	For FEV_1 AUC_{12-24} response, olodaterol 10 µg showed statistically significant increases compared with tiotropium 18 µg (difference of 30 mL [98 vs. 68 mL]; p=0.0306) and compared with olodaterol 5 µg (difference of 31 mL [98 vs. 66 mL]; p=0.0224). There was no statistically significant difference between olodaterol 5 µg and tiotropium 18 µg for FEV_1 AUC_{12-24} response (difference of -2 mL [66 vs. 68 mL]; p=0.9093). For FEV_1 AUC_{0-24} response after six weeks of treatment, there were no statistically significant differences between the active treatment groups. The difference in FEV_1 AUC_{0-24} response was 21 mL (139 vs. 118 mL; p=0.1088) between olodaterol 10 µg qd and tiotropium, -4 mL (114 vs. 118 mL; p=0.7382) between olodaterol 5 µg qd and tiotropium, and 25 mL (139 vs. 114; p=0.0524) between olodaterol 10 µg qd and olodaterol 5 µg qd.
Safety results:	Safety results are presented in the individual reports (Study 1222.39 [U10-3198-01] and Study 1222.40 [U10-3199-01]).
Conclusions:	The comparison of the 24-hour FEV_1-time profile of olodaterol administered once daily with the 24-hour FEV_1-time profile of tiotropium HandiHaler® administered once daily supports the once daily posology of olodaterol. A small difference was seen in favour of olodaterol 10 µg versus olodaterol 5 µg and versus tiotropium. However, evaluation of the preferred dose of olodaterol for long term maintenance treatment will be based on the totality of data in the summary documents and clinical overview.

Trial Synopsis - Appendix

The results table on the following page supplement the trial results presented in the Trial Synopsis. The appended tables provide detailed results for patient disposition, secondary endpoints, and adverse events for the combined analysis in the synopsis.

Results for	**presented in**
Patient Disposition	Table 15.1.1: 1
FEV_1 $AUC_{(0–12)}$, $AUC_{(12–24)}$ and $AUC_{(0–24)}$ response and treatment comparisons after 6 weeks	Table 15.2.1.1: 2
AE Summary Table	Table 15.3.2: 1

Table 15.1.1: 1 Disposition of patients

	Placebo	Olo 5ug	Olo 10ug	Tio HH 18ug	Total
Enrolled					302
Not entered/randomsed					72
Entered/randomised					230
Not treated					0
Treated	212(100.00)	217(100.00)	214(100.00)	214(100.00)	230(100.00)
Not prematurely discontinued from trial medication #	201(94.81)	205(94.47)	202(94.39)	207(96.73)	187(81.30)
Prematurely discontinued from trial medication	11(5.19)	12(5.53)	12(5.61)	7(3.27)	
Adverse event	9(4.25)	2(0.92)	8(3.74)	4(1.87)	
AE study dis. worse	5(2.36)	1(0.46)	2(0.93)	0(0.00)	
AE-oth. dis. worse	0(0.00)	1(0.46)	0(0.00)	0(0.00)	
AE-other	4(1.89)	0(0.00)	6(2.80)	4(1.87)	
Lack of efficacy	1(0.47)	2(0.92)	0(0.00)	0(0.00)	
Non compl prot.	0(0.00)	4(1.84)	0(0.00)	0(0.00)	
Consent withdrawn	1(0.47)	1(0.46)	2(0.93)	1(0.47)	
Other	0(0.00)	3(1.38)	2(0.93)	2(0.93)	

The total column for this row counts all patients who did not discontinue from any treatment (i.e., completed all treatments)

Table 15.2.1.1: 2 Adjusted mean* (SE) FEV1 AUC(0-12), AUC(12-24) and AUC(0-24) response [L] and treatment comparisons after 6 weeks - analysis with imputation (FAS)

Time interval	Comparison	Treatment difference		
		Mean (SE)	P-value	95% CI
0-12 hr	Olo 10ug - Olo 5ug	0.023 (0.013)	0.0855	(-0.003, 0.049)
	Olo 10ug - Tio HH 18ug	0.016 (0.013)	0.2372	(-0.010, 0.042)
	Olo 5ug - Tio HH 18ug	-0.007 (0.013)	0.5900	(-0.033, 0.019)
12-24 hr	Olo 10ug - Olo 5ug	0.031 (0.014)	0.0224	(0.004, 0.058)
	Olo 10ug - Tio HH 18ug	0.030 (0.014)	0.0306	(0.003, 0.057)
	Olo 5ug - Tio HH 18ug	-0.002 (0.014)	0.9093	(-0.028, 0.025)
0-24 hr	Olo 10ug - Olo 5ug	0.025 (0.013)	0.0524	(-0.000, 0.050)
	Olo 10ug - Tio HH 18ug	0.021 (0.013)	0.1088	(-0.005, 0.046)
	Olo 5ug - Tio HH 18ug	-0.004 (0.013)	0.7382	(-0.029, 0.021)

* Based on a mixed effects repeated measures model.

Table 15.3.2: 1 Adverse event overall summary - treated set

	Placebo N (%)	Olo 5ug N (%)	Olo 10ug N (%)	Tio HH 18ug N (%)	Total N (%)
Number of subjects	211 (100.0)	216 (100.0)	214 (100.0)	214 (100.0)	230 (100.0)
Subjects with any AE	72 (34.1)	73 (33.8)	78 (36.4)	73 (34.1)	156 (67.8)
Subjects with severe AEs	8 (3.8)	3 (1.4)	7 (3.3)	7 (3.3)	23 (10.0)
Subjects with investigator defined drug-related AEs	3 (1.4)	3 (1.4)	6 (2.8)	3 (1.4)	11 (4.8)
Subjects with other significant AEs (according to ICH E3)	5 (2.4)	2 (0.9)	3 (1.4)	3 (1.4)	13 (5.7)
Subjects with AEs leading to discontinuation of trial drug	8 (3.8)	3 (1.4)	7 (3.3)	6 (2.8)	24 (10.4)
Subjects with significant AEs (pre-specified events)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Subjects with serious AEs	10 (4.7)	4 (1.9)	8 (3.7)	7 (3.3)	27 (11.7)
Fatal	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Imm life-threatening	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Disability/incap.	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Req.hospitalisation	10 (4.7)	4 (1.9)	6 (2.8)	6 (2.8)	25 (10.9)
Prol.hospitalisation	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Congenital anomaly	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Other	0 (0.0)	0 (0.0)	2 (0.9)	1 (0.5)	3 (1.3)

A subject may be counted in more than one seriousness criterion.
Percentages are calculated using total number of subjects per treatment as the denominator.
Containing data from studies 1222_0039 and 1222_0040
MedDRA version used for reporting: 14.0
Since this is a crossover trial, the total will not be the sum of the individual treatments.