Boehringer Ingelheim

Clinical Study Synopsis for Public Disclosure

This clinical study synopsis is provided in line with **Boehringer Ingelheim's *Policy on Transparency and Publication of Clinical Study Data***.

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..

Additional information on this study and the drug concerned may be provided upon request based on **Boehringer Ingelheim's Policy on Transparency and Publication of Clinical Study Data**.

Name of company: Boehringer Ingelheim		**Tabulated Trial Report**	Boehringer Ingelheim
Name of finished product: Not applicable		**EudraCT No.:** 2009-014416-35	
Name of active ingredient: Olodaterol (BI 1744 CL)		**Page:** 1 of 6	**Synopsis No.:**
Module:		**Volume:**	
Report date: 20 MAR 2012	**Trial No. / U No.:** 1222.38 / U10-3197-01	**Date of trial:** 27 January 2010 – 5 April 2011	**Date of revision:** Not applicable

Title of trial:	Randomised, double-blind, placebo-controlled, 3-way cross-over study to determine the effect of 6 weeks treatment of orally inhaled BI 1744 CL (5 µg [2 actuations of 2.5µg] and 10 µg [2 actuations of 5 µg]) delivered by the Respimat® Inhaler on exercise endurance time during constant work rate cycle ergometry in patients with Chronic Obstructive Pulmonary Disease (COPD)
Coordinating Investigator:	[redacted]
Trial sites:	Multicentre study, cf. Appendix 16.1.4
Publication (reference):	Data of this study have not been published
Clinical phase:	III
Objectives:	The primary objective was to compare the effects of olodaterol with placebo on constant work rate exercise endurance after 6 weeks of treatment in patients with COPD. Secondary objectives were to compare the effects of olodaterol versus placebo on lung hyperinflation during constant work rate exercise in patients with COPD as measured by inspiratory capacity (IC), and the intensity of breathing discomfort experienced during constant work rate exercise in patients with COPD. The intensity of breathing discomfort was rated by the patients using the Borg Category-Ratio Scale.
Methodology:	Randomised, double-blind, placebo-controlled, 3-way cross-over design
No. of subjects:	
planned:	entered: 150 enrolled: 196

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actual:	Treatment Olodaterol 5 µg: entered: 150 treated: 150 analyzed (for primary endpoint): 141 Treatment Olodaterol 10µg entered: 147 treated: 147 analyzed (for primary endpoint): 140 Treatment Placebo: entered: 149 treated: 149 analyzed (for primary endpoint): 146
Diagnosis and main criteria for inclusion:	Outpatients of either sex, aged ≥40 and ≤75 years with a diagnosis of COPD; smoking history >10 pack years, post-bronchodilator FEV_1 <80% predicted; post-bronchodilator FEV_1/FVC <70%
Test product:	Olodaterol (as hydrochloride)
dose:	5 µg (ex mouthpiece [2 actuations of 2.5 µg]) once daily (calculated as free base)
mode of admin.:	Oral inhalation
batch no.:	B072000346
Test product:	Olodaterol (as hydrochloride)
dose:	10 µg (ex mouthpiece [2 actuations of 5 µg]) once daily (calculated as free base)
mode of admin.:	Oral inhalation
batch no.:	B072000356
Reference therapy:	Placebo inhalation matching olodaterol
dose:	Not applicable
mode of admin.:	Oral inhalation
batch no.:	B082000136
Duration of treatment:	3 x 6-week treatment periods (total treatment duration of 18 weeks)

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Criteria for evaluation:

Efficacy / clinical pharmacology:	Constant work rate exercise endurance time, inspiratory capacity (IC) during constant work rate exercise, intensity of breathing discomfort and leg discomfort during constant work rate exercise, body plethysmographic parameters [functional residual capacity (FRC), inspiratory capacity (IC), total lung capacity (TLC)], spirometric parameters [forced expiratory volume in one second (FEV_1), forced vital capacity (FVC), peak expiratory flow (PEF)]. For the primary and key secondary endpoints, subgroups were analyzed by baseline endurance time (quartiles) and by baseline locus of symptom limitation (breathing discomfort, leg discomfort, breath and leg discomfort).
Safety:	Adverse events (including physical exam), vital signs, laboratory evaluations, 12-lead ECG.
Statistical methods:	For the analysis of the primary endpoint, a mixed effect repeated measures model (MMRM) with treatment and period as fixed effects and patient as a random effect was utilized. In order to validate the normality assumption in the MMRM model, a log10 transformation was applied to the endurance time prior to the analysis of the primary endpoint; log_{10} baseline endurance time was used as a covariate. The actual response, instead of change from baseline, was used. This model was used for secondary and other endpoints as appropriate. Descriptive statistics were conducted for safety parameters.

SUMMARY – CONCLUSIONS:

Efficacy / clinical pharmacology results:

Primary endpoint

At baseline, the geometric mean endurance time (ET) during constant work rate cycle ergometry to symptom limitation at 75% of maximal work capacity was 374 seconds (sec). After six weeks of treatment, the mean ET was 354 sec for placebo, 396 sec for olodaterol 5 µg and 391 sec for olodaterol 10 µg. Compared with placebo, the 11.8% improvement in ET for olodaterol 5 µg (95% CI: 4.3%, 19.9%) and 10.5% improvement for olodaterol 10 µg (95% CI 3.0%, 18.4%) were statistically significant ($p \leq 0.0052$). There was no significant difference between olodaterol 5 µg and 10 µg in ET after six weeks.

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Key secondary endpoints

- For the key secondary endpoint, IC at isotime after 6 weeks, both olodaterol 5 µg and 10 µg significantly increased adjusted mean IC, compared with placebo, with adjusted mean differences of 0.084 L (p=0.0155) for olodaterol 5 µg and 0.166 L (p<0.0001) for olodaterol 10 µg. In addition, compared with placebo, both olodaterol 5 µg and 10 µg increased adjusted mean IC at pre-exercise (p<0.0001), and at end of exercise (p≤0.0245). There was no significant difference between olodaterol 5 µg and olodaterol 10 µg at any of the three time points.
- For intensity of breathing discomfort (Borg Category Ratio Scale) measured at isotime during exercise, after six weeks the difference between olodaterol 5 µg and placebo was -0.336 (p=0.1176) and between olodaterol 10 µg and placebo was -0.066 (p=0.7591). At the end of exercise, the difference between olodaterol 5 µg and placebo was 0.091 (p=0.5313) and between olodaterol 10 µg and placebo was 0.341 (p=0.0198). There were no differences between olodaterol 5 µg and 10 µg for intensity of breathing discomfort.

Other secondary endpoints:

- After six weeks of treatment, 30 minutes pre-dose there was a statistically significant decrease in mean FRC response for olodaterol 10 µg compared with placebo (-0.120 L; p = 0.0246); the decrease in mean FRC response for olodaterol 5 mg, compared with placebo, did not reach statistical significance (-0.086 L; p=0.1048). One hour post-dose, there was a statistically significant decrease in adjusted mean FRC response for olodaterol 5 µg (p<0.0001) and for olodaterol 10 µg (p=0.0005), compared with placebo.
- After six weeks of treatment, there were statistically significant increases (p≤0.0002) in adjusted mean IC responses observed for olodaterol 5 µg and olodaterol 10 µg, compared with placebo, 30 minutes pre-dose and one hour post-dose.
- After six weeks, treatment with olodaterol 5 µg and 10 µg resulted in adjusted mean FEV_1, and FVC responses that were statistically significantly greater than placebo 30 minutes pre-dose and one hour post-dose. After six weeks, PEF responses were also statistically significantly greater for olodaterol 5 µg and 10 µg compared with placebo 30 minutes pre-dose and one hour post-

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	dose.
Safety results:	In this six-week crossover study, olodaterol was generally safe and well tolerated. During the treatment phase, the overall occurrence of AEs was low and similar across treatments, with no apparent dose relationship observed for any AE: 22.8% placebo, 28.8% olodaterol 5 µg, and 21.1% olodaterol 10 µg. As expected in this population, the most frequently reported treated emergent adverse events were respiratory events: 10.7% placebo, 8.0% olodaterol 5 µg and 4.8% olodaterol 10 µg. The most common AEs overall (AEs with an incidence > 5% overall) were COPD exacerbation (12.7% overall; 5.7% placebo, 6.0% olodaterol 5 µg, 2.7% olodaterol 10 µg), and nasopharyngitis (7.6% overall; 4.7% placebo, 4.7% olodaterol 5 µg, 8.2% olodaterol 10 µg). The majority of AEs were mild to moderate in intensity, with severe AEs reported for 12 patients (7.6%) overall: one patient receiving placebo, six patients receiving olodaterol 5 µg and five patients receiving olodaterol 10 µg. There was one death reported for a patient receiving olodaterol 10 µg. The patient received five days of study treatment; the investigator reported the event upon reading of the death in an obituary and confirming the death with the patient's family doctor. No further information was available. An additional death was reported for a patient during screening; the patient did not receive study medication. Serious AEs during treatment were reported for 14 patients (8.9%). All but one SAE were considered not related to study drug; one patient receiving olodaterol 5 µg was reported with atrial fibrillation that was considered related to study drug. All patients recovered from their SAEs, except for one patient who died. The only SAE to occur in more than one patient was COPD exacerbation (two patients). The overall occurrence of SAEs and drug-related AEs was low and was similar between treatments. Three patients (one patient receiving placebo and two patients receiving olodaterol 5 µg) discontinued study drug due to AEs: one patient receiving placebo discontinued due to the SAE COPD exacerbation; one patient receiving olodaterol 5 µg discontinued due to the SAE atrial fibrillation and one patient discontinued due to the AE COPD exacerbation. An AE of COPD was classified as "other significant" AEs according to ICH E3 criteria. No changes indicative of an adverse effect were seen on any laboratory parameters, vital signs, or ECG parameters.

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Conclusions:

The primary objective of the present study was met, with olodaterol 5 µg once daily and olodaterol 10 µg once daily showing a statistically significant increase compared to placebo for the primary endpoint of exercise endurance time during constant work rate cycle ergometry at 75% maximal work capacity on Day 43. One of the secondary objectives of the study was also met, with olodaterol 5 µg once daily and olodaterol 10 µg once daily showing statistically significant increases compared to placebo in inspiratory capacity at isotime. The other secondary objective was not met since there were no statistically significant decreases compared to placebo in the intensity of breathing discomfort at isotime during constant work rate cycle ergometry at 75% maximal work capacity on Day 43. For the primary endpoint, the magnitude of response for olodaterol 5 µg and olodaterol 10 µg was similar. Olodaterol 5 µg once daily and olodaterol 10 µg once daily were generally safe and well tolerated; there were no safety concerns identified.

Trial Synopsis - Appendix

The result tables on the following pages supplement the trial results presented in the Trial Synopsis. The appended tables provide complete disposition results and results of secondary endpoints, as summarised below. The number of secondary endpoints defined for this trial was too large to allow meaningful presentation in this format; therefore, results for at least 10 secondary endpoints are provided in the Trial Synopsis and the following tables.

Results for	**presented in**
Disposition of patients	Table 15.1.1: 1
IC response at -30 minutes pre-dose after 6 weeks IC response at 1-hour post-dose after 6 weeks	Table 15.2.4.1: 3
FRC response at -30 minutes pre-dose after 6 weeks FRC response at 1-hour post-dose after 6 weeks	Table 15.2.4.1: 1
FEV_1 response at -30 minutes pre-dose after 6 weeks FEV_1 response at 1-hour post-dose after 6 weeks	Table 15.2.4.2: 1
FVC response at -30 minutes pre-dose after 6 weeks FVC response at 1-hour post-dose after 6 weeks	Table 15.2.4.2: 3

Table 15.1.1: 1 Disposition of patients

	Placebo	Olo 5ug	Olo 10ug	Total
Enrolled				204
Not entered/randomsed				47
Entered/randomised				157
Not treated				0
Treated	149(100.00)	150(100.00)	147(100.00)	157(100.00)
Not prematurely discontinued from trial medication #	144(96.64)	142(94.67)	138(93.88)	133(84.71)
Prematurely discontinued from trial medication	5(3.36)	8(5.33)	9(6.12)	
Adverse event	3(2.01)	8(5.33)	5(3.40)	
AE study dis. worse	1(0.67)	1(0.67)	2(1.36)	
AE-oth. dis. worse	1(0.67)	2(1.33)	0(0.00)	
AE-other	1(0.67)	5(3.33)	3(2.04)	
Non compl prot.	1(0.67)	0(0.00)	1(0.68)	
Lost to follow-up	1(0.67)	0(0.00)	0(0.00)	
Consent withdrawn	0(0.00)	0(0.00)	1(0.68)	
Other	0(0.00)	0(0.00)	2(1.36)	

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

Source data: Appendix 16.2.1, Listing 1 ctr\eot-t20-disp.sas 14JUN2011

Table 15.2.4.1: 3 Adjusted mean* (SE) IC response [L] after 6 weeks - analysis with imputation (FAS)

				Difference to Placebo		
Planned time	Treatment	N	Treatment mean (SE)	Mean (SE)	P-value	95% CI
-0:30	Placebo	147	2.463 (0.041)			
	Olo 5ug	146	2.613 (0.041)	0.150 (0.040)	0.0002	(0.071, 0.228)
	Olo 10ug	142	2.618 (0.042)	0.154 (0.040)	0.0001	(0.076, 0.233)
1:00	Placebo	147	2.493 (0.040)			
	Olo 5ug	146	2.725 (0.040)	0.232 (0.036)	<.0001	(0.162, 0.303)
	Olo 10ug	142	2.696 (0.040)	0.203 (0.036)	<.0001	(0.133, 0.273)

Based on a mixed effects repeated measures model. The model includes treatment, baseline and period as fixed effects and patient as a random effect, along with compound symmetry as a covariance structure for within-patient variation.

Common baseline mean: 2.503 (0.062)

Source data: Appendix 16.1.9.2, Statdoc 6.4.1.2 ctr\bodybox-adjmean-mmrm-time.sas 14JUN2011

Table 15.2.4.1: 1 Adjusted mean* (SE) FRC response [L] after 6 weeks - analysis with imputation (FAS)

				Difference to Placebo		
Planned time	Treatment	N	Treatment mean (SE)	Mean (SE)	P-value	95% CI
-0:30	Placebo	147	4.842 (0.062)			
	Olo 5ug	145	4.757 (0.063)	-0.086 (0.053)	0.1048	(-0.190, 0.018)
	Olo 10ug	141	4.723 (0.063)	-0.120 (0.053)	0.0246	(-0.224, -0.015)
1:00	Placebo	147	4.770 (0.065)			
	Olo 5ug	145	4.557 (0.065)	-0.213 (0.053)	<.0001	(-0.318, -0.108)
	Olo 10ug	141	4.583 (0.065)	-0.187 (0.054)	0.0005	(-0.293, -0.082)

Based on a mixed effects repeated measures model. The model includes treatment, baseline and period as fixed effects and patient as a random effect, along with compound symmetry as a covariance structure for within-patient variation.

Common baseline mean: 4.801 (0.102)

Source data: Appendix 16.1.9.2, Statdoc 6.4.1.1 ctr\bodybox-adjmean-mmrm-time.sas 14JUN2011

Table 15.2.4.2: 1 Adjusted mean* (SE) FEV1 response [L] after 6 weeks - analysis with imputation (FAS)

				Difference to Placebo		
Planned time	Treatment	N	Treatment mean (SE)	Mean (SE)	P-value	95% CI
-0:30	Placebo	146	1.520 (0.024)			
	Olo 5ug	143	1.630 (0.025)	0.110 (0.019)	<.0001	(0.073, 0.148)
	Olo 10ug	139	1.630 (0.025)	0.110 (0.019)	<.0001	(0.073, 0.148)
1:00	Placebo	146	1.577 (0.026)			
	Olo 5ug	143	1.768 (0.026)	0.192 (0.021)	<.0001	(0.151, 0.233)
	Olo 10ug	139	1.771 (0.026)	0.195 (0.021)	<.0001	(0.153, 0.236)

Based on a mixed effects repeated measures model. The model includes treatment, baseline and period as fixed effects and patient as a random effect, along with compound symmetry as a covariance structure for within-patient variation.

Common baseline mean: 1.553 (0.043)

Source data: Appendix 16.1.9.2, Statdoc 6.4.2.1 ctr\eot-t4-pft-adjmean-time.sas 14JUN2011

Table 15.2.4.2: 3 Adjusted mean* (SE) FVC response [L] after 6 weeks - analysis with imputation (FAS)

				Difference to Placebo		
Planned time	Treatment	N	Treatment mean (SE)	Mean (SE)	P-value	95% CI
-0:30	Placebo	146	3.103 (0.039)			
	Olo 5ug	143	3.222 (0.040)	0.119 (0.036)	0.0013	(0.047, 0.191)
	Olo 10ug	139	3.222 (0.040)	0.119 (0.037)	0.0013	(0.047, 0.191)
1:00	Placebo	146	3.144 (0.039)			
	Olo 5ug	143	3.409 (0.040)	0.265 (0.035)	<.0001	(0.196, 0.333)
	Olo 10ug	139	3.425 (0.040)	0.281 (0.035)	<.0001	(0.212, 0.350)

Based on a mixed effects repeated measures model. The model includes treatment, baseline and period as fixed effects and patient as a random effect, along with compound symmetry as a covariance structure for within-patient variation.

Common baseline mean: 3.160 (0.072)

Source data: Appendix 16.1.9.2, Statdoc 6.4.2.2 ctr\eot-t4-pft-adjmean-time.sas 14JUN2011