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.:** 2009-014395-21	
Name of active ingredient: Olodaterol, BI 1744 CL		**Page:** 1 of 6	**Synopsis No.:**
Module:		**Volume:**	
Report date: 28 March 2012	**Trial No. / U No.:** 1222.37 / U10-3196-02	**Date of trial:** 23 JAN 2010 – 16 APR 2011	**Date of revision:** 11 April 2012

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 1744CL (5 µg [2 actuations of 2.5µg] and 10 µg [2 actuations of 5µg]) 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 oladaterol with placebo on constant work rate exercise tolerance after 6 weeks of treatment in patients with COPD. Secondary objectives were to compare the effects of oladaterol 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

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Name of active ingredient: Olodaterol, BI 1744 CL		**Page:** 2 of 6	**Synopsis No.:**
Module:		**Volume:**	
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actual:	enrolled: 201 Treatment Olodaterol 5 µg: entered: 147 treated: 147 analyzed (for primary endpoint): 140 Treatment Olodaterol 10µg: entered: 143 treated: 143 analyzed (for primary endpoint): 136 Treatment Placebo: entered: 143 treated: 143 analyzed (for primary endpoint): 136
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 inhalation solution – Respimat®
dose:	5 µg once daily (ex mouthpiece: calculated as free base BI 1744 BS)
mode of admin.:	Oral inhalation
batch no.:	B072000346
Test product:	Olodaterol inhalation solution – Respimat®
dose:	10 µg once daily (ex mouthpiece: calculated as free base BI 1744 BS)
mode of admin.:	Oral inhalation
batch no.:	B072000356
Reference therapy:	Placebo - inhalation solution – Respimat®
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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Name of active ingredient: Olodaterol, BI 1744 CL		**Page:** 3 of 6	**Synopsis No.:**
Module:		**Volume:**	
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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)]. Subgroups were analyzed by baseline endurance time (quartiles) and by baseline locus of symptom limitation (breathing discomfort, leg discomfort, breathing 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 $\log_{10}$ transformation was applied to the endurance time prior to the analysis of the primary endpoint; log10 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 during constant work rate cycle ergometry to symptom limitation at 75% of maximal work capacity (ET) was 414 seconds (sec) (6 minutes [min]: 54 sec). After six weeks of treatment, the mean ET was 370 sec for placebo, 422 sec for olodaterol 5 µg, and 421 sec for olodaterol 10 µg. Compared with placebo, the 14.0% improvement in ET for olodaterol 5 µg (95% CI = 1.065, 1.221) and the 13.8% improvement in ET for olodaterol 10 µg (95% CI = 1.062, 1.219) were statistically significant ($p \leq 0.0003$). There was no significant difference in ET between the olodaterol 5 µg and10 µg after six weeks.

Key secondary endpoints

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Name of active ingredient: Olodaterol, BI 1744 CL		**Page:** 4 of 6	**Synopsis No.:**
Module:		**Volume:**	
Report date: 28 March 2012	**Trial No. / U No.:** 1222.37 / U10-3196-02	**Date of trial:** 23 JAN 2010 – 16 APR 2011	**Date of revision:** 11 April 2012

- For the key secondary endpoint, IC at isotime after six weeks, both olodaterol 5 µg and olodaterol 10 µg increased adjusted mean IC, compared with placebo, with adjusted mean differences of 0.182 L ($p < 0.0001$) and 0.174 L ($p < 0.0001$), respectively. In addition, compared with placebo, both olodaterol 5 µg and olodaterol 10 µg increased adjusted mean IC at pre-exercise ($p < 0.0001$) and at end of exercise ($p < 0.0001$ for olodaterol 5 µg and $p = 0.0003$ for olodaterol 10 µg). There was no significant difference between olodaterol doses at any of the three time points.
- For intensity of breathing discomfort (Borg Category Ratio Scale) measured at isotime during exercise, after six weeks of treatment, the difference between olodaterol 5 µg and placebo was -0.766 ($p=0.0007$) and the difference between olodaterol 10 µg and placebo was -0.634 ($p=0.0051$). At the end of exercise, the difference between olodaterol 5 µg and placebo was -0.088 ($p=0.5698$) and the difference between olodaterol 10 µg and placebo was 0.256 ($p=0.1003$). There was no significant difference between olodaterol doses on breathing discomfort.

Other secondary endpoints:

- Using body plethysmography, both olodaterol doses had significant effects, compared with placebo, on FRC at 1 hour post-dose and on IC at both 30 minutes pre-dose and 1 hour post-dose.
- FEV_1 and FVC were significantly increased, compared with placebo, by both olodaterol doses at both 30 minutes pre-dose and at 1 hour post-dose.

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Module:		**Volume:**	
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Safety results:

In this six-week crossover study, olodaterol was generally safe and well tolerated. During the treatment phase, the overall occurrence of adverse events (AEs) was low and similar across the three treatments, ranging from 26.6% in placebo to 33.3% in olodaterol 5 µg. As expected in this population, the most frequently reported treatment emergent adverse events (TEAEs) were respiratory events. The most common AEs overall (AEs with an incidence > 4% overall) were (placebo, olodaterol 5 µg, olodaterol 10 µg) COPD exacerbation (7.0%, 7.5%, 4.9%), dyspnea (2.1%, 2.7%, 1.4%), nasopharyngitis (2.8%, 2.0%, 0.7%), and cough (1.4%, 0.7%, 2.1%). The majority of AEs were mild to moderate in intensity, with severe AEs reported for eight patients (5.3% overall): one patient (0.7%) for placebo, four patients (2.7%) for olodaterol 5 µg, and three patients (2.1%) for olodaterol 10 µg. The percentage of patients reporting any AE was low and comparable across treatments, with no apparent dose relationship observed for any AE.

There were no deaths in the study. Serious AEs during treatment were reported for nine patients (6.0%), none of which were considered related to study drug; all patients recovered from their SAEs. The only SAE to occur in more than one patient was COPD exacerbation (five patients). The overall occurrence of SAEs and drug-related AEs was low and was similar between treatments.

Ten patients discontinued study drug due to AEs, including three who discontinued due to SAEs. Adverse events of anxiety, COPD exacerbation, constipation, lung neoplasm, headache, and prostatitis were 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 with placebo for the primary endpoint of exercise endurance time during constant work rate cycle ergometry at 75% maximal work capacity on Day 43. The secondary objectives of the study were also met, with olodaterol 5 µg once daily and olodaterol 10 µg once daily showing statistically significant increases compared with placebo in inspiratory capacity at isotime and statistically significant decreases compared with 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 and both key secondary endpoints, 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 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 up to a total of 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 at pre-exercise after 6 weeks IC at end-of-exercise after 6 weeks	Table 15.2.2: 1
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				201
Not entered/randomsed				50
Entered/randomised				151
Not treated				0
Treated	143(100.00)	147(100.00)	143(100.00)	151(100.00)
Not prematurely discontinued from trial medication #	137(95.80)	139(94.56)	140(97.90)	133(88.08)
Prematurely discontinued from trial medication	6(4.20)	8(5.44)	3(2.10)	
Adverse event	4(2.80)	4(2.72)	2(1.40)	
AE study dis. worse	2(1.40)	1(0.68)	0(0.00)	
AE-oth. dis. worse	0(0.00)	1(0.68)	0(0.00)	
AE-other	2(1.40)	2(1.36)	2(1.40)	
Non compl prot.	1(0.70)	1(0.68)	0(0.00)	
Consent withdrawn	1(0.70)	0(0.00)	0(0.00)	
Other	0(0.00)	3(2.04)	1(0.70)	

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

Table 15.2.2: 1 Adjusted mean* (SE) IC during exercise [L] and comparisons to placebo after 6 weeks - analysis with imputation (FAS)

					Difference to Placebo		
Time point	Treatment	N	Time[mm:ss]	Treatment mean (SE)	Mean (SE)	P-value	95% CI
Pre-exercise	Placebo	134	00:00	2.220 (0.032)			
	Olo 5ug	139	00:00	2.478 (0.032)	0.258 (0.034)	<.0001	(0.191, 0.325)
	Olo 10ug	133	00:00	2.513 (0.032)	0.294 (0.035)	<.0001	(0.226, 0.362)
Isotime	Placebo	136	05:58	1.917 (0.038)			
	Olo 5ug	140	06:02	2.099 (0.038)	0.182 (0.036)	<.0001	(0.112, 0.252)
	Olo 10ug	135	06:03	2.091 (0.038)	0.174 (0.036)	<.0001	(0.104, 0.245)
End-exercise	Placebo	136	07:26	1.887 (0.035)			
	Olo 5ug	140	08:13	2.067 (0.035)	0.180 (0.037)	<.0001	(0.107, 0.252)
	Olo 10ug	135	08:18	2.024 (0.035)	0.137 (0.037)	0.0003	(0.064, 0.210)

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 within-patient variation.
Pre-exercise common baseline mean(se) = 2.293 (0.061)
Isotime common baseline mean(se) = 2.035 (0.066)
End-exercise common baseline mean(se) = 1.995 (0.064)

Source data: Appendix 16.1.9.2, Statdoc 6.2.1 ctr\ic-adjmean-mmrm.sas 11NOV2011

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	134	4.977 (0.062)			
	Olo 5ug	139	4.855 (0.061)	-0.122 (0.069)	0.0784	(-0.258, 0.014)
	Olo 10ug	134	4.862 (0.062)	-0.115 (0.070)	0.1013	(-0.252, 0.023)
1:00	Placebo	134	4.950 (0.064)			
	Olo 5ug	139	4.740 (0.063)	-0.210 (0.066)	0.0015	(-0.339, -0.081)
	Olo 10ug	134	4.577 (0.064)	-0.373 (0.066)	<.0001	(-0.503, -0.243)

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: 5.017 (0.116)

Source data: Appendix 16.1.9.2, Statdoc 6.4.1.1 ctr\bodybox-adjmean-mmrm-time.sas 15JUN2011

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	136	1.475 (0.017)			
	Olo 5ug	137	1.564 (0.017)	0.089 (0.017)	<.0001	(0.056, 0.123)
	Olo 10ug	137	1.576 (0.017)	0.101 (0.017)	<.0001	(0.068, 0.134)
1:00	Placebo	136	1.473 (0.019)			
	Olo 5ug	137	1.698 (0.019)	0.224 (0.017)	<.0001	(0.191, 0.258)
	Olo 10ug	137	1.699 (0.019)	0.226 (0.017)	<.0001	(0.193, 0.259)

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: 1.478 (0.043)

Source data: Appendix 16.1.9.2, Statdoc 6.4.2.1 ctr\eot-t4-pft-adjmean-time.sas 15JUN2011

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	135	3.212 (0.037)			
	Olo 5ug	136	3.319 (0.037)	0.107 (0.031)	0.0006	(0.046, 0.167)
	Olo 10ug	136	3.310 (0.037)	0.098 (0.031)	0.0017	(0.037, 0.158)
1:00	Placebo	135	3.187 (0.034)			
	Olo 5ug	136	3.471 (0.034)	0.285 (0.029)	<.0001	(0.227, 0.342)
	Olo 10ug	136	3.477 (0.034)	0.290 (0.029)	<.0001	(0.233, 0.348)

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: 3.221 (0.073)

Source data: Appendix 16.1.9.2, Statdoc 6.4.2.2 ctr\eot-t4-pft-adjmean-time.sas 15JUN2011