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:		**EudraCT No.:** 2008-000562-23	
Name of active ingredient: BI 1744 plus tiotropium		**Page:** 1 of 3	**Synopsis No.:**
Module:		**Volume:**	
Report date: 15 JUL 2010	**Trial No. / U No.:** 1237.9/ U10-3444-01	**Date of trial:** 14 JUL 2008 – 20 FEB 2009	**Date of revision:** Not applicable

Title of trial:	Randomised, double-blind, cross-over study to assess the efficacy and safety of 4 weeks of once daily treatment of 2 doses of orally inhaled BI 1744 CL, each in fixed dose combination (FDC) with 5 µg tiotropium bromide (delivered by the respimat® inhaler) in patients with COPD
Coordinating Investigator:	[redacted]
Trial sites:	Multicentre Study, [redacted]
Publication (reference):	Data from this study have not been published.
Clinical phase:	IIb
Objectives:	To determine the optimum dose(s) of BI 1744 administered as a FDC with 5 µg tiotropium (Tio 5) delivered by the RESPIMAT I inhaler, once daily for 4 weeks in patients with chronic obstructive pulmonary disease (COPD).
Methodology:	Randomised, double-blind, cross-over study. Patients were randomized to 1 of 2 treatment regimens (BI 1744 2 µg FDC followed by BI 1744 5 µg FDC or BI 1744 5 µg FDC followed by BI 1744 2 µg FDC) There was a 14-day Washout Period before initiation of the second treatment.
No. of subjects:	
planned:	entered: 120
actual:	enrolled: 183; entered: 141 treated set (TS): 141; full analysis set (FAS): 136 per-protocol set (PPS): 96; analysed (for primary endpoint): 136
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 ≥30% and <80% predicted [ECSC criteria]; post-bronchodilator FEV_1/FVC <70%.
Test product:	BI 1744 plus tiotropium inhalation solution via RESPIMAT
dose:	2 µg BI 1744 plus 5 µg tiotropium (BI 1744 2/T5) 5 µg BI 1744 plus 5 µg tiotropium (BI 1744 5/T5)
mode of admin.:	Oral inhalation
batch no.:	2 µg BI 1744 : B072000288, 5 µg BI 1744: B072000300

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Reference therapy:	Not applicable. Each patient served as their own control.
dose:	
mode of admin.:	
batch no.:	
Duration of treatment:	4 weeks of once daily treatment with each study medication
	Other treatment: 5 µg tiotropium administered daily during the Run-In and Washout Periods (Batch No. 609410-6L0034)
Criteria for evaluation:	
Efficacy / clinical pharmacology results:	FEV_1, FVC, a m. PEFR, p m. PEFR, rescue medication use, Physician Global Evaluation, Patient Global Rating
Safety:	Adverse events, laboratory tests, vital signs, 12-lead electrocardiogram (ECG), and physical examination.
Statistical methods:	Analysis of covariance with terms for center, patient within center, treatment, and treatment period as fixed classification effects, and period baseline as a linear covariate; descriptive statistics

SUMMARY – CONCLUSIONS:

Efficacy / clinical pharmacology results:	For the primary efficacy endpoint (trough FEV_1 response [L] after 4 weeks of treatment), the difference between treatments was not statistically significant. There was some evidence of dose separation on Day 15 for FEV_1 and FVC.
Safety results:	BI 1744 (2 and 5 µg) in combination with 5 µg of tiotropium taken once daily for 4 weeks (Treatment Period 1) followed by a 2-week Washout Period, and treatment with the alternate BI 1744 FDC once daily for 4 weeks (Treatment Period 2) was well tolerated in adult COPD patients. The safety profile of BI 1744 FDC with tiotropium was consistent with the patient population and the known adverse event (AE) profiles for BI 1744 and tiotropium monotherapies, with no unexpected safety findings.

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Safety results (cont):	AEs were primarily mild to moderate in intensity and were occurred in a greater percentage of patients in the lower FDC (BI 1744 2/T5) treatment group than in the higher FDC (BI 1744 5/T5) treatment group (44% vs. 38%, respectively). There were few patients with related AEs (2.2%, 3/139). As expected in this patient population, AEs were primarily respiratory-related. Eight (8) patients reported 1 or more SAE during the Treatment Period; none were considered related to the study medications. SAEs appeared balanced across treatment groups (3 and 5 SAEs in the BI 1744 2/T5 and BI 1744 5/T5 treatment groups, respectively). Two additional SAEs were reported during the Screening Period. There were no deaths, and few discontinuations due to AEs. There were no significant safety findings with respect to AEs, laboratory evaluations, vital signs, ECGs, or physical examinations.
Conclusions:	**Primary Endpoint:** Clinically relevant improvements from baseline for the primary efficacy endpoint (trough FEV_1 response [L] after 4 weeks of treatment) were observed following treatment with both FDC dose levels of BI 1744 studied in this trial (BI 1744 2/T5 and BI 1744 5/T5). The degree of bronchodilation compared to baseline was similar between the 2 dose levels and similar to that observed for these dose levels in a parallel, supportive study that included a third BI 1744 FDC level, 10 µg (Study 1237.4, [U09 1588-01]). However, the primary endpoint and primary objective of the current study were not met as the improvement in FEV_1 in the BI 1744 5/T5 group was not statistically significantly greater than the improvement in FEV1 in the BI 1744 2/T5 group. There was some evidence of dose separation at Day 15 in FEV_1 and FVC. Full interpretation of the results of this study (in the context of the dose response of BI 1744 in fixed combination with tiotropium 5 µg) requires additional consideration of the results of the supportive study, 1237.4, which included a third dose level (10 µg) of BI 1744. **Safety:** The safety profile of once daily administration of BI 1744 (2 and 5 µg) in combination with 5 µg tiotropium bromide via the RESPIMAT Inhaler over 4 weeks was consistent with the patient population and known safety profiles of each study medication; there were no unexpected safety findings. As expected in this patient population, AEs were primarily respiratory-related. There were few patients with related AEs or with SAEs (none related).

Trial Synopsis – Appendix

The result tables on the following pages supplement the trial results presented in the Trial Synopsis. The appended tables provide the specific data results for patient disposition, adverse events and for the primary and many secondary endpoints. The number of secondary endpoints (EPs) defined for this trial was too large to allow meaningful presentation in this format; therefore, results for up to 12 secondary endpoints are provided in the Trial Synopsis and the following tables.

Results for	**presented in**
Patient Disposition	Table 15.1.1:1
Trough FEV_1 response after 4 weeks of treatment (Primary EP) Trough FEV_1 response after 2 weeks of treatment (Secondary EP)	Table 15.2.1.1.1: 1
Trough FVC response after 2 and 4 weeks of treatment (Secondary EP)	Table 15.2.1.2.1: 1
FEV_1 AUC_{0-3h} response after first dose and 2 weeks of treatment (Secondary EP) FEV_1 AUC_{0-3h} response after 4 weeks of treatment (Secondary EP)	Table 15.2.1.1.3: 1
FEV_1 AUC_{0-6h} response after 4 weeks of treatment (Secondary EP)	Table 15.2.1.1.3: 4
FVC AUC_{0-3h} response after first dose and 2 weeks of treatment (Secondary EP) FVC AUC_{0-3h} response after 4 weeks of treatment (Secondary EP)	Table 15.2.1.2.3: 1
FVC AUC_{0-6h} response after 4 weeks of treatment (Secondary EP)	Table 15.2.1.2.3: 4
Weekly Pre-dose Morning PEF over 4 weeks of treatment (Secondary EP)	Table 15.2.2.1: 1
Weekly Pre-dose Evening PEF over 4 weeks of treatment (Secondary EP)	Table 15.2.2.2: 1
Weekly Mean Number of Occasions Rescue Salbutamol Used Per Day over 4 weeks of treatment (Secondary EP)	Table 15.2.3: 2
Patients Global Rating Scores after 4 weeks of treatment (Secondary EP)	Table 15.2.4: 1
Adverse Events Summary	Table 15.3.2: 1

Table 15.1.1: 1 Disposition of patients

	Total
Enrolled	183
Not entered/randomised	42
Entered/randomised	141(100.00)
Treated	141(100.00)
Not prematurely discontinued from trial medication	131(92.91)
Prematurely discontinued from trial medication	10(7.09)
Adverse event	7(4.96)
AE study dis. worse	1(0.71)
AE-oth. dis. worse	2(1.42)
AE-other	4(2.84)
Non compl prot.	3(2.13)
Plan. time reached	0(0.00)
Lack of efficacy	0(0.00)
Lost to follow-up	0(0.00)
Consent withdrawn	0(0.00)
Other	0(0.00)

Table 15.2.1.1.1: 1 Adjusted mean* (SE) BI 1744 CL FEV1 trough response [L] treatment comparison over 4 weeks - analysis with imputation (FAS)

Test day	Mean (SE) BI1744 2/T5	Mean (SE) BI1744 5/T5	Difference Mean (SE)	Difference p-value	Difference 95% C.I.
15	0.037 (0.015)	0.059 (0.015)	0.023 (0.019)	0.2425	(-0.015, 0.061)
29	0.057 (0.013)	0.055 (0.013)	-0.002 (0.017)	0.8937	(-0.035, 0.031)

* Based on an ANCOVA with terms for baseline, treatment, centre, patient within centre and period (all effects fixed).
Number of patients : BI1744 2/T5 (136), BI1744 5/T5 (136)
Baseline mean (se) = at visit 2 (1.387 (0.502)), at visit 5 (1.359 (0.499))

Source data: Appendix 16.1.9.2, Statdoc 6.1.1.1 eot\type10.sas 30JUN2009

Table 15.2.1.2.1: 1 Adjusted mean* (SE) BI 1744 CL FVC trough response [L] treatment comparison over 4 weeks - analysis with imputation (FAS)

Test day	Mean (SE) BI1744 2/T5	Mean (SE) BI1744 5/T5	Difference Mean (SE)	Difference p-value	Difference 95% C.I.
15	0.072 (0.024)	0.104 (0.025)	0.032 (0.031)	0.2944	(-0.029, 0.094)
29	0.066 (0.022)	0.076 (0.023)	0.010 (0.028)	0.7180	(-0.046, 0.066)

* Based on an ANCOVA with terms for baseline, treatment, centre, patient within centre and period (all effects fixed).
Number of patients : BI1744 2/T5 (136), BI1744 5/T5 (136)
Baseline mean (se) = at visit 2 (2.843 (0.870)), at visit 5 (2.811 (0.871))

Source data: Appendix 16.1.9.2, Statdoc 6.1.2.1 eot\type10.sas 01JUL2009

Table 15.2.1.1.3: 1 Adjusted mean* (SE) BI 1744 CL FEV1 AUC(0-3h) response [L] treatment comparison over 4 weeks - analysis with imputation (FAS)

Test day	Mean (SE) BI1744 2/T5	Mean (SE) BI1744 5/T5	Difference Mean (SE)	Difference p-value	Difference 95% C.I.
1	0.168 (0.006)	0.173 (0.006)	0.005 (0.008)	0.5198	(-0.010, 0.021)
15	0.174 (0.012)	0.194 (0.012)	0.020 (0.016)	0.2110	(-0.011, 0.051)
29	0.201 (0.011)	0.200 (0.011)	-0.001 (0.014)	0.9368	(-0.029, 0.027)

* Based on an ANCOVA with terms for baseline, treatment, centre, patient within centre and period (all effects fixed).
Number of patients : BI1744 2/T5 (136), BI1744 5/T5 (136)
Baseline mean (se) = at visit 2 (1.387 (0.502)), at visit 5 (1.359 (0.499))

Source data: Appendix 16.1.9.2, Statdoc 6.1.1.3 eot\type10.sas 30JUN2009

Table 15.2.1.1.3: 4 Adjusted mean* (SE) BI 1744 CL FEV1 AUC(0-6h) response [L] treatment comparison after 4 weeks - analysis with imputation (FAS)

Mean (SE)		Difference		
BI1744 2/T5	BI1744 5/T5	Mean (SE)	p-value	95% C.I.
0.202 (0.012)	0.206 (0.012)	0.004 (0.015)	0.7906	(-0.026, 0.034)

* Based on an ANCOVA with terms for baseline, treatment, centre, patient within centre and period (all effects fixed).
Number of patients : BI1744 2/T5 (136), BI1744 5/T5 (136)
Baseline mean (se) = at visit 2 (1.387 (0.502)), at visit 5 (1.359 (0.499))

Table 15.2.1.2.3: 1 Adjusted mean* (SE) BI 1744 CL FVC AUC(0-3h) response [L] treatment comparisons over 4 weeks - analysis with imputation (FAS)

Test day	Mean (SE) BI1744 2/T5	Mean (SE) BI1744 5/T5	Difference Mean (SE)	Difference p-value	Difference 95% C.I.
1	0.273 (0.012)	0.275 (0.012)	0.001 (0.015)	0.9384	(-0.029, 0.032)
15	0.271 (0.020)	0.308 (0.021)	0.037 (0.026)	0.1583	(-0.014, 0.088)
29	0.275 (0.021)	0.303 (0.022)	0.029 (0.027)	0.2914	(-0.025, 0.082)

* Based on an ANCOVA with terms for baseline, treatment, centre, patient within centre and period (all effects fixed).
Number of patients : BI1744 2/T5 (136), BI1744 5/T5 (136)
Baseline mean (se) = at visit 2 (2.843 (0.870)), at visit 5 (2.811 (0.871))

Source data: Appendix 16.1.9.2, Statdoc 6.1.2.2 eot\type10.sas 01JUL2009

Table 15.2.1.2.3: 4 Adjusted mean* (SE) BI 1744 CL FVC AUC(0-6h) response [L] treatment comparisons after 4 weeks - analysis with imputation (FAS)

Mean (SE)		Difference		
BI1744 2/T5	BI1744 5/T5	Mean (SE)	p-value	95% C.I.
0.283 (0.023)	0.318 (0.024)	0.035 (0.030)	0.2485	(-0.024, 0.094)

* Based on an ANCOVA with terms for baseline, treatment, centre, patient within centre and period (all effects fixed).
Number of patients : BI1744 2/T5 (136), BI1744 5/T5 (136)
Baseline mean (se) = at visit 2 (2.843 (0.870)), at visit 5 (2.811 (0.871))

Table 15.2.2.1: 1 Adjusted mean* (SE) (of weekly mean) pre-dose morning PEFR [L/min] treatment comparison over 4 weeks - analysis with imputation (FAS)

	Mean (SE)		Difference		
Week	BI1744 2/T5	BI1744 5/T5	Mean (SE)	p-value	95% C.I.
1	244.16 (1.713)	245.28 (1.693)	1.119 (2.177)	0.6081	(-3.190, 5.429)
2	242.38 (1.842)	243.72 (1.821)	1.339 (2.342)	0.5686	(-3.296, 5.973)
3	242.31 (1.805)	242.97 (1.784)	0.653 (2.294)	0.7765	(-3.888, 5.194)
4	242.90 (2.000)	244.56 (1.977)	1.654 (2.543)	0.5166	(-3.379, 6.686)

* Based on an ANCOVA with terms for baseline, treatment, centre, patient within centre and period (all effects fixed).
Number of patients : BI1744 2/T5 (131), BI1744 5/T5 (132)
Baseline mean (se) = at visit 2 (238.767 (96.907)), at visit 5 (237.225 (96.939))

Source data: Appendix 16.1.9.2, Statdoc 6.2.1 eot\type20.sas 27MAY2010

Table 15.2.2.2: 1 Adjusted mean* (SE) (of weekly mean) evening PEFR [L/min] treatment comparison over 4 weeks - analysis with imputation (FAS)

	Mean (SE)		Difference		
Week	BI1744 2/T5	BI1744 5/T5	Mean (SE)	p-value	95% C.I.
1	262.21 (2.026)	265.51 (2.024)	3.303 (2.585)	0.2037	(-1.813, 8.418)
2	261.08 (2.146)	262.47 (2.144)	1.393 (2.738)	0.6118	(-4.027, 6.813)
3	258.62 (1.959)	260.32 (1.956)	1.695 (2.498)	0.4988	(-3.251, 6.640)
4	261.38 (1.942)	260.34 (1.940)	-1.039 (2.478)	0.6757	(-5.944, 3.865)

* Based on an ANCOVA with terms for baseline, treatment, centre, patient within centre and period (all effects fixed).
Number of patients : BI1744 2/T5 (131), BI1744 5/T5 (130)
Baseline mean (se) = at visit 2 (253.069 (100.019)), at visit 5 (253.052 (101.068))

Source data: Appendix 16.1.9.2, Statdoc 6.2.2 eot\type20.sas 27MAY2010

Table 15.2.3: 2 Adjusted mean* (SE) (of weekly mean) number of occasions of rescue salbutamol used per day treatment comparison over 4 - analysis with imputation (FAS)

	Mean (SE)		Difference		
Week	BI1744 2/T5	BI1744 5/T5	Mean (SE)	p-value	95% C.I.
1	1.294 (0.063)	1.305 (0.062)	0.011 (0.080)	0.8901	(-0.147, 0.169)
2	1.472 (0.068)	1.352 (0.067)	-0.120 (0.086)	0.1647	(-0.290, 0.050)
3	1.369 (0.071)	1.367 (0.070)	-0.002 (0.090)	0.9822	(-0.180, 0.176)
4	1.403 (0.071)	1.363 (0.069)	-0.040 (0.090)	0.6542	(-0.218, 0.137)

* Based on an ANCOVA with terms for baseline, treatment, centre, patient within centre and period (all effects fixed).
Number of patients : BI1744 2/T5 (131), BI1744 5/T5 (132)
Baseline mean (se) = at visit 2 (1.529 (2.136)), at visit 5 (1.533 (1.948))

Source data: Appendix 16.1.9.2, Statdoc 6.3.1 eot\type20.sas 27MAY2010

Table 15.2.4: 1 Adjusted mean* (SE) Patients Global Rating scores treatment comparison after 4 weeks - observed case analysis (FAS)

Mean (SE)		Difference		
BI1744 2/T5	BI1744 5/T5	Mean (SE)	p-value	95% C.I.
3.207 (0.091)	3.093 (0.090)	-0.114 (0.116)	0.3269	(-0.342, 0.115)

* Based on an ANOVA with terms for treatment, centre, patient within centre and period (all effects fixed).
Number of patients : BI1744 2/T5 (133), BI1744 5/T5 (135)

Source data: Appendix 16.1.9.2, Statdoc 6.4.1 eot\pgr_oc.sas 30JUN2009

Table 15.3.2: 1 Adverse event overall summary - treated set

Treatment analysis: TEEA trt emergent AEs (WO=21d)

	BI1744 2/T5 N (%)	BI1744 5/T5 N (%)
Number of patients	139 (100.0)	138 (100.0)
Patients with any AE	61 (43.9)	52 (37.7)
Patients with severe AEs	3 (2.2)	5 (3.6)
Patients with investigator defined drug-related AEs	3 (2.2)	0 (0.0)
Patients with other significant AEs (according to ICH E3)	4 (2.9)	0 (0.0)
Patients with AEs leading to discontinuation of trial drug	5 (3.6)	2 (1.4)
Patients with serious AEs	3 (2.2)	5 (3.6)
Fatal	0 (0.0)	0 (0.0)
Imm life-threatening	0 (0.0)	1 (0.7)
Disability/incap.	0 (0.0)	0 (0.0)
Req.hospitalisation	3 (2.2)	3 (2.2)
Prol.hospitalisation	0 (0.0)	0 (0.0)
Congenital anomaly	0 (0.0)	0 (0.0)
Other	0 (0.0)	1 (0.7)

A patient may be counted in more than one seriousness criterion.
Percentages are calculated using total number of patients per treatment as the denominator.
MedDRA version used for reporting: 11.1