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.:** 2007-005087-26	
Name of active ingredient: BI 1744 plus tiotropium; tiotropium		**Page:** 1 of 6	**Synopsis No.:**
Module:		**Volume:**	
Report date: 7 April 2010	**Trial No. / U No.:** 1237.4 / U09-1588-01	**Date of trial:** 25 JUN 2008 – 10 FEB 2009	**Date of revision:** Not applicable

Title of trial:	Randomised, Double-Blind, Parallel Group Study to Assess the Efficacy and Safety of 4 Weeks of Once Daily Treatment of 3 Doses of Orally Inhaled BI 1744 CL, each in fixed dose combination with 5 µg Tiotropium Bromide (Delivered by the Respimat® Inhaler) compared with 5µg Tiotropium Bromide Monoproduct (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 of BI 1744 in fixed dose combination with tiotropium (5 µg) delivered by the Respimat Inhaler once daily for 4 weeks in patients with chronic obstructive pulmonary disease (COPD).
Methodology:	Randomised, double-blind, parallel group comparing 4 groups over 4 weeks
No. of subjects:	
planned:	entered: 320
actual:	enrolled: 537 treated set (TS): 360 full analysis set (FAS): 360 entered: 360 per-protocol set (PPS): 284 post-treated set (PTRT): 346 **2 µg BI 1744 plus 5µg tiotropium (BI 1744 2/T5):** entered: 89; treated: 89; analysed (for primary endpoint): 89 (FAS), 70 (PPS) **5 µg BI 1744 plus 5µg tiotropium (BI 1744 5/T5):** entered: 93; treated: 93; analysed (for primary endpoint): 93 (FAS), 75 (PPS) **10 µg BI 1744 plus 5µg tiotropium (BI 1744 10/T5):** entered: 88; treated: 88; analysed (for primary endpoint): 88 (FAS), 70 (PPS) **5 µg tiotropium (Tio 5):** entered: 90; treated: 90; analysed (for primary endpoint): 90 (FAS), 69 (PPS)

Name of company: Boehringer Ingelheim		**Tabulated Trial Report**	Boehringer Ingelheim
Name of finished product:		**EudraCT No.:** 2007-005087-26	
Name of active ingredient: BI 1744 plus tiotropium; tiotropium		**Page:** 2 of 6	**Synopsis No.:**
Module:		**Volume:**	
Report date: 7 April 2010	**Trial No. / U No.:** 1237.4 / U09-1588-01	**Date of trial:** 25 JUN 2008 – 10 FEB 2009	**Date of revision:** Not applicable

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% predicted and <80% predicted [ECSC criteria]; post-bronchodilator FEV_1/FVC <70%.
Test product:	BI 1744 plus tiotropium inhalation solution via RESPIMAT
dose:	2 µg, 5 µg, or 10 µg BI 1744 plus 5 µg tiotropium
mode of admin.:	Oral inhalation
batch no.	2 µg; B072000288, 5 µg: B072000300, 10 µg: B72000320
Reference therapy:	tiotropium inhalation solution via RESPIMAT
dose:	5 µg tiotropium
mode of admin.:	Oral inhalation
batch no.	609410-6L0034
Duration of treatment:	4 weeks
Criteria for evaluation:	
Efficacy / clinical pharmacology:	
Efficacy:	Trough FEV_1 response, FEV_1, FVC, a m. PEF, p.m. PEF, rescue medication use, Physician Global Evaluation, Patient Global Evaluation.
Pharmacokinetics:	Plasma and urine concentrations of BI 1744 BS and tiotropium.
Safety:	Adverse events, laboratory tests, vital signs, 12-lead electrocardiogram (ECG), physical examination.
Statistical methods:	Analysis of covariance with terms for centre, treatment, and baseline; descriptive statistics.

Name of company: Boehringer Ingelheim		**Tabulated Trial Report**	Boehringer Ingelheim
Name of finished product:		**EudraCT No.:** 2007-005087-26	
Name of active ingredient: BI 1744 plus tiotropium; tiotropium		**Page:** 3 of 6	**Synopsis No.:**
Module:		**Volume:**	
Report date: 7 April 2010	**Trial No. / U No.:** 1237.4 / U09-1588-01	**Date of trial:** 25 JUN 2008 – 10 FEB 2009	**Date of revision:** Not applicable

SUMMARY – CONCLUSIONS:

Efficacy / clinical pharmacology results:

Efficacy

After 4 weeks of once daily treatment with fixed dose combinations (FDC) of BI 1744 2 µg, 5 µg, or 10 µg with 5 µg tiotropium (BI 1744 2/T5, BI 1744 5/T5, and BI 1744 10/T5, respectively) compared to monotherapy with tiotropium 5 µg (Tio 5) delivered by the Respimat Inhaler dose-ordering was observed for pre- and post-dose FEV_1; the dose-separation was more pronounced for pre- and post-dose FVC.

For the primary efficacy endpoint (trough FEV_1 response [L] after 4 weeks of treatment), only the highest FDC (BI 1744 10/T5) resulted in a statistically significant improvement compared with Tio 5 monotherapy (0.168 [0.021] L vs. 0.110 [0.021] L; treatment difference: 0.057 [0.027] L, p = 0.0337). For BI 1744 10/T5, there were also statistically significant improvements (compared with Tio 5 monotherapy) in FEV_1 $peak_{0-3h}$ response (0.410 (0.024) L vs. 0.266 (0.024) L, treatment difference: 0.144 (0.033) L, p <0.0001), and FEV_1 AUC_{0-6h} response (0.322 [0.024] L vs. 0.194 [0.023] L); treatment difference: 0.128 (0.031), p <0.0001), and in trough FVC response, FVC $peak_{0-3h}$ response, and FVC AUC_{0-6h} response. Results from other secondary efficacy endpoints (weekly mean morning and evening peak flow, rescue medication use, Patient Global Rating) were consistent with the results for FEV_1 and FVC.

Increases in trough FEV_1 response compared with Tio 5 reached statistical significance for BI 1744 5/T5 on Days 8 and 15, and for BI 1744 2/T5 on Day 8. Overall, the dose-response relationship was consistent with a previous 4-week study with BI 1744 monotherapy, in which BI 1744 (2 µg) was shown to be on the steep part of the dose-response curve. Furthermore, the middle dose in the current study (BI 1744 5/T5) showed some variability of response (i.e., at 1 timepoint or endpoint) similar to BI 1744 2/T5 or BI 1744 10/T5, while in other cases between that for BI 1744 2/T5 and 10/T5. Similar variability of response has previously been observed with BI 1744 5 µg monotherapy.

Name of company: Boehringer Ingelheim		**Tabulated Trial Report**	Boehringer Ingelheim
Name of finished product:		**EudraCT No.:** 2007-005087-26	
Name of active ingredient: BI 1744 plus tiotropium; tiotropium		**Page:** 4 of 6	**Synopsis No.:**
Module:		**Volume:**	
Report date: 7 April 2010	**Trial No. / U No.:** 1237.4 / U09-1588-01	**Date of trial:** 25 JUN 2008 – 10 FEB 2009	**Date of revision:** Not applicable

Efficacy / clinical pharmacology results (continued):

Pharmacokinetics

BI 1744

Plasma concentrations of BI 1744 BS after repeated treatment with the lowest FDC (BI 1744 CL 2/T5) generally were too low to quantify. After repeated treatment with BI 1744 CL 5/T5 and BI 1744 CL 10/T5, plasma concentrations were sufficiently high to calculate a limited set of PK parameters. Geometric mean maximum plasma concentrations (gMean $C_{max,ss}$) -were observed around 10 minutes (min) after dosing and amounted to 4.39 pg/mL (gCV 49.2%; BI 1744 CL 5/T5) and 6.87 pg/mL (gCV 56.1%, BI 1744 CL 10/T5). The corresponding gMean $AUC_{0-1,ss}$ values were 3.97 pg·h/mL (gCV 49.4%) and 5.82 pg·h/mL (gCV 50.5%), respectively. Dose-normalized $AUC_{0-1,ss}$ and $C_{max,ss}$ values were slightly higher following BI 1744 CL 5/T5 treatment compared with BI 1744 CL 10/T5. This finding was most likely due to the fact that the parameter estimates for the BI 1744 CL 5/T5 treatment group were based on a smaller number of patients ($AUC_{0-1,ss}$: N = 28/93, $C_{max,ss}$: N = 42/93) than in the BI 1744 CL 10/T5 treatment group ($AUC_{0-1,ss}$: N = 52/88, $C_{max,ss}$: N = 59/88), which represented those with relatively high systemic exposure, while patients with plasma concentrations below the limit of quantification were not taken into account.

Urinary excretion of BI 1744 BS up to 6 h after dosing in all 3 dose groups accounted for 1.11 to 1.20% of the dose, supporting the assumption that systemic exposure to BI 1744 BS increases proportionally within the dose range 2 to 10 µg BI 1744 CL in combination with 5 µg tiotropium.

Tiotropium

Plasma concentration profiles and PK parameters of tiotropium following repeated treatment with each BI 1744 CL FDC were similar and comparable to findings following treatment with Tio 5 monotherapy. Maximum plasma concentrations of tiotropium following repeated inhalation of all FDCs (BI 1744 CL 2/T5, 5/T5, and 10/T5) and Tio 5 monotherap were observed around 5 to 8 min after dosing. Geometric mean $C_{max,ss}$ values amounted to 12.4 to 14.4 pg/mL (gCV 64.7 to 75.3%), and gMean $AUC_{0-3,ss}$ values were 21.0 to 21.9 pg/h/mL (gCV 42.8 to 47.9%). Urinary excretion of tiotropium up to 6 h after dosing accounted for 5.58 to 6.59% of the dose.

Name of company: Boehringer Ingelheim		**Tabulated Trial Report**	Boehringer Ingelheim
Name of finished product:		**EudraCT No.:** 2007-005087-26	
Name of active ingredient: BI 1744 plus tiotropium; tiotropium		**Page:** 5 of 6	**Synopsis No.:**
Module:		**Volume:**	
Report date: 7 April 2010	**Trial No. / U No.:** 1237.4 / U09-1588-01	**Date of trial:** 25 JUN 2008 – 10 FEB 2009	**Date of revision:** Not applicable

Safety results:	BI 1744 (2, 5, and 10 µg) in combination with 5 µg of tiotropium taken once daily for 4 weeks was well tolerated in adult COPD patients. The safety profile of BI 1744 in fixed dose combination with tiotropium was consistent with the patient population and the known AE profiles for BI 1744 and tiotropium monotherapies, with no unexpected safety findings. AEs were primarily mild to moderate in intensity and were equally distributed across treatment groups. There were few patients with related AEs (4.2%, 15/360). As expected in this patient population, AEs (including SAEs) were primarily respiratory events. Nine patients reported 1 or more SAEs; none were considered related to study drug. SAEs appeared balanced across the treatment groups (0 to 4 SAEs per group), with no SAE reported in the highest FDC group (BI 1744 10/T5). The single fatal SAE (esophageal cancer) occurred after the Follow-up Period in a patient treated with Tio 5 monotherapy. There were no significant safety findings with respect to AEs, laboratory evaluations, vital signs, ECGs, or physical examination.
Conclusions:	**Primary Endpoint:** The primary efficacy endpoint (trough FEV_1 response [L] after 4 weeks of treatment) was met for BI 1744 10/T5. After 4 weeks once daily treatment, BI 1744 10/T5 showed statistically significant increases compared with tiotropium (5 µg) monotherapy (Tio 5) in FEV_1 and FVC, pre-dose (trough), and throughout the 6-hour post-dose period. These observations demonstrated that additional bronchodilator efficacy can be achieved when combining BI 1744 (a LABA) and tiotropium (a LAAC) compared with tiotropium monotherapy. **Dose-response:** BI 1744 doses in fixed combination with tiotropium showed dose ordering. The doses to be investigated in further studies were determined (BI 1744 10/T5 and BI 1744 5/T5). Therefore, the primary objective of the study was met.

Name of company: Boehringer Ingelheim		**Tabulated Trial Report**	Boehringer Ingelheim
Name of finished product:		**EudraCT No.:** 2007-005087-26	
Name of active ingredient: BI 1744 plus tiotropium; tiotropium		**Page:** 6 of 6	**Synopsis No.:**
Module:		**Volume:**	
Report date: 7 April 2010	**Trial No. / U No.:** 1237.4 / U09-1588-01	**Date of trial:** 25 JUN 2008 – 10 FEB 2009	**Date of revision:** Not applicable

Conclusions (continued)

Pharmacokinetics: Plasma concentration-time profiles of BI 1744 BS and tiotropium observed in the present study were consistent with those observed in previous studies in healthy volunteers and COPD patients.

Plasma concentration profiles and PK parameters of tiotropium following inhalation of each FDC (BI 1744 CL 2/T5, 5/T5, and 10/T5) and Tio 5 monotherapy were comparable. This finding is consistent with the results from a dedicated PK interaction study in COPD patients, which provided evidence that there is no relevant influence of BI 1744 BS on the PK of tiotropium and vice versa.

Systemic exposure to BI 1744 BS in this study was comparable to that observed in studies of BI 1744 CL monotherapy.

Safety: The safety profile of once daily administration of BI 1744 (up to 10 µg) in combination with 5 µg tiotropium 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 (including SAEs) were primarily respiratory events. There were few patients with related AEs (4.2%, 15/360) and few patients with SAEs (2.5%, 9/360; none related). The single fatal SAE (esophageal cancer) occurred after the Follow-up Period in a patient treated with Tio 5 monotherapy. In addition, there were few discontinuations due to AEs (none in the highest FDC).

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 16 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 1 and 2 weeks of treatment (Secondary EP)	Table 15.2.1.1.1: 1
Trough FVC response after 1, 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 1and 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: 5
FEV_1 $Peak_{0-3h}$ response after first dose and 1 and 2 weeks of treatment (Secondary EP) FEV_1 $Peak_{0-3h}$ response after 4 weeks of treatment (Secondary EP)	Table 15.2.1.1.4: 1
FVC AUC_{0-3h} response after first dose and 1and 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: 5
FVC $Peak_{0-3h}$ response after first dose and 1 and 2 weeks of treatment (Secondary EP) FVC $Peak_{0-3h}$ response after 4 weeks of treatment (Secondary EP)	Table 15.2.1.2.4: 1
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

	Tio 5	BI1744 2/T5	BI1744 5/T5	BI1744 10/T5	Total
Enrolled					537
Not entered/randomised					177
Entered/randomised	90(100.00)	89(100.00)	93(100.00)	88(100.00)	360(100.00)
Treated	90(100.00)	89(100.00)	93(100.00)	88(100.00)	360(100.00)
Not prematurely discontinued from trial medication	86(95.56)	87(97.75)	90(96.77)	84(95.45)	347(96.39)
Prematurely discontinued from trial medication	4(4.44)	2(2.25)	3(3.23)	4(4.55)	13(3.61)
Adverse event	3(3.33)	1(1.12)	2(2.15)	1(1.14)	7(1.94)
AE study dis. worse	1(1.11)	1(1.12)	0(0.00)	0(0.00)	2(0.56)
AE-other	2(2.22)	0(0.00)	2(2.15)	1(1.14)	5(1.39)
Lack of efficacy	1(1.11)	0(0.00)	0(0.00)	0(0.00)	1(0.28)
Non compl prot.	0(0.00)	0(0.00)	0(0.00)	1(1.14)	1(0.28)
Consent withdrawn	0(0.00)	1(1.12)	0(0.00)	1(1.14)	2(0.56)
Other	0(0.00)	0(0.00)	1(1.08)	1(1.14)	2(0.56)

Table 15.2.1.1.1: 1 Adjusted mean* (SE) FEV1 trough response [L] and comparison to Tiotropium bromide 5 mcg over 4 weeks - analysis with imputation (FAS)

Test day	Treatment	Treatment Mean (SE)	Difference from Tio 5 Mean (SE)	p-value	95% C.I.
8	Tio 5	0.093 (0.020)			
	BI1744 2/T5	0.149 (0.020)	0.056 (0.026)	0.0302	(0.005, 0.107)
	BI1744 5/T5	0.154 (0.019)	0.061 (0.026)	0.0177	(0.011, 0.111)
	BI1744 10/T5	0.166 (0.020)	0.073 (0.026)	0.0053	(0.022, 0.124)
15	Tio 5	0.099 (0.020)			
	BI1744 2/T5	0.141 (0.020)	0.042 (0.026)	0.1163	(-0.010, 0.093)
	BI1744 5/T5	0.159 (0.020)	0.060 (0.026)	0.0224	(0.009, 0.111)
	BI1744 10/T5	0.154 (0.021)	0.055 (0.026)	0.0380	(0.003, 0.107)
29	Tio 5	0.110 (0.021)			
	BI1744 2/T5	0.134 (0.021)	0.024 (0.027)	0.3791	(-0.029, 0.076)
	BI1744 5/T5	0.143 (0.020)	0.033 (0.027)	0.2133	(-0.019, 0.085)
	BI1744 10/T5	0.168 (0.021)	0.057 (0.027)	0.0337	(0.004, 0.110)

* Based on an ANCOVA with terms for baseline, treatment, centre (centre random, all other effects fixed)
Number of patients : Tio 5 (90), BI1744 2/T5 (89), BI1744 5/T5 (93), BI1744 10/T5(88)
Common baseline mean (se) = 1.239 (0.481)

Source data: Appendix 16.1.9.2, Statdoc 6.1.1.1 eot\type10.sas 12FEB2010

Table 15.2.1.2.1: 1 Adjusted mean* (SE) FVC trough response [L] and comparison to Tiotropium bromide 5 mcg over 4 weeks - analysis with imputation (FAS)

Test day	Treatment	Treatment Mean (SE)	Difference from Tio 5 Mean (SE)	p-value	95% C.I.
8	Tio 5	0.156 (0.033)			
	BI1744 2/T5	0.215 (0.033)	0.059 (0.044)	0.1792	(-0.027, 0.146)
	BI1744 5/T5	0.265 (0.032)	0.110 (0.043)	0.0120	(0.024, 0.195)
	BI1744 10/T5	0.275 (0.033)	0.119 (0.044)	0.0070	(0.033, 0.206)
15	Tio 5	0.171 (0.034)			
	BI1744 2/T5	0.196 (0.034)	0.025 (0.044)	0.5714	(-0.061, 0.111)
	BI1744 5/T5	0.280 (0.033)	0.109 (0.043)	0.0120	(0.024, 0.194)
	BI1744 10/T5	0.285 (0.034)	0.114 (0.044)	0.0098	(0.028, 0.199)
29	Tio 5	0.189 (0.036)			
	BI1744 2/T5	0.191 (0.036)	0.002 (0.047)	0.9573	(-0.089, 0.094)
	BI1744 5/T5	0.288 (0.036)	0.099 (0.046)	0.0321	(0.009, 0.189)
	BI1744 10/T5	0.306 (0.037)	0.117 (0.047)	0.0125	(0.025, 0.209)

* Based on an ANCOVA with terms for baseline, treatment, centre (centre random, all other effects fixed)
Number of patients : Tio 5 (90), BI1744 2/T5 (89), BI1744 5/T5 (93), BI1744 10/T5(88)
Common baseline mean (se) = 2.522 (0.805)

Source data: Appendix 16.1.9.2, Statdoc 6.1.2.1 eot\type10.sas 12FEB2010

Table 15.2.1.1.3: 1 Adjusted mean* (SE) FEV1 AUC(0-3 h) response [L] and comparison to Tiotropium bromide 5 mcg over 4 weeks - analysis with imputation (FAS)

Test day	Treatment	Treatment Mean (SE)	Difference from Tio 5 Mean (SE)	p-value	95% C.I.
1	Tio 5	0.161 (0.016)			
	BI1744 2/T5	0.201 (0.016)	0.040 (0.022)	0.0674	(-0.003, 0.082)
	BI1744 5/T5	0.229 (0.016)	0.068 (0.021)	0.0016	(0.026, 0.110)
	BI1744 10/T5	0.225 (0.016)	0.064 (0.022)	0.0033	(0.022, 0.107)
8	Tio 5	0.204 (0.024)			
	BI1744 2/T5	0.289 (0.024)	0.086 (0.030)	0.0044	(0.027, 0.145)
	BI1744 5/T5	0.302 (0.023)	0.098 (0.030)	0.0010	(0.040, 0.156)
	BI1744 10/T5	0.315 (0.024)	0.111 (0.030)	0.0003	(0.052, 0.170)
15	Tio 5	0.201 (0.024)			
	BI1744 2/T5	0.288 (0.024)	0.087 (0.031)	0.0055	(0.026, 0.148)
	BI1744 5/T5	0.305 (0.024)	0.105 (0.031)	0.0007	(0.044, 0.165)
	BI1744 10/T5	0.309 (0.025)	0.108 (0.031)	0.0006	(0.047, 0.169)
29	Tio 5	0.191 (0.023)			
	BI1744 2/T5	0.276 (0.023)	0.085 (0.030)	0.0052	(0.026, 0.145)
	BI1744 5/T5	0.270 (0.022)	0.079 (0.030)	0.0086	(0.020, 0.138)
	BI1744 10/T5	0.316 (0.023)	0.125 (0.030)	<.0001	(0.066, 0.185)

* Based on an ANCOVA with terms for baseline, treatment, centre (centre random, all other effects fixed)
Number of patients : Tio 5 (90), BI1744 2/T5 (89), BI1744 5/T5 (93), BI1744 10/T5(88)
Common baseline mean (se) = 1.239 (0.481)

Source data: Appendix 16.1.9.2, Statdoc 6.1.1.3 eot\type10.sas 12FEB2010

Table 15.2.1.1.3: 5 Adjusted mean* (SE) FEV1 AUC(0-6 h) response [L] and comparison to Tiotropium bromide 5 mcg after 4 weeks - analysis with imputation (FAS)

Treatment	Treatment Mean (SE)	Difference from Tio 5 Mean (SE)	p-value	95% C.I.
Tio 5	0.194 (0.023)			
BI1744 2/T5	0.282 (0.023)	0.088 (0.031)	0.0048	(0.027, 0.149)
BI1744 5/T5	0.280 (0.023)	0.086 (0.031)	0.0056	(0.025, 0.146)
BI1744 10/T5	0.322 (0.024)	0.128 (0.031)	<.0001	(0.066, 0.189)

* Based on an ANCOVA with terms for baseline, treatment, centre (centre random, all other effects fixed)
Number of patients : Tio 5 (90), BI1744 2/T5 (89), BI1744 5/T5 (93), BI1744 10/T5(88)
Common baseline mean (se) = 1.239 (0.481)

Source data: Appendix 16.1.9.2, Statdoc 6.1.1.4 eot\type13.sas 21APR2009

Table 15.2.1.1.4: 1 Adjusted mean* (SE) FEV1 peak(0-3 h) response [L] and comparison to Tiotropium bromide 5 mcg over 4 weeks - analysis with imputation (FAS)

Test day	Treatment	Treatment Mean (SE)	Difference from Tio 5 Mean (SE)	p-value	95% C.I.
1	Tio 5	0.249 (0.019)			
	BI1744 2/T5	0.284 (0.019)	0.035 (0.025)	0.1614	(-0.014, 0.085)
	BI1744 5/T5	0.311 (0.019)	0.063 (0.025)	0.0126	(0.013, 0.112)
	BI1744 10/T5	0.321 (0.019)	0.072 (0.025)	0.0049	(0.022, 0.121)
8	Tio 5	0.276 (0.025)			
	BI1744 2/T5	0.359 (0.025)	0.083 (0.032)	0.0101	(0.020, 0.146)
	BI1744 5/T5	0.378 (0.024)	0.102 (0.032)	0.0014	(0.040, 0.164)
	BI1744 10/T5	0.397 (0.025)	0.121 (0.032)	0.0002	(0.058, 0.184)
15	Tio 5	0.276 (0.026)			
	BI1744 2/T5	0.361 (0.026)	0.085 (0.034)	0.0127	(0.018, 0.151)
	BI1744 5/T5	0.391 (0.026)	0.115 (0.033)	0.0007	(0.049, 0.180)
	BI1744 10/T5	0.386 (0.027)	0.110 (0.034)	0.0013	(0.043, 0.176)
29	Tio 5	0.266 (0.024)			
	BI1744 2/T5	0.353 (0.024)	0.088 (0.033)	0.0079	(0.023, 0.152)
	BI1744 5/T5	0.348 (0.024)	0.082 (0.032)	0.0120	(0.018, 0.146)
	BI1744 10/T5	0.410 (0.024)	0.144 (0.033)	<.0001	(0.080, 0.209)

* Based on an ANCOVA with terms for baseline, treatment, centre (centre random, all other effects fixed)
Number of patients : Tio 5 (90), BI1744 2/T5 (89), BI1744 5/T5 (93), BI1744 10/T5(88)
Common baseline mean (se) = 1.239 (0.481)

Source data: Appendix 16.1.9.2, Statdoc 6.1.1.5 eot\type10.sas 12FEB2010

Table 15.2.1.2.3: 1 Adjusted mean* (SE) FVC AUC(0-3 h) response [L] and comparison to Tiotropium bromide 5 mcg over 4 weeks - analysis with imputation (FAS)

Test day	Treatment	Treatment Mean (SE)	Difference from Tio 5 Mean (SE)	p-value	95% C.I.
1	Tio 5	0.268 (0.032)			
	BI1744 2/T5	0.331 (0.032)	0.063 (0.042)	0.1359	(-0.020, 0.146)
	BI1744 5/T5	0.413 (0.031)	0.145 (0.042)	0.0006	(0.062, 0.227)
	BI1744 10/T5	0.410 (0.032)	0.142 (0.042)	0.0009	(0.059, 0.225)
8	Tio 5	0.310 (0.042)			
	BI1744 2/T5	0.441 (0.042)	0.131 (0.053)	0.0141	(0.027, 0.236)
	BI1744 5/T5	0.493 (0.041)	0.183 (0.052)	0.0006	(0.080, 0.286)
	BI1744 10/T5	0.537 (0.042)	0.228 (0.053)	<.0001	(0.123, 0.332)
15	Tio 5	0.327 (0.044)			
	BI1744 2/T5	0.437 (0.044)	0.110 (0.054)	0.0437	(0.003, 0.217)
	BI1744 5/T5	0.513 (0.043)	0.186 (0.054)	0.0006	(0.081, 0.291)
	BI1744 10/T5	0.554 (0.044)	0.226 (0.054)	<.0001	(0.120, 0.333)
29	Tio 5	0.308 (0.043)			
	BI1744 2/T5	0.424 (0.043)	0.116 (0.056)	0.0384	(0.006, 0.225)
	BI1744 5/T5	0.492 (0.043)	0.184 (0.055)	0.0009	(0.076, 0.292)
	BI1744 10/T5	0.547 (0.044)	0.239 (0.056)	<.0001	(0.130, 0.349)

* Based on an ANCOVA with terms for baseline, treatment, centre (centre random, all other effects fixed)
Number of patients : Tio 5 (90), BI1744 2/T5 (89), BI1744 5/T5 (93), BI1744 10/T5(88)
Common baseline mean (se) = 2.522 (0.805)

Source data: Appendix 16.1.9.2, Statdoc 6.1.2.2 eot\type10.sas 12FEB2010

Table 15.2.1.2.3: 5 Adjusted mean* (SE) FVC AUC(0-6 h) response [L] and comparison to Tiotropium bromide 5 mcg after 4 weeks - analysis with imputation (FAS)

Treatment	Treatment Mean (SE)	Difference from Tio 5 Mean (SE)	p-value	95% C.I.
Tio 5	0.309 (0.044)			
BI1744 2/T5	0.429 (0.044)	0.120 (0.056)	0.0332	(0.010, 0.230)
BI1744 5/T5	0.492 (0.043)	0.183 (0.055)	0.0011	(0.074, 0.292)
BI1744 10/T5	0.547 (0.044)	0.238 (0.056)	<.0001	(0.128, 0.349)

* Based on an ANCOVA with terms for baseline, treatment, centre (centre random, all other effects fixed)
Number of patients : Tio 5 (90), BI1744 2/T5 (89), BI1744 5/T5 (93), BI1744 10/T5(88)
Common baseline mean (se) = 2.522 (0.805)

Source data: Appendix 16.1.9.2, Statdoc 6.1.2.3 eot\type13.sas 21APR2009

Table 15.2.1.2.4: 1 Adjusted mean* (SE) FVC peak(0-3 h) response [L] and comparison to Tiotropium bromide 5 mcg over 4 weeks - analysis with imputation (FAS)

Test day	Treatment	Treatment Mean (SE)	Difference from Tio 5 Mean (SE)	p-value	95% C.I.
1	Tio 5	0.428 (0.037)			
	BI1744 2/T5	0.476 (0.037)	0.049 (0.049)	0.3262	(-0.049, 0.146)
	BI1744 5/T5	0.576 (0.036)	0.148 (0.049)	0.0025	(0.052, 0.244)
	BI1744 10/T5	0.583 (0.037)	0.155 (0.049)	0.0019	(0.057, 0.252)
8	Tio 5	0.437 (0.043)			
	BI1744 2/T5	0.560 (0.043)	0.123 (0.057)	0.0311	(0.011, 0.235)
	BI1744 5/T5	0.615 (0.042)	0.179 (0.056)	0.0016	(0.068, 0.289)
	BI1744 10/T5	0.690 (0.043)	0.254 (0.057)	<.0001	(0.142, 0.366)
15	Tio 5	0.465 (0.047)			
	BI1744 2/T5	0.586 (0.047)	0.121 (0.059)	0.0414	(0.005, 0.237)
	BI1744 5/T5	0.648 (0.046)	0.183 (0.058)	0.0019	(0.068, 0.298)
	BI1744 10/T5	0.697 (0.047)	0.232 (0.059)	0.0001	(0.116, 0.348)
29	Tio 5	0.431 (0.045)			
	BI1744 2/T5	0.562 (0.045)	0.131 (0.060)	0.0296	(0.013, 0.249)
	BI1744 5/T5	0.634 (0.044)	0.204 (0.059)	0.0007	(0.087, 0.320)
	BI1744 10/T5	0.696 (0.046)	0.265 (0.060)	<.0001	(0.147, 0.383)

* Based on an ANCOVA with terms for baseline, treatment, centre (centre random, all other effects fixed)
Number of patients : Tio 5 (90), BI1744 2/T5 (89), BI1744 5/T5 (93), BI1744 10/T5(88)
Common baseline mean (se) = 2.522 (0.805)

Source data: Appendix 16.1.9.2, Statdoc 6.1.2.4 eot\type10.sas 12FEB2010

Table 15.2.2.1: 1 Adjusted mean* (SE) (of weekly mean) pre-dose morning PEFR [L/min] and comparison to Tiotropium bromide 5 mcg over 4 - analysis with imputation (FAS)

Week	Treatment	Treatment Mean (SE)	Difference from Tio 5 Mean (SE)	p-value	95% C.I.
1	Tio 5	227.81 (3.198)			
	BI1744 2/T5	244.43 (3.208)	16.621 (4.299)	0.0001	(8.163, 25.080)
	BI1744 5/T5	248.84 (3.174)	21.034 (4.278)	<.0001	(12.615, 29.452)
	BI1744 10/T5	248.76 (3.310)	20.949 (4.382)	<.0001	(12.326, 29.572)
2	Tio 5	228.57 (3.401)			
	BI1744 2/T5	240.87 (3.415)	12.303 (4.664)	0.0088	(3.126, 21.481)
	BI1744 5/T5	249.99 (3.377)	21.422 (4.642)	<.0001	(12.287, 30.556)
	BI1744 10/T5	247.77 (3.524)	19.205 (4.754)	<.0001	(9.850, 28.559)
3	Tio 5	228.82 (3.663)			
	BI1744 2/T5	239.61 (3.684)	10.793 (5.188)	0.0383	(0.584, 21.002)
	BI1744 5/T5	249.39 (3.639)	20.577 (5.165)	<.0001	(10.413, 30.741)
	BI1744 10/T5	248.33 (3.800)	19.510 (5.288)	0.0003	(9.104, 29.915)
4	Tio 5	226.49 (3.678)			
	BI1744 2/T5	234.14 (3.699)	7.647 (5.210)	0.1432	(-2.604, 17.899)
	BI1744 5/T5	249.17 (3.654)	22.674 (5.187)	<.0001	(12.467, 32.880)
	BI1744 10/T5	247.30 (3.816)	20.808 (5.310)	0.0001	(10.359, 31.256)

* Based on an ANCOVA with terms for baseline, treatment, centre (centre random, all other effects fixed)
Number of patients : Tio 5 (89), BI1744 2/T5 (88), BI1744 5/T5 (90), BI1744 10/T5(83)
Common baseline mean (se) = 220.70 (99.666)

Source data: Appendix 16.1.9.2, Statdoc 6.2.1 eot\type20.sas 21APR2009

Table 15.2.2.2: 1 Adjusted mean* (SE) (of weekly mean) evening PEFR [L/min] and comparison to Tiotropium bromide 5 mcg over 4 weeks - analysis with imputation (FAS)

Week	Treatment	Treatment Mean (SE)	Difference from Tio 5 Mean (SE)	p-value	95% C.I.
1	Tio 5	249.10 (3.419)			
	BI1744 2/T5	260.86 (3.425)	11.757 (4.387)	0.0078	(3.124, 20.390)
	BI1744 5/T5	267.47 (3.360)	18.365 (4.336)	<.0001	(9.832, 26.897)
	BI1744 10/T5	268.58 (3.510)	19.478 (4.453)	<.0001	(10.716, 28.241)
2	Tio 5	247.10 (3.804)			
	BI1744 2/T5	260.73 (3.814)	13.627 (4.983)	0.0066	(3.822, 23.431)
	BI1744 5/T5	267.31 (3.738)	20.204 (4.926)	<.0001	(10.511, 29.897)
	BI1744 10/T5	266.40 (3.909)	19.300 (5.057)	0.0002	(9.349, 29.251)
3	Tio 5	249.78 (3.765)			
	BI1744 2/T5	258.20 (3.791)	8.425 (5.323)	0.1145	(-2.048, 18.899)
	BI1744 5/T5	268.16 (3.702)	18.386 (5.267)	0.0006	(8.022, 28.751)
	BI1744 10/T5	265.67 (3.884)	15.888 (5.401)	0.0035	(5.260, 26.515)
4	Tio 5	246.77 (3.777)			
	BI1744 2/T5	253.12 (3.803)	6.350 (5.354)	0.2365	(-4.185, 16.886)
	BI1744 5/T5	266.61 (3.714)	19.841 (5.299)	0.0002	(9.415, 30.267)
	BI1744 10/T5	265.50 (3.896)	18.730 (5.433)	0.0006	(8.039, 29.421)

* Based on an ANCOVA with terms for baseline, treatment, centre (centre random, all other effects fixed)
Number of patients : Tio 5 (89), BI1744 2/T5 (88), BI1744 5/T5 (92), BI1744 10/T5(84)
Common baseline mean (se) = 234.39 (101.50)

Source data: Appendix 16.1.9.2, Statdoc 6.2.2 eot\type20.sas 21APR2009

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

Week	Treatment	Treatment Mean (SE)	Difference from Tio 5 Mean (SE)	p-value	95% C.I.
1	Tio 5	1.905 (0.155)			
	BI1744 2/T5	1.512 (0.155)	-0.393 (0.207)	0.0581	(-0.800, 0.014)
	BI1744 5/T5	1.504 (0.152)	-0.402 (0.205)	0.0510	(-0.805, 0.002)
	BI1744 10/T5	1.669 (0.159)	-0.237 (0.210)	0.2600	(-0.650, 0.176)
2	Tio 5	1.784 (0.178)			
	BI1744 2/T5	1.610 (0.177)	-0.174 (0.211)	0.4095	(-0.589, 0.241)
	BI1744 5/T5	1.476 (0.175)	-0.308 (0.209)	0.1411	(-0.718, 0.103)
	BI1744 10/T5	1.477 (0.182)	-0.306 (0.214)	0.1533	(-0.727, 0.115)
3	Tio 5	1.947 (0.183)			
	BI1744 2/T5	1.650 (0.182)	-0.297 (0.227)	0.1914	(-0.743, 0.149)
	BI1744 5/T5	1.492 (0.180)	-0.455 (0.225)	0.0437	(-0.897, -0.013)
	BI1744 10/T5	1.563 (0.187)	-0.384 (0.230)	0.0965	(-0.837, 0.069)
4	Tio 5	2.017 (0.172)			
	BI1744 2/T5	1.615 (0.172)	-0.402 (0.222)	0.0715	(-0.840, 0.035)
	BI1744 5/T5	1.602 (0.169)	-0.416 (0.220)	0.0601	(-0.849, 0.018)
	BI1744 10/T5	1.482 (0.176)	-0.535 (0.226)	0.0182	(-0.979, -0.092)

* Based on an ANCOVA with terms for baseline, treatment, centre (centre random, all other effects fixed)
Number of patients : Tio 5 (89), BI1744 2/T5 (89), BI1744 5/T5 (92), BI1744 10/T5(84)
Common baseline mean (se) = 2.531 (2.648)

Source data: Appendix 16.1.9.2, Statdoc 6.3.1 eot\type20.sas 21APR2009

Table 15.2.4: 1 Adjusted mean* (SE) Patients Global Rating scores and comparison to Tiotropium bromide 5 mcg after 4 weeks - observed case analysis (FAS)

Treatment	Treatment Mean (SE)	Difference from Tio 5 Mean (SE)	p-value	95% C.I.
Tio 5	2.866 (0.112)			
BI1744 2/T5	2.598 (0.111)	-0.268 (0.148)	0.0706	(-0.559, 0.023)
BI1744 5/T5	2.368 (0.109)	-0.498 (0.147)	0.0008	(-0.786, -0.209)
BI1744 10/T5	2.377 (0.113)	-0.489 (0.149)	0.0012	(-0.782, -0.195)

* Based on an ANCOVA with terms for treatment, centre (centre random, treatment effect fixed)
Number of patients : Tio 5 (86), BI1744 2/T5 (87), BI1744 5/T5 (90), BI1744 10/T5(84)

Table 15.3.2: 1 Adverse event overall summary - treated set

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

	Tio 5 N (%)	BI1744 2/T5 N (%)	BI1744 5/T5 N (%)	BI1744 10/T5 N (%)
Number of patients	90 (100.0)	89 (100.0)	93 (100.0)	88 (100.0)
Patients with any AE	31 (34.4)	30 (33.7)	27 (29.0)	29 (33.0)
Patients with severe AEs	3 (3.3)	4 (4.5)	2 (2.2)	0 (0.0)
Patients with investigator defined drug-related AEs	3 (3.3)	5 (5.6)	4 (4.3)	3 (3.4)
Patients with other significant AEs (according to ICH E3)	2 (2.2)	0 (0.0)	1 (1.1)	0 (0.0)
Patients with AEs leading to discontinuation of trial drug	3 (3.3)	1 (1.1)	2 (2.2)	0 (0.0)
Patients with serious AEs	2 (2.2)	3 (3.4)	1 (1.1)	0 (0.0)
Fatal	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)
Disability/incap.	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Req.hospitalisation	2 (2.2)	3 (3.4)	1 (1.1)	0 (0.0)
Prol.hospitalisation	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)
Other	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)

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