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: BI 1744 CL		**EudraCT No.:** 2006-004828-36	
Name of active ingredient: BI 1744 CL		**Page:** 1 of 5	**Synopsis No.:**
Module:		**Volume:**	
Report date: 26 MAR 2009	**Trial No. / U No.:** 1222.5 / U09-3125-01	**Date of trial:** 12 MAR 2007 – 14 JAN 2008	**Date of revision** (if applicable)**:** Not applicable

Title of trial:	Randomised, Double-Blind, Placebo-Controlled, Parallel Group Study to Assess the Efficacy and Safety of 4 Weeks of Once Daily Treatment of Orally Inhaled BI 1744 CL (2 µg, 5 µg, 10 µg, 20 µg) Delivered by the Respimat® Inhaler in Patients with COPD
Principal/Coordinating Investigator:	[redacted]
Trial sites:	Multicenter, c f. Appendix 16.1.4
Publication (reference):	Data of this study has not been published
Clinical phase:	II
Objectives:	To determine the optimum dose of BI 1744 CL inhalation solution delivered by the Respimat® inhaler once daily for four weeks in patients with COPD
Methodology:	Randomised, double-blind, placebo-controlled, parallel group design comparing 5 groups over 4 weeks
No. of subjects:	
planned:	entered: 400
actual:	enrolled: 621 entered: 405 Treatment 2 µg: entered: 81 treated: 81 analysed (for primary endpoint): Treatment 5 µg: entered: 80 treated: 80 analysed (for primary endpoint): Treatment 10 µg: entered: 86 treated: 86 analysed (for primary endpoint): Treatment 20 µg: entered: 79 treated: 79 analysed (for primary endpoint): Treatment placebo: entered: 79 treated: 79 analysed (for primary endpoint):

Name of company: Boehringer Ingelheim		**Tabulated Trial Report**	Boehringer Ingelheim
Name of finished product: BI 1744 CL		**EudraCT No.:** 2006-004828-36	
Name of active ingredient: BI 1744 CL		**Page:** 2 of 5	**Synopsis No.:**
Module:		**Volume:**	
Report date: 26 MAR 2009	**Trial No. / U No.:** 1222.5 / U09-3125-01	**Date of trial:** 12 MAR 2007 – 14 JAN 2008	**Date of revision** (if applicable)**:** 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; post-bronchodilator FEV_1/FVC <70%.
Test product:	BI 1744 CL inhalation solution via RESPIMAT®
dose:	2 µg, 5 µg, 10 µg, 20 µg (calculated as BI 1744 CL nominal dose)
mode of admin.:	Oral inhalation
batch no.:	2 µg: B062000158, 5 µg: B062000170, 10 µg: B062000283, 20 µg: B062000289
Reference therapy:	Placebo inhalation solution via RESPIMAT®
dose:	N/A
mode of admin.:	Oral inhalation
batch no.:	B062000159
Duration of treatment:	4 weeks
Criteria for evaluation:	
Efficacy / clinical pharmacology:	FEV_1, FVC, a m. / p m. PEFR, rescue medication use, COPD symptoms, Global Evaluation
Pharmacokinetics:	Plasma and urine concentrations of BI 1744 BS and selected metabolites
Safety:	Vital signs, 12-lead ECG, laboratory tests, adverse events, physical examinations
Statistical methods:	Analysis of covariance with terms for center, treatment and baseline; descriptive statistics
SUMMARY – CONCLUSIONS:	
Efficacy / clinical pharmacology results:	<u>Efficacy</u> Study 1222.3 had previously provided evidence of the bronchodilator efficacy of single doses of BI 1744 CL (2 µg, 5 µg, 10 µg, 20 µg) over the full 24-hour dosing interval in patients with COPD. The present study has provided further confirmation of the 24-hour bronchodilator efficacy of once daily administration with BI 1744 CL in patients with COPD, with statistically significant improvements in trough (pre-dose) FEV_1, FEV_1 peak $_{0\text{-}3h}$ and FEV_1 $AUC_{0\text{-}6h}$

Name of company: Boehringer Ingelheim		**Tabulated Trial Report**	Boehringer Ingelheim
Name of finished product: BI 1744 CL		**EudraCT No.:** 2006-004828-36	
Name of active ingredient: BI 1744 CL		**Page:** 3 of 5	**Synopsis No.:**
Module:		**Volume:**	
Report date: 26 MAR 2009	**Trial No. / U No.:** 1222.5 / U09-3125-01	**Date of trial:** 12 MAR 2007 – 14 JAN 2008	**Date of revision** (if applicable)**:** Not applicable

after 4 weeks of once daily treatment with BI 1744 CL (2 µg, 5 µg, 10 µg, 20 µg). Differences in trough FEV_1 (primary endpoint) compared with placebo after four weeks of treatment were: 0.061 L for 2 µg BI 1744 CL (p=0.02), 0.097 L for 5 µg BI 1744 CL (p=0.0003), 0.123 L for 10 µg BI 1744 CL (p<0.0001), and 0.132 L for 20 µg BI 1744 CL (p<0.0001). Differences in FEV_1 peak $_{0\text{-}3h}$ compared with placebo after four weeks of treatment were: 0.164 L for 2 µg BI 1744 CL, 0.169 L for 5 µg BI 1744 CL, 0.218 L for 10 µg BI 1744 CL, and 0.225 L for 20 µg BI 1744 CL (p<0.0001 for all doses). Differences in FEV_1 $AUC_{0\text{-}6h}$ compared with placebo after four weeks of treatment were: 0.141 L for 2 µg BI 1744 CL, 0.162 L for 5 µg BI 1744 CL, 0.213 L for 10 µg BI 1744 CL, and 0.214 L for 20 µg BI 1744 CL (p<0.0001 for all doses).

A clear dose-response relationship was observed with respect to pulmonary function. Doses of 10 µg and 20 µg BI 1744 CL showed a consistent increase in efficacy compared with 2 µg BI 1744 CL, suggesting that 2 µg BI 1744 CL is on the steep portion of the dose-response curve. When considering all the available data from the various pulmonary function parameters across the 4 weeks of treatment, the efficacy of 10 µg and 20 µg BI 1744 CL was quite similar, suggesting that both doses were on, or close to, the plateau of the dose-response curve. The relative efficacy of 5 µg BI 1744 CL compared with 2 µg and 10 µg BI 1744 CL was variable; in some cases, similar efficacy was observed with 2 µg and 5 µg BI 1744 CL; in some cases, similar efficacy was observed with 5 µg and 10 µg BI 1744 CL; and in some cases, the efficacy 5 µg BI 1744 CL was between the efficacy with 2 µg and the efficacy with 10 µg BI 1744 CL.

Pharmacokinetics

Steady state of BI 1744 BS and BI 1744 BS – glucuronide was reached on Day 8. Accumulation of BI 1744 BS based on C_{max} accounted for a factor of 1.12 (gCV 54.6%) to 1.34 (gCV 54.1%). Estimation based on $AUC_{0\text{-}3}$ provided a similar value, i.e. 1.37 (gCV 67.5%). Accumulation of BI 1744 BS – glucuronide based on C_{max} was in a comparable range, i.e. 1.04 (gCV 71.3%) to 1.13 (gCV 99.0%). $C_{max,ss}$ and $AUC_{0\text{-}1,ss}$ values of BI 1744 BS increased proportionally within the dose range 5 – 20 µg BI 1744 CL. The ratio between BI 1744 BS – glucuronide and BI 1744 BS at Day 29 was 0.592 (gCV 75.0%) to 0.697 (gCV 85.1%) based on $AUC_{0\text{-}6,ss}$. SOM 1522 BS could not be quantified in the majority of plasma and urine samples.

Name of company: Boehringer Ingelheim		**Tabulated Trial Report**	Boehringer Ingelheim
Name of finished product: BI 1744 CL		**EudraCT No.:** 2006-004828-36	
Name of active ingredient: BI 1744 CL		**Page:** 4 of 5	**Synopsis No.:**
Module:		**Volume:**	
Report date: 26 MAR 2009	**Trial No. / U No.:** 1222.5 / U09-3125-01	**Date of trial:** 12 MAR 2007 – 14 JAN 2008	**Date of revision** (if applicable)**:** Not applicable

	The small difference in systemic exposure to BI 1744 BS ($AUC_{0-6,ss}$, $AUC_{0-24,ss}$, and Cmax,ss) observed in patients with moderately impaired renal function as opposed to patients with normal renal function was not of concern. In addition, the differences in systemic exposure to BI 1744 BS related to age, weight, race (restricted to the comparison Black/White), and sex were not of concern. Systemic exposure ($AUC_{0-6,ss}$, $C_{max,ss}$) to BI 1744 BS in six patients with a predicted decreased CYP2C9 enzyme activity (*2/*2 and *2/*3) was not different from systemic exposure to BI 1744 BS observed in homozygote wild-type patients (CYP2C9*1/*1) and heterozygote patients (CYP2C9*1/*2, CYP2C9*1/*3). There was no trend towards an increase in systemic exposure to BI 1744 BS with decreased enzyme activity when comparing homozygote wild-type patients (CYP2C9*1/*1) with heterozygote allele carriers (CYP2C9*1/*3, CYP2C9*1/*2). Systemic exposure ($AUC_{0-6,ss}$, $C_{max,ss}$) to BI 1744 BS in one patient homozygous for *3 (CYP2C8*3/*3) was not different from systemic exposure to BI 1744 BS observed in homozygote wild-type patients (CYP2C8*1/*1) and heterozygote allele carriers (CYP2C8*1/*3). There was no trend towards an increase in systemic exposure to BI 1744 BS with decreased enzyme activity when comparing homozygote wild-type patients (CYP2C8*1/*1) with heterozygote allele carriers (CYP2C8*1/*3).
Safety results:	Adverse events were mostly mild to moderate in intensity and were equally distributed across all treatment groups. Eight patients experienced a serious adverse event. None were considered related to the study drug. There was a small increase in the 5 µg group in the number of patients that experienced a significant adverse event (as defined by ICH 3) and in adverse events leading to discontinuation. All doses showed a satisfactory safety and tolerability profile with respect to vital signs, laboratory evaluations, 12-lead ECGs and physical examination. There was no indication of effects of 2 µg, 5 µg, and 10 µg BI 1744 CL on systemic pharmacodynamic parameters known to be sensitive to β_2-agonists (potassium, heart rate, creatine phosphokinase). There was some indication that there was a pharmacodynamic effect on these two indicators at the 20 µg level.

Name of company: Boehringer Ingelheim		**Tabulated Trial Report**	Boehringer Ingelheim
Name of finished product: BI 1744 CL		**EudraCT No.:** 2006-004828-36	
Name of active ingredient: BI 1744 CL		**Page:** 5 of 5	**Synopsis No.:**
Module:		**Volume:**	
Report date: 26 MAR 2009	**Trial No. / U No.:** 1222.5 / U09-3125-01	**Date of trial:** 12 MAR 2007 – 14 JAN 2008	**Date of revision** (if applicable)**:** Not applicable

Conclusions:

In the present study, both primary objectives were met: (i) for all doses, significant increases in trough FEV_1 were observed after four weeks of once daily administration of BI 1744 CL, confirming the 24 hour duration of action of BI 1744 CL after chronic dosing, (ii) a clear dose-response relationship was observed with respect to pulmonary function; the 2 µg dose of BI 1744 CL was clearly on the steep part of the dose-response curve, while the similarity in effect of the 10 µg and 20 µg doses suggests that the plateau of the dose-response curve is reached at 10 µg BI 1744 CL.

All doses showed a satisfactory safety and tolerability profile with respect to adverse events, vital signs, laboratory evaluations and 12-lead ECGs and physical examination. There was no indication of effects of 2 µg, 5 µg, and 10 µg BI 1744 CL on systemic pharmacodynamic parameters known to be sensitive to β_2-agonists (potassium, heart rate, creatine phosphokinase). Small, and at certain time-points statistically significant, effects of 20 µg BI 1744 CL on these parameters suggest that the threshold of systemic pharmacodynamic activity is about 20 µg in patients with COPD, consistent with results in healthy volunteers and patients with asthma.

The results from the present study support the safety and tolerability of four weeks of once daily administration of BI 1744 CL up to 20 µg in patients with COPD. There were no safety or tolerability concerns that would preclude further clinical evaluation of BI 1744 CL in patients with COPD.

Pharmacokinetic data of BI 1744 BS, BI 1744 BS – glucuronide and SOM 1522 BS were consistent with the results of previous studies in healthy volunteers, COPD and asthma patients. Steady state of BI 1744 BS and BI 1744 BS – glucuronide was reached on Day 8. Accumulation of BI 1744 BS and BI 1744 BS – glucuronide in plasma was low and in the same range for both analytes. $C_{max,ss}$ and $AUC_{0-1,ss}$ values of BI 1744 BS increased proportionally within the dose range 5 – 20 µg BI 1744 CL. Small differences in systemic exposure related to certain covariates were not regarded of concern.

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, 11 additional secondary efficacy endpoints, and a summary of adverse events as summarised below.

Results for	**presented in**
Disposition of patients	Table 15.1.1: 1
Trough FEV_1 response at week 1 Trough FEV_1 response at week 2	Table 15.2.1.1.1: 1
FEV_1 $AUC_{(0-3h)}$ response after the first dose FEV_1 $AUC_{(0-3h)}$ response at week 1 FEV_1 $AUC_{(0-3h)}$ response at week 2	Table 15.2.1.1.3: 1
Trough FVC response at week 1 Trough FVC response at week 2 Trough FVC response at week 4	Table 15.2.1.2.1: 1
FVC $AUC_{(0-6h)}$ response at week 4	Table 15.2.1.2.3: 1
Peak $FEV_{1\ (0-3h)}$ response at Week 1 Peak $FEV_{1\ (0-3h)}$ response at Week 2	Table 15.2.1.1.4: 1
Adverse Events overall summary	Table 15.3.2: 1

Table 15.1.1: 1 Disposition of patients

	R Placebo	BI 1744 R2	BI 1744 R5	BI 1744 R10	BI 1744 R20	Total
Enrolled						621
Not entered/randomsed						216
Entered/randomised	79(100.00)	81(100.00)	80(100.00)	86(100.00)	79(100.00)	405(100.00)
Treated	79(100.00)	81(100.00)	80(100.00)	86(100.00)	79(100.00)	405(100.00)
Not prematurely discontinued from trial medication	74(93.67)	80(98.77)	73(91.25)	85(98.84)	76(96.20)	388(95.80)
Prematurely discontinued from trial medication	5(6.33)	1(1.23)	7(8.75)	1(1.16)	3(3.80)	17(4.20)
Adverse event	1(1.27)	1(1.23)	5(6.25)	0(0.00)	2(2.53)	9(2.22)
AE study dis. worse	1(1.27)	0(0.00)	1(1.25)	0(0.00)	1(1.27)	3(0.74)
AE-oth. dis. worse	0(0.00)	1(1.23)	2(2.50)	0(0.00)	0(0.00)	3(0.74)
AE-other	0(0.00)	0(0.00)	2(2.50)	0(0.00)	1(1.27)	3(0.74)
Lack of efficacy	2(2.53)	0(0.00)	0(0.00)	0(0.00)	0(0.00)	2(0.49)
Non compl prot.	0(0.00)	0(0.00)	1(1.25)	0(0.00)	0(0.00)	1(0.25)
Lost to follow-up	1(1.27)	0(0.00)	0(0.00)	0(0.00)	0(0.00)	1(0.25)
Consent withdrawn	1(1.27)	0(0.00)	1(1.25)	0(0.00)	0(0.00)	2(0.49)
Other	0(0.00)	0(0.00)	0(0.00)	1(1.16)	1(1.27)	2(0.49)

Patients [redacted] were discontinued after Visit 2 due to dosing error and re-randomized. These patients are only included once in all displays under patient numbers [redacted]. Separate listings of their safety data from the first to second randomization visits are given in the Appendix under patient numbers [redacted].

Source data: Appendix 16.2, Listing 1.1 disp_sa.sas 30SEP2008

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

Test day	Treatment	Treatment Mean (SE)	Difference from R Placebo Mean (SE)	p-value	95% C.I.
8	R Placebo	-0.029 (0.019)			
	BI 1744 R2	0.059 (0.018)	0.088 (0.025)	0.0004	(0.039, 0.137)
	BI 1744 R5	0.108 (0.019)	0.137 (0.025)	<.0001	(0.088, 0.186)
	BI 1744 R10	0.099 (0.018)	0.128 (0.024)	<.0001	(0.080, 0.176)
	BI 1744 R20	0.140 (0.019)	0.169 (0.025)	<.0001	(0.120, 0.218)
15	R Placebo	-0.023 (0.020)			
	BI 1744 R2	0.062 (0.020)	0.085 (0.026)	0.0011	(0.034, 0.136)
	BI 1744 R5	0.099 (0.020)	0.121 (0.026)	<.0001	(0.070, 0.173)
	BI 1744 R10	0.102 (0.020)	0.125 (0.026)	<.0001	(0.075, 0.175)
	BI 1744 R20	0.105 (0.020)	0.128 (0.026)	<.0001	(0.077, 0.179)
29	R Placebo	-0.014 (0.021)			
	BI 1744 R2	0.046 (0.021)	0.061 (0.027)	0.0233	(0.008, 0.113)
	BI 1744 R5	0.082 (0.021)	0.097 (0.027)	0.0003	(0.044, 0.149)
	BI 1744 R10	0.109 (0.021)	0.123 (0.026)	<.0001	(0.072, 0.175)
	BI 1744 R20	0.118 (0.021)	0.132 (0.027)	<.0001	(0.080, 0.185)

* Based on an ANCOVA with terms for baseline, treatment, centre (centre random, all other effects fixed)
Number of patients : R Placebo (79), BI 1744 R2 (81), BI 1744 R5 (80), BI 1744 R10 (86), BI 1744 R20 (79)
Common baseline mean (se) = 1.253 (0.479)

Source data: Appendix 16.1.9.2, Statdoc 6.1.1.1 type10.sas 11MAR2009

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

Test day	Treatment	Treatment Mean (SE)	Difference from R Placebo Mean (SE)	p-value	95% C.I.
1	R Placebo	0.031 (0.017)			
	BI 1744 R2	0.165 (0.017)	0.133 (0.022)	<.0001	(0.090, 0.176)
	BI 1744 R5	0.203 (0.017)	0.172 (0.022)	<.0001	(0.128, 0.215)
	BI 1744 R10	0.236 (0.017)	0.204 (0.022)	<.0001	(0.162, 0.247)
	BI 1744 R20	0.234 (0.017)	0.203 (0.022)	<.0001	(0.159, 0.246)
8	R Placebo	-0.000 (0.022)			
	BI 1744 R2	0.186 (0.022)	0.187 (0.028)	<.0001	(0.131, 0.243)
	BI 1744 R5	0.215 (0.022)	0.215 (0.029)	<.0001	(0.159, 0.271)
	BI 1744 R10	0.218 (0.021)	0.218 (0.028)	<.0001	(0.163, 0.273)
	BI 1744 R20	0.247 (0.022)	0.247 (0.029)	<.0001	(0.191, 0.304)
15	R Placebo	0.006 (0.024)			
	BI 1744 R2	0.166 (0.024)	0.159 (0.030)	<.0001	(0.100, 0.219)
	BI 1744 R5	0.200 (0.024)	0.194 (0.030)	<.0001	(0.134, 0.253)
	BI 1744 R10	0.209 (0.023)	0.203 (0.030)	<.0001	(0.144, 0.262)
	BI 1744 R20	0.211 (0.024)	0.204 (0.030)	<.0001	(0.145, 0.264)
29	R Placebo	0.016 (0.024)			
	BI 1744 R2	0.158 (0.024)	0.142 (0.031)	<.0001	(0.081, 0.203)
	BI 1744 R5	0.174 (0.024)	0.158 (0.031)	<.0001	(0.097, 0.219)
	BI 1744 R10	0.221 (0.024)	0.205 (0.031)	<.0001	(0.145, 0.265)
	BI 1744 R20	0.226 (0.024)	0.210 (0.031)	<.0001	(0.148, 0.271)

* Based on an ANCOVA with terms for baseline, treatment, centre (centre random, all other effects fixed)
Number of patients : R Placebo (79), BI 1744 R2 (81), BI 1744 R5 (80), BI 1744 R10 (86), BI 1744 R20 (79)
Common baseline mean (se) = 1.253 (0.479)

Source data: Appendix 16.1.9.2, Statdoc 6.1.1.4 type10.sas 11MAR2009

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

Test day	Treatment	Treatment Mean (SE)	Difference from R Placebo Mean (SE)	p-value	95% C.I.
8	R Placebo	-0.020 (0.033)			
	BI 1744 R2	0.090 (0.033)	0.110 (0.044)	0.0127	(0.024, 0.197)
	BI 1744 R5	0.154 (0.033)	0.174 (0.044)	<.0001	(0.087, 0.261)
	BI 1744 R10	0.149 (0.032)	0.170 (0.043)	0.0001	(0.084, 0.255)
	BI 1744 R20	0.151 (0.033)	0.171 (0.044)	0.0001	(0.084, 0.258)
15	R Placebo	-0.000 (0.040)			
	BI 1744 R2	0.090 (0.040)	0.090 (0.052)	0.0836	(-0.012, 0.192)
	BI 1744 R5	0.171 (0.040)	0.171 (0.052)	0.0011	(0.068, 0.274)
	BI 1744 R10	0.149 (0.039)	0.150 (0.051)	0.0037	(0.049, 0.250)
	BI 1744 R20	0.148 (0.040)	0.148 (0.052)	0.0047	(0.046, 0.251)
29	R Placebo	-0.026 (0.040)			
	BI 1744 R2	0.068 (0.040)	0.094 (0.051)	0.0695	(-0.008, 0.195)
	BI 1744 R5	0.136 (0.040)	0.162 (0.052)	0.0018	(0.061, 0.264)
	BI 1744 R10	0.146 (0.039)	0.172 (0.051)	0.0008	(0.072, 0.272)
	BI 1744 R20	0.153 (0.040)	0.179 (0.052)	0.0006	(0.077, 0.281)

* Based on an ANCOVA with terms for baseline, treatment, centre (centre random, all other effects fixed)
Number of patients : R Placebo (79), BI 1744 R2 (81), BI 1744 R5 (80), BI 1744 R10 (86), BI 1744 R20 (79)
Common baseline mean (se) = 2.598 (0.863)

Source data: Appendix 16.1.9.2, Statdoc 6.1.2.1 type10.sas 11MAR2009

Table 15.2.1.2.3: 1 Adjusted mean* (SE) FVC AUC(0-6) response [L] and comparison to placebo after 4 weeks - analysis with imputation (FAS)

Treatment	Treatment Mean (SE)	Difference from R Placebo Mean (SE)	p-value	95% C.I.
R Placebo	0.009 (0.044)			
BI 1744 R2	0.271 (0.043)	0.262 (0.057)	<.0001	(0.150, 0.373)
BI 1744 R5	0.292 (0.044)	0.283 (0.057)	<.0001	(0.171, 0.395)
BI 1744 R10	0.320 (0.042)	0.311 (0.056)	<.0001	(0.201, 0.421)
BI 1744 R20	0.313 (0.044)	0.304 (0.057)	<.0001	(0.192, 0.416)

* Based on an ANCOVA with terms for baseline, treatment, centre (centre random, all other effects fixed)
Number of patients : R Placebo (79), BI 1744 R2 (81), BI 1744 R5 (80), BI 1744 R10 (86), BI 1744 R20 (79)
Common baseline mean (se) = 2.598 (0.863)

Source data: Appendix 16.1.9.2, Statdoc 6.1.2.3 type13.sas 30SEP2008

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

Test day	Treatment	Treatment Mean (SE)	Difference from R Placebo Mean (SE)	p-value	95% C.I.
1	R Placebo	0.104 (0.021)			
	BI 1744 R2	0.259 (0.021)	0.155 (0.027)	<.0001	(0.101, 0.209)
	BI 1744 R5	0.288 (0.021)	0.185 (0.027)	<.0001	(0.131, 0.239)
	BI 1744 R10	0.335 (0.020)	0.231 (0.027)	<.0001	(0.178, 0.284)
	BI 1744 R20	0.335 (0.021)	0.231 (0.028)	<.0001	(0.177, 0.286)
8	R Placebo	0.062 (0.024)			
	BI 1744 R2	0.264 (0.023)	0.202 (0.032)	<.0001	(0.140, 0.264)
	BI 1744 R5	0.293 (0.024)	0.231 (0.032)	<.0001	(0.169, 0.294)
	BI 1744 R10	0.295 (0.023)	0.233 (0.031)	<.0001	(0.172, 0.295)
	BI 1744 R20	0.321 (0.024)	0.259 (0.032)	<.0001	(0.197, 0.322)
15	R Placebo	0.079 (0.025)			
	BI 1744 R2	0.243 (0.025)	0.165 (0.032)	<.0001	(0.101, 0.228)
	BI 1744 R5	0.267 (0.025)	0.189 (0.032)	<.0001	(0.125, 0.252)
	BI 1744 R10	0.282 (0.024)	0.203 (0.032)	<.0001	(0.140, 0.266)
	BI 1744 R20	0.280 (0.025)	0.201 (0.033)	<.0001	(0.137, 0.265)
29	R Placebo	0.078 (0.026)			
	BI 1744 R2	0.242 (0.026)	0.164 (0.034)	<.0001	(0.097, 0.231)
	BI 1744 R5	0.247 (0.026)	0.169 (0.034)	<.0001	(0.102, 0.237)
	BI 1744 R10	0.295 (0.025)	0.218 (0.034)	<.0001	(0.152, 0.284)
	BI 1744 R20	0.303 (0.026)	0.225 (0.034)	<.0001	(0.157, 0.292)

* Based on an ANCOVA with terms for baseline, treatment, centre (centre random, all other effects fixed)
Number of patients : R Placebo (79), BI 1744 R2 (81), BI 1744 R5 (80), BI 1744 R10 (86), BI 1744 R20 (79)
Common baseline mean (se) = 1.253 (0.479)

Source data: Appendix 16.1.9.2, Statdoc 6.1.1.7 type10.sas 11MAR2009

Table 15.3.2: 1 Adverse event overall summary - treated set

Treatment analysis: All periods(trt incl 12 days)

	BI 1744 R2 N (%)	BI 1744 R5 N (%)	BI 1744 R10 N (%)	BI 1744 R20 N (%)	R Placebo N (%)
Number of patients	81 (100.0)	80 (100.0)	86 (100.0)	79 (100.0)	79 (100.0)
Patients with any AE	30 (37.0)	33 (41.3)	26 (30.2)	30 (38.0)	29 (36.7)
Patients with severe AEs	3 (3.7)	2 (2.5)	2 (2.3)	3 (3.8)	1 (1.3)
Patients with investigator defined drug-related AEs	4 (4.9)	3 (3.8)	2 (2.3)	1 (1.3)	5 (6.3)
Patients with other significant AEs (according to ICH E3)	1 (1.2)	4 (5.0)	0 (0.0)	0 (0.0)	1 (1.3)
Patients with AEs leading to discontinuation of trial drug	1 (1.2)	5 (6.3)	0 (0.0)	2 (2.5)	1 (1.3)
Patients with significant AEs (pre-specified events)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Patients with serious AEs	2 (2.5)	2 (2.5)	2 (2.3)	2 (2.5)	0 (0.0)
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)	1 (1.3)	0 (0.0)
Disability/incap.	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Req.hospitalisation	1 (1.2)	2 (2.5)	2 (2.3)	1 (1.3)	0 (0.0)
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	1 (1.2)	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: 10.1