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.:** 2006-04829-29	
Name of active ingredient: BI 1744 CL inhalation solution – Respimat® Inhaler		**Page:** 1 of 6	**Synopsis No.:**
Module:		**Volume:**	
Report date: 28 October 2009	**Trial No. / U No.:** 1222.6/ U09-1850-01	**Date of trial:** 09 May 2007 – 03 October 2008	**Date of revision:** Not applicable

Title of trial:	Randomised, double-blind, placebo-controlled, parallel group study to assess the efficacy (bronchodilation) 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 asthma
Coordinating Investigator:	[redacted]
Trial sites:	Multicentre study.
Publication (reference):	Data of this study have not been published.
Clinical phase:	IIb
Objectives:	To determine the optimum dose of BI 1744 CL inhalation solution delivered by the Respimat® inhaler once daily for 4 weeks in patients with asthma.
Methodology:	Randomised, double-blind, placebo-controlled, parallel group design comparing 5 groups over 4 weeks.
No. of patients:	
planned:	300 (60 per group)
actual:	Enrolled: 426 Entered: 296 Placebo: entered: 54 treated: 54 analysed for the primary endpoint: 54 2 µg BI 1744: entered: 61 treated: 61 analysed for the primary endpoint: 61 5 µg BI 1744: entered: 60 treated: 60 analysed for the primary endpoint: 60 10 µg BI 1744: entered: 60 treated: 60 analysed for the primary endpoint: 60 20 µg BI 1744: entered: 61 treated: 61 analysed for the primary endpoint: 61
Diagnosis and main criteria for inclusion:	Outpatients of either sex, aged ≥18 years with a diagnosis of asthma (based on Global Initiative for Asthma [GINA] criteria); pre-bronchodilator forced expiratory volume in 1 second (FEV_1) ≥60% predicted and <90% predicted (based on European Coal and Steel Community [ECSC] criteria); increase in FEV_1 ≥12% and 200 mL 15 minutes after 400 µg salbutamol (albuterol); low/moderate stable dose inhaled corticosteroids (ICS) for at least 6 weeks prior to Visit 1; no long-acting β-agonists (LABAs) for 2 weeks prior to Visit 1.

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Test product:	BI 1744 CL inhalation solution - Respimat® Inhaler
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, inhaler: B062000122, mouthpieces for inhaler: B062000668
Reference therapy:	Placebo inhalation solution - Respimat® Inhaler
dose:	Not applicable
mode of admin.:	Oral inhalation
batch no.:	Placebo solution: B062000133, inhaler: B062000122, mouthpieces for inhaler: B062000668
Duration of treatment:	4 weeks
Criteria for evaluation:	
Efficacy:	FEV_1, peak expiratory flow rate (PEF) in the morning (am) and in the evening (pm), forced vital capacity (FVC), area under the curve (AUC), peak response, rescue medication use, asthma control questionnaire (ACQ)
Pharmacokinetics:	Plasma and urine concentrations of BI 1744 BS and its metabolites SOM 1522 BS and BI 1744 BS - glucuronide.
Safety:	Adverse events (AEs), laboratory tests, vital signs, 12-lead electrocardiogram (ECG), physical examinations
Statistical methods:	The primary analysis used the mixed effects linear model comparing the bronchodilator efficacy among the 5 treatment groups. In the mixed effects model, baseline values, treatment groups, test day, baseline-by-test-day and test-day-by-treatment interaction were fixed effects and centres were assumed to be random effects. The baseline values were included in the model as covariates. The secondary efficacy endpoints were analysed using the same statistical model as for the primary endpoint.

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SUMMARY – CONCLUSIONS:

Efficacy / clinical pharmacology results:

Efficacy: The primary endpoint of trough FEV_1 response after 4 weeks of treatment was 0.083 L for the 2 µg BI 1744 treatment group, 0.090 L for the 5 µg group, 0.080 L for the 10 µg group, 0.150 L for the 20 µg group and 0.004 L for placebo (all treatments were given in conjunction with an inhaled corticosteroid). The differences between the 20 µg BI 1744 dose group and placebo were statistically significant (p = 0.0011). Thus, for the primary endpoint trough FEV_1 response BI 1744 treatment was superior to placebo for the 20 µg dose administered by inhalation of solution delivered by the Respimat® inhaler in patients with asthma.

Pre-dose morning peak expiratory flow response after 4 weeks of treatment comprised a key secondary endpoint. The pre-dose morning PEF treatment difference compared with placebo was 16.2 L/min for the 2 µg BI 1744 group, 27.9 L/min for the 5 µg group, 36.1 L/min for the 10 µg group, and 42.9 L/min for the 20 µg group. The differences between all BI 1744 dose groups and placebo were statistically significant. In addition, pre-dose morning PEF showed statistically significant differences from placebo for all BI 1744 doses after 1, 2 and 3 weeks of treatment. Evening PEF response was assessed weekly over the 4-week treatment period and showed a statistically significant treatment benefit for all BI 1744 dose groups at all assessment timepoints. Statistically significant reductions in PEF variability were observed for the 5 µg, 10 µg and 20 µg after 2 and 4 weeks of treatment but not after 1 and 3 weeks.

Other secondary endpoints (trough FVC response, AUC_{0-6} FVC, $peak_{0-3}$ FVC, mean post-dose FVC) only showed a consistent treatment benefit versus placebo for patients in the 20 µg BI 1744 dose group.

All BI 1744 dose groups achieved a statistically significant reduction in the weekly mean number of doses of rescue medication (range 0.733 to 0.983 doses per day) used over the first 3 weeks of treatment, as compared with the placebo group. The 5 µg (-0.526 doses per day; p = 0.0423) and 20 µg (-0.593 doses per day; p = 0.0218) BI 1744 doses also reduced rescue medication use over Week 4.

A statistically significant reduction in ACQ scores after 4 weeks of treatment was achieved for the 10 µg (-0.328; p = 0.0044) and 20 µg (-0.276; p = 0.0158) BI 1744 dose groups. The difference in scores was less than 0.5, which is considered a minimal clinically important difference.

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	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 1.13 (gCV 50.5%) to 1.48 (gCV 64.2%) throughout the different dose groups. Estimation based on AUC_{0-3} provided a similar value, i.e. 1.46 (gCV 45.5%). Accumulation of BI 1744 BS - glucuronide based on C_{max} was slightly lower, i.e. 0.966 (gCV 61.7%) to 1.29 (gCV 84.5%). $C_{max,ss}$ and $AUC_{0-1,ss}$ values of BI 1744 BS increased proportionally within the dose range 5 - 20 µg BI 1744 CL. Plasma concentrations following inhalation of 2 µg BI 1744 CL were below the limit of quantification in 60 of 61 patients. Urinary excretion increased proportionally within the dose range 2 - 20 µg BI 1744 CL. The ratio between BI 1744 BS - glucuronide and BI 1744 BS at Day 29 was 0.630 (gCV 70.3%) based on $AUC_{0-6,ss}$. Exploratory analysis showed that mean systemic exposure was higher by 7% (based on $C_{max,ss\ norm}$) to 19% (based on $AUC_{0-24,ss,norm}$) in females compared with males. However, individual $C_{max,ss\ norm}$ and $AUC_{0-24,ss,norm}$ values were largely overlapping. For all other covariates (body weight, age, race, CYP2C8/CYP2C9 polymorphisms, kidney, liver, lung function) there was either no clear relationship observed or the distribution of covariates was not suitable to draw a firm conclusion (e.g. the number of White patients exceeded by far the number of Asian patients). No clear relationship between systemic exposure and body weight was observed. There was no clear relationship between systemic exposure and age. Only a few patients older than 65 years were included in the analysis, precluding a firm conclusion on the influence of age on systemic exposure to BI 1744 BS.
Safety results:	The results of this study show that BI 1744 was generally safe and well tolerated. During the treatment phase, the overall occurrence of AEs was slightly higher in the active treatment groups (37.7% of patients reported at least one AE in the 2 µg BI 1744 dose group, 40.0% in the 5 µg group, 30.0% in the 10 µg group and 39.3% in the 20 µg group) than in the placebo group (27.8%). The 20 µg BI 1744 group had a notably higher number of patients with drug-related AEs compared to the lower dose groups (16.4% compared to 3.3% to 8.3% in the other groups). The most common treatment-emergent AEs were headache and nasopharyngitis, which occurred with a similar incidence in all treatment groups.

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Exacerbation of asthma occurred at a higher incidence in the placebo treatment group (7.4% compared with 1.7% to 3.3% in the BI 1744 dose groups). Most other AEs also occurred with a comparable incidence in the different study treatment groups. However, tremor and anxiety only occurred in patients in the 20 µg BI 1744 group (5 patients: 8.2%, and 2 patients: 3.3%, respectively) and palpitations was also seen with a slightly higher frequency in the 20 µg group.

Drug-related AEs were experienced by 2 patients (3.7%) in the placebo group, 2 patients (3.3%) in the 2 µg BI 1744 dose group, 5 patients (8.3%) in the 5 µg and 10 µg groups, and 10 patients (16.4%) in the 20 µg group. The most common drug-related AEs were tremor (only seen in the 20 µg BI 1744 group), headache, dizziness, palpitations and anxiety.

One patient in the 5 µg BI 1744 dose group was withdrawn from the study due to an AE of premature ventricular contractions. This event was also classified as an 'other significant AE' based on ICH E3.

Two patients experienced at least one SAE during the study. One patient in the 10 µg BI 1744 group experienced an SAE of pneumonia and 1 patient in the 20 µg BI 1744 group experienced SAEs of dizziness, palpitations, hyperhidrosis and chest pain. The dizziness, palpitations, hyperhidrosis and chest pain were considered drug-related. None of the SAEs were fatal or life-threatening.

A slightly higher incidence of possibly clinically relevant changes in serum creatine phosphokinase was seen in patients in the 10 µg and 20 µg BI 1744 dose groups compared to the lower dose groups. A consistent and statistically significant reduction in mean potassium level was seen in patients in the 20 µg BI 1744 dose group following treatment on Day 1. However, no significant treatment difference between placebo and any active treatment dose group was apparent on Days 8, 15 or 29.

Changes in line with known systemic sympathomimetic effects were observed (increased heart rate at ≥10 µg, shortened uncorrected QT interval, and increased QTcB at ≥10 µg). In addition, T-waves abnormalities were observed at doses of BI 1744 ≥10 µg.

No evidence of symptom rebound was seen in patients in the BI 1744 treatment groups following discontinuation of the study medication.

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Conclusions:

All doses of BI 1744 treatment showed an improvement in trough and peak FEV_1 over 4 weeks of treatment but only improvements following administration of 20 µg were statistically significant. For trough FEV_1, the 2 µg, 5 µg and 10 µg doses showed a similar degree of improvement, but the 20 µg dose provided the largest effect. The home-measured weekly means of PEF showed dose-ordering and a typical dose-response relationship more appropriate for dose selection.

The results of this study showed that BI 1744 was generally safe and well tolerated. The overall occurrence of AEs was slightly higher in the active treatment groups than in the placebo group, with the 20 µg BI 1744 group having a notably higher number of patients with drug-related AEs compared to the lower dose groups. Most AEs occurred with a comparable incidence in the different treatment groups, however, tremor and anxiety only occurred in patients in the 20 µg BI 1744 group and palpitations was also seen with a slightly higher frequency in the 20 µg group. Changes in vital signs and ECG parameters were also seen more frequently in the higher dose groups (10 µg and 20 µg).

The pharmacokinetics in plasma of BI 7144 BS, BI 1744 BS - glucuronide and SOM 1522 BS were consistent with the results of previous studies in healthy volunteers 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. Based on exploratory analysis, systemic exposure in females tended to be slightly higher than in males. However, the magnitude of this difference was not of concern. For all other covariates (body weight, age, race, CYP2C8/CYP2C9 polymorphisms, kidney, liver, and lung function) no firm conclusion with regard to the influence on the PK of BI 1744 could be drawn.

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 additional 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 additional secondary endpoints are provided in the following tables.

Results for	**presented in**
Patient disposition	Table 15.1.1: 1
Weekly mean pre-dose morning PEFR	Table 15.2.2.1: 1
Weekly mean evening PEFR	Table 15.2.2.2: 1
PEFR variability	Table 15.2.2.3: 1
Trough FEV_1 response at week 1 Trough FEV_1 response at week 2 Trough FEV_1 response at week 4	Table 15.2.1.1.1: 1
FEV_1 AUC_{0-3h} response after first dose FEV_1 AUC_{0-3h} response at week 1 FEV_1 AUC_{0-3h} response at week 2 FEV_1 AUC_{0-3h} response at week 4	Table 15.2.1.1.3: 3
FEV_1 AUC_{0-6h} response after 4 weeks	Table 15.2.1.1.3: 6
FEV_1 $peak_{0-3h}$ after first dose FEV_1 $peak_{0-3h}$ at week 1 FEV_1 $peak_{0-3h}$ at week 2 FEV_1 $peak_{0-3h}$ at week 4	Table 15.2.1.1.4: 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						426
Not entered/randomsed						130
Entered/randomised	54(100.00)	61(100.00)	60(100.00)	60(100.00)	61(100.00)	296(100.00)
Treated	54(100.00)	61(100.00)	60(100.00)	60(100.00)	61(100.00)	296(100.00)
Not prematurely discontinued from trial medication	53(98.15)	58(95.08)	58(96.67)	59(98.33)	61(100.00)	289(97.64)
Prematurely discontinued from trial medication	1(1.85)	3(4.92)	2(3.33)	1(1.67)	0(0.00)	7(2.36)
Adverse event	0(0.00)	0(0.00)	1(1.67)	0(0.00)	0(0.00)	1(0.34)
AE study dis. worse	0(0.00)	0(0.00)	0(0.00)	0(0.00)	0(0.00)	0(0.00)
AE-oth. dis. worse	0(0.00)	0(0.00)	1(1.67)	0(0.00)	0(0.00)	1(0.34)
AE-other	0(0.00)	0(0.00)	0(0.00)	0(0.00)	0(0.00)	0(0.00)
Lack of efficacy	0(0.00)	1(1.64)	0(0.00)	0(0.00)	0(0.00)	1(0.34)
Non compl prot.	0(0.00)	0(0.00)	1(1.67)	0(0.00)	0(0.00)	1(0.34)
Lost to follow-up	0(0.00)	1(1.64)	0(0.00)	0(0.00)	0(0.00)	1(0.34)
Consent withdrawn	1(1.85)	1(1.64)	0(0.00)	1(1.67)	0(0.00)	3(1.01)
Other	0(0.00)	0(0.00)	0(0.00)	0(0.00)	0(0.00)	0(0.00)

Table 15.2.2.1: 1 MMRM* for weekly mean pre-dose morning PEFR [L/min] and comparison to placebo over 4 weeks - observed case analysis (FAS)

Week	Treatment	Treatment Mean (SE)	Difference from R Placebo Mean (SE)	p-value	95% C.I.
1	R Placebo	362.25 (4.591)			
	BI 1744 R2	391.33 (4.322)	29.077 (6.303)	<.0001	(16.671, 41.483)
	BI 1744 R5	400.51 (4.355)	38.261 (6.329)	<.0001	(25.804, 50.717)
	BI 1744 R10	407.57 (4.391)	45.314 (6.353)	<.0001	(32.810, 57.819)
	BI 1744 R20	420.47 (4.323)	58.214 (6.308)	<.0001	(45.797, 70.630)
2	R Placebo	363.94 (4.968)			
	BI 1744 R2	384.11 (4.676)	20.162 (6.820)	0.0034	(6.739, 33.585)
	BI 1744 R5	402.64 (4.712)	38.692 (6.848)	<.0001	(25.214, 52.169)
	BI 1744 R10	405.87 (4.752)	41.923 (6.874)	<.0001	(28.392, 55.453)
	BI 1744 R20	413.03 (4.677)	49.089 (6.825)	<.0001	(35.656, 62.521)
3	R Placebo	366.83 (4.985)			
	BI 1744 R2	388.51 (4.693)	21.678 (6.844)	0.0017	(8.207, 35.149)
	BI 1744 R5	397.98 (4.729)	31.151 (6.872)	<.0001	(17.625, 44.677)
	BI 1744 R10	403.33 (4.769)	36.505 (6.899)	<.0001	(22.926, 50.083)
	BI 1744 R20	413.39 (4.693)	46.559 (6.849)	<.0001	(33.078, 60.039)
4	R Placebo	368.18 (5.713)			
	BI 1744 R2	384.42 (5.377)	16.238 (7.843)	0.0393	(0.801, 31.675)
	BI 1744 R5	396.06 (5.419)	27.878 (7.875)	0.0005	(12.379, 43.378)
	BI 1744 R10	404.26 (5.465)	36.072 (7.906)	<.0001	(20.512, 51.633)
	BI 1744 R20	411.13 (5.377)	42.943 (7.848)	<.0001	(27.498, 58.389)
4 week average**	R Placebo	365.30 (4.442)			
	BI 1744 R2	387.09 (4.182)	21.789 (6.098)	0.0004	(9.786, 33.792)
	BI 1744 R5	399.30 (4.214)	33.995 (6.124)	<.0001	(21.943, 46.048)
	BI 1744 R10	405.26 (4.249)	39.954 (6.147)	<.0001	(27.854, 52.053)
	BI 1744 R20	414.50 (4.183)	49.201 (6.104)	<.0001	(37.187, 61.215)

* Mixed effect model with repeated measures using terms for baseline, treatment, test day, baseline-by-test-day, treatment-by-test-day and center as random effect.
** Average treatment effect during the 4-week treatment period.
Number of patients : R Placebo (54), BI 1744 R2 (61), BI 1744 R5 (60), BI 1744 R10 (59), BI 1744 R20 (61)
Common baseline mean (se) = 373.90 (111.88)
Source data: Appendix 16.1.9.2, Statdoc 6.2.1 type20.sas 26AUG2009

Table 15.2.2.2: 1 MMRM* for weekly mean evening PEFR [L/min] and comparison to placebo over 4 weeks - observed case analysis (FAS)

Week	Treatment	Treatment Mean (SE)	Difference from R Placebo Mean (SE)	p-value	95% C.I.
1	R Placebo	378.24 (5.031)			
	BI 1744 R2	418.24 (4.736)	39.995 (6.905)	<.0001	(26.404, 53.586)
	BI 1744 R5	416.81 (4.772)	38.566 (6.937)	<.0001	(24.913, 52.219)
	BI 1744 R10	426.14 (4.811)	47.899 (6.961)	<.0001	(34.199, 61.600)
	BI 1744 R20	434.52 (4.738)	56.276 (6.916)	<.0001	(42.664, 69.888)
2	R Placebo	376.77 (5.368)			
	BI 1744 R2	410.70 (5.052)	33.930 (7.367)	<.0001	(19.429, 48.430)
	BI 1744 R5	416.49 (5.092)	39.716 (7.401)	<.0001	(25.150, 54.281)
	BI 1744 R10	425.10 (5.133)	48.332 (7.427)	<.0001	(33.714, 62.949)
	BI 1744 R20	425.85 (5.054)	49.081 (7.378)	<.0001	(34.560, 63.601)
3	R Placebo	382.63 (5.174)			
	BI 1744 R2	413.19 (4.870)	30.558 (7.102)	<.0001	(16.581, 44.535)
	BI 1744 R5	411.44 (4.908)	28.806 (7.134)	<.0001	(14.766, 42.847)
	BI 1744 R10	424.49 (4.948)	41.862 (7.159)	<.0001	(27.772, 55.951)
	BI 1744 R20	421.77 (4.872)	39.138 (7.112)	<.0001	(25.140, 53.135)
4	R Placebo	384.08 (5.585)			
	BI 1744 R2	407.05 (5.256)	22.970 (7.665)	0.0030	(7.883, 38.057)
	BI 1744 R5	408.68 (5.297)	24.600 (7.700)	0.0016	(9.446, 39.754)
	BI 1744 R10	420.88 (5.341)	36.806 (7.727)	<.0001	(21.598, 52.015)
	BI 1744 R20	426.58 (5.258)	42.505 (7.675)	<.0001	(27.399, 57.611)
4 week average**	R Placebo	380.43 (4.697)			
	BI 1744 R2	412.29 (4.422)	31.863 (6.446)	<.0001	(19.176, 44.550)
	BI 1744 R5	413.35 (4.455)	32.922 (6.476)	<.0001	(20.176, 45.668)
	BI 1744 R10	424.16 (4.491)	43.725 (6.498)	<.0001	(30.935, 56.514)
	BI 1744 R20	427.18 (4.424)	46.750 (6.458)	<.0001	(34.040, 59.459)

* Mixed effect model with repeated measures using terms for baseline, treatment, test day, baseline-by-test-day, treatment-by-test-day and center as random effect.
** Average treatment effect during the 4-week treatment period.
Number of patients : R Placebo (54), BI 1744 R2 (61), BI 1744 R5 (60), BI 1744 R10 (59), BI 1744 R20 (61)
Common baseline mean (se) = 385.73 (113.46)
Source data: Appendix 16.1.9.2, Statdoc 6.2.3 type20.sas 26AUG2009

Table 15.2.2.3: 1 MMRM* for weekly mean PEFR variability [L/min] and comparison to placebo over 4 weeks - observed case analysis (FAS)

Week	Treatment	Treatment Mean (SE)	Difference from R Placebo Mean (SE)	p-value	95% C.I.
1	R Placebo	11.115 (0.786)			
	BI 1744 R2	10.730 (0.742)	-0.385 (1.063)	0.7171	(-2.477, 1.706)
	BI 1744 R5	9.572 (0.745)	-1.544 (1.066)	0.1486	(-3.641, 0.554)
	BI 1744 R10	9.425 (0.752)	-1.690 (1.072)	0.1158	(-3.799, 0.419)
	BI 1744 R20	9.372 (0.739)	-1.744 (1.061)	0.1015	(-3.832, 0.345)
2	R Placebo	11.862 (0.789)			
	BI 1744 R2	11.037 (0.745)	-0.824 (1.067)	0.4404	(-2.925, 1.276)
	BI 1744 R5	8.922 (0.748)	-2.940 (1.070)	0.0064	(-5.046, -0.833)
	BI 1744 R10	8.607 (0.755)	-3.255 (1.076)	0.0027	(-5.373, -1.137)
	BI 1744 R20	9.557 (0.742)	-2.304 (1.066)	0.0314	(-4.402, -0.207)
3	R Placebo	11.299 (0.827)			
	BI 1744 R2	10.577 (0.781)	-0.722 (1.120)	0.5198	(-2.927, 1.483)
	BI 1744 R5	9.153 (0.784)	-2.147 (1.124)	0.0571	(-4.358, 0.065)
	BI 1744 R10	9.104 (0.792)	-2.195 (1.130)	0.0530	(-4.419, 0.028)
	BI 1744 R20	9.749 (0.778)	-1.550 (1.119)	0.1670	(-3.753, 0.652)
4	R Placebo	11.694 (0.780)			
	BI 1744 R2	10.575 (0.736)	-1.118 (1.055)	0.2898	(-3.194, 0.957)
	BI 1744 R5	9.343 (0.739)	-2.351 (1.057)	0.0270	(-4.432, -0.269)
	BI 1744 R10	8.649 (0.747)	-3.045 (1.063)	0.0045	(-5.138, -0.952)
	BI 1744 R20	8.756 (0.733)	-2.937 (1.053)	0.0056	(-5.010, -0.865)
4 week average**	R Placebo	11.492 (0.620)			
	BI 1744 R2	10.730 (0.586)	-0.763 (0.831)	0.3594	(-2.398, 0.873)
	BI 1744 R5	9.247 (0.588)	-2.245 (0.832)	0.0074	(-3.883, -0.607)
	BI 1744 R10	8.946 (0.594)	-2.546 (0.838)	0.0026	(-4.196, -0.897)
	BI 1744 R20	9.359 (0.583)	-2.134 (0.829)	0.0105	(-3.765, -0.502)

* Mixed effect model with repeated measures using terms for baseline, treatment, test day, baseline-by-test-day, treatment-by-test-day and center as random effect.
** Average treatment effect during the 4-week treatment period.
Number of patients : R Placebo (54), BI 1744 R2 (61), BI 1744 R5 (60), BI 1744 R10 (59), BI 1744 R20 (61)
Common baseline mean (se) = 10.828 (6.460)
Source data: Appendix 16.1.9.2, Statdoc 6.2.4 type20.sas 26AUG2009

Table 15.2.1.1.1: 1 MMRM* for FEV1 trough response [L] and comparison to placebo over 4 weeks - observed cases analyses (FAS)

Test day	Treatment	Treatment Mean (SE)	Difference from R Placebo Mean (SE)	p-value	95% C.I.
8	R Placebo	-0.007 (0.033)			
	BI 1744 R2	0.060 (0.031)	0.067 (0.044)	0.1264	(-0.019, 0.154)
	BI 1744 R5	0.094 (0.032)	0.101 (0.044)	0.0232	(0.014, 0.188)
	BI 1744 R10	0.106 (0.031)	0.114 (0.044)	0.0106	(0.027, 0.200)
	BI 1744 R20	0.166 (0.031)	0.173 (0.044)	0.0001	(0.087, 0.260)
15	R Placebo	-0.009 (0.036)			
	BI 1744 R2	0.094 (0.034)	0.103 (0.048)	0.0329	(0.008, 0.198)
	BI 1744 R5	0.080 (0.034)	0.089 (0.048)	0.0666	(-0.006, 0.184)
	BI 1744 R10	0.034 (0.034)	0.043 (0.048)	0.3738	(-0.052, 0.137)
	BI 1744 R20	0.131 (0.034)	0.140 (0.048)	0.0037	(0.046, 0.234)
29	R Placebo	0.004 (0.034)			
	BI 1744 R2	0.083 (0.032)	0.080 (0.045)	0.0754	(-0.008, 0.167)
	BI 1744 R5	0.090 (0.032)	0.086 (0.045)	0.0571	(-0.003, 0.174)
	BI 1744 R10	0.080 (0.032)	0.076 (0.045)	0.0906	(-0.012, 0.164)
	BI 1744 R20	0.150 (0.032)	0.147 (0.044)	0.0011	(0.059, 0.234)
4 week average**	R Placebo	-0.004 (0.030)			
	BI 1744 R2	0.079 (0.028)	0.083 (0.039)	0.0347	(0.006, 0.161)
	BI 1744 R5	0.088 (0.029)	0.092 (0.040)	0.0209	(0.014, 0.170)
	BI 1744 R10	0.073 (0.028)	0.077 (0.039)	0.0504	(-0.000, 0.155)
	BI 1744 R20	0.149 (0.028)	0.153 (0.039)	0.0001	(0.076, 0.231)

* Mixed effect model with repeated measures using terms for baseline, treatment, test day, baseline-by-test-day, treatment-by-test-day and center as random effect.
** Average treatment effect during the 4-week treatment period.
Number of patients : R Placebo (53), BI 1744 R2 (61), BI 1744 R5 (59), BI 1744 R10 (60), BI 1744 R20 (61)
Common baseline mean (se) = 2.327 (0.680)
Source data: Appendix 16.1.9.2, Statdoc 6.1.1.1 type10a_t1.sas 26AUG2009

Table 15.2.1.1.3: 3 Adjusted mean* (SE) BI 1744 CL FEV1 AUC(0-3) response [L] and comparison to placebo over 4 weeks - individual ANCOVA analysis with imputation (FAS)

Test day	Treatment	Treatment Mean (SE)	Difference from R Placebo Mean (SE)	p-value	95% C.I.
1	R Placebo	0.095 (0.030)			
	BI 1744 R2	0.273 (0.028)	0.178 (0.039)	<.0001	(0.102, 0.254)
	BI 1744 R5	0.278 (0.029)	0.183 (0.039)	<.0001	(0.107, 0.259)
	BI 1744 R10	0.268 (0.029)	0.173 (0.039)	<.0001	(0.097, 0.249)
	BI 1744 R20	0.386 (0.028)	0.291 (0.039)	<.0001	(0.215, 0.367)
8	R Placebo	0.059 (0.034)			
	BI 1744 R2	0.249 (0.032)	0.190 (0.045)	<.0001	(0.101, 0.279)
	BI 1744 R5	0.255 (0.032)	0.196 (0.045)	<.0001	(0.107, 0.285)
	BI 1744 R10	0.214 (0.032)	0.156 (0.045)	0.0007	(0.066, 0.245)
	BI 1744 R20	0.321 (0.032)	0.262 (0.045)	<.0001	(0.173, 0.351)
15	R Placebo	0.077 (0.037)			
	BI 1744 R2	0.288 (0.034)	0.210 (0.050)	<.0001	(0.112, 0.309)
	BI 1744 R5	0.235 (0.035)	0.158 (0.050)	0.0018	(0.060, 0.257)
	BI 1744 R10	0.165 (0.035)	0.088 (0.050)	0.0799	(-0.011, 0.187)
	BI 1744 R20	0.300 (0.034)	0.223 (0.050)	<.0001	(0.125, 0.321)
29	R Placebo	0.088 (0.037)			
	BI 1744 R2	0.260 (0.034)	0.172 (0.048)	0.0004	(0.077, 0.268)
	BI 1744 R5	0.224 (0.035)	0.136 (0.049)	0.0056	(0.040, 0.232)
	BI 1744 R10	0.188 (0.035)	0.101 (0.049)	0.0398	(0.005, 0.196)
	BI 1744 R20	0.323 (0.034)	0.236 (0.048)	<.0001	(0.140, 0.331)

* Based on an ANCOVA with terms for baseline, treatment, centre (centre random, all other effects fixed)
Number of patients : R Placebo (54), BI 1744 R2 (61), BI 1744 R5 (60), BI 1744 R10 (60), BI 1744 R20 (61)
Common baseline mean (se) = 2.327 (0.680)

Table 15.2.1.1.3: 6 Adjusted mean* (SE) FEV1 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	0.091 (0.037)			
BI 1744 R2	0.269 (0.035)	0.178 (0.050)	0.0005	(0.079, 0.277)
BI 1744 R5	0.229 (0.035)	0.137 (0.051)	0.0070	(0.038, 0.237)
BI 1744 R10	0.190 (0.035)	0.099 (0.050)	0.0512	(-0.001, 0.198)
BI 1744 R20	0.323 (0.035)	0.232 (0.050)	<.0001	(0.133, 0.331)

* Based on an ANCOVA with terms for baseline, treatment, centre (centre random, all other effects fixed)
Number of patients : R Placebo (54), BI 1744 R2 (61), BI 1744 R5 (60), BI 1744 R10 (60), BI 1744 R20 (61)
Common baseline mean (se) = 2.327 (0.680)

Table 15.2.1.1.4: 1 MMRM* for FEV1 peak(0-3) response [L] and comparison to placebo over 4 weeks - observed case analysis (FAS)

Test day	Treatment	Treatment Mean (SE)	Difference from R Placebo Mean (SE)	p-value	95% C.I.
1	R Placebo	0.203 (0.036)			
	BI 1744 R2	0.372 (0.034)	0.169 (0.048)	0.0005	(0.074, 0.263)
	BI 1744 R5	0.378 (0.034)	0.174 (0.048)	0.0003	(0.080, 0.269)
	BI 1744 R10	0.376 (0.034)	0.173 (0.048)	0.0004	(0.078, 0.268)
	BI 1744 R20	0.499 (0.034)	0.296 (0.048)	<.0001	(0.202, 0.390)
8	R Placebo	0.170 (0.036)			
	BI 1744 R2	0.343 (0.034)	0.173 (0.048)	0.0004	(0.078, 0.268)
	BI 1744 R5	0.355 (0.034)	0.185 (0.048)	0.0002	(0.090, 0.281)
	BI 1744 R10	0.308 (0.034)	0.138 (0.048)	0.0047	(0.043, 0.233)
	BI 1744 R20	0.407 (0.034)	0.237 (0.048)	<.0001	(0.142, 0.332)
15	R Placebo	0.182 (0.041)			
	BI 1744 R2	0.386 (0.039)	0.204 (0.055)	0.0002	(0.096, 0.312)
	BI 1744 R5	0.335 (0.039)	0.153 (0.055)	0.0057	(0.045, 0.261)
	BI 1744 R10	0.261 (0.038)	0.079 (0.055)	0.1513	(-0.029, 0.186)
	BI 1744 R20	0.403 (0.038)	0.221 (0.055)	<.0001	(0.114, 0.328)
29	R Placebo	0.198 (0.040)			
	BI 1744 R2	0.363 (0.038)	0.166 (0.054)	0.0022	(0.060, 0.271)
	BI 1744 R5	0.315 (0.038)	0.117 (0.054)	0.0307	(0.011, 0.223)
	BI 1744 R10	0.279 (0.038)	0.081 (0.054)	0.1320	(-0.025, 0.187)
	BI 1744 R20	0.430 (0.038)	0.232 (0.054)	<.0001	(0.127, 0.337)
4 week average**	R Placebo	0.188 (0.034)			
	BI 1744 R2	0.366 (0.032)	0.178 (0.045)	0.0001	(0.089, 0.267)
	BI 1744 R5	0.346 (0.033)	0.157 (0.046)	0.0006	(0.068, 0.247)
	BI 1744 R10	0.306 (0.032)	0.118 (0.046)	0.0102	(0.028, 0.207)
	BI 1744 R20	0.435 (0.032)	0.246 (0.045)	<.0001	(0.157, 0.336)

* Mixed effect model with repeated measures using terms for baseline, treatment, test day, baseline-by-test-day, treatment-by-test-day and center as random effect.
** Average treatment effect during the 4-week treatment period.
Number of patients : R Placebo (54), BI 1744 R2 (61), BI 1744 R5 (60), BI 1744 R10 (60), BI 1744 R20 (61)
Common baseline mean (se) = 2.327 (0.680)
Source data: Appendix 16.1.9.2, Statdoc 6.1.1.11 type10a_t1.sas 26AUG2009