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.:** 2008-006334-10	
Name of active ingredient: BI 1744CL Inhalation Solution – Respimat®		**Page:** 1 of 6	**Synopsis No.:**
Module:		**Volume:** {hyperlink }	
Disclosure Synopsis date : 20 FEB 2014	**Trial No. / U No.:** 1222.26 / U10-1155-01	**Date of trial:** 16 FEB 2009 – 20 JUL 2009	**Date of revision** (if applicable): Not applicable

Title of trial:	Randomised, double-blind, 4-way cross-over study to determine the 24-hour FEV_1-time profile of orally inhaled BI 1744 CL, delivered with the Respimat® inhaler, after 3 weeks of once daily (5 µg [2 actuations of 2.5 µg], 10 µg [2 actuations of 5 µg]) or twice daily (2 µg [2 actuations of 1 µg], 5 µg [2 actuations of 2.5 µg]) administration in patients with chronic obstructive pulmonary disease (COPD)
Principal/Coordinating Investigator:	[redacted]
Trial sites:	Multicentre study, see Appendix 16.1.4
Publication (reference):	Data have not been published.
Clinical phase:	IIb
Objectives:	The objective of the trial was to determine the 24-hour FEV_1-time profile of BI 1744 CL inhalation solution administered once daily (5 µg and 10 µg) or twice daily (2 µg and 5 µg) using the Respimat® Inhaler after 3-week treatment periods.
Methodology:	Randomised, double-blind, 4-way cross-over design
No. of subjects:	
planned:	entered: 44 patients
actual:	enrolled: 56 patients treated: 47 patients - analysed for primary endpoint: 47 patients
Diagnosis and main criteria for inclusion:	COPD diagnosis with relatively stable airway obstruction with post-bronchodilator FEV_1 <80% of predicted and <70% of FVC; males or females, age ≥40 years; cigarette smoking history >10 pack-years
Test product:	BI 1744 CL Inhalation Solution – Respimat®

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Name of active ingredient: BI 1744CL Inhalation Solution – Respimat®		Page: 2 of 6	
Module:		**Volume:** {hyperlink }	
Disclosure Synopsis date: 20 FEB 2014	**Trial No. / U No.:** 1222.26 / U10-1155-01	**Date of trial:** 16 FEB 2009 – 20 JUL 2009	**Date of revision** (if applicable)**:** Not applicable

dose:	Treatments: - BI 1744 CL 10 µg once daily - BI 1744 CL 5 µg once daily - BI 1744 CL 5 µg twice daily - BI 1744 CL 2 µg twice daily
mode of admin.:	Oral inhalation with Respimat® device
batch no.:	BI 1744 CL 1 µg per actuation (for 2 µg dose): B072000344 BI 1744 CL 2.5 µg per actuation (for 5 µg dose): B072000346 BI 1744 CL 5 µg per actuation (for 10 µg doses): B072000356 Placebo: B082000136
Reference therapy:	Not Applicable
Duration of treatment:	3 weeks for each treatment arm (no wash-out between treatments)
Criteria for evaluation:	
Efficacy / clinical pharmacology:	**Primary:** FEV_1 AUC_{0-12} response and FEV_1 AUC_{12-24} response after 3 weeks of treatment **Secondary:** FEV_1 AUC_{0-24}, peak FEV_1 and trough FEV_1 after 3 weeks of treatment. Individual FEV_1 and FVC measurements at each time point over 24 hours after 3 weeks of treatment. FVC AUC_{0-12}, FVC AUC_{12-24}, FVC AUC_{0-24}, peak FVC and trough FVC after 3 weeks treatment.
Safety:	Vital signs (blood pressure, pulse rate), 12-lead ECG, clinical laboratory tests, adverse events (AEs).

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Name of active ingredient: BI 1744CL Inhalation Solution – Respimat®		Page: 3 of 6	
Module:		**Volume:** {hyperlink }	
Disclosure Synopsis date: 20 FEB 2014	**Trial No. / U No.:** 1222.26 / U10-1155-01	**Date of trial:** 16 FEB 2009 – 20 JUL 2009	**Date of revision** (if applicable)**:** Not applicable

Statistical methods:	A mixed effect repeated measures model (MMRM) with treatment and period as fixed effects and period as a repeated effect with patient as the repeated subject and a compound symmetry covariance structure.

SUMMARY – CONCLUSIONS:

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Name of active ingredient: BI 1744CL Inhalation Solution – Respimat®		Page: 4 of 6	
Module:		**Volume:** {hyperlink }	
Disclosure Synopsis date: 20 FEB 2014	**Trial No. / U No.:** 1222.26 / U10-1155-01	**Date of trial:** 16 FEB 2009 – 20 JUL 2009	**Date of revision** (if applicable)**:** Not applicable

Efficacy / clinical pharmacology results:

Efficacy:

All BI 1744 dose regimens showed a significant increase in FEV_1 AUC_{0-12} and FEV_1 AUC_{12-24} compared with baseline ($p < 0.001$).

BI 1744 10 µg once daily (qd) vs. BI 1744 5 µg once daily (qd): The FEV_1-time profiles for BI 1744 10 µg qd and BI 1744 5 µg qd were almost identical, with no significant differences in FEV_1 AUC_{0-12} and FEV_1 AUC_{12-24} responses (−0. 006 (0.015) L, p = 0.7046; −0.006 (0.015) L, p = 0.7090, respectively).

BI 1744 5 µg twice daily (bid) vs. BI 1744 2 µg twice daily (bid): FEV_1 AUC_{0-12} and FEV_1 AUC_{12-24} responses for BI 1744 5 µg bid were significantly increased compared with BI 1744 2 µg bid (0.033 (0.015) L, p = 0.0248; 0.035 (0.015) L, p = 0.0211, respectively).

BI 1744 5 µg once daily (qd) vs. BI 1744 2 µg twice daily (bid): FEV_1 AUC_{0-12} response for BI 1744 5 µg once daily (qd) was significantly increased compared with BI 1744 2 µg twice daily (bid) (0.054 (0.015) L, p = 0.0003). There was no significant difference in FEV_1 AUC_{12-24} response between BI 1744 5 µg once daily (qd) and BI 1744 2 µg twice daily (bid) (−0.012 (0.015) L, p = 0.4111).

BI 1744 5 µg once daily (qd) vs. BI 1744 5 µg twice daily (bid): FEV_1 AUC_{0-12} response for BI 1744 5 µg twice daily (bid) was slightly reduced (non-significant) compared with BI 1744 5 µg once daily (qd), indicating that there was no carry-over effect of the evening dose of BI 1744 5 µg with respect to FEV_1 response after the morning dose. As expected, FEV_1 AUC_{12-24} response for BI 1744 5 µg twice daily was significantly increased compared with BI 1744 5 µg once daily (qd), due to the second peak from the twice daily administration (0.047 (0.015) L, p = 0.0019).

BI 1744 10 µg once daily (qd) vs. BI 1744 5 µg twice daily (bid): In the present study, 10 µg once daily did not show any increased efficacy compared to 5 µg once daily; as such, a second dose of 5 µg in the evening provided additional bronchodilation compared with both 5 µg once daily and 10 µg once daily [FEV_1 AUC_{12-24} response for BI 1744 5 µg twice daily significantly increased compared with BI 1744 10 µg once daily (qd): 0.052 (0.015) L, p = 0.0006].

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Name of active ingredient: BI 1744CL Inhalation Solution – Respimat®		Page: 5 of 6	
Module:		**Volume:** {hyperlink }	
Disclosure Synopsis date: 20 FEB 2014	**Trial No. / U No.:** 1222.26 / U10-1155-01	**Date of trial:** 16 FEB 2009 – 20 JUL 2009	**Date of revision** (if applicable)**:** Not applicable

Pharmacokinetics

After 3 weeks inhalation of 2 µg bid and 5 µg qd BI 1744 CL, trough plasma concentrations of BI 1744 BS were mostly below the limit of quantification (LOQ: 2.0 pg/mL); hence (geometric) mean $C_{pre,ss}$ was not calculated. After inhalation of 5 µg bid and 10 µg qd, respectively, trough plasma concentrations were quantifiable in at least ⅓ of the patients and geometric mean values were comparable between both treatments (gMean 2.92 pg/mL, gCV: 24.3%, N=24 and gMean 2.97 pg/mL, gCV: 23.2%, N=19, respectively).

BI 1744 BS concentrations at 10 minutes post dosing ($C_{0\ 167,ss}$) after inhalation of 2 µg bid were mostly below the LOQ. Geometric mean $C_{0\ 167,ss}$ values in the 5 µg qd, 5 µg bid and 10 µg qd groups were 3.52 pg/mL (gCV: 35.9%, N=25), 4.28 pg/mL (gCV: 42.0%, N=36) and 5.78 pg/mL (gCV: 62.1%, N=41), respectively.

The fraction of the dose excreted via the urine within the dosing interval was similar in all dose groups (3.27–3.61%), suggesting dose-linear PK.

Safety results:

BI 1744 was generally safe and well tolerated. During the treatment phase, the overall occurrence of AEs was slightly higher in the 5 µg bid dose group (28.3% of patients reported at least one AE) compared to the other dose groups (19.3% to 23.4%). No relation to total daily dose was evident. The most common treatment-emergent AEs were were nasopharyngitis, cough and dyspnoea. Nasopharyngitis was more frequently reported in the 5 µg BI 1744 bid and 10µg BI 1744 qd groups (each 3 patients (6.5%) compared to 1 patient (2.1%) in the other groups). Most other AEs occurred with a comparable incidence in the different study treatment groups.

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Module:		**Volume:** {hyperlink }	
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Conclusions:

BI 1744 2 µg and 5 µg, when administered twice daily, and BI 1744 5 µg and 10 µg, when administered once daily, provided significant bronchodilation over a complete 24 hour period.

Based on a comparison of BI 1744 5 µg once daily dosing vs. BI 1744 5 µg twice daily dosing, there was no evidence of an accumulation or carry over effect with respect to efficacy during the period 0-12 hrs post-morning dose with twice daily dosing compared with once daily dosing.

Under conditions where at least one dose lies on the steep part of the dose-response curve (BI 1744 5 µg once daily vs. BI 1744 2 µg twice daily), there was a statistically significant increase in efficacy during the period 0 – 12 hrs post-morning dose (FEV_1 AUC_{0-12}, FVC AUC_{0-12}) with a once daily dosing regimen compared with a twice daily dosing regimen. Furthermore, the efficacy during the period 12 – 24 hrs post-morning dose (0 – 12 hrs post-evening dose) with a once daily dosing regimen was comparable to the efficacy with a twice daily dosing regimen.

In the present study, 10 µg once daily did not show any increased efficacy compared to 5 µg once daily; as such, a second dose of 5 µg in the evening provided additional bronchodilation compared with both 5 µg once daily and 10 µg once daily. The equivalence of 5 µg once daily and10 µg once daily contrasts with results from other studies, and is not likely to be predictive regarding the sensitive (steep) part of the dose-response curve.

BI 1744 was generally safe and well tolerated.

Total daily systemic exposure to BI 1744 BS based on the amounts excreted in the urine was proportional to the dose, and was comparable if the dose was given as a single daily dose, or split into a bid regimen.

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, 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
FEV_1 $AUC_{(0-12h)}$ response after 3 weeks of treatment FEV_1 $AUC_{(12-24h)}$ response after 3 weeks of treatment (Co-Primary Endpoints) FEV_1 $AUC_{(0-24h)}$ response after 3 weeks of treatment (Secondary Efficacy Endpoint)	Table 15.2.1.1: 1
Peak $FEV_{1\ (0-3h)}$ response after 3 weeks of treatment (Secondary Efficacy Endpoint)	Table 15.2.1.4: 1
Trough FEV_1 response after 3 weeks of treatment (Secondary Efficacy Endpoint)	Table 15.2.1.3: 1
$FVC_{(0-12h)}$ response after 3 weeks of treatment $FVC_{(12-24h)}$ response after 3 weeks of treatment $FVC_{(0-24h)}$ response after 3 weeks of treatment (Secondary Efficacy Endpoints)	Table 15.2.2.1: 1
Peak FVC response after 3 weeks of treatment (Secondary Efficacy Endpoint)	Table 15.2.2.4: 1
Trough FVC response after 3 weeks of treatment (Secondary Efficacy Endpoint)	Table 15.2.2.3: 1
Adverse Events overall summary	Table 15.3.2: 1

Table 15.1.1: 1 Disposition of patients

	BI 1744 R2B	BI 1744 R5Q	BI 1744 R5B	BI 1744 R10Q	Total
Enrolled					56
Not entered/randomsed					9
Entered/randomised					47
Not treated					0
Treated	47(100.00)	47(100.00)	46(100.00)	46(100.00)	47(100.00)
Not prematurely discontinued from trial medication	46(97.87)	47(100.00)	46(100.00)	46(100.00)	46(97.87)
Prematurely discontinued from trial medication	1(2.13)	0(0.00)	0(0.00)	0(0.00)	1(2.13)
Adverse event	1(2.13)	0(0.00)	0(0.00)	0(0.00)	1(2.13)
AE study dis. worse	1(2.13)	0(0.00)	0(0.00)	0(0.00)	1(2.13)

Table 15.2.1.1: 1 Adjusted mean# (SE) FEV1 AUC(0-12), AUC(12-24) and AUC(0-24) response [L] after 3 weeks
- analysis with imputation (FAS)

Time Interval	Dose A	Dose B	Dose A Mean (SE)	Dose B Mean (SE)	Difference Mean (SE)	Difference P-value	Difference 95% C.I.
0-12 hr	BI 1744 R10Q	BI 1744 R5B	0.204 (0.024) ***	0.189 (0.024) ***	0.015 (0.015)	0.3011	(-0.014, 0.044)
	BI 1744 R10Q	BI 1744 R2B	0.204 (0.024) ***	0.155 (0.024) ***	0.049 (0.015)	0.0012	(0.019, 0.078)
	BI 1744 R5Q	BI 1744 R5B	0.209 (0.024) ***	0.189 (0.024) ***	0.021 (0.015)	0.1582	(-0.008, 0.050)
	BI 1744 R5Q	BI 1744 R2B	0.209 (0.024) ***	0.155 (0.024) ***	0.054 (0.015)	0.0003	(0.025, 0.083)
	BI 1744 R10Q	BI 1744 R5Q	0.204 (0.024) ***	0.209 (0.024) ***	-0.006 (0.015)	0.7046	(-0.034, 0.023)
	BI 1744 R5B	BI 1744 R2B	0.189 (0.024) ***	0.155 (0.024) ***	0.033 (0.015)	0.0248	(0.004, 0.063)
12-24 hr	BI 1744 R10Q	BI 1744 R5B	0.149 (0.022) ***	0.201 (0.022) ***	-0.052 (0.015)	0.0006	(-0.081,-0.023)
	BI 1744 R10Q	BI 1744 R2B	0.149 (0.022) ***	0.167 (0.022) ***	-0.018 (0.015)	0.2333	(-0.047, 0.012)
	BI 1744 R5Q	BI 1744 R5B	0.155 (0.022) ***	0.201 (0.022) ***	-0.047 (0.015)	0.0019	(-0.076,-0.017)
	BI 1744 R5Q	BI 1744 R2B	0.155 (0.022) ***	0.167 (0.022) ***	-0.012 (0.015)	0.4111	(-0.041, 0.017)
	BI 1744 R10Q	BI 1744 R5Q	0.149 (0.022) ***	0.155 (0.022) ***	-0.006 (0.015)	0.7090	(-0.035, 0.024)
	BI 1744 R5B	BI 1744 R2B	0.201 (0.022) ***	0.167 (0.022) ***	0.035 (0.015)	0.0211	(0.005, 0.064)
0-24 hr	BI 1744 R10Q	BI 1744 R5B	0.176 (0.022) ***	0.195 (0.022) ***	-0.019 (0.014)	0.1753	(-0.045, 0.008)
	BI 1744 R10Q	BI 1744 R2B	0.176 (0.022) ***	0.160 (0.022) ***	0.016 (0.014)	0.2445	(-0.011, 0.043)
	BI 1744 R5Q	BI 1744 R5B	0.182 (0.022) ***	0.195 (0.022) ***	-0.013 (0.014)	0.3444	(-0.040, 0.014)
	BI 1744 R5Q	BI 1744 R2B	0.182 (0.022) ***	0.160 (0.022) ***	0.022 (0.014)	0.1161	(-0.005, 0.049)
	BI 1744 R10Q	BI 1744 R5Q	0.176 (0.022) ***	0.182 (0.022) ***	-0.006 (0.014)	0.6789	(-0.033, 0.021)
	BI 1744 R5B	BI 1744 R2B	0.195 (0.022) ***	0.160 (0.022) ***	0.035 (0.014)	0.0129	(0.007, 0.062)

Based on a mixed effects repeated measures model.
Number of patients: BI 1744 R2B (46), BI 1744 R5Q (47), BI 1744 R5B (46), BI 1744 R10Q (46)
Common baseline mean (se): AUC (0-12h) = 1.187 (0.052), AUC (0-24h) = 1.160 (0.050), AUC (12-24h) = 1.132 (0.048)
* p < 0.05 vs. baseline, ** p < 0.01 vs. baseline, *** p < 0.001 vs. baseline
Since patient [redacted] had missing data prior to 2 hours post-dose for period 4, treatment BI 1744 R2B has N=45 for AUC(0-12) and AUC(0-24)

Source data: Appendix 16.1.9.2, Statdoc 6.1.1 pft_adjmn1.sas 20OCT2009

Table 15.2.1.4: 1 Adjusted mean# (SE) FEV1 peak(0-3) response [L] after 3 weeks - analysis with imputation (FAS)

Dose A	Dose B	Dose A Mean (SE)	Dose B Mean (SE)	Difference Mean (SE)	Difference P-value	Difference 95% C.I.
BI 1744 R10Q	BI 1744 R5B	0.242 (0.029) ***	0.230 (0.029) ***	0.012 (0.017)	0.4931	(-0.023, 0.047)
BI 1744 R10Q	BI 1744 R2B	0.242 (0.029) ***	0.187 (0.029) ***	0.054 (0.018)	0.0025	(0.020, 0.089)
BI 1744 R5Q	BI 1744 R5B	0.249 (0.029) ***	0.230 (0.029) ***	0.020 (0.017)	0.2597	(-0.015, 0.054)
BI 1744 R5Q	BI 1744 R2B	0.249 (0.029) ***	0.187 (0.029) ***	0.062 (0.018)	0.0006	(0.027, 0.097)
BI 1744 R10Q	BI 1744 R5Q	0.242 (0.029) ***	0.249 (0.029) ***	-0.008 (0.017)	0.6578	(-0.042, 0.027)
BI 1744 R5B	BI 1744 R2B	0.230 (0.029) ***	0.187 (0.029) ***	0.042 (0.018)	0.0175	(0.008, 0.077)

Based on a mixed effects repeated measures model.
Number of patients: BI 1744 R2B (45), BI 1744 R5Q (47), BI 1744 R5B (46), BI 1744 R10Q (46)
Common baseline mean (se): 1.276 (0.054)
* p < 0.05 vs. baseline, ** p < 0.01 vs. baseline, *** p < 0.001 vs. baseline

Table 15.2.1.3: 1 Adjusted mean# (SE) FEV1 trough response [L] after 3 weeks - analysis with imputation (FAS)

Dose A	Dose B	Dose A Mean (SE)	Dose B Mean (SE)	Difference Mean (SE)	Difference P-value	Difference 95% C.I.
BI 1744 R10Q	BI 1744 R5B	0.087 (0.028) **	0.129 (0.028) ***	-0.042 (0.020)	0.0353	(-0.081,-0.003)
BI 1744 R10Q	BI 1744 R2B	0.087 (0.028) **	0.093 (0.028) **	-0.006 (0.020)	0.7606	(-0.045, 0.033)
BI 1744 R5Q	BI 1744 R5B	0.108 (0.028) ***	0.129 (0.028) ***	-0.021 (0.020)	0.2875	(-0.060, 0.018)
BI 1744 R5Q	BI 1744 R2B	0.108 (0.028) ***	0.093 (0.028) **	0.015 (0.020)	0.4553	(-0.024, 0.054)
BI 1744 R10Q	BI 1744 R5Q	0.087 (0.028) **	0.108 (0.028) ***	-0.021 (0.020)	0.2902	(-0.060, 0.018)
BI 1744 R5B	BI 1744 R2B	0.129 (0.028) ***	0.093 (0.028) **	0.036 (0.020)	0.0731	(-0.003, 0.075)

Based on a mixed effects repeated measures model.
Number of patients: BI 1744 R2B (45), BI 1744 R5Q (47), BI 1744 R5B (46), BI 1744 R10Q (46)
Common baseline mean (se): 1.202 (0.051)
* p < 0.05 vs. baseline, ** p < 0.01 vs. baseline, *** p < 0.001 vs. baseline

Table 15.2.2.1: 1 Adjusted mean# (SE) FVC AUC(0-12), AUC(12-24) and AUC(0-24) response [L] after 3 weeks
- analysis with imputation (FAS)

Time Interval	Dose A	Dose B	Dose A Mean (SE)	Dose B Mean (SE)	Difference Mean (SE)	Difference P-value	Difference 95% C.I.
0-12 hr	BI 1744 R10Q	BI 1744 R5B	0.340 (0.043) ***	0.294 (0.043) ***	0.046 (0.027)	0.0917	(-0.008, 0.099)
	BI 1744 R10Q	BI 1744 R2B	0.340 (0.043) ***	0.262 (0.043) ***	0.078 (0.027)	0.0050	(0.024, 0.131)
	BI 1744 R5Q	BI 1744 R5B	0.335 (0.043) ***	0.294 (0.043) ***	0.041 (0.027)	0.1273	(-0.012, 0.095)
	BI 1744 R5Q	BI 1744 R2B	0.335 (0.043) ***	0.262 (0.043) ***	0.073 (0.027)	0.0080	(0.019, 0.127)
	BI 1744 R10Q	BI 1744 R5Q	0.340 (0.043) ***	0.335 (0.043) ***	0.004 (0.027)	0.8683	(-0.049, 0.058)
	BI 1744 R5B	BI 1744 R2B	0.294 (0.043) ***	0.262 (0.043) ***	0.032 (0.027)	0.2444	(-0.022, 0.086)
12-24 hr	BI 1744 R10Q	BI 1744 R5B	0.219 (0.043) ***	0.318 (0.043) ***	-0.099 (0.032)	0.0023	(-0.162,-0.036)
	BI 1744 R10Q	BI 1744 R2B	0.219 (0.043) ***	0.239 (0.043) ***	-0.020 (0.032)	0.5229	(-0.083, 0.043)
	BI 1744 R5Q	BI 1744 R5B	0.215 (0.043) ***	0.318 (0.043) ***	-0.103 (0.032)	0.0015	(-0.165,-0.040)
	BI 1744 R5Q	BI 1744 R2B	0.215 (0.043) ***	0.239 (0.043) ***	-0.024 (0.032)	0.4508	(-0.087, 0.039)
	BI 1744 R10Q	BI 1744 R5Q	0.219 (0.043) ***	0.215 (0.043) ***	0.004 (0.032)	0.9087	(-0.059, 0.066)
	BI 1744 R5B	BI 1744 R2B	0.318 (0.043) ***	0.239 (0.043) ***	0.079 (0.032)	0.0146	(0.016, 0.142)
0-24 hr	BI 1744 R10Q	BI 1744 R5B	0.279 (0.041) ***	0.306 (0.041) ***	-0.027 (0.027)	0.3291	(-0.080, 0.027)
	BI 1744 R10Q	BI 1744 R2B	0.279 (0.041) ***	0.249 (0.041) ***	0.030 (0.027)	0.2733	(-0.024, 0.084)
	BI 1744 R5Q	BI 1744 R5B	0.275 (0.041) ***	0.306 (0.041) ***	-0.030 (0.027)	0.2638	(-0.084, 0.023)
	BI 1744 R5Q	BI 1744 R2B	0.275 (0.041) ***	0.249 (0.041) ***	0.026 (0.027)	0.3386	(-0.028, 0.080)
	BI 1744 R10Q	BI 1744 R5Q	0.279 (0.041) ***	0.275 (0.041) ***	0.004 (0.027)	0.8877	(-0.050, 0.057)
	BI 1744 R5B	BI 1744 R2B	0.306 (0.041) ***	0.249 (0.041) ***	0.057 (0.027)	0.0402	(0.003, 0.111)

Based on a mixed effects repeated measures model.
Number of patients: BI 1744 R2B (46), BI 1744 R5Q (47), BI 1744 R5B (46), BI 1744 R10Q (46)
Common baseline mean (se): AUC (0-12h) = 2.774 (0.102), AUC (0-24h) = 2.740 (0.100), AUC (12-24h) = 2.705 (0.099)
* p < 0.05 vs. baseline, ** p < 0.01 vs. baseline, *** p < 0.001 vs. baseline
Since patient [redacted] had missing data prior to 2 hours post-dose for period 4, treatment BI 1744 R2B has N=45 for AUC(0-12) and AUC(0-24)

Source data: Appendix 16.1.9.2, Statdoc 6.2.1 pft_adjmn1.sas 20OCT2009

Table 15.2.2.4: 1 Adjusted mean# (SE) FVC peak(0-3) response [L] after 3 weeks - analysis with imputation (FAS)

Dose A	Dose B	Dose A Mean (SE)	Dose B Mean (SE)	Difference Mean (SE)	Difference P-value	Difference 95% C.I.
BI 1744 R10Q	BI 1744 R5B	0.433 (0.049) ***	0.349 (0.049) ***	0.084 (0.034)	0.0133	(0.018, 0.151)
BI 1744 R10Q	BI 1744 R2B	0.433 (0.049) ***	0.325 (0.049) ***	0.108 (0.034)	0.0018	(0.041, 0.175)
BI 1744 R5Q	BI 1744 R5B	0.417 (0.049) ***	0.349 (0.049) ***	0.068 (0.034)	0.0450	(0.002, 0.135)
BI 1744 R5Q	BI 1744 R2B	0.417 (0.049) ***	0.325 (0.049) ***	0.092 (0.034)	0.0078	(0.025, 0.159)
BI 1744 R10Q	BI 1744 R5Q	0.433 (0.049) ***	0.417 (0.049) ***	0.016 (0.034)	0.6268	(-0.050, 0.083)
BI 1744 R5B	BI 1744 R2B	0.349 (0.049) ***	0.325 (0.049) ***	0.024 (0.034)	0.4891	(-0.044, 0.091)

Based on a mixed effects repeated measures model.
Number of patients: BI 1744 R2B (45), BI 1744 R5Q (47), BI 1744 R5B (46), BI 1744 R10Q (46)
Common baseline mean (se): 2.925 (0.105)
* p < 0.05 vs. baseline, ** p < 0.01 vs. baseline, *** p < 0.001 vs. baseline

Table 15.2.2.3: 1 Adjusted mean# (SE) FVC trough response [L] after 3 weeks - analysis with imputation (FAS)

Dose A	Dose B	Dose A Mean (SE)	Dose B Mean (SE)	Difference Mean (SE)	Difference P-value	Difference 95% C.I.
BI 1744 R10Q	BI 1744 R5B	0.162 (0.054) **	0.181 (0.054) **	-0.019 (0.040)	0.6259	(-0.097, 0.059)
BI 1744 R10Q	BI 1744 R2B	0.162 (0.054) **	0.111 (0.054) *	0.051 (0.040)	0.2034	(-0.028, 0.130)
BI 1744 R5Q	BI 1744 R5B	0.177 (0.054) **	0.181 (0.054) **	-0.004 (0.039)	0.9190	(-0.082, 0.074)
BI 1744 R5Q	BI 1744 R2B	0.177 (0.054) **	0.111 (0.054) *	0.066 (0.040)	0.0985	(-0.012, 0.145)
BI 1744 R10Q	BI 1744 R5Q	0.162 (0.054) **	0.177 (0.054) **	-0.015 (0.039)	0.6991	(-0.093, 0.063)
BI 1744 R5B	BI 1744 R2B	0.181 (0.054) **	0.111 (0.054) *	0.070 (0.040)	0.0802	(-0.009, 0.149)

Based on a mixed effects repeated measures model.
Number of patients: BI 1744 R2B (45), BI 1744 R5Q (47), BI 1744 R5B (46), BI 1744 R10Q (46)
Common baseline mean (se): 2.781 (0.108)
* p < 0.05 vs. baseline, ** p < 0.01 vs. baseline, *** p < 0.001 vs. baseline

Table 15.3.2: 1 Adverse event overall summary - treated set

Treatment analysis: Trt+total incl 12 day washout

	BI 1744 R2B N (%)	BI 1744 R5Q N (%)	BI 1744 R5B N (%)	BI 1744 R10Q N (%)	Total N (%)
Number of patients	47 (100.0)	47 (100.0)	46 (100.0)	46 (100.0)	47 (100.0)
Patients with any AE	11 (23.4)	11 (23.4)	13 (28.3)	9 (19.6)	29 (61.7)
Patients with severe AEs	1 (2.1)	0 (0.0)	0 (0.0)	0 (0.0)	1 (2.1)
Patients with investigator defined drug-related AEs	1 (2.1)	2 (4.3)	2 (4.3)	6 (13.0)	7 (14.9)
Patients with other significant AEs (according to ICH E3)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Patients with AEs leading to discontinuation of trial drug	1 (2.1)	0 (0.0)	0 (0.0)	0 (0.0)	1 (2.1)
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	1 (2.1)	0 (0.0)	0 (0.0)	0 (0.0)	1 (2.1)
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)	0 (0.0)	0 (0.0)
Disability/incap.	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Req.hospitalisation	1 (2.1)	0 (0.0)	0 (0.0)	0 (0.0)	1 (2.1)
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	0 (0.0)	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: 12.0
Since this is a crossover trial, the total will not be the sum of the individual treatments.