Name of company: Boehringer Ingelheim		**Tabulated Trial Report**	Boehringer Ingelheim
Name of finished product: Not applicable		**EudraCT No.:** 2009-014417-27	
Name of active ingredient: BI 1744 CL Olodaterol RESPIMAT		**Page:** 1 of 6	**Synopsis No.:**
Module:		**Volume:**	
Report date: 11 January 2012	**Trial No. / U No.:** 1222.39/ U10-3198-01	**Date of trial:** 08 Jan 2011 – 04 Jan 2011	**Date of revision:** Not applicable

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Title of trial:	Randomised, double-blind, double-dummy, placebo-controlled, 4-way cross-over study to characterise the 24-hour FEV_1-time profiles of BI 1744 CL 5µg and 10µg (oral inhalation, delivered by the Respimat® Inhaler) and tiotropium bromide 18µg (oral inhalation, delivered by the HandiHaler®) after 6 weeks of treatment in patients with Chronic Obstructive Pulmonary Disease (COPD)
Coordinating Investigator:	Peter Lange, MD
Trial sites:	Multicentre study, cf. Appendix 16.1.4.
Publication (reference):	Data of this study have not been published.
Clinical phase:	III
Objectives:	The primary objective was to evaluate whether once daily treatment with olodaterol (5 µg [two actuations of 2.5 µg] and 10 µg [two actuations of 5 µg]) is superior to placebo (both delivered by the RESPIMAT inhaler) using area under the curve FEV_1 calculated from zero time to 12 hours (AUC_{0-12}) and area under the curve for FEV_1 calculated from hour 12 to 24 hours (AUC_{12-24}) responses after six weeks of treatment. The coprimary efficacy endpoints were FEV_1 AUC_{0-12} response and FEV1 AUC_{12-24} response after 6 weeks of treatment. A secondary objective was to compare the 24-hour FEV_1-time profile of olodaterol (5 µg and 10 µg) administered once daily by the RESPIMAT Inhaler with the 24-hour FEV_1-time profile of tiotropium powder capsule (18 µg) administered once daily via the HandiHaler® after 6 weeks of treatment.
Methodology:	Randomized, double-blind, double-dummy, placebo-controlled, 4-way cross-over design

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No. of subjects:	
planned:	Enrolled: 108 Entered: 100
actual:	Enrolled: 147 Entered/randomized: 108 Olodaterol 5 µg: treated: 101; analysed (for primary endpoint): 100 Olodaterol 10 µg: treated: 101; analysed (for primary endpoint): 99 Tiotropium bromide: treated: 101; analysed (for primary endpoint): 99 Placebo: treated: 102; analysed (for primary endpoint): 99
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 <80% predicted; post-bronchodilator FEV_1/FVC <70%
Test product (1):	Olodaterol inhalation solution – RESPIMAT
dose:	5 µg once daily (ex mouthpiece: 2 actuations of 2.5 µg once daily)
mode of admin.:	Oral inhalation
batch no.:	2.5 µg: B072000346, B082000026, B082000007
Test product (2):	Olodaterol inhalation solution – RESPIMAT
dose:	10 µg once daily (ex mouthpiece: 2 actuations of 5 µg once daily)
mode of admin.:	Oral inhalation
batch no.:	5 µg: B072000356, B082000029, B072000354

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Reference therapy (1):	Matching placebo to olodaterol inhalation solution – RESPIMAT
dose:	once daily
mode of admin.:	Oral inhalation
batch no.:	B082000136
Reference therapy (2):	Tiotropium bromide powder capsules – HandiHaler®
dose:	18 µg once daily
mode of admin.:	Oral inhalation
batch no.:	B102000006
Reference therapy (3):	Placebo – RESPIMAT and Placebo – HandiHaler®
dose:	N/A
mode of admin.:	Oral inhalation
batch no.:	B092000133
Duration of treatment:	4 x 6-week treatment periods, with a 3 week wash-out between each treatment period (total treatment duration of 24 weeks)
Criteria for evaluation:	
Efficacy / clinical pharmacology:	FEV_1 AUC_{0-12}, FEV_1 AUC_{12-24}, FEV_1 AUC_{0-24} and FEV_1 AUC_{0-3} responses. FVC AUC_{0-12}, FVC AUC_{12-24}, FVC AUC_{0-24} and FVC AUC_{0-3} responses. FEV_1 and FVC at individual time-points. Peak and trough FEV_1 and FVC responses
Safety:	Adverse events (AEs) (including physical exam), vital signs, laboratory evaluations, 12-lead ECG
Statistical methods:	Mixed effect repeated measures model (MMRM) with treatment and period as fixed effects, patient as a random effect, and study baseline as a continuous covariate. Descriptive statistics for safety endpoints.

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SUMMARY – CONCLUSIONS:

Efficacy/clinical pharmacology results:

For the first co-primary efficacy endpoint of FEV_1 AUC_{0-12} response after six weeks of treatment, both olodaterol 5 µg and /olodaterol 10 µg demonstrated a statistically significant increase compared with placebo (p<.0001), with a difference of 185 mL (131 vs. –54 mL) for olodaterol 5 µg and a difference of 207 mL (152 vs. –54 mL) for olodaterol 10 µg.

For the second co-primary efficacy endpoint of FEV_1 AUC_{12-24} response after six weeks of treatment, both olodaterol 5 µg and /olodaterol 10 µg demonstrated a statistically significant increase compared with placebo (p<.0001), with a difference of 131 mL (36 vs. –95 mL) for olodaterol 5 µg and a difference of 178 mL (82 vs. –95 mL) for olodaterol 10 µg.

There were also statistically significant increases in mean FEV_1 AUC_{0-12} response and FEV_1 AUC_{12-24} response for tiotropium 18 µg compared with placebo (p<.0001), with differences of 173 mL (119 vs. –54 mL) and 123 mL (27 vs. –95 mL), respectively.

Both doses of olodaterol and tiotropium 18 µg showed a statistically significant increase in adjusted mean FEV_1 AUC_{0-24} response compared to placebo (p<.0001), with differences of 158 mL (83 vs. –75 mL, p<.0001) for olodaterol 5 µg, 192 mL (117 vs. –75 mL, p<.0001) for olodaterol 10 µg, and 148 mL (73 vs. –75 mL, p<.0001) for tiotropium 18 µg.

There was a statistically significant increase in adjusted mean FEV_1 AUC_{0-3} response at six weeks for both doses of olodaterol and tiotropium 18 µg compared with placebo (p<.0001), with differences of 206 mL (161 vs. –45 mL) for olodaterol 5 µg, 215 mL (170 vs. –45 mL) for olodaterol 10 µg, and 182 mL (137 vs. –45 mL) for tiotropium 18 µg.

Both olodaterol doses and tiotropium 18 µg showed a statistically significant increase in FEV_1 peak and FEV_1 trough compared with placebo (p<.0001). The difference in FEV_1 peak compared with placebo was 213 mL (232 vs. 19 mL) for olodaterol 5 µg, 234 mL (253 vs. 19 mL) for olodaterol 10 µg and 201 mL (220 vs. 19 mL) for tiotropium 18 µg. The difference in FEV_1 trough compared with placebo was 133 mL (90 vs. –43 mL) for olodaterol 5 µg, 147 mL (104 vs. –43 mL) for olodaterol 10 µg and 97 mL (54 vs. –43 mL) for tiotropium 18 µg.

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Efficacy/clinical pharmacology results (continued):	Analyses of FVC AUC responses and of $FEV_1$and FVC responses throughout the 24-hour post-dose evaluation period supported analyses of the primary and key secondary analyses. There were no statistically significant differences between the active treatment groups in any efficacy parameter, except between olodaterol 10 µg and tiotropium 18 µg for mean FEV_1 AUC_{12-24} (55 mL, p=.0100), mean FEV_1 AUC_{0-24} (44 mL, p=.0209),mean FEV_1 trough response (50 mL, p=.0084), mean FVC AUC_{12-24} response (69 mL, p=.0414), and mean FVC trough response (84 mL, p=.0198).
Safety results:	Overall, 66.7% patients reported at least one AE during the study. The percentages of patients who experienced at least one AE were balanced across treatment groups, ranging from 31.7% in the olodaterol 5 µg group to 34.7% in the tiotropium 18 µg group. The majority of AEs were mild to moderate in intensity, with severe AEs reported for 8 (7.4%) of patients overall. SAEs were reported for 10 (9.3%) patients. One patient in the olodaterol 10 µg group experienced severe pain in her knee, groin, and shoulder, which was considered by the investigator to be related to study drug; she was discontinued from the study and recovered without treatment All other severe AEs and SAEs were considered not related to study drug by the investigator. There were no deaths reported for this trial. The most frequently reported treatment-emergent AEs (TEAEs) in at least 5% of patients were nasopharyngitis (19.4%), COPD exacerbation coded as chronic obstructive pulmonary disease (13.9%), dyspnea (6.5%), and cough (5.6%). The percentage of patients reporting each TEAE was generally comparable across the treatment groups, and no dose relationship was seen for any TEAE. Most TEAEs were mild or moderate in intensity. TEAEs that were considered severe were reported for 7.4% of patients overall: 3.9% of patients in the placebo group, none in the olodaterol 5 µg group, 1.0% in the olodaterol 10 µg group, and 4.0% in the tiotropium 18 µg group.

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Safety results (continued):	Ten patients were reported with at least one serious AE (SAE) during the treatment period. There were 5 patients reported with an SAE while receiving placebo, 1 patient while receiving olodaterol 5 µg, 0 patients while receiving olodaterol 10 µg and 5 patients while receiving tiotropium 18 µg. None were considered by the investigator to be related to study drug. One patient had an SAE while receiving olodaterol; atrial fibrillation was reported for one patient in the olodaterol 5 µg treatment group. TEAEs leading to discontinuation of the study drug were reported for eight patients: three patients in the placebo group, one patient in the olodaterol 5 µg group, one patient in the olodaterol 10 µg group, and three patients in the tiotropium 18 µg group. All events that led to discontinuation were considered by the investigator to be not related to the study drug except for arthralgia in one patient in the olodaterol 10 µg group; all patients recovered. AEs of COPD exacerbation in two patients in the placebo group and one patient in the olodaterol 5 µg group were classified as "other significant" according to ICH E3 criteria. All four discontinued the study drug because of this event and recovered. Clinical laboratory results, vital signs measurements, and electrocardiogram (ECG) findings were similar between treatment groups. No changes indicative of an adverse effect were seen on any laboratory parameters, vital signs or ECG
Conclusions:	The primary objective of the study was met, with statistically significant increases compared with placebo for the co-primary efficacy endpoints of FEV_1 AUC_{0-12} response and FEV_1 AUC_{12-24} response after six weeks of once daily treatment with olodaterol 5 µg and olodaterol 10 µg. The results for the analyses of the secondary endpoints supported the results observed for the co-primary endpoints. Olodaterol was generally safe and well tolerated; no safety trends were noted for this trial. Conclusions regarding the comparison of the 24-hour FEV_1-time profile of olodaterol once daily and the 24-hour FEV_1-time profile of tiotropium 18 µg once daily which was a secondary objective of the study, are described in the accompanying combined clinical trial report (1222.9994).

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 and for additional secondary endpoints mentioned in the results section.

Results for	**presented in**
Patient Disposition	Table 15.1.1: 1
FVC $AUC_{(0-12),}$ $AUC_{(12-24),}$ and $AUC_{(0-24)}$ response after 6 weeks of treatment	Table 15.2.2.1: 1
FVC $AUC_{(0-3)}$ response after 6 weeks of treatment	Table 15.2.2.1: 5
FVC peak response after 6 weeks of treatment	Table 15.2.2.4: 1
FVC trough response after 6 weeks of treatment	Table 15.2.2.3: 1
FEV_1 response throughout the 24 hour post dose evaluation after 6 weeks of treatment	Table 15.2.1.2: 1
FVC response throughout the 24 hour post dose evaluation after 6 weeks of treatment	Table 15.2.2.2: 1

Table 15.1.1: 1 Disposition of patients

	Placebo	Olo 5ug	Olo 10ug	Tio HH 18ug	Total
Enrolled					147
Not entered/randomsed					39
Entered/randomised					108
Not treated					0
Treated	102(100.00)	101(100.00)	101(100.00)	101(100.00)	108(100.00)
Not prematurely discontinued from trial medication #	98(96.08)	99(98.02)	98(97.03)	96(95.05)	91(84.26)
Prematurely discontinued from trial medication	4(3.92)	2(1.98)	3(2.97)	5(4.95)	
Adverse event	3(2.94)	1(0.99)	1(0.99)	3(2.97)	
AE study dis. worse	2(1.96)	1(0.99)	0(0.00)	0(0.00)	
AE-other	1(0.98)	0(0.00)	1(0.99)	3(2.97)	
Lack of efficacy	0(0.00)	1(0.99)	0(0.00)	0(0.00)	
Consent withdrawn	1(0.98)	0(0.00)	1(0.99)	1(0.99)	
Other	0(0.00)	0(0.00)	1(0.99)	1(0.99)	

The total column for this row counts all patients who did not discontinue from any treatment (i.e., completed all treatments)

Source data: Appendix 16.2.1, Listing 1 ctr\eot-t20-disp.sas 29JUL2011

Table 15.2.2.1: 1 Adjusted mean* (SE) FVC AUC(0-12), AUC(12-24) and AUC(0-24) response [L] and comparisons to placebo after 6 weeks - analysis with imputation (FAS)

Time interval	Treatment	N	Treatment mean (SE)	Difference to Placebo		
				Mean (SE)	P-value	95% CI
0-12 hr	Placebo	99	-0.110 (0.038)			
	Olo 5ug	100	0.172 (0.038)	0.282 (0.034)	<.0001	(0.216, 0.348)
	Olo 10ug	99	0.192 (0.038)	0.303 (0.033)	<.0001	(0.237, 0.368)
	Tio HH 18ug	99	0.166 (0.038)	0.276 (0.034)	<.0001	(0.210, 0.342)
12-24 hr	Placebo	99	-0.166 (0.039)			
	Olo 5ug	100	0.030 (0.039)	0.196 (0.033)	<.0001	(0.131, 0.262)
	Olo 10ug	99	0.086 (0.039)	0.252 (0.033)	<.0001	(0.187, 0.318)
	Tio HH 18ug	99	0.018 (0.039)	0.184 (0.033)	<.0001	(0.118, 0.249)
0-24 hr	Placebo	99	-0.138 (0.037)			
	Olo 5ug	100	0.101 (0.037)	0.240 (0.031)	<.0001	(0.178, 0.301)
	Olo 10ug	99	0.139 (0.037)	0.278 (0.031)	<.0001	(0.216, 0.339)
	Tio HH 18ug	99	0.091 (0.037)	0.230 (0.031)	<.0001	(0.168, 0.291)

* Based on a mixed effects repeated measures model.

Source data: Appendix 16.1.9.2, Statdoc 6.2.1 ctr\eot-t4-pft-adjmean-refcomp.sas 29JUL2011

Table 15.2.2.1: 5 Adjusted mean* (SE) FVC AUC(0-3) response [L] and comparisons to placebo after first dose - analysis with imputation (FAS)

			Difference to Placebo		
Treatment	N	Treatment mean (SE)	Mean (SE)	P-value	95% CI
Placebo	101	-0.024 (0.037)			
Olo 5ug	101	0.244 (0.037)	0.268 (0.031)	<.0001	(0.207, 0.330)
Olo 10ug	100	0.288 (0.037)	0.312 (0.031)	<.0001	(0.251, 0.374)
Tio HH 18ug	98	0.191 (0.037)	0.215 (0.031)	<.0001	(0.153, 0.277)

* Based on a mixed effects repeated measures model.

Source data: Appendix 16.1.9.2, Statdoc 6.2.2 ctr\eot-t4-pft-adjmean-refcomp.sas 29JUL2011

Table 15.2.2.4: 1 Adjusted mean* (SE) FVC peak(0-3) response [L] and comparisons to placebo after 6 weeks - analysis with imputation (FAS)

			Difference to Placebo		
Treatment	N	Treatment mean (SE)	Mean (SE)	P-value	95% CI
Placebo	99	0.086 (0.043)			
Olo 5ug	100	0.386 (0.043)	0.300 (0.040)	<.0001	(0.222, 0.378)
Olo 10ug	99	0.383 (0.043)	0.297 (0.040)	<.0001	(0.220, 0.375)
Tio HH 18ug	99	0.381 (0.043)	0.295 (0.040)	<.0001	(0.217, 0.373)

* Based on a mixed effects repeated measures model.

Source data: Appendix 16.1.9.2, Statdoc 6.2.5 ctr\eot-t4-pft-adjmean-refcomp.sas 29JUL2011

Table 15.2.2.3: 1 Adjusted mean* (SE) FVC trough response [L] and comparisons to placebo after 6 weeks - analysis with imputation (FAS)

			Difference to Placebo		
Treatment	N	Treatment mean (SE)	Mean (SE)	P-value	95% CI
Placebo	99	-0.082 (0.041)			
Olo 5ug	100	0.103 (0.041)	0.185 (0.036)	<.0001	(0.115, 0.255)
Olo 10ug	99	0.130 (0.041)	0.212 (0.036)	<.0001	(0.143, 0.282)
Tio HH 18ug	99	0.046 (0.041)	0.129 (0.036)	0.0003	(0.059, 0.199)

* Based on a mixed effects repeated measures model.

Source data: Appendix 16.1.9.2, Statdoc 6.2.4 ctr\eot-t4-pft-adjmean-refcomp.sas 29JUL2011

Table 15.2.1.2: 1 Adjusted mean* (SE) FEV1 [L] and comparisons to placebo over time - analysis with imputation (FAS)

				Difference to Placebo		
Planned time	Treatment	N	Treatment mean (SE)	Mean (SE)	P-value	95% CI
-0:30	Placebo	98	1.432 (0.019)			
	Olo 5ug	100	1.550 (0.019)	0.118 (0.020)	<.0001	(0.080, 0.156)
	Olo 10ug	99	1.550 (0.019)	0.118 (0.019)	<.0001	(0.079, 0.156)
	Tio HH 18ug	99	1.522 (0.019)	0.090 (0.020)	<.0001	(0.051, 0.128)
0:30	Placebo	99	1.429 (0.019)			
	Olo 5ug	100	1.638 (0.019)	0.208 (0.019)	<.0001	(0.170, 0.247)
	Olo 10ug	99	1.636 (0.019)	0.207 (0.019)	<.0001	(0.168, 0.245)
	Tio HH 18ug	99	1.607 (0.019)	0.178 (0.019)	<.0001	(0.139, 0.216)
1:00	Placebo	99	1.422 (0.020)			
	Olo 5ug	100	1.631 (0.020)	0.209 (0.020)	<.0001	(0.169, 0.249)
	Olo 10ug	99	1.640 (0.020)	0.218 (0.020)	<.0001	(0.179, 0.258)
	Tio HH 18ug	99	1.604 (0.020)	0.182 (0.020)	<.0001	(0.143, 0.222)
2:00	Placebo	99	1.443 (0.020)			
	Olo 5ug	100	1.662 (0.020)	0.219 (0.020)	<.0001	(0.179, 0.259)
	Olo 10ug	99	1.672 (0.020)	0.229 (0.020)	<.0001	(0.189, 0.269)
	Tio HH 18ug	99	1.641 (0.020)	0.198 (0.020)	<.0001	(0.157, 0.238)
3:00	Placebo	99	1.456 (0.023)			
	Olo 5ug	100	1.662 (0.022)	0.205 (0.023)	<.0001	(0.159, 0.251)
	Olo 10ug	99	1.684 (0.023)	0.228 (0.023)	<.0001	(0.182, 0.274)
	Tio HH 18ug	99	1.643 (0.023)	0.187 (0.024)	<.0001	(0.141, 0.233)
4:00	Placebo	99	1.453 (0.023)			
	Olo 5ug	100	1.655 (0.023)	0.202 (0.024)	<.0001	(0.155, 0.248)
	Olo 10ug	99	1.665 (0.023)	0.212 (0.024)	<.0001	(0.165, 0.258)
	Tio HH 18ug	99	1.630 (0.023)	0.177 (0.024)	<.0001	(0.131, 0.224)
6:00	Placebo	99	1.428 (0.022)			
	Olo 5ug	100	1.615 (0.022)	0.187 (0.023)	<.0001	(0.142, 0.232)
	Olo 10ug	99	1.631 (0.022)	0.203 (0.023)	<.0001	(0.158, 0.248)
	Tio HH 18ug	99	1.607 (0.022)	0.179 (0.023)	<.0001	(0.134, 0.224)

* Based on a mixed effects repeated measures model.

Source data: Appendix 16.1.9.2, Statdoc 6.1.4 ctr\eot-t4-pft-adjmean-time.sas 03AUG2011

Table 15.2.1.2: 1 Adjusted mean* (SE) FEV1 [L] and comparisons to placebo over time - analysis with imputation (FAS)

				Difference to Placebo		
Planned time	Treatment	N	Treatment mean (SE)	Mean (SE)	P-value	95% CI
8:00	Placebo	99	1.406 (0.023)			
	Olo 5ug	100	1.582 (0.023)	0.176 (0.026)	<.0001	(0.125, 0.226)
	Olo 10ug	99	1.621 (0.023)	0.216 (0.026)	<.0001	(0.165, 0.266)
	Tio HH 18ug	99	1.572 (0.023)	0.166 (0.026)	<.0001	(0.116, 0.217)
10:00	Placebo	99	1.407 (0.024)			
	Olo 5ug	100	1.585 (0.024)	0.177 (0.026)	<.0001	(0.126, 0.229)
	Olo 10ug	99	1.600 (0.024)	0.192 (0.026)	<.0001	(0.140, 0.244)
	Tio HH 18ug	99	1.571 (0.024)	0.164 (0.026)	<.0001	(0.112, 0.216)
12:00	Placebo	99	1.416 (0.028)			
	Olo 5ug	100	1.523 (0.028)	0.107 (0.034)	0.0017	(0.040, 0.174)
	Olo 10ug	99	1.594 (0.028)	0.178 (0.034)	<.0001	(0.111, 0.245)
	Tio HH 18ug	99	1.561 (0.028)	0.145 (0.034)	<.0001	(0.078, 0.211)
22:00	Placebo	99	1.343 (0.021)			
	Olo 5ug	100	1.494 (0.021)	0.150 (0.020)	<.0001	(0.112, 0.189)
	Olo 10ug	99	1.527 (0.021)	0.184 (0.020)	<.0001	(0.145, 0.222)
	Tio HH 18ug	99	1.452 (0.021)	0.108 (0.020)	<.0001	(0.070, 0.147)
23:00	Placebo	99	1.411 (0.021)			
	Olo 5ug	100	1.562 (0.021)	0.151 (0.020)	<.0001	(0.111, 0.191)
	Olo 10ug	99	1.575 (0.021)	0.164 (0.020)	<.0001	(0.124, 0.204)
	Tio HH 18ug	99	1.522 (0.021)	0.112 (0.020)	<.0001	(0.072, 0.151)
23:50	Placebo	99	1.462 (0.021)			
	Olo 5ug	100	1.576 (0.021)	0.115 (0.019)	<.0001	(0.077, 0.153)
	Olo 10ug	99	1.591 (0.021)	0.129 (0.019)	<.0001	(0.092, 0.167)
	Tio HH 18ug	99	1.544 (0.021)	0.082 (0.019)	<.0001	(0.044, 0.120)

* Based on a mixed effects repeated measures model.

Source data: Appendix 16.1.9.2, Statdoc 6.1.4 ctr\eot-t4-pft-adjmean-time.sas 03AUG2011

Table 15.2.2.2: 1 Adjusted mean* (SE) FVC [L] over time and comparisons to placebo - analysis with imputation (FAS)

Planned time	Treatment	N	Treatment mean (SE)	Difference to Placebo		
				Mean (SE)	P-value	95% CI
-0:30	Placebo	98	3.124 (0.038)			
	Olo 5ug	100	3.308 (0.038)	0.184 (0.036)	<.0001	(0.113, 0.256)
	Olo 10ug	99	3.302 (0.038)	0.178 (0.036)	<.0001	(0.107, 0.250)
	Tio HH 18ug	99	3.312 (0.038)	0.188 (0.037)	<.0001	(0.116, 0.260)
0:30	Placebo	99	3.103 (0.041)			
	Olo 5ug	100	3.440 (0.041)	0.338 (0.041)	<.0001	(0.258, 0.418)
	Olo 10ug	99	3.431 (0.041)	0.328 (0.041)	<.0001	(0.248, 0.408)
	Tio HH 18ug	99	3.437 (0.041)	0.335 (0.041)	<.0001	(0.255, 0.414)
1:00	Placebo	99	3.105 (0.043)			
	Olo 5ug	100	3.415 (0.043)	0.310 (0.041)	<.0001	(0.229, 0.390)
	Olo 10ug	99	3.429 (0.043)	0.324 (0.041)	<.0001	(0.244, 0.404)
	Tio HH 18ug	99	3.406 (0.043)	0.301 (0.041)	<.0001	(0.221, 0.382)
2:00	Placebo	99	3.142 (0.043)			
	Olo 5ug	100	3.487 (0.043)	0.344 (0.040)	<.0001	(0.265, 0.424)
	Olo 10ug	99	3.480 (0.043)	0.337 (0.040)	<.0001	(0.258, 0.417)
	Tio HH 18ug	99	3.456 (0.043)	0.313 (0.040)	<.0001	(0.234, 0.393)
3:00	Placebo	99	3.165 (0.044)			
	Olo 5ug	100	3.461 (0.044)	0.296 (0.042)	<.0001	(0.214, 0.378)
	Olo 10ug	99	3.471 (0.044)	0.306 (0.042)	<.0001	(0.225, 0.388)
	Tio HH 18ug	99	3.438 (0.044)	0.273 (0.042)	<.0001	(0.191, 0.354)
4:00	Placebo	99	3.143 (0.042)			
	Olo 5ug	100	3.465 (0.042)	0.323 (0.041)	<.0001	(0.243, 0.402)
	Olo 10ug	99	3.428 (0.042)	0.285 (0.040)	<.0001	(0.205, 0.365)
	Tio HH 18ug	99	3.422 (0.042)	0.279 (0.041)	<.0001	(0.199, 0.359)
6:00	Placebo	99	3.092 (0.042)			
	Olo 5ug	100	3.378 (0.042)	0.286 (0.042)	<.0001	(0.204, 0.368)
	Olo 10ug	99	3.395 (0.042)	0.302 (0.042)	<.0001	(0.220, 0.384)
	Tio HH 18ug	99	3.377 (0.042)	0.284 (0.042)	<.0001	(0.202, 0.367)

* Based on a mixed effects repeated measures model.

Source data: Appendix 16.1.9.2, Statdoc 6.2.3 ctr\eot-t4-pft-adjmean-time.sas 03AUG2011

Table 15.2.2.2: 1 Adjusted mean* (SE) FVC [L] over time and comparisons to placebo - analysis with imputation (FAS)

				Difference to Placebo		
Planned time	Treatment	N	Treatment mean (SE)	Mean (SE)	P-value	95% CI
8:00	Placebo	99	3.062 (0.042)			
	Olo 5ug	100	3.326 (0.042)	0.265 (0.040)	<.0001	(0.185, 0.344)
	Olo 10ug	99	3.385 (0.042)	0.323 (0.040)	<.0001	(0.244, 0.402)
	Tio HH 18ug	99	3.323 (0.042)	0.262 (0.040)	<.0001	(0.182, 0.341)
10:00	Placebo	99	3.067 (0.039)			
	Olo 5ug	100	3.316 (0.039)	0.249 (0.038)	<.0001	(0.175, 0.323)
	Olo 10ug	99	3.354 (0.039)	0.287 (0.038)	<.0001	(0.213, 0.361)
	Tio HH 18ug	99	3.335 (0.039)	0.268 (0.038)	<.0001	(0.194, 0.342)
12:00	Placebo	99	3.058 (0.041)			
	Olo 5ug	100	3.243 (0.041)	0.185 (0.039)	<.0001	(0.109, 0.262)
	Olo 10ug	99	3.321 (0.041)	0.264 (0.039)	<.0001	(0.187, 0.340)
	Tio HH 18ug	99	3.271 (0.041)	0.213 (0.039)	<.0001	(0.137, 0.290)
22:00	Placebo	99	3.005 (0.044)			
	Olo 5ug	100	3.211 (0.044)	0.206 (0.040)	<.0001	(0.127, 0.284)
	Olo 10ug	99	3.256 (0.044)	0.251 (0.040)	<.0001	(0.172, 0.330)
	Tio HH 18ug	99	3.176 (0.044)	0.171 (0.040)	<.0001	(0.092, 0.250)
23:00	Placebo	99	3.104 (0.043)			
	Olo 5ug	100	3.301 (0.043)	0.198 (0.040)	<.0001	(0.118, 0.277)
	Olo 10ug	99	3.317 (0.043)	0.213 (0.040)	<.0001	(0.134, 0.293)
	Tio HH 18ug	99	3.228 (0.043)	0.124 (0.040)	0.0024	(0.044, 0.204)
23:50	Placebo	99	3.145 (0.042)			
	Olo 5ug	100	3.316 (0.042)	0.171 (0.036)	<.0001	(0.100, 0.243)
	Olo 10ug	99	3.355 (0.042)	0.210 (0.036)	<.0001	(0.139, 0.282)
	Tio HH 18ug	99	3.278 (0.042)	0.133 (0.036)	0.0003	(0.062, 0.205)

* Based on a mixed effects repeated measures model.