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.:** 2009-014418-86	
Name of active ingredient: BI 1744 CL Olodaterol RESPIMAT		**Page:** 1 of 8	**Synopsis No.:**
Module:		**Volume:**	
Report date: 11 January 2012	**Trial No. / U No.:** 1222.40 / U10-3199-01	**Date of trial:** 12 Jan 2010 – 10 Jan 2011	**Date of revision** : Not applicable

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:	[redacted]
Trial sites:	Multicentre Study, cf. Appendix 16.1.4.
Publication (reference):	Data from 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 FEV_1 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:	entered: 100 enrolled: 109
actual:	Olodaterol 5 µg: entered: 116 treated: 116 analysed (for primary endpoint): 115 Olodaterol 10 µg: entered: 113 treated: 113 analysed (for primary endpoint): 106 Tiotropium bromide: entered: 113 treated: 113 analysed (for primary endpoint): 112 Placebo: entered: 110 treated: 110 analysed (for primary endpoint): 105
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.:	B072000346 B082000026
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.:	B072000356 B082000029

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Reference therapy (1):	Tiotropium bromide powder capsules – HandiHaler®
dose:	18 µg once daily
mode of admin.:	Oral inhalation
batch no.:	B072000252
	B092000098
Reference therapy (2):	Placebo – RESPIMAT
dose:	Not applicable
mode of admin.:	Oral inhalation
batch no.:	Placebo matching RESPIMAT
	B082000136
	B082000022
Reference therapy (3):	Placebo – HandiHaler®
dose:	Not applicable
mode of admin.:	Oral inhalation
batch no.:	Placebo matching HandiHaler®
	B092000010
Duration of treatment:	Four six-week treatment periods with a 3 week wash-out between each treatment period (total treatment duration of 24 weeks)

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Criteria for evaluation:

Efficacy / clinical pharmacology:

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 co-primary efficacy endpoints were FEV_1 AUC_{0-12} response and FEV_1 AUC_{12-24} response after 6 weeks of treatment.

Secondary endpoints included:

- FEV_1 AUC_{0-24} response after 6 weeks treatment
- FVC AUC_{0-12}, FVC AUC_{12-24} and FVC AUC_{0-24} responses after 6 weeks treatment
- Trough FEV_1 and FVC responses after 6 weeks treatment
- FEV_1 AUC_{0-3} and FVC AUC_{0-3} responses after 1st dose and after 6 weeks treatment
- Peak FEV_1 and FVC responses after first dose and after 6 weeks treatment
- Individual FEV_1 and FVC measurements at each time point after first dose (up to 3 hours) and after 6 weeks (over 24 hours) of treatment

Safety:

Adverse events (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 10 µg and olodaterol 5µg demonstrated a statistically significant increase compared with placebo ($p<0.0001$), with a difference of 221 mL (213 vs. -8 mL) for olodaterol 10 µg and a difference of 197 mL (189 vs. -8 mL) for olodaterol 5 µg. A statistically significant increase ($p<0.0001$), compared with placebo, was also observed for tiotropium 18 µg, with a difference in adjusted means of 221 mL.

For the second co-primary efficacy endpoint of FEV_1 AUC_{12-24} response after six weeks of treatment, both olodaterol 10 µg and olodaterol 5 µg demonstrated a statistically significant increase compared with placebo ($p<0.0001$), with a difference of 170 mL (111 vs. -59 mL) for olodaterol 10 µg and a difference of 153 mL (94 vs. -59 mL) for olodaterol 5 µg. A statistically significant increase ($p<0.0001$), compared with placebo, was also observed for tiotropium 18 µg, with a difference in adjusted means of 164 mL.

For the secondary endpoint, FEV_1 AUC_{0-24} response after six weeks of treatment, both olodaterol 10 µg and olodaterol 5 µg demonstrated a statistically significant increase compared with placebo ($p<0.0001$), with a difference of 191 mL (158 vs. -33 mL) for olodaterol 10 µg and a difference of 175 mL (142 vs. -33 mL) for olodaterol 5 µg. A statistically significant increase ($p<0.0001$), compared with placebo, was also observed for tiotropium 18 µg, with a difference in adjusted means of 192 mL.

For FEV_1 AUC_{0-3} response after six weeks of treatment, both olodaterol 10 µg and olodaterol 5 µg demonstrated a statistically significant increase compared with placebo ($p<0.0001$), with a difference of 238 mL (256 vs. 18 mL) for olodaterol 10 µg and a difference of 214 mL (232 vs. 18 mL) for olodaterol 5 µg. A statistically significant increase ($p<0.0001$), compared with placebo, was also observed for tiotropium 18 µg, with a difference in adjusted means of 235 mL. The FEV_1 AUC_{0-3} response after the first dose supported these results.

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Efficacy/clinical pharmacology results (continued):

Peak FEV_1 response and trough FEV_1 response after six weeks were consistent with the primary analysis, with statistically significant increases observed for both olodaterol doses compared with placebo. Peak FEV_1 response was 325 mL for olodaterol 10 µg and 290 mL for olodaterol 5 µg qd with differences of 243 mL and 208 mL, respectively, compared with placebo. The results for the peak FEV1 response after the first dose supported these results. Trough FEV_1 response was similar for olodaterol 10 µg and olodaterol 5 µg qd, (differences of 143 mL and 134 mL, respectively, compared with placebo), consistent with results observed in previous studies.

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.

No differences were observed between olodaterol 5 µg, olodaterol 10 µg and tiotropium 18 µg for FEV_1 AUC_{0-12} response, for FEV_1 AUC_{12-24} response, or for FEV_1 AUC_{0-24} response.

Safety results:

Overall, 68.9% of patients reported at least one treatment-emergent AE during the study. The percentages of patients who experienced at least one AE were balanced across the treatment groups: 33.9% in the placebo group, 35.7% in the olodaterol 5 µg group, 38.9% in the olodaterol 10 µg group, and 33.6% in the tiotropium 18 µg group. The majority of AEs were mild to moderate in intensity; severe AEs were reported for 12.3% of patients, overall. One AE, kidney dysfunction, reported for a patient receiving placebo, and one SAE, atrial fibrillation, reported for a patient receiving olodaterol 10 µg, were of severe intensity and considered by the investigator to be related to study drug. All other severe AEs and SAEs reported were considered not related to study drug by the investigator. There was no evidence of a dose relationship for any AE or category of AEs (SAEs, etc.); small differences between treatment groups were considered consequent to variability related to the overall small number of events. There were no deaths reported for this study.

The most frequently reported AEs were respiratory events. The most commonly reported AEs overall (AEs with an incidence >5%), by preferred term (PT) were COPD exacerbation coded as the PT chronic obstructive pulmonary disease (14.8%), nasopharyngitis (14.8%), cough (9.0%), and dyspnoea (9.0%). The percentage of patients reporting each AE was generally comparable across the treatment groups, and no dose relationship was seen for any AE.

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Safety results (continued):

Most of the AEs reported for the trial were not considered by the investigator to be related to the study drug. Adverse Events that were considered drug-related according to the investigator were reported for five patients in total : two AEs (kidney dysfunction and potassium increased) in one patient in the placebo group; none in the olodaterol 5 µg group; one AE (atrial fibrillation) in one patient and two AEs (hair loss and palpitations) in one patient in the olodaterol 10 µg group; two AEs (dyspnea exacerbated and fatigueability generalised) in one patient and one AE (irratitative cough) in one patient in the tiotropium 18 µg group. All of these events assessed by the investigator to be drug-related were of mild or moderate intensity, except the kidney dysfunction reported for the patient in the placebo group and the atrial fibrillation reported for the patient in the olodaterol 10 µg group, which were severe in intensity. The atrial fibrillation led to discontinuation of study drug and was reported as an SAE. The kidney dysfunction led to discontinuation of study medication but was not reported as an SAE.

A total of 17 patients (13.9% overall) were reported with at least one SAE during the treatment period of the study. There were 5 patients reported with an SAE while receiving placebo, 3 patients while receiving olodaterol 5 µg, 8 patients while receiving olodaterol 10 µg and 2 patients while receiving tiotropium 18 µg. The only SAE to occur in more than one patient was COPD exacerbation in seven patients. One SAE of atrial fibrillation reported for one patient in the olodaterol 10 µg group was considered by the investigator to be related to the study drug. All of the patients with SAEs recovered from the event(s) except neuroendocrine carcinoma, which was reported for a patient in the olodaterol 10 µg group.

AEs leading to discontinuation of the study drug were reported for a total of 16 patients (13.1%): 5 patients (4.6%) in the placebo group, 2 patients (1.7%) in the olodaterol 5 µg group, 6 patients (5.3%) in the olodaterol 10 µg group, and 3 patients (2.7%) 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 two AEs: renal impairment, reported for one patient in the placebo group, and atrial fibrillation, reported for one patient in the olodaterol 10 µg group.

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Safety results (continued):	There were 8 patients (6.6%) reported with AEs that were "other significant" AEs according to ICH E3 criteria. In the placebo group, one patient was reported with anaemia, two patients were reported with COPD, and one patient was reported with renal impairment. In the olodaterol 5 µg group, one patient was reported with nausea. In the olodaterol 10 µg group, one patient was reported with atrial fibrillation, and one patient was reported with blood creatinine increased. In the tiotropium 18 µg group, there was one patient reported with back pain and one patient reported with rheumatoid arthritis. Clinical laboratory results, vital signs measurements, and ECG findings were similar between the treatment groups. No changes of clinical significance were observed for any laboratory parameters, vital signs or ECG parameters measured for the study.
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 and no safety trends were noted in 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, 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
FEV_1 $AUC_{(0-3)}$ response after first dose	Table 15.2.1.1: 5
FEV_1 peak response after 6 weeks	Table 15.2.1.4: 1
FEV_1 trough response after 6 weeks	Table 15.2.1.3: 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					155
Not entered/randomsed					33
Entered/randomised					122
Not treated					0
Treated	110(100.00)	116(100.00)	113(100.00)	113(100.00)	122(100.00)
Not prematurely discontinued from trial medication #	103(93.64)	106(91.38)	104(92.04)	111(98.23)	96(78.69)
Prematurely discontinued from trial medication	7(6.36)	10(8.62)	9(7.96)	2(1.77)	
Adverse event	6(5.45)	1(0.86)	7(6.19)	1(0.88)	
AE study dis. worse	3(2.73)	0(0.00)	2(1.77)	0(0.00)	
AE-oth. dis. worse	0(0.00)	1(0.86)	0(0.00)	0(0.00)	
AE-other	3(2.73)	0(0.00)	5(4.42)	1(0.88)	
Lack of efficacy	1(0.91)	1(0.86)	0(0.00)	0(0.00)	
Non compl prot.	0(0.00)	4(3.45)	0(0.00)	0(0.00)	
Consent withdrawn	0(0.00)	1(0.86)	1(0.88)	0(0.00)	
Other	0(0.00)	3(2.59)	1(0.88)	1(0.88)	

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 15.2.1.1: 5 Adjusted mean* (SE) FEV1 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	107	0.018 (0.018)			
Olo 5ug	113	0.232 (0.017)	0.214 (0.017)	<.0001	(0.181, 0.248)
Olo 10ug	113	0.256 (0.017)	0.238 (0.017)	<.0001	(0.205, 0.272)
Tio HH 18ug	111	0.169 (0.018)	0.152 (0.017)	<.0001	(0.119, 0.185)

* Based on a mixed effects repeated measures model.

Source data: Appendix 16.1.9.2, Statdoc 6.1.2 ctr\eot-t4-pft-adjmean-refcomp.sas 29JUL2011

Table 15.2.1.4: 1 Adjusted mean* (SE) FEV1 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	105	0.082 (0.020)			
Olo 5ug	115	0.290 (0.020)	0.208 (0.019)	<.0001	(0.169, 0.246)
Olo 10ug	106	0.325 (0.020)	0.243 (0.020)	<.0001	(0.205, 0.282)
Tio HH 18ug	112	0.325 (0.020)	0.244 (0.019)	<.0001	(0.205, 0.282)

* Based on a mixed effects repeated measures model.

Source data: Appendix 16.1.9.2, Statdoc 6.1.6 ctr\eot-t4-pft-adjmean-refcomp.sas 29JUL2011

Table 15.2.1.3: 1 Adjusted mean* (SE) FEV1 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	105	0.003 (0.019)			
Olo 5ug	115	0.137 (0.019)	0.134 (0.019)	<.0001	(0.097, 0.171)
Olo 10ug	107	0.146 (0.019)	0.143 (0.019)	<.0001	(0.105, 0.181)
Tio HH 18ug	112	0.161 (0.019)	0.158 (0.019)	<.0001	(0.120, 0.195)

* Based on a mixed effects repeated measures model.

Source data: Appendix 16.1.9.2, Statdoc 6.1.5 ctr\eot-t4-pft-adjmean-refcomp.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	105	-0.006 (0.035)			
	Olo 5ug	115	0.324 (0.034)	0.330 (0.028)	<.0001	(0.276, 0.384)
	Olo 10ug	106	0.321 (0.035)	0.326 (0.028)	<.0001	(0.272, 0.381)
	Tio HH 18ug	112	0.364 (0.035)	0.370 (0.027)	<.0001	(0.316, 0.424)
12-24 hr	Placebo	105	-0.109 (0.036)			
	Olo 5ug	115	0.169 (0.035)	0.278 (0.033)	<.0001	(0.214, 0.342)
	Olo 10ug	107	0.155 (0.036)	0.264 (0.033)	<.0001	(0.200, 0.329)
	Tio HH 18ug	112	0.192 (0.035)	0.302 (0.033)	<.0001	(0.238, 0.366)
0-24 hr	Placebo	105	-0.057 (0.036)			
	Olo 5ug	115	0.247 (0.035)	0.304 (0.030)	<.0001	(0.244, 0.363)
	Olo 10ug	107	0.226 (0.036)	0.283 (0.031)	<.0001	(0.222, 0.343)
	Tio HH 18ug	112	0.278 (0.035)	0.335 (0.030)	<.0001	(0.275, 0.395)

* 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	107	0.053 (0.035)			
Olo 5ug	113	0.423 (0.034)	0.370 (0.031)	<.0001	(0.309, 0.430)
Olo 10ug	113	0.419 (0.034)	0.366 (0.030)	<.0001	(0.306, 0.426)
Tio HH 18ug	111	0.316 (0.034)	0.262 (0.030)	<.0001	(0.202, 0.322)

* 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	105	0.191 (0.037)			
Olo 5ug	115	0.526 (0.036)	0.334 (0.031)	<.0001	(0.272, 0.396)
Olo 10ug	106	0.537 (0.037)	0.346 (0.032)	<.0001	(0.283, 0.408)
Tio HH 18ug	112	0.569 (0.037)	0.378 (0.031)	<.0001	(0.316, 0.440)

* 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	105	-0.001 (0.037)			
Olo 5ug	115	0.243 (0.036)	0.244 (0.033)	<.0001	(0.179, 0.309)
Olo 10ug	107	0.215 (0.037)	0.216 (0.033)	<.0001	(0.150, 0.282)
Tio HH 18ug	112	0.255 (0.037)	0.256 (0.033)	<.0001	(0.191, 0.321)

* 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	105	1.189 (0.019)			
	Olo 5ug	115	1.299 (0.018)	0.111 (0.020)	<.0001	(0.071, 0.150)
	Olo 10ug	106	1.336 (0.019)	0.147 (0.020)	<.0001	(0.107, 0.187)
	Tio HH 18ug	112	1.348 (0.018)	0.159 (0.020)	<.0001	(0.120, 0.199)
0:30	Placebo	105	1.225 (0.020)			
	Olo 5ug	115	1.423 (0.019)	0.197 (0.021)	<.0001	(0.157, 0.238)
	Olo 10ug	106	1.462 (0.020)	0.236 (0.021)	<.0001	(0.195, 0.277)
	Tio HH 18ug	112	1.436 (0.020)	0.210 (0.021)	<.0001	(0.170, 0.251)
1:00	Placebo	105	1.215 (0.020)			
	Olo 5ug	115	1.443 (0.020)	0.229 (0.020)	<.0001	(0.189, 0.268)
	Olo 10ug	106	1.477 (0.020)	0.262 (0.020)	<.0001	(0.222, 0.302)
	Tio HH 18ug	112	1.457 (0.020)	0.242 (0.020)	<.0001	(0.202, 0.281)
2:00	Placebo	105	1.227 (0.021)			
	Olo 5ug	115	1.463 (0.020)	0.236 (0.020)	<.0001	(0.197, 0.275)
	Olo 10ug	106	1.488 (0.021)	0.261 (0.020)	<.0001	(0.222, 0.301)
	Tio HH 18ug	112	1.482 (0.020)	0.255 (0.020)	<.0001	(0.216, 0.294)
3:00	Placebo	105	1.230 (0.021)			
	Olo 5ug	115	1.446 (0.021)	0.216 (0.020)	<.0001	(0.176, 0.257)
	Olo 10ug	106	1.475 (0.021)	0.245 (0.021)	<.0001	(0.205, 0.286)
	Tio HH 18ug	112	1.478 (0.021)	0.249 (0.020)	<.0001	(0.208, 0.289)
4:00	Placebo	105	1.229 (0.022)			
	Olo 5ug	115	1.453 (0.021)	0.223 (0.021)	<.0001	(0.183, 0.264)
	Olo 10ug	106	1.462 (0.021)	0.233 (0.021)	<.0001	(0.192, 0.274)
	Tio HH 18ug	112	1.472 (0.021)	0.243 (0.021)	<.0001	(0.202, 0.284)
6:00	Placebo	105	1.216 (0.023)			
	Olo 5ug	115	1.392 (0.022)	0.176 (0.023)	<.0001	(0.131, 0.220)
	Olo 10ug	106	1.437 (0.023)	0.221 (0.023)	<.0001	(0.176, 0.266)
	Tio HH 18ug	112	1.432 (0.022)	0.216 (0.023)	<.0001	(0.172, 0.261)

* 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	105	1.184 (0.020)			
	Olo 5ug	115	1.379 (0.019)	0.195 (0.018)	<.0001	(0.159, 0.231)
	Olo 10ug	106	1.395 (0.020)	0.211 (0.019)	<.0001	(0.175, 0.248)
	Tio HH 18ug	112	1.392 (0.019)	0.208 (0.018)	<.0001	(0.172, 0.244)
10:00	Placebo	105	1.172 (0.021)			
	Olo 5ug	115	1.358 (0.020)	0.186 (0.020)	<.0001	(0.147, 0.225)
	Olo 10ug	106	1.374 (0.021)	0.202 (0.020)	<.0001	(0.162, 0.241)
	Tio HH 18ug	112	1.388 (0.020)	0.216 (0.020)	<.0001	(0.177, 0.255)
12:00	Placebo	105	1.163 (0.019)			
	Olo 5ug	115	1.330 (0.019)	0.167 (0.018)	<.0001	(0.132, 0.202)
	Olo 10ug	106	1.348 (0.019)	0.185 (0.018)	<.0001	(0.150, 0.220)
	Tio HH 18ug	112	1.348 (0.019)	0.185 (0.018)	<.0001	(0.150, 0.219)
22:00	Placebo	105	1.123 (0.020)			
	Olo 5ug	115	1.268 (0.019)	0.145 (0.021)	<.0001	(0.103, 0.187)
	Olo 10ug	107	1.301 (0.019)	0.178 (0.022)	<.0001	(0.135, 0.220)
	Tio HH 18ug	112	1.271 (0.019)	0.147 (0.021)	<.0001	(0.105, 0.190)
23:00	Placebo	105	1.201 (0.019)			
	Olo 5ug	115	1.333 (0.019)	0.133 (0.020)	<.0001	(0.093, 0.172)
	Olo 10ug	107	1.348 (0.019)	0.147 (0.020)	<.0001	(0.107, 0.187)
	Tio HH 18ug	112	1.348 (0.019)	0.147 (0.020)	<.0001	(0.108, 0.187)
23:50	Placebo	105	1.225 (0.020)			
	Olo 5ug	115	1.361 (0.020)	0.135 (0.020)	<.0001	(0.097, 0.174)
	Olo 10ug	107	1.364 (0.020)	0.139 (0.020)	<.0001	(0.100, 0.178)
	Tio HH 18ug	112	1.393 (0.020)	0.168 (0.020)	<.0001	(0.129, 0.207)

* 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	105	2.797 (0.035)			
	Olo 5ug	115	2.982 (0.034)	0.186 (0.035)	<.0001	(0.118, 0.254)
	Olo 10ug	106	2.991 (0.035)	0.195 (0.035)	<.0001	(0.126, 0.264)
	Tio HH 18ug	112	3.054 (0.034)	0.258 (0.035)	<.0001	(0.190, 0.326)
0:30	Placebo	105	2.828 (0.037)			
	Olo 5ug	115	3.185 (0.036)	0.357 (0.033)	<.0001	(0.292, 0.423)
	Olo 10ug	106	3.177 (0.037)	0.349 (0.034)	<.0001	(0.283, 0.416)
	Tio HH 18ug	112	3.193 (0.036)	0.365 (0.033)	<.0001	(0.300, 0.431)
1:00	Placebo	105	2.821 (0.037)			
	Olo 5ug	115	3.199 (0.036)	0.378 (0.033)	<.0001	(0.313, 0.444)
	Olo 10ug	106	3.205 (0.037)	0.384 (0.034)	<.0001	(0.318, 0.451)
	Tio HH 18ug	112	3.213 (0.036)	0.392 (0.033)	<.0001	(0.327, 0.458)
2:00	Placebo	105	2.845 (0.038)			
	Olo 5ug	115	3.197 (0.037)	0.352 (0.034)	<.0001	(0.286, 0.418)
	Olo 10ug	106	3.225 (0.038)	0.380 (0.034)	<.0001	(0.313, 0.447)
	Tio HH 18ug	112	3.223 (0.037)	0.378 (0.033)	<.0001	(0.312, 0.444)
3:00	Placebo	105	2.851 (0.038)			
	Olo 5ug	115	3.196 (0.037)	0.345 (0.036)	<.0001	(0.275, 0.415)
	Olo 10ug	106	3.197 (0.038)	0.346 (0.036)	<.0001	(0.275, 0.417)
	Tio HH 18ug	112	3.241 (0.037)	0.390 (0.036)	<.0001	(0.320, 0.460)
4:00	Placebo	105	2.813 (0.039)			
	Olo 5ug	115	3.201 (0.038)	0.388 (0.033)	<.0001	(0.323, 0.454)
	Olo 10ug	106	3.159 (0.039)	0.346 (0.034)	<.0001	(0.280, 0.412)
	Tio HH 18ug	112	3.208 (0.038)	0.395 (0.033)	<.0001	(0.330, 0.461)
6:00	Placebo	105	2.799 (0.044)			
	Olo 5ug	115	3.103 (0.043)	0.304 (0.044)	<.0001	(0.217, 0.390)
	Olo 10ug	106	3.138 (0.044)	0.339 (0.045)	<.0001	(0.251, 0.426)
	Tio HH 18ug	112	3.173 (0.043)	0.373 (0.044)	<.0001	(0.287, 0.460)

* 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	105	2.755 (0.037)			
	Olo 5ug	115	3.063 (0.036)	0.307 (0.032)	<.0001	(0.245, 0.370)
	Olo 10ug	106	3.065 (0.037)	0.310 (0.032)	<.0001	(0.246, 0.373)
	Tio HH 18ug	112	3.121 (0.036)	0.366 (0.032)	<.0001	(0.303, 0.428)
10:00	Placebo	105	2.724 (0.038)			
	Olo 5ug	115	3.048 (0.037)	0.324 (0.034)	<.0001	(0.257, 0.391)
	Olo 10ug	106	3.017 (0.038)	0.293 (0.035)	<.0001	(0.225, 0.361)
	Tio HH 18ug	112	3.088 (0.038)	0.364 (0.034)	<.0001	(0.297, 0.431)
12:00	Placebo	105	2.703 (0.037)			
	Olo 5ug	115	3.006 (0.036)	0.303 (0.033)	<.0001	(0.238, 0.367)
	Olo 10ug	106	3.007 (0.037)	0.304 (0.033)	<.0001	(0.238, 0.369)
	Tio HH 18ug	112	3.046 (0.036)	0.343 (0.033)	<.0001	(0.278, 0.407)
22:00	Placebo	105	2.629 (0.038)			
	Olo 5ug	115	2.895 (0.037)	0.266 (0.038)	<.0001	(0.191, 0.340)
	Olo 10ug	107	2.913 (0.038)	0.284 (0.038)	<.0001	(0.208, 0.359)
	Tio HH 18ug	112	2.907 (0.037)	0.278 (0.038)	<.0001	(0.204, 0.353)
23:00	Placebo	105	2.757 (0.038)			
	Olo 5ug	115	3.008 (0.037)	0.251 (0.036)	<.0001	(0.180, 0.322)
	Olo 10ug	107	2.992 (0.038)	0.236 (0.036)	<.0001	(0.164, 0.307)
	Tio HH 18ug	112	3.023 (0.037)	0.266 (0.036)	<.0001	(0.196, 0.337)
23:50	Placebo	105	2.819 (0.039)			
	Olo 5ug	115	3.055 (0.038)	0.236 (0.035)	<.0001	(0.168, 0.304)
	Olo 10ug	107	3.016 (0.039)	0.197 (0.035)	<.0001	(0.128, 0.265)
	Tio HH 18ug	112	3.064 (0.038)	0.246 (0.034)	<.0001	(0.178, 0.313)

* Based on a mixed effects repeated measures model.