Boehringer Ingelheim

Clinical Study Synopsis for Public Disclosure

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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..

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Name of company: Boehringer Ingelheim		**Tabulated Trial Report**	Boehringer Ingelheim
Name of finished product: Not applicable		**EudraCT No.:** 2009-013395-48	
Name of active ingredient: Olodaterol		**Page:** 1 of 7	**Synopsis No.:**
Module:		**Volume:**	
Report date: 25 JAN 2012	**Trial No. / U No.:** 1222.27 / U11-2137-01	**Dates of trial:** 22 FEB 2010 – 14 JAN 2011	**Date of revision:** Not applicable

Title of trial:	A Randomised, Double-Blind, Placebo- and Active-Controlled, Incomplete Crossover Efficacy and Safety Comparison of 4-week Treatment Periods of Once Daily Treatment of 4 Doses of BI 1744 CL Inhalation Solution Delivered by the Respimat® in Patients with Asthma
Coordinating Investigator:	[redacted]
Trial sites:	Multinational, multi-centre trial in 27 sites in Austria, Germany, Poland, Romania, Slovakia, and Slovenia
Publication (reference):	Data from this trial have not been published.
Clinical phase:	II
Objectives:	The primary objective of this study was to determine the efficacy and safety of 4 doses of olodaterol (BI 1744 CL) inhalation solution (2 µg, 5 µg, 10 µg, and 20 µg) delivered by the Respimat® inhaler once daily in the evening for 4 weeks in patients with asthma in comparison with placebo. The primary variable to assess bronchodilator efficacy was the forced expiratory volume in 1 second (FEV_1). The study aimed to select an optimum dose of olodaterol based on bronchodilator efficacy and safety evaluations. A secondary objective of this study was to compare the 24-h FEV_1 time profile of olodaterol administered once daily by the Respimat® inhaler with the 24-h FEV_1 time profile of formoterol fumarate powder capsule (Foradil®, 12 µg) administered twice daily via the Aerolizer® inhaler after 4 weeks of treatment.
Methodology:	Randomised, placebo- and active-controlled, double-blind, double-dummy 4-period incomplete block design crossover study with 6 possible treatments

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No. of subjects:	
planned:	entered: 190
actual:	enrolled: 317 entered: 198 Olodaterol 2 µg: treated: 121, analysed (for primary endpoint): 119 Olodaterol 5 µg: treated: 130, analysed (for primary endpoint): 126 Olodaterol 10 µg: treated: 127, analysed (for primary endpoint): 121 Olodaterol 20 µg: treated: 124, analysed (for primary endpoint): 119 Formoterol 12 µg: treated: 125, analysed (for primary endpoint): 122 Placebo: treated: 125, analysed (for primary endpoint): 122 Since this was a crossover trial and every patient was supposed to receive 4 treatments, the total number of patients is not the sum of the number of patients on each treatment.
Diagnosis and main criteria for inclusion:	Outpatients of either sex, aged 18 to 70 years with a current diagnosis and a documented history of asthma of at least 3 months (Global Initiative for Asthma [GINA] treatment steps 3 or 4), pre-bronchodilator FEV_1 ≥60% and <90% of the predicted FEV_1 (calculated according to ECSC), and an increase in FEV_1 of at least 12% and at least 200 ml 15 min after administration of 400 µg salbutamol at the Screening Visit

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Test product:	Olodaterol (as hydrochloride) inhalation solution delivered by the Respimat® inhaler
dose:	2 µg (ex mouthpiece [2 actuations of 1.0 µg]) once daily in the evening 5 µg (ex mouthpiece [2 actuations of 2.5 µg]) once daily in the evening 10 µg (ex mouthpiece [2 actuations of 5.0 µg]) once daily in the evening 20 µg (ex mouthpiece [2 actuations of 10.0 µg]) once daily in the evening (calculated as free base)
mode of admin.:	Oral inhalation
batch no.:	Inhalation solution/Respimat® inhalers: B072000344/B082000007 (1 µg/actuation), B072000346/B082000007 (2.5 µg/actuation), B072000356/B072000354 (5 µg/actuation), B072000357/B072000354 (10 µg/actuation)
Reference therapy 1:	Placebo
dose:	Not applicable
mode of admin.:	Oral inhalation
batch no.:	Placebo matching olodaterol inhalation solution delivered by the Respimat® inhaler (inhalation solution/Respimat® inhalers): B082000136/B072000350 Placebo matching formoterol fumarate powder in capsules delivered by the Aerolizer® inhaler (Capsules/Aerolizer® inhalers): B092000046/070039, B102000086/B0489B01
Reference therapy 2:	Formoterol fumarate powder in capsules (Foradil®) delivered by the Aerolizer® inhaler
dose:	12 µg twice daily
mode of admin.:	Oral inhalation
batch no.:	Capsules/Aerolizer® inhalers: U0057/B092000090, U0063/B102000173
Duration of treatment:	One 2-week baseline period, 4 treatment periods of 4 weeks without intermittent wash-out periods, and a 2-week follow-up period Patients had to take ICS throughout the trial as background medication.

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Criteria for evaluation:

Efficacy:

Primary endpoint:

FEV_1 area under the curve from 0 to 24 h (AUC_{0-24}) after 4 weeks of treatment, divided by 24 h to report in litres; baseline FEV_1 (assessed before administration of any trial treatment) was subtracted from the FEV_1 AUC_{0-24} at the end of each 4-week treatment period. This quantity is subsequently referred to as FEV_1 AUC_{0-24} response after 4 weeks of treatment.

Secondary endpoints:

Clinic spirometry at the end of each 4-week treatment period: FEV_1 AUC_{0-12} response, FEV_1 AUC_{12-24} response, forced vital capacity (FVC) AUC_{0-24} response, FVC AUC_{0-12} response, FVC AUC_{12-24} response, peak expiratory flow (PEF) AUC_{0-24} response, PEF AUC_{0-12} response, PEF AUC_{12-24} response, peak FEV_1 response within 24 h post-dose, peak FVC response within 24 h post-dose, peak PEF response within 24 h post-dose, trough FEV_1 response, trough FVC response, trough PEF response; individual FEV_1, FVC and PEF values at the following time points relative to pm trial drug administration: -1:00, -0:10, 0:30, 1:00, 2:00, 3:00, 4:00, 11:50, 12:30, 13:00, 14:00, 15:00, 16:00, 18:00, 20:00, 22:00, 23:00, 23:50

Patient diary: For each treatment period, means for Week 3 and Week 4 and overall means excluding the first 2 weeks of treatment of the following parameters: morning PEF, evening PEF, PEF daily variability, morning FEV_1, evening FEV_1, daily use of rescue medication, nighttime use of rescue medication, daytime use of rescue medication; weekly and overall worst category of number of nighttime awakenings, daytime and nighttime asthma symptoms; percentage of asthma sympton-free days

Questionnaires: Total Asthma Quality of Life Questionnaire (AQLQ(S)) and individual domain scores (symptoms, activity limitation, emotional function, environmental stimuli) at the end of each treatment period, total Asthma Control Questionnaire (ACQ) score at the end of each treatment period

Safety:

Adverse events (AEs), vital signs (pulse rate and blood pressure), routine blood chemistry, haematology and urinalysis, 12-lead electrocardiogram (ECG), blood potassium concentrations

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Pharmacokinetics:	If feasible, plasma concentrations of olodaterol at steady state 20 min ($C_{0\ 333,ss}$), 1 h ($C_{1,ss}$), and 3 h ($C_{3,ss}$) after dosing were determined at the end of each treatment period.
Statistical methods:	The primary endpoint was analysed using a mixed model with treatment, period, and baseline FEV_1 as fixed effects, and patient as a random effect. Continuous secondary endpoints were analysed similarly to the primary endpoint. Other secondary endpoints were summarised descriptively only. Potassium was analysed similarly to the primary endpoint. Other safety endpoints were presented descriptively only.

SUMMARY – CONCLUSIONS:

Efficacy results:

Out of the 198 treated patients, 182 patients (91.9%) completed the planned treatment time, i.e. 16 patients (8.1%) discontinued study treatment prematurely. The number of patients who stopped study treatment ranged from none while treated with 2 µg olodaterol to 5 while treated with 10 µg olodaterol. The most frequent reasons for premature discontinuation were AEs (8 patients, 4.0%) followed by non-compliance with the trial protocol (3 patients, 1.5%). The treated population consisted almost exclusively of white patients (99.0%); the overall proportion of female patients was 56.6%. The mean age in the treated set was 45.0 years and the mean duration of asthma was 20.4 years. Half of the patients had had asthma for at least 20 years (50.0%).

For the primary endpoint FEV_1 AUC_{0-24} response after 4 weeks of treatment, the adjusted mean treatment difference vs. placebo was 0.140 L for treatment with 2 µg olodaterol (95% CI 0.097, 0.182), 0.182 L for 5 µg olodaterol (95% CI 0.140, 0.224), 0.205 L for 10 µg olodaterol (95% CI 0.163, 0.248), and 0.229 L for 20 µg olodaterol (95% CI 0.186, 0.272); for formoterol, it was 0.169 L (95% CI 0.126, 0.211). The mean differences between each olodaterol dose and placebo and also between formoterol and placebo were statistically significant ($p<0.0001$). Thus, for the primary endpoint mean FEV_1 AUC_{0-24} response, olodaterol treatment was superior to placebo for all doses administered. These results were supported by several sensitivity analyses. Furthermore, the treatment effect of olodaterol increased with the olodaterol dose with regard to the primary endpoint.

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Efficacy results: (continued)

Analyses of the secondary endpoints FEV_1 AUC_{0-12} response and FEV_1 AUC_{12-24} response showed consistent results with those for the primary endpoint. Furthermore, mean FEV_1 values assessed at individual time points pre- and post-dose showed efficacy of all olodaterol doses at each point over the 24-h interval. In addition, mean FEV_1 increased with the olodaterol dose at every single time point and hence strict dose ordering was apparent over the complete 24-h period observed in this study. This was also reflected in mean FEV_1 peak and trough responses which were statistically significantly different from placebo ($p<0.0001$) for all doses of olodaterol and which showed a strict dose ordering. Treatment with formoterol also led to a statistically significant improvement over placebo ($p<0.005$ in the FEV_1 AUC_{0-12} response, the FEV_1 AUC_{12-24} response, in mean FEV_1 at all observed time points, and in mean FEV_1 peak and trough responses. Secondary endpoints derived from FVC and PEF measurements at clinic visits were broadly consistent with the results of FEV_1 endpoints.

Week 3, week 4, and overall mean morning and evening PEF and FEV_1 measurements at home using the AM2+® device showed improvements in mean compared with placebo for all active treatments. Therefore, results were consistent with the results of endpoints derived from FEV_1 and PEF measured at the clinic visits after 4 weeks.

Safety results:

The mean exposure to study treatment was comparable for all treatments, ranging from 29.8 days for placebo treatment to 30.5 days for 5 µg olodaterol. The mean total exposure to study medication was 111.5 days.

During the treatment phase, the overall occurrence of AEs was higher during treatment with olodaterol (9.9%, 13.8%, 15.7%, and 12.9% for treatment with 2 µg, 5 µg, 10 µg, and 20 µg olodaterol, respectively) than during treatment with placebo (4.8%) or formoterol (6.4%). The most common treatment-emergent AEs by SOC were infections and infestations with nasopharyngitis as the most frequently reported AE and respiratory, thoracic, and mediastinal disorders with dyspnoea as the most frequently reported AE. The most frequent AEs on the preferred term level were nasopharyngitis and headache; the incidence of both was low for all treatments. By-gender analysis of AEs showed that on olodaterol treatment, the frequency of female patients with any AE (11.4% to 22.2%) was higher than the frequency of male patients with any AE (3.4% to 13.2%) for all doses except 20 µg olodaterol. A total of 8 AEs in 7 patients were considered

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Safety results: (continued)	study drug-related by the investigators; all but 1 occurred on treatment with olodaterol. The most frequent AEs considered drug-related were muscle spasms and palpitations (2 patients each). Two SAEs were reported during the study, appendicitis on treatment with 10 µg olodaterol and cerebral infarction in the post-treatment period (last treatment received 2 µg olodaterol). Both patients recovered, the latter with sequelae. Neither SAE was considered to be study drug-related by the investigator. Other significant AEs were reported for 8 patients, i.e. non-serious AEs that led to discontinuation of trial treatment. (For 2 of these 8 patients, the AE started during the screening period but subsequently led to discontinuation from treatment.) No notable findings with regard to the laboratory assessments were observed. At the end of the 4-week treatment period, slightly but statistically significantly lower mean blood potassium concentration were seen in patients 1 h after administration of 5 µg, 10 µg, or 20 µg olodaterol compared with placebo; the size of these differences was not considered clinically relevant. No statistically significant differences from placebo were seen predose and 3 h post-dose. No relationship was observed between olodaterol plasma concentrations 20 min post-dose (which is close to the expected t_{max} for olodaterol) and blood potassium.
Conclusions:	All doses of olodaterol (2 µg, 5 µg, 10 µg, 20 µg) showed superiority over placebo with regard to the mean FEV_1 AUC_{0-24} response after 4 weeks of treatment in this incomplete block crossover trial in patients with asthma. Furthermore, there was a clear dose-response relationship, with the mean FEV_1 AUC_{0-24} response increasing with increasing dose. The mean FEV_1 AUC_{0-24} response for formoterol was located between the mean responses for the 2 µg and the 5 µg olodaterol doses. Assessment of the 24-h FEV_1 profile confirmed a 24-h duration of bronchodilation for all olodaterol doses. These findings were supported by the results of the secondary endpoints derived from clinic visit and home-based spirometry measurements. The results of this study showed that olodaterol was generally safe and well tolerated. The overall occurrence of AEs was higher for treatment with olodaterol than for treatment with placebo or formoterol. This observation will be further assessed in the context of overall olodaterol safety data.

Trial Synopsis – Appendix

The result tables on the following pages supplement the trial results presented in the Trial Synopsis. The number of secondary endpoints defined for this trial was too large to allow meaningful presentation in this format. The appended tables provide complete disposition results and results of additional secondary endpoints, as summarised below.

Results for	**presented in**
Disposition of patients	Table 15.1.1: 1
FEV_1 $AUC_{0\text{-}24h}$ response after 4 weeks FEV_1 $AUC_{0\text{-}12h}$ response after 4 weeks FEV_1 $AUC_{12\text{-}24h}$ response after 4 weeks	Table 15.2.1.1: 1
Peak FEV_1 response (within 24 hours after dosing) after 4 weeks	Table 15.2.1.3: 1
Trough FEV_1 response (within 24 hours after dosing) after 4 weeks	Table 15.2.1.4: 1
FVC $AUC_{0\text{-}24h}$ response after 4 weeks FVC $AUC_{0\text{-}12h}$ response after 4 weeks FVC $AUC_{12\text{-}24h}$ response after 4 weeks	Table 15.2.2.1: 1
PEF $AUC_{0\text{-}24h}$ response after 4 weeks PEF $AUC_{0\text{-}12h}$ response after 4 weeks PEF $AUC_{12\text{-}24h}$ response after 4 weeks	Table 15.2.3.1: 1

Table 15.1.1: 1 Disposition of patients

	Placebo	Olo 2ug	Olo 5ug	Olo 10ug	Olo 20ug	Form 12ug	Total
Enrolled							317
Not entered/randomised							119
Entered/randomised							198
Treated	125(100.00)	121(100.00)	130(100.00)	127(100.00)	124(100.00)	125(100.00)	198(100.00)
Not prematurely discontinued from trial medication #	123(98.40)	121(100.00)	127(97.69)	122(96.06)	120(96.77)	123(98.40)	182(91.92)
Prematurely discontinued from trial medication	2(1.60)	0(0.00)	3(2.31)	5(3.94)	4(3.23)	2(1.60)	16(8.08)
Adverse event	2(1.60)	0(0.00)	3(2.31)	2(1.57)	1(0.81)	0(0.00)	8(4.04)
AE-oth. dis. worse	1(0.80)	0(0.00)	0(0.00)	1(0.79)	0(0.00)	0(0.00)	2(1.01)
AE-other	1(0.80)	0(0.00)	3(2.31)	1(0.79)	1(0.81)	0(0.00)	6(3.03)
Non compl prot.	0(0.00)	0(0.00)	0(0.00)	2(1.57)	0(0.00)	1(0.80)	3(1.52)
Lost to follow-up	0(0.00)	0(0.00)	0(0.00)	1(0.79)	0(0.00)	0(0.00)	1(0.51)
Consent withdrawn	0(0.00)	0(0.00)	0(0.00)	0(0.00)	2(1.61)	0(0.00)	2(1.01)
Other	0(0.00)	0(0.00)	0(0.00)	0(0.00)	1(0.81)	1(0.80)	2(1.01)

Table 15.2.1.1: 1 Adjusted mean* (SE) FEV1 AUC(0-12), AUC(12-24) and AUC(0-24) response [L] and comparisons to placebo after 4 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	122	-0.039 (0.026)			
	Olo 2ug	119	0.124 (0.026)	0.163 (0.024)	<.0001	(0.116, 0.211)
	Olo 5ug	126	0.173 (0.026)	0.212 (0.024)	<.0001	(0.166, 0.259)
	Olo 10ug	121	0.194 (0.026)	0.233 (0.024)	<.0001	(0.186, 0.280)
	Olo 20ug	119	0.211 (0.026)	0.250 (0.024)	<.0001	(0.203, 0.298)
	Form 12ug	122	0.145 (0.026)	0.184 (0.024)	<.0001	(0.137, 0.231)
12-24 hr	Placebo	122	0.031 (0.026)			
	Olo 2ug	119	0.147 (0.026)	0.115 (0.022)	<.0001	(0.073, 0.158)
	Olo 5ug	126	0.183 (0.025)	0.151 (0.021)	<.0001	(0.110, 0.193)
	Olo 10ug	121	0.208 (0.026)	0.177 (0.022)	<.0001	(0.135, 0.219)
	Olo 20ug	119	0.238 (0.026)	0.207 (0.022)	<.0001	(0.164, 0.250)
	Form 12ug	122	0.183 (0.026)	0.152 (0.022)	<.0001	(0.110, 0.194)
0-24 hr	Placebo	122	-0.004 (0.025)			
	Olo 2ug	119	0.135 (0.025)	0.140 (0.022)	<.0001	(0.097, 0.182)
	Olo 5ug	126	0.178 (0.025)	0.182 (0.021)	<.0001	(0.140, 0.224)
	Olo 10ug	121	0.201 (0.025)	0.205 (0.022)	<.0001	(0.163, 0.248)
	Olo 20ug	119	0.225 (0.025)	0.229 (0.022)	<.0001	(0.186, 0.272)
	Form 12ug	122	0.164 (0.025)	0.169 (0.022)	<.0001	(0.126, 0.211)

*adjusted using a mixed model with treatment, period and baseline value as fixed effects; and patient as a random effect.

Source data: Appendix 16.1.9.2, Statdoc 6.1.1 ctr\eot-t4-pft-adjmean-refcomp.sas 31MAR2011

Table 15.2.1.3: 1 Adjusted mean* (SE) FEV1 peak response [L] and comparisons to placebo after 4 weeks - analysis with imputation (FAS)

			Difference to Placebo		
Treatment	N	Treatment mean (SE)	Mean (SE)	P-value	95% CI
Placebo	122	0.224 (0.026)			
Olo 2ug	119	0.326 (0.027)	0.102 (0.023)	<.0001	(0.056, 0.148)
Olo 5ug	126	0.359 (0.026)	0.135 (0.023)	<.0001	(0.090, 0.180)
Olo 10ug	121	0.385 (0.027)	0.161 (0.023)	<.0001	(0.116, 0.207)
Olo 20ug	119	0.404 (0.027)	0.180 (0.023)	<.0001	(0.134, 0.226)
Form 12ug	122	0.390 (0.026)	0.166 (0.023)	<.0001	(0.120, 0.211)

*adjusted using a mixed model with treatment, period and baseline value as fixed effects; and patient as a random effect.

Source data: Appendix 16.1.9.2, Statdoc 6.1.7 ctr\eot-t4-pft-adjmean-refcomp.sas 31MAR2011

Table 15.2.1.4: 1 Adjusted mean* (SE) FEV1 trough response [L] and comparisons to placebo after 4 weeks - analysis with imputation (FAS)

			Difference to Placebo		
Treatment	N	Treatment mean (SE)	Mean (SE)	P-value	95% CI
Placebo	122	0.013 (0.026)			
Olo 2ug	119	0.116 (0.026)	0.103 (0.023)	<.0001	(0.058, 0.148)
Olo 5ug	126	0.146 (0.026)	0.133 (0.023)	<.0001	(0.088, 0.177)
Olo 10ug	121	0.182 (0.026)	0.169 (0.023)	<.0001	(0.124, 0.214)
Olo 20ug	119	0.211 (0.026)	0.199 (0.023)	<.0001	(0.153, 0.244)
Form 12ug	122	0.115 (0.026)	0.103 (0.023)	<.0001	(0.058, 0.147)

*adjusted using a mixed model with treatment, period and baseline value as fixed effects; and patient as a random effect.

Source data: Appendix 16.1.9.2, Statdoc 6.1.8 ctr\eot-t4-pft-adjmean-refcomp.sas 31MAR2011

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 4 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	122	-0.047 (0.029)			
	Olo 2ug	119	0.056 (0.029)	0.103 (0.026)	<.0001	(0.052, 0.154)
	Olo 5ug	126	0.109 (0.029)	0.156 (0.026)	<.0001	(0.106, 0.207)
	Olo 10ug	121	0.094 (0.029)	0.141 (0.026)	<.0001	(0.091, 0.192)
	Olo 20ug	119	0.122 (0.029)	0.169 (0.026)	<.0001	(0.118, 0.221)
	Form 12ug	122	0.055 (0.029)	0.102 (0.026)	<.0001	(0.051, 0.153)
12-24 hr	Placebo	122	-0.005 (0.029)			
	Olo 2ug	119	0.055 (0.029)	0.061 (0.024)	0.0107	(0.014, 0.107)
	Olo 5ug	126	0.109 (0.028)	0.115 (0.023)	<.0001	(0.069, 0.160)
	Olo 10ug	121	0.110 (0.029)	0.115 (0.024)	<.0001	(0.069, 0.161)
	Olo 20ug	119	0.139 (0.029)	0.144 (0.024)	<.0001	(0.098, 0.191)
	Form 12ug	122	0.085 (0.029)	0.091 (0.024)	0.0001	(0.044, 0.137)
0-24 hr	Placebo	122	-0.026 (0.028)			
	Olo 2ug	119	0.056 (0.028)	0.082 (0.023)	0.0005	(0.036, 0.128)
	Olo 5ug	126	0.109 (0.028)	0.136 (0.023)	<.0001	(0.090, 0.181)
	Olo 10ug	121	0.102 (0.028)	0.128 (0.023)	<.0001	(0.083, 0.174)
	Olo 20ug	119	0.131 (0.028)	0.157 (0.023)	<.0001	(0.111, 0.203)
	Form 12ug	122	0.070 (0.028)	0.097 (0.023)	<.0001	(0.051, 0.143)

*adjusted using a mixed model with treatment, period and baseline value as fixed effects; and patient as a random effect.

Source data: Appendix 16.1.9.2, Statdoc 6.2.1 ctr\eot-t4-pft-adjmean-refcomp.sas 31MAR2011

Table 15.2.3.1: 1 Adjusted mean* (SE) PEF AUC(0-12), AUC(12-24) and AUC(0-24) response [L/sec] and comparisons to placebo after 4 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	122	-0.117 (0.076)			
	Olo 2ug	119	0.291 (0.077)	0.408 (0.067)	<.0001	(0.277, 0.539)
	Olo 5ug	126	0.449 (0.076)	0.566 (0.066)	<.0001	(0.438, 0.695)
	Olo 10ug	121	0.495 (0.077)	0.612 (0.066)	<.0001	(0.482, 0.743)
	Olo 20ug	119	0.553 (0.077)	0.670 (0.067)	<.0001	(0.539, 0.801)
	Form 12ug	122	0.471 (0.076)	0.588 (0.066)	<.0001	(0.457, 0.718)
12-24 hr	Placebo	122	0.043 (0.075)			
	Olo 2ug	119	0.380 (0.075)	0.337 (0.063)	<.0001	(0.213, 0.461)
	Olo 5ug	126	0.528 (0.075)	0.485 (0.062)	<.0001	(0.363, 0.606)
	Olo 10ug	121	0.575 (0.075)	0.531 (0.063)	<.0001	(0.408, 0.655)
	Olo 20ug	119	0.692 (0.075)	0.648 (0.063)	<.0001	(0.524, 0.772)
	Form 12ug	122	0.594 (0.075)	0.551 (0.063)	<.0001	(0.428, 0.674)
0-24 hr	Placebo	122	-0.038 (0.074)			
	Olo 2ug	119	0.336 (0.074)	0.373 (0.061)	<.0001	(0.253, 0.493)
	Olo 5ug	126	0.489 (0.074)	0.527 (0.060)	<.0001	(0.409, 0.645)
	Olo 10ug	121	0.534 (0.074)	0.572 (0.061)	<.0001	(0.453, 0.692)
	Olo 20ug	119	0.623 (0.074)	0.660 (0.061)	<.0001	(0.540, 0.781)
	Form 12ug	122	0.532 (0.074)	0.570 (0.061)	<.0001	(0.451, 0.689)

*adjusted using a mixed model with treatment, period and baseline value as fixed effects; and patient as a random effect.

Source data: Appendix 16.1.9.2, Statdoc 6.3.1 ctr\eot-t4-pft-adjmean-refcomp.sas 31MAR2011