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:		**EudraCT No.:** 2008-003704-67	
Name of active ingredient: Olodaterol (BI 1744)		**Page:** 1 of 8	**Synopsis No.:**
Module:		**Volume:**	
Report date: 09 JAN 2012	**Trial No. / U No.:** 1222.12 / U10-3193-01	**Date of trial:** 05 Feb 2009 – 27 Sep 2010	**Date of revision:** Not applicable

Title of trial:	Randomised, double-blind, placebo-controlled, parallel group study to assess the efficacy and safety of 48 weeks of once daily treatment of orally inhaled BI 1744 CL (5 µg [2 actuations of 2.5 µg] and 10 µg [2 actuations of 5 µg]) delivered by the Respimat® inhaler, in patients with Chronic Obstructive Pulmonary Disease (COPD)
Coordinating Investigator:	[redacted]
Trial sites:	Multi-centre, multinational, cf. Appendix 16.1.4
Publication (reference):	None
Clinical phase:	III
Objective:	The primary objective of this study was to assess the long-term efficacy and safety of once daily treatment of olodaterol (BI 1744) inhalation solution (5 µg [2 actuations of 2.5 µg] and 10 µg [2 actuations of 5 µg]) compared to placebo (delivered by the RESPIMAT inhaler) in patients with COPD.
Methodology:	Randomised, double-blind, placebo-controlled, parallel group design
No. of patients:	
planned:	600 (200 per treatment group)
actual:	enrolled: 892; entered/randomised: 644; treated: 642* (*Not treated = 2 patients, 1 randomised and not treated due to an AE; 1 treated and not included due to lack of Health Insurance Portability and Accountability Act authorization) placebo: treated: 216 • analyzed for co-primary endpoint forced expiratory volume in 1 second (FEV_1) area under the curve (AUC) over 0 to 3 hours (0-3h) response at Day 85: 215 • analyzed for co-primary endpoint trough FEV_1 response at Day 85: 205 olodaterol 5 µg: treated: 209 • analyzed for co-primary endpoint FEV_1 AUC_{0-3h}: response at Day 85: 207 • analyzed for co-primary endpoint trough FEV_1 response at Day 85: 205

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	olodaterol 10 µg: treated: 217 • analyzed for co-primary endpoint FEV_1 AUC_{0-3h}: response at Day 85: 215 • analyzed for co-primary endpoint trough FEV_1 response at Day 85: 207
Diagnosis and main criteria for inclusion:	Male or female patients, aged ≥40 years with a diagnosis of COPD; smoking history >10 pack years, post-bronchodilator FEV_1 <80% predicted; post-bronchodilator FEV_1/forced vital capacity (FVC) <70%.
Test product:	Olodaterol (as hydrochloride)
dose:	5 µg (ex mouthpiece [2 actuations of 2.5 µg]) once daily 10 µg (ex mouthpiece [2 actuations of 5 µg]) once daily (calculated as free base)
mode of admin.:	Oral inhalation
batch no.:	B072000346 (5 µg); B072000356 (10 µg)
Reference therapy:	Placebo inhalation matching olodaterol
dose:	Not applicable
mode of admin.:	Oral inhalation
batch no.:	B082000136
Duration of treatment:	48 weeks

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Criteria for evaluation:

Efficacy / clinical pharmacology:

Efficacy parameters included: FEV_1 AUC_{0-3h} response, trough FEV_1 response, FEV_1 AUC_{0-12h} response (in a subset of patients), FEV_1 $peak_{0-3h}$ response, FVC AUC_{0-3h} response, trough FVC response, FVC AUC_{0-12h} response (in a subset of patients), FVC $peak_{0-3h}$ response, FEV_1 and FVC at individual time points, peak expiratory flow (PEF), rescue medication use, patient's global rating (PGR), time to first COPD exacerbation, time to first moderate COPD exacerbation, time to first COPD exacerbation leading to hospitalisation, number of COPD exacerbations per patient year, number of moderate COPD exacerbations, and number of COPD exacerbations leading to hospitalisation per patient year.

Pharmacokinetics (PK) was assessed by plasma concentrations of olodaterol from blood samples drawn prior to dosing at Visit 2, and 10 minutes post dosing at Visits 4, 5, and 6. Systemic pharmacodynamics (PD) was evaluated by values of potassium from blood samples drawn at 1 h and 3 h post dosing at Visits 4 and 5.

Safety:

Adverse events, including administration related bronchoconstriction, vital signs, laboratory evaluations, ECG (12-lead) and Holter monitoring.

Statistical methods:

Likelihood-based mixed effects models with repeated measures (MMRM), Analysis of Covariance (ANCOVA), Cox regression, log-rank test, Kaplan-Meier estimation of the survival function, negative binomial models, and descriptive statistics.

SUMMARY – CONCLUSIONS:

Efficacy / clinical pharmacology results:

Co-primary endpoints:

Statistically significant increases were observed for the co-primary endpoints of FEV_1 AUC_{0-3h} response and trough FEV_1 response at Day 85, for both doses of olodaterol (5 µg and 10 µg) compared with placebo.

- For FEV_1 AUC_{0-3} response, the estimated adjusted means at Day 85 were: 5 µg, 0.151 L difference (0.159 L vs. 0.008 L, $p<0.0001$); 10 µg, 0.143 L difference (0.152 L vs. 0.008 L, $p<0.0001$).
- For trough FEV_1 response, the estimated adjusted means at Day 85 were: 5 µg, 0.047 L difference (0.044 L vs. -0.003 L), $p=0.0116$; 10 µg, 0.048 L difference (0.045 L vs. -0.003 L, $p=0.0095$).

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Efficacy / clinical pharmacology results (continued):

Since patients taking tiotropium at screening continued with tiotropium as concomitant therapy throughout the trial, randomisation was stratified by concomitant tiotropium use, and tiotropium use stratum was included as a covariate in the model for the primary analyses. The results were dominated by the subgroup of patients who did not concomitantly use tiotropium (about 80% patients). The patients who used tiotropium concomitantly also showed improvement with olodaterol; however, due to the smaller sample size, the results were imprecise and not always statistically significant.

An analysis by tiotropium stratum based on the combined dataset from this study (1222.12) and the replicate Study 1222.11 is presented in a separate report (Study 1222.9992).

Secondary endpoints:

For FEV_1 AUC_{0-12} response in the subset of patients completing the 12 hr Pulmonary Function Tests on Day 85, both doses of olodaterol had estimated adjusted means that were statistically significantly greater than placebo (5 µg, 0.110 L difference [0.120 L vs. placebo, 0.010 L, $p<0.0001$]; 10 µg, 0.089 L difference [0.100 L vs. 0.010 L, $p=0.0011$]). For additional spirometry endpoints measured at individual test days over 48 weeks (FEV_1 AUC_{0-3h} response, trough FEV_1 response, FEV_1 $peak_{0-3h}$ response) responses were similar to those at the primary endpoint visit (Day 85).

Both olodaterol dose groups showed a statistically significant increase in FVC AUC_{0-3h} response compared to placebo over 48 weeks and FVC AUC_{0-12h} response compared to placebo at Day 85 (Week 12) ($p<0.0001$ to $p=0.0028$). The FVC responses at individual test days over 48 weeks were similar to those at the primary endpoint visit (Day 85). FVC $Peak_{0-3h}$ responses over 48 weeks were consistent with those of the primary analysis, with both olodaterol dose groups showing a statistically significant improvement compared with placebo ($p<0.0001$ for each group). Differences between the olodaterol treatment group and placebo in trough FVC response over 48 weeks were generally not statistically significant.

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Efficacy / clinical pharmacology results (continued):

Morning and evening PEFR were statistically significantly greater in both olodaterol treatment groups compared with placebo at all assessments over 48 weeks ($p<0.0001$ to $p=0.0168$ and $p<0.0001$ to $p=0.0325$, respectively). Adjusted mean differences from placebo for morning PEFR ranged from 14.177 sec to 16.549 L/min for the 5 µg olodaterol treatment group and 18.412 to 20.934 L/min for the 10 µg olodaterol treatment group whereas evening PEFR ranged from 12.456 sec to 17.278 L/min for the 5 µg olodaterol treatment group and 19.582 sec to 20.800 L/min for the 10 µg olodaterol treatment group.

The adjusted mean daily (24 hour) use of rescue medication ranged approximately 0.575 puffs/day to 1.340 puffs/day lower in the olodaterol groups than in the placebo group ($p<0.0001$ to $p=0.0062$), which was associated with reductions in both daytime and nighttime rescue medication use. The magnitude of the mean differences from placebo at key study time points (Weeks 1, 12, 24, and 48) were -0.594 ($p=0.0016$), -0.694 ($p=0.0035$), -0.847 ($p=0.0004$), and -0.837 ($p=0.0010$) puffs/day for the olodaterol 5µg group, respectively, and -0.619 ($p=0.0009$), -1.058 ($p<0.0001$), -1.145 ($p<0.0001$), and -1.278 ($p<0.0001$) puffs/day for the olodaterol 10 µg group, respectively.

The increases in the Patient's Global Rating were significantly greater in both olodaterol treatment groups compared with placebo, with 2.9 to 3.1 ("a little better") for the olodaterol treatment groups and 3.2 to 3.3 for the placebo group ($p=0.0008$ to $p=0.0180$), over all time points except for an isolated time point at test day 337 for the olodaterol 5 µg group ($p=0.1313$).

There were no statistically significant differences in time to first COPD exacerbation, time to moderate COPD exacerbation, and time to COPD exacerbation leading to hospitalisation in the olodaterol treatment groups compared with placebo. The hazard ratios for mean time to first COPD exacerbation compared to placebo were 0.993 ($p = 0.9853$) for the olodaterol 5 µg treatment group and 1.241 ($p=0.2344$) for the olodaterol 10 µg treatment group. There were no statistically significant differences in the mean numbers of COPD exacerbations, moderate COPD exacerbations, and COPD exacerbations leading to hospitalisation per patient/year in the olodaterol treatment groups compared with placebo.

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Efficacy / clinical pharmacology results (continued):	**Clinical Pharmacology:** Overall, the geometric mean (gMean) $C_{0.167,ss}$ value of the olodaterol 10 µg treatment group (7.34 pg/mL) was 1.8-fold higher than that of the olodaterol 5 µg treatment group (4.07 pg/mL). The reason for this less than dose-proportional increase is the higher incidence of plasma concentrations below the limit of quantification in the olodaterol 5 µg treatment group (BLQ, NOP: N=155) than in the 10 µg group (BLQ, NOP: N=62). As these data are omitted in the calculation of the descriptive statistics, the gMean value of the olodaterol 5 µg treatment group is more pronouncedly prone to certain overestimation than the gMean value of the olodaterol 10 µg treatment group. Olodaterol plasma concentrations in Asians were slightly higher than in Whites (factor of 1.2). There was no evidence of a relationship between blood potassium levels and olodaterol plasma concentrations, after daily inhalations of 5 µg or 10 µg olodaterol.
Safety results:	In this 48-week study that investigated the use of 5 µg or 10 µg olodaterol compared with placebo, no safety concerns were identified. • There were 11 deaths; 5 during treatment (1 in the placebo treatment group and 4 in the olodaterol 10 µg treatment group), 5 post study (4 patients [2 in the placebo treatment group, 1 each in the olodaterol 5 µg and 10 µg treatment groups], in patients who discontinued the study and the death was reported as a result of vital status follow-up within the planned observation period, and 1 patient in the olodaterol 10 µg treatment group who completed the study and the death occurred 1 month outside of the vital status follow-up period) and 1 in a patient who was a screen failure and who was not treated. No deaths were considered to be related to study drug. • There were 101 patients (15.7%) with 1 or more SAEs, 32 (14.8%) patients in the placebo group, 32 (15.3%) in the olodaterol 5 µg group, and 37 (17.1%) in the olodaterol 10 µg group. SAEs that occurred in more than 2 patients included COPD exacerbation (4.8%), pneumonia (1.9%), pneumothorax (0.8%), respiratory failure (0.6%), coronary artery disease (0.6%), aortic aneurysm (0.5%), road traffic accident (0.5%), and lung infection (0.5%).

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Safety results (continued):

- There were 5 patients with SAEs considered by the investigator to be related to the study drug: 2 patients in the olodaterol 5 µg treatment group (chest pain and ventricular tachycardia), and 1 patient in the olodaterol 10 µg treatment group (respiratory failure), and 2 patients in the placebo treatment group (staphylococcal sepsis and atrial fibrillation). Adverse events were reported in 67.9% of patients in the olodaterol 5 µg treatment group, 75.1% in the olodaterol 10 µg treatment group, and 67.6% in the placebo treatment group.
- Overall, the most frequently reported AEs were COPD (reported as COPD exacerbation or worsening of COPD, 24.9%), nasopharyngitis (9.7%), and upper respiratory tract infection (9.2%).
- Forty-nine patients (7.6%) experienced a study drug-administration-related respiratory event indicative of bronchoconstriction. Of these, 46 patients (7.2%) reported a ≥15% decrease from trough FEV1 (placebo, 28 patients [13.0%]; olodaterol 5 µg, 7 patients [3.3%]; olodaterol 10 µg, 11 patients [5.1%]), and 3 patients (0.5%; placebo, 2 patients [0.9%]; olodaterol 10 µg, 1 patient [0.5%]) required rescue medication within 30 minutes of study drug inhalation at a clinic visit.
- The majority of AEs were mild to moderate in intensity, with severe AEs reported in 11.5% of patients. Most AEs were considered unrelated to study drug; less than 10% of patients (8.1%) of patients had any related AE.
- There were 47 patients (7.3%) who discontinued study drug due to AEs; 4.3% in the olodaterol 5 µg treatment group and 8.8% in each of the olodaterol 10 µg and placebo treatment groups.
- No consistent trends suggesting an adverse effect of treatment were evident in vital signs, laboratory parameters (except CPK), ECG results, Holter monitoring, and physical examination findings.
- Using maximum values on treatment, upward shifts from baseline exceeding the upper limit of normal were noted for CPK; 12/192 (6.3%) for the placebo group, 19/183 (10.4%) for olodaterol 5 µg group, and 35/187 (18.7%) for the olodaterol 10 µg treatment group.
- Olodaterol treatment yielded no statistically significant differences in potassium levels compared to placebo.

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Conclusions:	The primary objective of the present study was met, with olodaterol 5 µg once daily and olodaterol 10µg once daily showing statistically significant improvements compared to placebo for the co-primary endpoints of FEV_1 AUC_{0-3} response at Day 85 and trough FEV_1 response at Day 85; the effect size compared with placebo was less than expected based on the results from Phase II, especially for olodaterol 10 µg. Olodaterol 5 µg once daily and olodaterol 10 µg once daily were generally safe and well tolerated; there were no safety concerns identified. An evaluation of the preferred dose for long-term maintenance treatment in COPD will be presented in an overall integrated summary based on a review of the complete information available within the clinical program.

Trial Synopsis - Appendix

The result tables on the following pages supplement the trial results presented in the Trial Synopsis. The appended tables provide complete disposition results and results of additional secondary endpoints, as summarised below. The number of secondary endpoints defined for this trial was too large to allow meaningful presentation in this format; therefore, results for up to a total of 11 secondary endpoints are provided in the Trial Synopsis and the following tables.

Results for	**presented in**
Patient disposition	Table 15.1.1: 1
FEV_1 AUC_{0-3h} over 48 weeks	Table 15.2.1.1.2: 1
Trough FEV_1 over 48 weeks	Table 15.2.1.1.3: 1
FEV_1 $peak_{0-3h}$ over 48 weeks	Table 15.2.1.1.4: 1
FVC AUC_{0-3h} over 48 weeks	Table 15.2.1.2.2: 1
FVC at all time points over 48 weeks	Table 15.2.1.2.1: 1
FVC AUC_{0-12h} on test day 85	Table 15.2.1.2.2: 4
FVC $peak_{0-3h}$ over 48 weeks	Table 15.2.1.2.4: 1
Trough FVC over 48 weeks	Table 15.2.1.2.3: 1
Morning Weekly PEFR, Weeks 1 to 48	Table 15.2.2.1: 1
Evening Weekly PEFR, Weeks 1 to 48	Table 15.2.2.1: 4

Table 15.1.1: 1 Disposition of patients

	Placebo	Olo 5ug	Olo 10ug	Total
Enrolled				892
Not entered/randomsed				248
Entered/randomised				644
Not treated				2
Treated	216(100.00)	209(100.00)	217(100.00)	642(100.00)
Not prematurely discontinued from trial medication #	175(81.02)	185(88.52)	181(83.41)	541(84.27)
Prematurely discontinued from trial medication	41(18.98)	24(11.48)	36(16.59)	101(15.73)
Adverse event	20(9.26)	10(4.78)	20(9.22)	50(7.79)
AE study dis. worse	8(3.70)	3(1.44)	2(0.92)	13(2.02)
AE-oth. dis. worse	3(1.39)	3(1.44)	2(0.92)	8(1.25)
AE-other	9(4.17)	4(1.91)	16(7.37)	29(4.52)
Lack of efficacy	10(4.63)	5(2.39)	2(0.92)	17(2.65)
Non compl prot.	2(0.93)	0(0.00)	0(0.00)	2(0.31)
Lost to follow-up	1(0.46)	2(0.96)	3(1.38)	6(0.93)
Consent withdrawn	3(1.39)	5(2.39)	8(3.69)	16(2.49)
Other	5(2.31)	2(0.96)	3(1.38)	10(1.56)

NOTE: All percentages based on the numbers of patients treated.
Not treated includes treated patient [redacted] who was excluded from analysis due to lack of HIPAA authorization.
Patient [redacted] discontinued the trial prior to taking the first dose of study drug.

Table 15.2.1.1.2: 1 Adjusted mean (SE) FEV1 AUC (0-3) response and comparisons to placebo over 48 weeks - analysis with imputation (FAS)

			Difference from Placebo		
Test day	Treatment	Treatment mean (SE)	Mean (SE)	P-value	95% CI
1	Placebo	0.025 (0.013)			
	Olo 5ug	0.189 (0.013)	0.164 (0.017)	<.0001	(0.131, 0.197)
	Olo 10ug	0.196 (0.013)	0.171 (0.017)	<.0001	(0.138, 0.204)
15	Placebo	0.025 (0.013)			
	Olo 5ug	0.188 (0.013)	0.163 (0.017)	<.0001	(0.130, 0.197)
	Olo 10ug	0.177 (0.013)	0.152 (0.017)	<.0001	(0.119, 0.186)
43	Placebo	0.010 (0.013)			
	Olo 5ug	0.180 (0.013)	0.169 (0.017)	<.0001	(0.135, 0.203)
	Olo 10ug	0.171 (0.013)	0.161 (0.017)	<.0001	(0.127, 0.195)
85	Placebo	0.008 (0.013)			
	Olo 5ug	0.159 (0.013)	0.151 (0.017)	<.0001	(0.116, 0.185)
	Olo 10ug	0.152 (0.013)	0.143 (0.017)	<.0001	(0.110, 0.177)
169	Placebo	-0.010 (0.013)			
	Olo 5ug	0.155 (0.013)	0.165 (0.018)	<.0001	(0.131, 0.200)
	Olo 10ug	0.126 (0.013)	0.136 (0.018)	<.0001	(0.102, 0.171)
337	Placebo	-0.030 (0.013)			
	Olo 5ug	0.132 (0.013)	0.161 (0.018)	<.0001	(0.127, 0.196)
	Olo 10ug	0.128 (0.013)	0.158 (0.018)	<.0001	(0.123, 0.193)

Results are from an MMRM model. Fixed effects include treatment, tiotropium strata, visit, treatment by visit interaction, baseline and baseline by visit interaction. Patient is considered random and a spatial power covariance structure was used.

Number of patients contributing to models: Placebo (215), Olo 5ug (207), Olo 10ug (215)
Common baseline mean (SE): 1.151 (0.020)

Source data: Appendix 16.1.9.2, Statdoc 6.1.1.2.1 ctr\pft-adjmean-mmrm.sas 10AUG2011

Table 15.2.1.1.3: 1 Adjusted mean (SE) trough FEV1 response and comparisons to placebo over 48 weeks - analysis with imputation (FAS)

			Difference from Placebo		
Test day	Treatment	Treatment mean (SE)	Mean (SE)	P-value	95% CI
15	Placebo	0.013 (0.014)			
	Olo 5ug	0.066 (0.014)	0.053 (0.018)	0.0043	(0.017, 0.089)
	Olo 10ug	0.078 (0.014)	0.065 (0.018)	0.0005	(0.028, 0.101)
43	Placebo	-0.002 (0.014)			
	Olo 5ug	0.071 (0.014)	0.073 (0.018)	<.0001	(0.037, 0.110)
	Olo 10ug	0.082 (0.014)	0.085 (0.018)	<.0001	(0.049, 0.121)
85	Placebo	-0.003 (0.014)			
	Olo 5ug	0.044 (0.014)	0.047 (0.019)	0.0116	(0.011, 0.084)
	Olo 10ug	0.045 (0.014)	0.048 (0.019)	0.0095	(0.012, 0.085)
127	Placebo	-0.007 (0.014)			
	Olo 5ug	0.062 (0.014)	0.069 (0.019)	0.0002	(0.032, 0.106)
	Olo 10ug	0.037 (0.014)	0.044 (0.019)	0.0186	(0.007, 0.081)
169	Placebo	-0.036 (0.014)			
	Olo 5ug	0.033 (0.014)	0.069 (0.019)	0.0003	(0.032, 0.106)
	Olo 10ug	0.022 (0.014)	0.058 (0.019)	0.0020	(0.021, 0.095)
225	Placebo	-0.029 (0.014)			
	Olo 5ug	0.029 (0.014)	0.058 (0.019)	0.0024	(0.020, 0.095)
	Olo 10ug	-0.002 (0.014)	0.027 (0.019)	0.1614	(-0.011, 0.064)
281	Placebo	-0.029 (0.014)			
	Olo 5ug	0.033 (0.014)	0.062 (0.019)	0.0012	(0.025, 0.099)
	Olo 10ug	0.043 (0.014)	0.072 (0.019)	0.0002	(0.034, 0.109)

Results are from an MMRM model. Fixed effects include treatment, tiotropium strata, visit, treatment by visit interaction, baseline and baseline by visit interaction. Patient is considered random and a spatial power covariance structure was used.

Number of patients contributing to models: Placebo (205), Olo 5ug (205), Olo 10ug (207)
Common baseline mean (SE): 1.153 (0.020)

Source data: Appendix 16.1.9.2, Statdoc 6.1.1.3.1 ctr\pft-adjmean-mmrm.sas 10AUG2011

Table 15.2.1.1.3: 1 Adjusted mean (SE) trough FEV1 response and comparisons to placebo over 48 weeks - analysis with imputation (FAS)

			Difference from Placebo		
Test day	Treatment	Treatment mean (SE)	Mean (SE)	P-value	95% CI
337	Placebo	-0.057 (0.014)			
	Olo 5ug	0.011 (0.014)	0.068 (0.019)	0.0004	(0.031, 0.106)
	Olo 10ug	0.014 (0.014)	0.071 (0.019)	0.0002	(0.033, 0.108)

Results are from an MMRM model. Fixed effects include treatment, tiotropium strata, visit, treatment by visit interaction, baseline and baseline by visit interaction. Patient is considered random and a spatial power covariance structure was used.

Number of patients contributing to models: Placebo (205), Olo 5ug (205), Olo 10ug (207)
Common baseline mean (SE): 1.153 (0.020)

Source data: Appendix 16.1.9.2, Statdoc 6.1.1.3.1 ctr\pft-adjmean-mmrm.sas 10AUG2011

Table 15.2.1.1.4: 1 Adjusted mean (SE) FEV1 peak (0-3) response and comparisons to placebo over 48 weeks - analysis with imputation (FAS)

			Difference from Placebo		
Test day	Treatment	Treatment mean (SE)	Mean (SE)	P-value	95% CI
1	Placebo	0.099 (0.014)			
	Olo 5ug	0.267 (0.014)	0.168 (0.018)	<.0001	(0.132, 0.203)
	Olo 10ug	0.276 (0.013)	0.177 (0.018)	<.0001	(0.142, 0.212)
15	Placebo	0.104 (0.014)			
	Olo 5ug	0.259 (0.014)	0.155 (0.018)	<.0001	(0.119, 0.190)
	Olo 10ug	0.251 (0.014)	0.147 (0.018)	<.0001	(0.111, 0.182)
43	Placebo	0.080 (0.014)			
	Olo 5ug	0.252 (0.014)	0.172 (0.018)	<.0001	(0.136, 0.209)
	Olo 10ug	0.246 (0.014)	0.166 (0.018)	<.0001	(0.130, 0.202)
85	Placebo	0.088 (0.014)			
	Olo 5ug	0.232 (0.014)	0.144 (0.018)	<.0001	(0.108, 0.180)
	Olo 10ug	0.217 (0.014)	0.130 (0.018)	<.0001	(0.094, 0.166)
169	Placebo	0.062 (0.014)			
	Olo 5ug	0.226 (0.014)	0.164 (0.019)	<.0001	(0.128, 0.201)
	Olo 10ug	0.197 (0.014)	0.135 (0.019)	<.0001	(0.098, 0.171)
337	Placebo	0.041 (0.014)			
	Olo 5ug	0.197 (0.014)	0.155 (0.019)	<.0001	(0.118, 0.192)
	Olo 10ug	0.198 (0.014)	0.157 (0.019)	<.0001	(0.120, 0.194)

Results are from an MMRM model. Fixed effects include treatment, tiotropium strata, visit, treatment by visit interaction, baseline and baseline by visit interaction. Patient is considered random and a spatial power covariance structure was used.

Number of patients contributing to models: Placebo (215), Olo 5ug (207), Olo 10ug (215)
Common baseline mean (SE): 1.151 (0.020)

Source data: Appendix 16.1.9.2, Statdoc 6.1.1.4.1 ctr\pft-adjmean-mmrm.sas 10AUG2011

Table 15.2.1.2.2: 1 Adjusted mean (SE) FVC AUC (0-3) response and comparisons to placebo over 48 weeks - analysis with imputation (FAS)

			Difference from Placebo		
Test day	Treatment	Treatment mean (SE)	Mean (SE)	P-value	95% CI
1	Placebo	0.052 (0.026)			
	Olo 5ug	0.383 (0.026)	0.331 (0.035)	<.0001	(0.263, 0.399)
	Olo 10ug	0.384 (0.026)	0.333 (0.034)	<.0001	(0.265, 0.400)
15	Placebo	0.096 (0.026)			
	Olo 5ug	0.338 (0.026)	0.242 (0.035)	<.0001	(0.174, 0.310)
	Olo 10ug	0.323 (0.026)	0.226 (0.035)	<.0001	(0.159, 0.294)
43	Placebo	0.048 (0.026)			
	Olo 5ug	0.312 (0.027)	0.263 (0.035)	<.0001	(0.195, 0.332)
	Olo 10ug	0.294 (0.026)	0.246 (0.035)	<.0001	(0.178, 0.315)
85	Placebo	0.046 (0.026)			
	Olo 5ug	0.284 (0.027)	0.239 (0.035)	<.0001	(0.170, 0.308)
	Olo 10ug	0.291 (0.026)	0.245 (0.035)	<.0001	(0.176, 0.314)
169	Placebo	0.062 (0.027)			
	Olo 5ug	0.303 (0.027)	0.241 (0.036)	<.0001	(0.171, 0.311)
	Olo 10ug	0.281 (0.026)	0.219 (0.035)	<.0001	(0.150, 0.289)
337	Placebo	0.053 (0.027)			
	Olo 5ug	0.271 (0.027)	0.217 (0.036)	<.0001	(0.147, 0.288)
	Olo 10ug	0.271 (0.027)	0.218 (0.036)	<.0001	(0.148, 0.288)

Results are from an MMRM model. Fixed effects include treatment, tiotropium strata, visit, treatment by visit interaction, baseline and baseline by visit interaction. Patient is considered random and a spatial power covariance structure was used.

Number of patients contributing to models: Placebo (215), Olo 5ug (207), Olo 10ug (215)
Common baseline mean (SE): 2.605 (0.032)

Source data: Appendix 16.1.9.2, Statdoc 6.1.2.2.1 ctr\pft-adjmean-mmrm.sas 10AUG2011

Table 15.2.1.2.1: 1 Adjusted mean (SE) FVC and comparisons to placebo over 48 weeks - analysis with imputation (FAS)

Test day	Planned time	Treatment	Treatment mean (SE)	Difference from Placebo		
				Mean (SE)	P-value	95% CI
1	-1:00	Placebo	2.583 (0.032)			
		Olo 5ug	2.583 (0.032)			
		Olo 10ug	2.583 (0.032)			
	-0:10	Placebo	2.627 (0.032)			
		Olo 5ug	2.627 (0.032)			
		Olo 10ug	2.627 (0.032)			
	0:05	Placebo	2.629 (0.025)			
		Olo 5ug	2.892 (0.026)	0.263 (0.034)	<.0001	(0.196, 0.330)
		Olo 10ug	2.899 (0.025)	0.270 (0.034)	<.0001	(0.204, 0.337)
	0:15	Placebo	2.631 (0.026)			
		Olo 5ug	2.953 (0.027)	0.322 (0.035)	<.0001	(0.253, 0.390)
		Olo 10ug	2.940 (0.026)	0.309 (0.035)	<.0001	(0.241, 0.376)
	0:30	Placebo	2.651 (0.027)			
		Olo 5ug	2.984 (0.027)	0.333 (0.036)	<.0001	(0.263, 0.403)
		Olo 10ug	2.971 (0.027)	0.320 (0.035)	<.0001	(0.250, 0.389)
	1:00	Placebo	2.658 (0.027)			
		Olo 5ug	2.994 (0.027)	0.336 (0.036)	<.0001	(0.266, 0.407)
		Olo 10ug	2.984 (0.027)	0.325 (0.036)	<.0001	(0.255, 0.395)
	2:00	Placebo	2.682 (0.027)			
		Olo 5ug	3.025 (0.028)	0.343 (0.037)	<.0001	(0.272, 0.415)
		Olo 10ug	3.036 (0.027)	0.354 (0.036)	<.0001	(0.283, 0.425)

Results are from an MMRM model. Fixed effects include treatment, tiotropium strata, visit, treatment by visit interaction, baseline and baseline by visit interaction. Patient is considered random and a spatial power covariance structure was used.

For pre-dose measures at Day 1 in this table, entries for differences from Placebo are omitted. The Day 1 pre-dose treatment mean and SE are observed values, pooled across all treatments.

Number of patients contributing to models: Placebo (215), Olo 5ug (207), Olo 10ug (215)
Common baseline mean (SE): 2.605 (0.032)

Source data: Appendix 16.1.9.2, Statdoc 6.1.2.1.1 ctr\pft-adjmean-mmrm-time.sas 10AUG2011

Table 15.2.1.2.1: 1 Adjusted mean (SE) FVC and comparisons to placebo over 48 weeks - analysis with imputation (FAS)

Test day	Planned time	Treatment	Treatment mean (SE)	Difference from Placebo		
				Mean (SE)	P-value	95% CI
1	3:00	Placebo	2.675 (0.027)			
		Olo 5ug	3.021 (0.028)	0.346 (0.037)	<.0001	(0.274, 0.418)
		Olo 10ug	3.038 (0.027)	0.363 (0.036)	<.0001	(0.292, 0.434)
15	-0:10	Placebo	2.668 (0.028)			
		Olo 5ug	2.727 (0.028)	0.060 (0.037)	0.1063	(-0.013, 0.132)
		Olo 10ug	2.755 (0.027)	0.087 (0.037)	0.0181	(0.015, 0.159)
	0:05	Placebo	2.695 (0.026)			
		Olo 5ug	2.894 (0.026)	0.199 (0.035)	<.0001	(0.131, 0.267)
		Olo 10ug	2.870 (0.026)	0.175 (0.034)	<.0001	(0.108, 0.243)
	0:15	Placebo	2.700 (0.026)			
		Olo 5ug	2.923 (0.027)	0.223 (0.035)	<.0001	(0.154, 0.292)
		Olo 10ug	2.895 (0.026)	0.195 (0.035)	<.0001	(0.127, 0.264)
	0:30	Placebo	2.704 (0.027)			
		Olo 5ug	2.927 (0.027)	0.223 (0.036)	<.0001	(0.152, 0.294)
		Olo 10ug	2.923 (0.027)	0.219 (0.036)	<.0001	(0.149, 0.290)
	1:00	Placebo	2.734 (0.027)			
		Olo 5ug	2.952 (0.028)	0.218 (0.036)	<.0001	(0.147, 0.290)
		Olo 10ug	2.950 (0.027)	0.216 (0.036)	<.0001	(0.145, 0.287)
	2:00	Placebo	2.704 (0.028)			
		Olo 5ug	2.974 (0.028)	0.270 (0.037)	<.0001	(0.198, 0.343)
		Olo 10ug	2.952 (0.028)	0.248 (0.037)	<.0001	(0.176, 0.320)

Results are from an MMRM model. Fixed effects include treatment, tiotropium strata, visit, treatment by visit interaction, baseline and baseline by visit interaction. Patient is considered random and a spatial power covariance structure was used.

For pre-dose measures at Day 1 in this table, entries for differences from Placebo are omitted. The Day 1 pre-dose treatment mean and SE are observed values, pooled across all treatments.

Number of patients contributing to models: Placebo (215), Olo 5ug (207), Olo 10ug (215)
Common baseline mean (SE): 2.605 (0.032)

Source data: Appendix 16.1.9.2, Statdoc 6.1.2.1.1 ctr\pft-adjmean-mmrm-time.sas 10AUG2011

Table 15.2.1.2.1: 1 Adjusted mean (SE) FVC and comparisons to placebo over 48 weeks - analysis with imputation (FAS)

Test day	Planned time	Treatment	Treatment mean (SE)	Difference from Placebo		
				Mean (SE)	P-value	95% CI
15	3:00	Placebo	2.703 (0.028)			
		Olo 5ug	2.966 (0.028)	0.263 (0.037)	<.0001	(0.190, 0.335)
		Olo 10ug	2.941 (0.027)	0.238 (0.037)	<.0001	(0.166, 0.310)
43	-1:00	Placebo	2.660 (0.027)			
		Olo 5ug	2.735 (0.027)	0.075 (0.036)	0.0370	(0.005, 0.145)
		Olo 10ug	2.758 (0.027)	0.098 (0.036)	0.0062	(0.028, 0.168)
	-0:10	Placebo	2.642 (0.028)			
		Olo 5ug	2.749 (0.028)	0.107 (0.037)	0.0038	(0.034, 0.179)
		Olo 10ug	2.776 (0.027)	0.134 (0.037)	0.0003	(0.061, 0.206)
	0:05	Placebo	2.644 (0.026)			
		Olo 5ug	2.869 (0.026)	0.225 (0.035)	<.0001	(0.156, 0.293)
		Olo 10ug	2.873 (0.026)	0.228 (0.035)	<.0001	(0.160, 0.296)
	0:15	Placebo	2.654 (0.027)			
		Olo 5ug	2.896 (0.027)	0.242 (0.035)	<.0001	(0.172, 0.311)
		Olo 10ug	2.882 (0.026)	0.228 (0.035)	<.0001	(0.159, 0.298)
	0:30	Placebo	2.650 (0.027)			
		Olo 5ug	2.922 (0.027)	0.272 (0.036)	<.0001	(0.201, 0.343)
		Olo 10ug	2.901 (0.027)	0.251 (0.036)	<.0001	(0.180, 0.322)
	1:00	Placebo	2.659 (0.028)			
		Olo 5ug	2.920 (0.028)	0.261 (0.037)	<.0001	(0.189, 0.333)
		Olo 10ug	2.910 (0.027)	0.251 (0.036)	<.0001	(0.180, 0.322)

Results are from an MMRM model. Fixed effects include treatment, tiotropium strata, visit, treatment by visit interaction, baseline and baseline by visit interaction. Patient is considered random and a spatial power covariance structure was used.

For pre-dose measures at Day 1 in this table, entries for differences from Placebo are omitted. The Day 1 pre-dose treatment mean and SE are observed values, pooled across all treatments.

Number of patients contributing to models: Placebo (215), Olo 5ug (207), Olo 10ug (215)
Common baseline mean (SE): 2.605 (0.032)

Source data: Appendix 16.1.9.2, Statdoc 6.1.2.1.1 ctr\pft-adjmean-mmrm-time.sas 10AUG2011

Table 15.2.1.2.1: 1 Adjusted mean (SE) FVC and comparisons to placebo over 48 weeks - analysis with imputation (FAS)

Test day	Planned time	Treatment	Treatment mean (SE)	Difference from Placebo		
				Mean (SE)	P-value	95% CI
43	2:00	Placebo	2.661 (0.028)			
		Olo 5ug	2.946 (0.028)	0.285 (0.037)	<.0001	(0.212, 0.358)
		Olo 10ug	2.925 (0.028)	0.265 (0.037)	<.0001	(0.192, 0.337)
	3:00	Placebo	2.683 (0.028)			
		Olo 5ug	2.931 (0.028)	0.248 (0.037)	<.0001	(0.175, 0.321)
		Olo 10ug	2.918 (0.028)	0.235 (0.037)	<.0001	(0.162, 0.307)
85	-1:00	Placebo	2.662 (0.028)			
		Olo 5ug	2.681 (0.027)	0.019 (0.036)	0.5993	(-0.052, 0.090)
		Olo 10ug	2.703 (0.027)	0.041 (0.036)	0.2569	(-0.030, 0.111)
	-0:10	Placebo	2.668 (0.028)			
		Olo 5ug	2.708 (0.028)	0.041 (0.037)	0.2751	(-0.032, 0.114)
		Olo 10ug	2.717 (0.028)	0.049 (0.037)	0.1834	(-0.023, 0.122)
	0:05	Placebo	2.646 (0.026)			
		Olo 5ug	2.829 (0.026)	0.183 (0.035)	<.0001	(0.115, 0.252)
		Olo 10ug	2.828 (0.026)	0.183 (0.035)	<.0001	(0.114, 0.251)
	0:15	Placebo	2.656 (0.027)			
		Olo 5ug	2.874 (0.027)	0.219 (0.036)	<.0001	(0.149, 0.289)
		Olo 10ug	2.860 (0.026)	0.204 (0.035)	<.0001	(0.135, 0.274)
	0:30	Placebo	2.679 (0.027)			
		Olo 5ug	2.883 (0.028)	0.204 (0.036)	<.0001	(0.132, 0.275)
		Olo 10ug	2.881 (0.027)	0.202 (0.036)	<.0001	(0.130, 0.273)

Results are from an MMRM model. Fixed effects include treatment, tiotropium strata, visit, treatment by visit interaction, baseline and baseline by visit interaction. Patient is considered random and a spatial power covariance structure was used.

For pre-dose measures at Day 1 in this table, entries for differences from Placebo are omitted. The Day 1 pre-dose treatment mean and SE are observed values, pooled across all treatments.

Number of patients contributing to models: Placebo (215), Olo 5ug (207), Olo 10ug (215)
Common baseline mean (SE): 2.605 (0.032)

Source data: Appendix 16.1.9.2, Statdoc 6.1.2.1.1 ctr\pft-adjmean-mmrm-time.sas 10AUG2011

Table 15.2.1.2.1: 1 Adjusted mean (SE) FVC and comparisons to placebo over 48 weeks - analysis with imputation (FAS)

Test day	Planned time	Treatment	Treatment mean (SE)	Difference from Placebo		
				Mean (SE)	P-value	95% CI
85	1:00	Placebo	2.662 (0.028)			
		Olo 5ug	2.892 (0.028)	0.231 (0.037)	<.0001	(0.159, 0.303)
		Olo 10ug	2.897 (0.027)	0.236 (0.037)	<.0001	(0.164, 0.307)
	2:00	Placebo	2.688 (0.028)			
		Olo 5ug	2.918 (0.028)	0.229 (0.037)	<.0001	(0.156, 0.303)
		Olo 10ug	2.939 (0.028)	0.250 (0.037)	<.0001	(0.177, 0.323)
	3:00	Placebo	2.673 (0.028)			
		Olo 5ug	2.921 (0.028)	0.248 (0.037)	<.0001	(0.174, 0.321)
		Olo 10ug	2.914 (0.028)	0.241 (0.037)	<.0001	(0.169, 0.314)
127	-0:10	Placebo	2.678 (0.028)			
		Olo 5ug	2.728 (0.028)	0.050 (0.037)	0.1824	(-0.023, 0.123)
		Olo 10ug	2.712 (0.028)	0.034 (0.037)	0.3690	(-0.040, 0.107)
169	-0:10	Placebo	2.635 (0.028)			
		Olo 5ug	2.680 (0.028)	0.045 (0.038)	0.2348	(-0.029, 0.119)
		Olo 10ug	2.706 (0.028)	0.071 (0.038)	0.0602	(-0.003, 0.144)
	0:05	Placebo	2.651 (0.027)			
		Olo 5ug	2.840 (0.026)	0.189 (0.035)	<.0001	(0.120, 0.259)
		Olo 10ug	2.852 (0.026)	0.201 (0.035)	<.0001	(0.132, 0.271)
	0:15	Placebo	2.655 (0.027)			
		Olo 5ug	2.871 (0.027)	0.217 (0.036)	<.0001	(0.146, 0.287)
		Olo 10ug	2.861 (0.027)	0.206 (0.036)	<.0001	(0.136, 0.277)

Results are from an MMRM model. Fixed effects include treatment, tiotropium strata, visit, treatment by visit interaction, baseline and baseline by visit interaction. Patient is considered random and a spatial power covariance structure was used.

For pre-dose measures at Day 1 in this table, entries for differences from Placebo are omitted. The Day 1 pre-dose treatment mean and SE are observed values, pooled across all treatments.

Number of patients contributing to models: Placebo (215), Olo 5ug (207), Olo 10ug (215)
Common baseline mean (SE): 2.605 (0.032)

Source data: Appendix 16.1.9.2, Statdoc 6.1.2.1.1 ctr\pft-adjmean-mmrm-time.sas 10AUG2011

Table 15.2.1.2.1: 1 Adjusted mean (SE) FVC and comparisons to placebo over 48 weeks - analysis with imputation (FAS)

Test day	Planned time	Treatment	Treatment mean (SE)	Difference from Placebo		
				Mean (SE)	P-value	95% CI
169	0:30	Placebo	2.674 (0.028)			
		Olo 5ug	2.897 (0.028)	0.223 (0.037)	<.0001	(0.151, 0.295)
		Olo 10ug	2.874 (0.027)	0.199 (0.037)	<.0001	(0.127, 0.271)
	1:00	Placebo	2.666 (0.028)			
		Olo 5ug	2.928 (0.028)	0.262 (0.037)	<.0001	(0.189, 0.335)
		Olo 10ug	2.894 (0.027)	0.228 (0.037)	<.0001	(0.155, 0.300)
	2:00	Placebo	2.691 (0.028)			
		Olo 5ug	2.935 (0.028)	0.244 (0.038)	<.0001	(0.169, 0.318)
		Olo 10ug	2.917 (0.028)	0.226 (0.038)	<.0001	(0.152, 0.300)
	3:00	Placebo	2.681 (0.028)			
		Olo 5ug	2.935 (0.028)	0.255 (0.038)	<.0001	(0.181, 0.329)
		Olo 10ug	2.907 (0.028)	0.227 (0.038)	<.0001	(0.153, 0.301)
225	-0:10	Placebo	2.675 (0.028)			
		Olo 5ug	2.713 (0.028)	0.038 (0.038)	0.3201	(-0.037, 0.112)
		Olo 10ug	2.673 (0.028)	-0.002 (0.038)	0.9497	(-0.077, 0.072)
281	-0:10	Placebo	2.676 (0.029)			
		Olo 5ug	2.718 (0.028)	0.041 (0.038)	0.2739	(-0.033, 0.116)
		Olo 10ug	2.746 (0.028)	0.070 (0.038)	0.0662	(-0.005, 0.144)
337	-0:10	Placebo	2.606 (0.029)			
		Olo 5ug	2.652 (0.029)	0.046 (0.038)	0.2274	(-0.029, 0.121)
		Olo 10ug	2.668 (0.028)	0.062 (0.038)	0.1012	(-0.012, 0.137)

Results are from an MMRM model. Fixed effects include treatment, tiotropium strata, visit, treatment by visit interaction, baseline and baseline by visit interaction. Patient is considered random and a spatial power covariance structure was used.

For pre-dose measures at Day 1 in this table, entries for differences from Placebo are omitted. The Day 1 pre-dose treatment mean and SE are observed values, pooled across all treatments.

Number of patients contributing to models: Placebo (215), Olo 5ug (207), Olo 10ug (215)
Common baseline mean (SE): 2.605 (0.032)

Source data: Appendix 16.1.9.2, Statdoc 6.1.2.1.1 ctr\pft-adjmean-mmrm-time.sas 10AUG2011

Table 15.2.1.2.1: 1 Adjusted mean (SE) FVC and comparisons to placebo over 48 weeks - analysis with imputation (FAS)

Test day	Planned time	Treatment	Treatment mean (SE)	Difference from Placebo		
				Mean (SE)	P-value	95% CI
337	0:05	Placebo	2.630 (0.027)			
		Olo 5ug	2.822 (0.027)	0.192 (0.036)	<.0001	(0.122, 0.262)
		Olo 10ug	2.811 (0.027)	0.181 (0.036)	<.0001	(0.111, 0.251)
	0:15	Placebo	2.649 (0.027)			
		Olo 5ug	2.851 (0.027)	0.202 (0.036)	<.0001	(0.131, 0.274)
		Olo 10ug	2.840 (0.027)	0.191 (0.036)	<.0001	(0.120, 0.262)
	0:30	Placebo	2.660 (0.028)			
		Olo 5ug	2.875 (0.028)	0.215 (0.037)	<.0001	(0.142, 0.288)
		Olo 10ug	2.861 (0.028)	0.201 (0.037)	<.0001	(0.128, 0.273)
	1:00	Placebo	2.667 (0.028)			
		Olo 5ug	2.891 (0.028)	0.224 (0.037)	<.0001	(0.150, 0.297)
		Olo 10ug	2.871 (0.028)	0.203 (0.037)	<.0001	(0.130, 0.277)
	2:00	Placebo	2.671 (0.029)			
		Olo 5ug	2.906 (0.029)	0.234 (0.038)	<.0001	(0.160, 0.309)
		Olo 10ug	2.916 (0.028)	0.244 (0.038)	<.0001	(0.170, 0.319)
	3:00	Placebo	2.681 (0.029)			
		Olo 5ug	2.888 (0.029)	0.208 (0.038)	<.0001	(0.133, 0.282)
		Olo 10ug	2.915 (0.028)	0.234 (0.038)	<.0001	(0.159, 0.309)

Results are from an MMRM model. Fixed effects include treatment, tiotropium strata, visit, treatment by visit interaction, baseline and baseline by visit interaction. Patient is considered random and a spatial power covariance structure was used.

For pre-dose measures at Day 1 in this table, entries for differences from Placebo are omitted. The Day 1 pre-dose treatment mean and SE are observed values, pooled across all treatments.

Number of patients contributing to models: Placebo (215), Olo 5ug (207), Olo 10ug (215)
Common baseline mean (SE): 2.605 (0.032)

Source data: Appendix 16.1.9.2, Statdoc 6.1.2.1.1 ctr\pft-adjmean-mmrm-time.sas 10AUG2011

Table 15.2.1.2.2: 4 Adjusted mean (SE) FVC AUC (0-12) response and comparisons to placebo after 12 weeks - analysis with imputation (FAS), 12 hour PFT subset

			Difference from Placebo		
Test day	Treatment	Treatment mean (SE)	Mean (SE)	P-value	95% CI
85	Placebo	0.057 (0.036)			
	Olo 5ug	0.199 (0.035)	0.142 (0.047)	0.0028	(0.049, 0.235)
	Olo 10ug	0.212 (0.036)	0.156 (0.048)	0.0013	(0.061, 0.250)

Results are from non-MMRM ANCOVA models by visit. Fixed effects include treatment, tiotropium strata, and baseline. No LOCF.

Number of patients contributing to models: Placebo (98), Olo 5ug (116), Olo 10ug (107)
Common baseline mean (SE): 2.668 (0.046)

Source data: Appendix 16.1.9.2, Statdoc 6.1.2.2.3 ctr\pft-adjmean-ancova.sas 10AUG2011

Table 15.2.1.2.4: 1 Adjusted mean (SE) FVC peak (0-3) response and comparisons to placebo over 48 weeks - analysis with imputation (FAS)

			Difference from Placebo		
Test day	Treatment	Treatment mean (SE)	Mean (SE)	P-value	95% CI
1	Placebo	0.202 (0.027)			
	Olo 5ug	0.534 (0.028)	0.332 (0.036)	<.0001	(0.261, 0.403)
	Olo 10ug	0.535 (0.027)	0.333 (0.036)	<.0001	(0.263, 0.403)
15	Placebo	0.254 (0.027)			
	Olo 5ug	0.479 (0.028)	0.225 (0.036)	<.0001	(0.153, 0.296)
	Olo 10ug	0.464 (0.027)	0.210 (0.036)	<.0001	(0.139, 0.281)
43	Placebo	0.183 (0.028)			
	Olo 5ug	0.451 (0.028)	0.268 (0.037)	<.0001	(0.196, 0.340)
	Olo 10ug	0.434 (0.027)	0.251 (0.037)	<.0001	(0.179, 0.323)
85	Placebo	0.213 (0.028)			
	Olo 5ug	0.439 (0.028)	0.226 (0.037)	<.0001	(0.154, 0.298)
	Olo 10ug	0.422 (0.027)	0.209 (0.037)	<.0001	(0.137, 0.281)
169	Placebo	0.223 (0.028)			
	Olo 5ug	0.449 (0.028)	0.226 (0.037)	<.0001	(0.153, 0.299)
	Olo 10ug	0.429 (0.028)	0.206 (0.037)	<.0001	(0.133, 0.279)
337	Placebo	0.208 (0.028)			
	Olo 5ug	0.415 (0.028)	0.207 (0.037)	<.0001	(0.133, 0.280)
	Olo 10ug	0.419 (0.028)	0.211 (0.037)	<.0001	(0.138, 0.285)

Results are from an MMRM model. Fixed effects include treatment, tiotropium strata, visit, treatment by visit interaction, baseline and baseline by visit interaction. Patient is considered random and a spatial power covariance structure was used.

Number of patients contributing to models: Placebo (215), Olo 5ug (207), Olo 10ug (215)
Common baseline mean (SE): 2.605 (0.032)

Source data: Appendix 16.1.9.2, Statdoc 6.1.2.4.1 ctr\pft-adjmean-mmrm.sas 10AUG2011

Table 15.2.1.2.3: 1 Adjusted mean (SE) trough FVC response and comparisons to placebo over 48 weeks - analysis with imputation (FAS)

			Difference from Placebo		
Test day	Treatment	Treatment mean (SE)	Mean (SE)	P-value	95% CI
15	Placebo	0.054 (0.028)			
	Olo 5ug	0.113 (0.028)	0.059 (0.037)	0.1040	(-0.012, 0.131)
	Olo 10ug	0.141 (0.027)	0.087 (0.036)	0.0172	(0.015, 0.158)
43	Placebo	0.029 (0.028)			
	Olo 5ug	0.122 (0.028)	0.094 (0.037)	0.0106	(0.022, 0.166)
	Olo 10ug	0.147 (0.027)	0.118 (0.037)	0.0013	(0.046, 0.190)
85	Placebo	0.043 (0.028)			
	Olo 5ug	0.075 (0.028)	0.032 (0.037)	0.3821	(-0.040, 0.105)
	Olo 10ug	0.091 (0.027)	0.048 (0.037)	0.1917	(-0.024, 0.120)
127	Placebo	0.064 (0.028)			
	Olo 5ug	0.114 (0.028)	0.050 (0.037)	0.1808	(-0.023, 0.123)
	Olo 10ug	0.098 (0.028)	0.033 (0.037)	0.3700	(-0.039, 0.106)
169	Placebo	0.021 (0.028)			
	Olo 5ug	0.066 (0.028)	0.045 (0.037)	0.2312	(-0.029, 0.118)
	Olo 10ug	0.091 (0.028)	0.070 (0.037)	0.0596	(-0.003, 0.144)
225	Placebo	0.061 (0.028)			
	Olo 5ug	0.099 (0.028)	0.038 (0.037)	0.3110	(-0.036, 0.111)
	Olo 10ug	0.058 (0.028)	-0.003 (0.038)	0.9426	(-0.076, 0.071)
281	Placebo	0.062 (0.028)			
	Olo 5ug	0.104 (0.028)	0.042 (0.038)	0.2680	(-0.032, 0.115)
	Olo 10ug	0.131 (0.028)	0.069 (0.038)	0.0662	(-0.005, 0.143)

Results are from an MMRM model. Fixed effects include treatment, tiotropium strata, visit, treatment by visit interaction, baseline and baseline by visit interaction. Patient is considered random and a spatial power covariance structure was used.

Number of patients contributing to models: Placebo (205), Olo 5ug (205), Olo 10ug (207)
Common baseline mean (SE): 2.608 (0.032)

Source data: Appendix 16.1.9.2, Statdoc 6.1.2.3.1 ctr\pft-adjmean-mmrm.sas 10AUG2011

Table 15.2.1.2.3: 1 Adjusted mean (SE) trough FVC response and comparisons to placebo over 48 weeks - analysis with imputation (FAS)

			Difference from Placebo		
Test day	Treatment	Treatment mean (SE)	Mean (SE)	P-value	95% CI
337	Placebo	-0.008 (0.028)			
	Olo 5ug	0.038 (0.028)	0.046 (0.038)	0.2249	(-0.028, 0.120)
	Olo 10ug	0.054 (0.028)	0.062 (0.038)	0.0994	(-0.012, 0.136)

Results are from an MMRM model. Fixed effects include treatment, tiotropium strata, visit, treatment by visit interaction, baseline and baseline by visit interaction. Patient is considered random and a spatial power covariance structure was used.

Number of patients contributing to models: Placebo (205), Olo 5ug (205), Olo 10ug (207)
Common baseline mean (SE): 2.608 (0.032)

Table 15.2.2.1: 1 Adjusted mean (SE) weekly mean morning PEFR and comparisons to placebo over 48 weeks - analysis with imputation (FAS)

			Difference from Placebo		
Week	Treatment	Treatment mean (SE)	Mean (SE)	P-value	95% CI
1	Placebo	194.166 (2.245)			
	Olo 5ug	208.343 (2.285)	14.177 (2.930)	<.0001	(8.424, 19.930)
	Olo 10ug	212.579 (2.220)	18.412 (2.891)	<.0001	(12.735, 24.090)
2	Placebo	192.878 (2.462)			
	Olo 5ug	207.350 (2.506)	14.472 (3.213)	<.0001	(8.163, 20.782)
	Olo 10ug	211.037 (2.434)	18.159 (3.171)	<.0001	(11.932, 24.386)
3	Placebo	190.836 (2.800)			
	Olo 5ug	208.658 (2.850)	17.822 (3.654)	<.0001	(10.647, 24.998)
	Olo 10ug	213.164 (2.769)	22.327 (3.606)	<.0001	(15.246, 29.409)
4	Placebo	191.713 (2.797)			
	Olo 5ug	206.908 (2.847)	15.195 (3.650)	<.0001	(8.027, 22.363)
	Olo 10ug	211.916 (2.766)	20.204 (3.602)	<.0001	(13.129, 27.278)
5	Placebo	192.012 (2.873)			
	Olo 5ug	208.120 (2.924)	16.108 (3.750)	<.0001	(8.745, 23.472)
	Olo 10ug	209.428 (2.841)	17.417 (3.700)	<.0001	(10.150, 24.684)
6	Placebo	192.136 (2.868)			
	Olo 5ug	207.374 (2.919)	15.237 (3.743)	<.0001	(7.888, 22.587)
	Olo 10ug	210.210 (2.836)	18.073 (3.694)	<.0001	(10.820, 25.327)
7	Placebo	188.703 (3.005)			
	Olo 5ug	207.508 (3.058)	18.805 (3.920)	<.0001	(11.106, 26.504)
	Olo 10ug	210.022 (2.970)	21.319 (3.869)	<.0001	(13.720, 28.917)
8	Placebo	189.450 (3.178)			
	Olo 5ug	206.561 (3.235)	17.111 (4.147)	<.0001	(8.967, 25.255)
	Olo 10ug	207.743 (3.142)	18.293 (4.093)	<.0001	(10.255, 26.331)

Results are from non-MMRM ANCOVA models by week, with LOCF up to each week. Fixed effects include treatment, tiotropium strata and baseline.

Number of patients contributing to models: Placebo (211), Olo 5ug (204), Olo 10ug (214)
Common baseline mean (SE): 194.065 (3.899)

Source data: Appendix 16.1.9.2, Statdoc 6.2.2.1 ctr\diary-adjmean-ancova.sas 10AUG2011

Table 15.2.2.1: 1 Adjusted mean (SE) weekly mean morning PEFR and comparisons to placebo over 48 weeks - analysis with imputation (FAS)

			Difference from Placebo		
Week	Treatment	Treatment mean (SE)	Mean (SE)	P-value	95% CI
9	Placebo	189.005 (3.212)			
	Olo 5ug	205.323 (3.269)	16.317 (4.191)	0.0001	(8.086, 24.548)
	Olo 10ug	207.499 (3.176)	18.494 (4.137)	<.0001	(10.371, 26.617)
10	Placebo	188.574 (3.242)			
	Olo 5ug	205.026 (3.299)	16.452 (4.230)	0.0001	(8.145, 24.760)
	Olo 10ug	208.197 (3.205)	19.623 (4.175)	<.0001	(11.425, 27.822)
11	Placebo	188.927 (3.255)			
	Olo 5ug	203.871 (3.312)	14.944 (4.247)	0.0005	(6.604, 23.284)
	Olo 10ug	206.043 (3.218)	17.116 (4.191)	<.0001	(8.885, 25.346)
12	Placebo	187.745 (3.200)			
	Olo 5ug	202.953 (3.257)	15.209 (4.176)	0.0003	(7.008, 23.409)
	Olo 10ug	206.967 (3.164)	19.222 (4.121)	<.0001	(11.129, 27.315)
13	Placebo	189.715 (3.298)			
	Olo 5ug	207.901 (3.356)	18.186 (4.304)	<.0001	(9.735, 26.638)
	Olo 10ug	209.191 (3.261)	19.476 (4.247)	<.0001	(11.135, 27.817)
14	Placebo	187.451 (3.393)			
	Olo 5ug	205.261 (3.453)	17.811 (4.427)	<.0001	(9.117, 26.505)
	Olo 10ug	207.457 (3.354)	20.006 (4.369)	<.0001	(11.426, 28.587)
15	Placebo	186.263 (3.431)			
	Olo 5ug	207.302 (3.492)	21.040 (4.477)	<.0001	(12.247, 29.832)
	Olo 10ug	207.887 (3.392)	21.624 (4.419)	<.0001	(12.947, 30.302)
16	Placebo	185.953 (3.376)			
	Olo 5ug	205.103 (3.435)	19.150 (4.405)	<.0001	(10.500, 27.799)
	Olo 10ug	206.856 (3.337)	20.903 (4.347)	<.0001	(12.366, 29.439)

Results are from non-MMRM ANCOVA models by week, with LOCF up to each week. Fixed effects include treatment, tiotropium strata and baseline.

Number of patients contributing to models: Placebo (211), Olo 5ug (204), Olo 10ug (214)
Common baseline mean (SE): 194.065 (3.899)

Source data: Appendix 16.1.9.2, Statdoc 6.2.2.1 ctr\diary-adjmean-ancova.sas 10AUG2011

Table 15.2.2.1: 1 Adjusted mean (SE) weekly mean morning PEFR and comparisons to placebo over 48 weeks - analysis with imputation (FAS)

			Difference from Placebo		
Week	Treatment	Treatment mean (SE)	Mean (SE)	P-value	95% CI
17	Placebo	184.528 (3.388)			
	Olo 5ug	205.611 (3.448)	21.083 (4.421)	<.0001	(12.401, 29.764)
	Olo 10ug	204.573 (3.350)	20.045 (4.363)	<.0001	(11.477, 28.612)
18	Placebo	185.331 (3.388)			
	Olo 5ug	204.804 (3.447)	19.473 (4.420)	<.0001	(10.792, 28.153)
	Olo 10ug	205.391 (3.349)	20.060 (4.362)	<.0001	(11.493, 28.627)
19	Placebo	184.865 (3.330)			
	Olo 5ug	203.119 (3.389)	18.254 (4.345)	<.0001	(9.722, 26.786)
	Olo 10ug	205.172 (3.292)	20.307 (4.288)	<.0001	(11.886, 28.727)
20	Placebo	182.526 (3.514)			
	Olo 5ug	202.172 (3.576)	19.647 (4.585)	<.0001	(10.642, 28.651)
	Olo 10ug	203.679 (3.474)	21.154 (4.525)	<.0001	(12.268, 30.040)
21	Placebo	184.588 (3.467)			
	Olo 5ug	201.866 (3.528)	17.278 (4.523)	0.0001	(8.395, 26.161)
	Olo 10ug	204.161 (3.427)	19.573 (4.464)	<.0001	(10.806, 28.340)
22	Placebo	182.861 (3.422)			
	Olo 5ug	201.034 (3.483)	18.173 (4.466)	<.0001	(9.403, 26.942)
	Olo 10ug	204.348 (3.384)	21.488 (4.407)	<.0001	(12.833, 30.143)
23	Placebo	185.627 (3.388)			
	Olo 5ug	203.226 (3.448)	17.599 (4.421)	<.0001	(8.916, 26.281)
	Olo 10ug	205.476 (3.350)	19.849 (4.364)	<.0001	(11.280, 28.418)
24	Placebo	186.207 (3.367)			
	Olo 5ug	202.756 (3.427)	16.549 (4.394)	0.0002	(7.920, 25.178)
	Olo 10ug	206.032 (3.329)	19.825 (4.337)	<.0001	(11.309, 28.341)

Results are from non-MMRM ANCOVA models by week, with LOCF up to each week. Fixed effects include treatment, tiotropium strata and baseline.

Number of patients contributing to models: Placebo (211), Olo 5ug (204), Olo 10ug (214)
Common baseline mean (SE): 194.065 (3.899)

Source data: Appendix 16.1.9.2, Statdoc 6.2.2.1 ctr\diary-adjmean-ancova.sas 10AUG2011

Table 15.2.2.1: 1 Adjusted mean (SE) weekly mean morning PEFR and comparisons to placebo over 48 weeks - analysis with imputation (FAS)

			Difference from Placebo		
Week	Treatment	Treatment mean (SE)	Mean (SE)	P-value	95% CI
25	Placebo	186.246 (3.404)			
	Olo 5ug	203.536 (3.465)	17.290 (4.442)	0.0001	(8.566, 26.013)
	Olo 10ug	207.836 (3.366)	21.590 (4.384)	<.0001	(12.981, 30.200)
26	Placebo	187.195 (3.462)			
	Olo 5ug	203.628 (3.524)	16.433 (4.518)	0.0003	(7.561, 25.305)
	Olo 10ug	206.703 (3.423)	19.509 (4.459)	<.0001	(10.752, 28.265)
27	Placebo	185.426 (3.472)			
	Olo 5ug	201.936 (3.533)	16.510 (4.530)	0.0003	(7.614, 25.406)
	Olo 10ug	206.666 (3.432)	21.240 (4.471)	<.0001	(12.460, 30.020)
28	Placebo	185.368 (3.572)			
	Olo 5ug	199.996 (3.636)	14.627 (4.661)	0.0018	(5.473, 23.782)
	Olo 10ug	205.939 (3.532)	20.571 (4.600)	<.0001	(11.537, 29.605)
29	Placebo	184.801 (3.538)			
	Olo 5ug	199.534 (3.601)	14.732 (4.617)	0.0015	(5.665, 23.800)
	Olo 10ug	207.734 (3.498)	22.933 (4.557)	<.0001	(13.985, 31.882)
30	Placebo	183.511 (3.324)			
	Olo 5ug	200.011 (3.383)	16.499 (4.338)	0.0002	(7.981, 25.017)
	Olo 10ug	205.110 (3.286)	21.598 (4.281)	<.0001	(13.192, 30.005)
31	Placebo	186.418 (3.424)			
	Olo 5ug	199.245 (3.484)	12.827 (4.467)	0.0042	(4.055, 21.600)
	Olo 10ug	203.644 (3.385)	17.227 (4.409)	0.0001	(8.569, 25.885)
32	Placebo	184.341 (3.459)			
	Olo 5ug	199.008 (3.520)	14.667 (4.513)	0.0012	(5.804, 23.530)
	Olo 10ug	203.497 (3.419)	19.156 (4.454)	<.0001	(10.409, 27.903)

Results are from non-MMRM ANCOVA models by week, with LOCF up to each week. Fixed effects include treatment, tiotropium strata and baseline.

Number of patients contributing to models: Placebo (211), Olo 5ug (204), Olo 10ug (214)
Common baseline mean (SE): 194.065 (3.899)

Source data: Appendix 16.1.9.2, Statdoc 6.2.2.1 ctr\diary-adjmean-ancova.sas 10AUG2011

Table 15.2.2.1: 1 Adjusted mean (SE) weekly mean morning PEFR and comparisons to placebo over 48 weeks - analysis with imputation (FAS)

			Difference from Placebo		
Week	Treatment	Treatment mean (SE)	Mean (SE)	P-value	95% CI
33	Placebo	184.440 (3.470)			
	Olo 5ug	199.900 (3.531)	15.460 (4.528)	0.0007	(6.568, 24.352)
	Olo 10ug	202.351 (3.431)	17.911 (4.469)	<.0001	(9.136, 26.687)
34	Placebo	185.757 (3.531)			
	Olo 5ug	197.739 (3.594)	11.982 (4.608)	0.0095	(2.933, 21.031)
	Olo 10ug	203.669 (3.491)	17.912 (4.547)	<.0001	(8.982, 26.842)
35	Placebo	184.563 (3.490)			
	Olo 5ug	198.400 (3.552)	13.837 (4.554)	0.0025	(4.894, 22.780)
	Olo 10ug	204.766 (3.450)	20.202 (4.494)	<.0001	(11.377, 29.028)
36	Placebo	184.671 (3.571)			
	Olo 5ug	198.677 (3.634)	14.006 (4.659)	0.0028	(4.856, 23.156)
	Olo 10ug	202.908 (3.530)	18.237 (4.598)	<.0001	(9.206, 27.267)
37	Placebo	184.900 (3.600)			
	Olo 5ug	198.705 (3.663)	13.804 (4.697)	0.0034	(4.580, 23.028)
	Olo 10ug	203.253 (3.559)	18.352 (4.636)	<.0001	(9.249, 27.456)
38	Placebo	185.386 (3.560)			
	Olo 5ug	200.101 (3.623)	14.715 (4.645)	0.0016	(5.594, 23.837)
	Olo 10ug	202.612 (3.519)	17.226 (4.584)	0.0002	(8.224, 26.228)
39	Placebo	185.152 (3.609)			
	Olo 5ug	198.525 (3.672)	13.374 (4.709)	0.0047	(4.127, 22.620)
	Olo 10ug	202.768 (3.568)	17.616 (4.647)	0.0002	(8.491, 26.742)
40	Placebo	185.739 (3.593)			
	Olo 5ug	197.846 (3.657)	12.107 (4.689)	0.0100	(2.900, 21.315)
	Olo 10ug	202.615 (3.552)	16.876 (4.627)	0.0003	(7.789, 25.963)

Results are from non-MMRM ANCOVA models by week, with LOCF up to each week. Fixed effects include treatment, tiotropium strata and baseline.

Number of patients contributing to models: Placebo (211), Olo 5ug (204), Olo 10ug (214)
Common baseline mean (SE): 194.065 (3.899)

Source data: Appendix 16.1.9.2, Statdoc 6.2.2.1 ctr\diary-adjmean-ancova.sas 10AUG2011

Table 15.2.2.1: 1 Adjusted mean (SE) weekly mean morning PEFR and comparisons to placebo over 48 weeks - analysis with imputation (FAS)

			Difference from Placebo		
Week	Treatment	Treatment mean (SE)	Mean (SE)	P-value	95% CI
41	Placebo	186.788 (3.661)			
	Olo 5ug	198.244 (3.726)	11.455 (4.777)	0.0168	(2.074, 20.837)
	Olo 10ug	202.515 (3.620)	15.727 (4.715)	0.0009	(6.468, 24.986)
42	Placebo	184.968 (3.682)			
	Olo 5ug	199.336 (3.747)	14.369 (4.804)	0.0029	(4.934, 23.803)
	Olo 10ug	203.839 (3.640)	18.872 (4.741)	<.0001	(9.561, 28.182)
43	Placebo	184.926 (3.754)			
	Olo 5ug	197.539 (3.820)	12.613 (4.898)	0.0103	(2.994, 22.232)
	Olo 10ug	204.133 (3.711)	19.207 (4.834)	<.0001	(9.713, 28.700)
44	Placebo	183.129 (3.723)			
	Olo 5ug	196.971 (3.789)	13.842 (4.858)	0.0045	(4.302, 23.382)
	Olo 10ug	204.438 (3.681)	21.308 (4.794)	<.0001	(11.894, 30.723)
45	Placebo	182.789 (3.704)			
	Olo 5ug	195.907 (3.770)	13.118 (4.834)	0.0068	(3.625, 22.610)
	Olo 10ug	202.791 (3.662)	20.002 (4.771)	<.0001	(10.634, 29.370)
46	Placebo	182.218 (3.681)			
	Olo 5ug	195.486 (3.746)	13.267 (4.803)	0.0059	(3.836, 22.699)
	Olo 10ug	204.315 (3.639)	22.097 (4.740)	<.0001	(12.788, 31.405)
47	Placebo	184.344 (3.713)			
	Olo 5ug	198.638 (3.779)	14.294 (4.845)	0.0033	(4.779, 23.809)
	Olo 10ug	204.964 (3.671)	20.621 (4.782)	<.0001	(11.230, 30.011)
48	Placebo	182.939 (3.800)			
	Olo 5ug	196.300 (3.868)	13.360 (4.959)	0.0072	(3.622, 23.099)
	Olo 10ug	203.873 (3.757)	20.934 (4.894)	<.0001	(11.323, 30.545)

Results are from non-MMRM ANCOVA models by week, with LOCF up to each week. Fixed effects include treatment, tiotropium strata and baseline.

Number of patients contributing to models: Placebo (211), Olo 5ug (204), Olo 10ug (214)
Common baseline mean (SE): 194.065 (3.899)

Source data: Appendix 16.1.9.2, Statdoc 6.2.2.1 ctr\diary-adjmean-ancova.sas 10AUG2011

Table 15.2.2.1: 4 Adjusted mean (SE) weekly mean evening PEFR and comparisons to placebo over 48 weeks - analysis with imputation (FAS)

			Difference from Placebo		
Week	Treatment	Treatment mean (SE)	Mean (SE)	P-value	95% CI
1	Placebo	208.749 (2.363)			
	Olo 5ug	224.465 (2.409)	15.716 (3.082)	<.0001	(9.663, 21.769)
	Olo 10ug	228.331 (2.340)	19.582 (3.041)	<.0001	(13.610, 25.555)
2	Placebo	206.601 (2.481)			
	Olo 5ug	222.883 (2.530)	16.282 (3.237)	<.0001	(9.925, 22.639)
	Olo 10ug	224.648 (2.457)	18.047 (3.194)	<.0001	(11.774, 24.319)
3	Placebo	208.025 (2.727)			
	Olo 5ug	223.190 (2.781)	15.164 (3.558)	<.0001	(8.177, 22.152)
	Olo 10ug	227.716 (2.701)	19.691 (3.511)	<.0001	(12.796, 26.585)
4	Placebo	207.143 (2.742)			
	Olo 5ug	221.429 (2.795)	14.286 (3.577)	<.0001	(7.262, 21.309)
	Olo 10ug	226.684 (2.715)	19.541 (3.529)	<.0001	(12.610, 26.471)
5	Placebo	206.824 (2.856)			
	Olo 5ug	220.030 (2.911)	13.205 (3.726)	0.0004	(5.889, 20.522)
	Olo 10ug	222.919 (2.828)	16.095 (3.676)	<.0001	(8.876, 23.314)
6	Placebo	205.941 (2.894)			
	Olo 5ug	220.439 (2.951)	14.499 (3.776)	0.0001	(7.084, 21.914)
	Olo 10ug	222.787 (2.866)	16.846 (3.726)	<.0001	(9.530, 24.163)
7	Placebo	202.780 (3.090)			
	Olo 5ug	221.470 (3.150)	18.690 (4.031)	<.0001	(10.774, 26.606)
	Olo 10ug	223.410 (3.060)	20.630 (3.977)	<.0001	(12.819, 28.441)
8	Placebo	202.734 (3.254)			
	Olo 5ug	218.348 (3.317)	15.613 (4.245)	0.0003	(7.277, 23.950)
	Olo 10ug	222.095 (3.222)	19.361 (4.189)	<.0001	(11.136, 27.587)

Results are from non-MMRM ANCOVA models by week, with LOCF up to each week. Fixed effects include treatment, tiotropium strata and baseline.

Number of patients contributing to models: Placebo (213), Olo 5ug (205), Olo 10ug (215)
Common baseline mean (SE): 209.196 (4.045)

Source data: Appendix 16.1.9.2, Statdoc 6.2.1.3 ctr\diary-adjmean-ancova.sas 10AUG2011

Table 15.2.2.1: 4 Adjusted mean (SE) weekly mean evening PEFR and comparisons to placebo over 48 weeks - analysis with imputation (FAS)

			Difference from Placebo		
Week	Treatment	Treatment mean (SE)	Mean (SE)	P-value	95% CI
9	Placebo	202.562 (3.272)			
	Olo 5ug	216.881 (3.336)	14.319 (4.269)	0.0008	(5.935, 22.702)
	Olo 10ug	221.231 (3.240)	18.669 (4.212)	<.0001	(10.397, 26.942)
10	Placebo	203.580 (3.376)			
	Olo 5ug	216.717 (3.442)	13.137 (4.405)	0.0030	(4.487, 21.787)
	Olo 10ug	221.417 (3.343)	17.836 (4.346)	<.0001	(9.302, 26.371)
11	Placebo	201.284 (3.337)			
	Olo 5ug	216.829 (3.402)	15.545 (4.354)	0.0004	(6.995, 24.095)
	Olo 10ug	218.801 (3.305)	17.517 (4.296)	<.0001	(9.081, 25.953)
12	Placebo	201.353 (3.258)			
	Olo 5ug	215.572 (3.322)	14.219 (4.251)	0.0009	(5.871, 22.567)
	Olo 10ug	221.444 (3.227)	20.091 (4.194)	<.0001	(11.854, 28.328)
13	Placebo	200.877 (3.369)			
	Olo 5ug	218.549 (3.435)	17.672 (4.396)	<.0001	(9.040, 26.304)
	Olo 10ug	220.171 (3.336)	19.294 (4.337)	<.0001	(10.776, 27.811)
14	Placebo	200.442 (3.524)			
	Olo 5ug	218.205 (3.593)	17.763 (4.597)	0.0001	(8.735, 26.790)
	Olo 10ug	221.569 (3.489)	21.126 (4.536)	<.0001	(12.219, 30.034)
15	Placebo	198.033 (3.562)			
	Olo 5ug	217.536 (3.632)	19.503 (4.647)	<.0001	(10.377, 28.629)
	Olo 10ug	222.198 (3.527)	24.165 (4.586)	<.0001	(15.160, 33.170)
16	Placebo	198.451 (3.541)			
	Olo 5ug	215.534 (3.610)	17.083 (4.619)	0.0002	(8.012, 26.154)
	Olo 10ug	220.862 (3.506)	22.411 (4.558)	<.0001	(13.461, 31.361)

Results are from non-MMRM ANCOVA models by week, with LOCF up to each week. Fixed effects include treatment, tiotropium strata and baseline.

Number of patients contributing to models: Placebo (213), Olo 5ug (205), Olo 10ug (215)
Common baseline mean (SE): 209.196 (4.045)

Source data: Appendix 16.1.9.2, Statdoc 6.2.1.3 ctr\diary-adjmean-ancova.sas 10AUG2011

Table 15.2.2.1: 4 Adjusted mean (SE) weekly mean evening PEFR and comparisons to placebo over 48 weeks - analysis with imputation (FAS)

			Difference from Placebo		
Week	Treatment	Treatment mean (SE)	Mean (SE)	P-value	95% CI
17	Placebo	195.971 (3.582)			
	Olo 5ug	214.440 (3.652)	18.468 (4.673)	<.0001	(9.292, 27.645)
	Olo 10ug	217.970 (3.547)	21.998 (4.611)	<.0001	(12.944, 31.053)
18	Placebo	196.584 (3.639)			
	Olo 5ug	215.783 (3.710)	19.200 (4.748)	<.0001	(9.876, 28.523)
	Olo 10ug	218.031 (3.604)	21.447 (4.685)	<.0001	(12.247, 30.647)
19	Placebo	198.325 (3.610)			
	Olo 5ug	214.632 (3.680)	16.307 (4.709)	0.0006	(7.059, 25.555)
	Olo 10ug	220.986 (3.574)	22.661 (4.647)	<.0001	(13.536, 31.786)
20	Placebo	196.217 (3.672)			
	Olo 5ug	213.164 (3.744)	16.947 (4.791)	0.0004	(7.539, 26.355)
	Olo 10ug	220.715 (3.636)	24.498 (4.727)	<.0001	(15.215, 33.781)
21	Placebo	194.950 (3.626)			
	Olo 5ug	213.691 (3.697)	18.741 (4.730)	<.0001	(9.451, 28.030)
	Olo 10ug	220.119 (3.590)	25.169 (4.668)	<.0001	(16.003, 34.335)
22	Placebo	197.177 (3.753)			
	Olo 5ug	212.416 (3.826)	15.239 (4.896)	0.0019	(5.624, 24.854)
	Olo 10ug	219.067 (3.716)	21.889 (4.831)	<.0001	(12.402, 31.377)
23	Placebo	197.828 (3.637)			
	Olo 5ug	213.357 (3.708)	15.530 (4.745)	0.0011	(6.211, 24.848)
	Olo 10ug	220.328 (3.602)	22.501 (4.682)	<.0001	(13.306, 31.695)
24	Placebo	199.222 (3.688)			
	Olo 5ug	216.500 (3.760)	17.278 (4.811)	0.0004	(7.830, 26.726)
	Olo 10ug	220.022 (3.652)	20.800 (4.747)	<.0001	(11.478, 30.122)

Results are from non-MMRM ANCOVA models by week, with LOCF up to each week. Fixed effects include treatment, tiotropium strata and baseline.

Number of patients contributing to models: Placebo (213), Olo 5ug (205), Olo 10ug (215)
Common baseline mean (SE): 209.196 (4.045)

Source data: Appendix 16.1.9.2, Statdoc 6.2.1.3 ctr\diary-adjmean-ancova.sas 10AUG2011

Table 15.2.2.1: 4 Adjusted mean (SE) weekly mean evening PEFR and comparisons to placebo over 48 weeks - analysis with imputation (FAS)

			Difference from Placebo		
Week	Treatment	Treatment mean (SE)	Mean (SE)	P-value	95% CI
25	Placebo	199.338 (3.712)			
	Olo 5ug	215.197 (3.784)	15.860 (4.842)	0.0011	(6.350, 25.369)
	Olo 10ug	220.855 (3.676)	21.518 (4.778)	<.0001	(12.135, 30.901)
26	Placebo	198.362 (3.723)			
	Olo 5ug	215.718 (3.796)	17.356 (4.857)	0.0004	(7.818, 26.895)
	Olo 10ug	221.431 (3.687)	23.069 (4.793)	<.0001	(13.658, 32.481)
27	Placebo	198.681 (3.747)			
	Olo 5ug	212.990 (3.820)	14.309 (4.888)	0.0035	(4.710, 23.908)
	Olo 10ug	220.904 (3.710)	22.223 (4.823)	<.0001	(12.752, 31.694)
28	Placebo	198.054 (3.867)			
	Olo 5ug	211.621 (3.943)	13.567 (5.045)	0.0074	(3.659, 23.475)
	Olo 10ug	220.691 (3.830)	22.636 (4.978)	<.0001	(12.860, 32.413)
29	Placebo	197.147 (3.808)			
	Olo 5ug	210.700 (3.882)	13.553 (4.968)	0.0065	(3.797, 23.309)
	Olo 10ug	221.693 (3.771)	24.547 (4.902)	<.0001	(14.921, 34.173)
30	Placebo	197.249 (3.639)			
	Olo 5ug	212.176 (3.710)	14.927 (4.747)	0.0017	(5.605, 24.249)
	Olo 10ug	220.194 (3.603)	22.945 (4.684)	<.0001	(13.746, 32.143)
31	Placebo	195.924 (3.705)			
	Olo 5ug	210.436 (3.777)	14.512 (4.833)	0.0028	(5.020, 24.003)
	Olo 10ug	218.954 (3.669)	23.030 (4.769)	<.0001	(13.664, 32.395)
32	Placebo	196.868 (3.729)			
	Olo 5ug	210.787 (3.802)	13.919 (4.865)	0.0044	(4.366, 23.472)
	Olo 10ug	217.906 (3.692)	21.038 (4.800)	<.0001	(11.612, 30.464)

Results are from non-MMRM ANCOVA models by week, with LOCF up to each week. Fixed effects include treatment, tiotropium strata and baseline.

Number of patients contributing to models: Placebo (213), Olo 5ug (205), Olo 10ug (215)
Common baseline mean (SE): 209.196 (4.045)

Source data: Appendix 16.1.9.2, Statdoc 6.2.1.3 ctr\diary-adjmean-ancova.sas 10AUG2011

Table 15.2.2.1: 4 Adjusted mean (SE) weekly mean evening PEFR and comparisons to placebo over 48 weeks - analysis with imputation (FAS)

			Difference from Placebo		
Week	Treatment	Treatment mean (SE)	Mean (SE)	P-value	95% CI
33	Placebo	197.745 (3.712)			
	Olo 5ug	209.768 (3.785)	12.023 (4.843)	0.0133	(2.512, 21.534)
	Olo 10ug	218.673 (3.676)	20.929 (4.779)	<.0001	(11.544, 30.313)
34	Placebo	196.187 (3.751)			
	Olo 5ug	208.757 (3.825)	12.570 (4.894)	0.0104	(2.960, 22.181)
	Olo 10ug	217.958 (3.715)	21.771 (4.829)	<.0001	(12.288, 31.254)
35	Placebo	196.086 (3.786)			
	Olo 5ug	208.481 (3.859)	12.394 (4.939)	0.0123	(2.696, 22.092)
	Olo 10ug	219.165 (3.749)	23.078 (4.873)	<.0001	(13.509, 32.647)
36	Placebo	196.741 (3.728)			
	Olo 5ug	209.535 (3.801)	12.793 (4.864)	0.0087	(3.242, 22.344)
	Olo 10ug	217.847 (3.692)	21.106 (4.799)	<.0001	(11.681, 30.530)
37	Placebo	198.265 (3.849)			
	Olo 5ug	209.022 (3.924)	10.758 (5.021)	0.0325	(0.898, 20.617)
	Olo 10ug	217.409 (3.811)	19.144 (4.954)	0.0001	(9.415, 28.872)
38	Placebo	196.896 (3.876)			
	Olo 5ug	210.869 (3.952)	13.973 (5.057)	0.0059	(4.043, 23.903)
	Olo 10ug	216.415 (3.838)	19.519 (4.990)	0.0001	(9.721, 29.317)
39	Placebo	194.961 (3.947)			
	Olo 5ug	210.044 (4.024)	15.083 (5.150)	0.0035	(4.970, 25.195)
	Olo 10ug	215.851 (3.909)	20.890 (5.081)	<.0001	(10.912, 30.868)
40	Placebo	197.356 (3.914)			
	Olo 5ug	211.849 (3.990)	14.493 (5.106)	0.0047	(4.467, 24.519)
	Olo 10ug	218.321 (3.875)	20.965 (5.038)	<.0001	(11.072, 30.858)

Results are from non-MMRM ANCOVA models by week, with LOCF up to each week. Fixed effects include treatment, tiotropium strata and baseline.

Number of patients contributing to models: Placebo (213), Olo 5ug (205), Olo 10ug (215)
Common baseline mean (SE): 209.196 (4.045)

Source data: Appendix 16.1.9.2, Statdoc 6.2.1.3 ctr\diary-adjmean-ancova.sas 10AUG2011

Table 15.2.2.1: 4 Adjusted mean (SE) weekly mean evening PEFR and comparisons to placebo over 48 weeks - analysis with imputation (FAS)

			Difference from Placebo		
Week	Treatment	Treatment mean (SE)	Mean (SE)	P-value	95% CI
41	Placebo	200.324 (3.865)			
	Olo 5ug	211.501 (3.940)	11.177 (5.042)	0.0270	(1.275, 21.079)
	Olo 10ug	217.800 (3.827)	17.476 (4.975)	0.0005	(7.706, 27.246)
42	Placebo	197.999 (3.929)			
	Olo 5ug	210.824 (4.005)	12.825 (5.125)	0.0126	(2.760, 22.890)
	Olo 10ug	216.489 (3.890)	18.490 (5.057)	0.0003	(8.559, 28.421)
43	Placebo	196.698 (3.935)			
	Olo 5ug	209.161 (4.012)	12.463 (5.134)	0.0155	(2.381, 22.545)
	Olo 10ug	218.215 (3.897)	21.517 (5.066)	<.0001	(11.570, 31.465)
44	Placebo	194.452 (3.982)			
	Olo 5ug	206.531 (4.059)	12.079 (5.194)	0.0204	(1.878, 22.279)
	Olo 10ug	218.026 (3.943)	23.574 (5.125)	<.0001	(13.509, 33.639)
45	Placebo	196.495 (3.917)			
	Olo 5ug	208.108 (3.993)	11.613 (5.110)	0.0234	(1.578, 21.647)
	Olo 10ug	218.470 (3.879)	21.975 (5.042)	<.0001	(12.074, 31.876)
46	Placebo	195.263 (3.937)			
	Olo 5ug	207.644 (4.013)	12.381 (5.136)	0.0162	(2.296, 22.466)
	Olo 10ug	217.500 (3.898)	22.237 (5.067)	<.0001	(12.286, 32.188)
47	Placebo	196.742 (4.029)			
	Olo 5ug	208.436 (4.108)	11.694 (5.256)	0.0265	(1.372, 22.016)
	Olo 10ug	217.447 (3.990)	20.704 (5.186)	<.0001	(10.519, 30.889)
48	Placebo	195.502 (3.987)			
	Olo 5ug	207.958 (4.065)	12.456 (5.201)	0.0169	(2.242, 22.670)
	Olo 10ug	216.155 (3.948)	20.653 (5.132)	<.0001	(10.574, 30.731)

Results are from non-MMRM ANCOVA models by week, with LOCF up to each week. Fixed effects include treatment, tiotropium strata and baseline.

Number of patients contributing to models: Placebo (213), Olo 5ug (205), Olo 10ug (215)
Common baseline mean (SE): 209.196 (4.045)

Source data: Appendix 16.1.9.2, Statdoc 6.2.1.3 ctr\diary-adjmean-ancova.sas 10AUG2011