Boehringer Ingelheim

Clinical Study Synopsis for Public Disclosure

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Name of company: Boehringer Ingelheim		**Tabulated Trial Report**	Boehringer Ingelheim
Name of finished product:		**EudraCT No.:** 2008-003647-36	
Name of active ingredient: Olodaterol (BI 1744)		**Page:** 1 of 7	**Synopsis No.:**
Module:		**Volume:**	
Report date: 28 DEC 2011	**Trial No. / U No.:** 1222.11 / U10-3192-01	**Date of trial:** 05 NOV 2008 – 21 SEP 2010	**Date of revision:** Not applicable

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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):	Data from this trial have not yet been published.
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: 859 ; entered/randomised: 625; treated: 624 [One patient was randomized to study drug (10 µg) prior to review of the screening ECG. The patient did not meet the creening criteria and was not treated] Treatment : placebo: entered: 209; treated: 209 analyzed for co-primary endpoint (forced expiratory volume in 1 second area under the curve over 0 to 3 hours (FEV_1 AUC_{0-3h}) response at Day 85: 208; analyzed for co-primary endpoint trough FEV_1 response at Day 85: 200

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No. of patients actual (continued):	Treatment: olodaterol 5 µg: entered: 208; treated: 208; analyzed for co-primary endpoint FEV_1 AUC_{0-3h}:response at Day 85: 206; analyzed for co-primary endpoint trough FEV_1 response at Day 85: 199 Treatment: olodaterol 10 µg: entered: 208; treated: 207; analyzed for co-primary endpoint FEV_1 AUC_{0-3h} response at Day 85: 206; analyzed for co-primary endpoint trough FEV_1 response at Day 85: 202
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.:	5 µg: B072000346; 10 µg: B072000356
Reference therapy:	Placebo inhalation matching olodaterol
dose:	not applicable (N/A)
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 $peak_{0-3h}$ response; FVC AUC_{0-12h} response(in a subset of patients); FEV_1 and FVC at individual time points; morning and evening peak expiratory flow (PEFR); daytime, nighttime, and daily (24-hour) 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 hospitalization, number of COPD exacerbations per patient year, number of COPD exacerbations leading to hospitalization per patient year, number of moderate COPD exacerbations per patient year.

Pharmacokinetics (PK) was assessed by plasma concentrations of olodaterol from blood samples drawn prior to dosing and 10 minutes post-dosing. Systemic pharmacodynamics (PD) was evaluated by values of potassium from blood samples drawn at 1 and 3 hours post-dosing.

Safety: Adverse events, administration related bronchoconstriction, vital signs, laboratory evaluations, 12-lead electrocardiogram (ECG), 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 survivor function, negative binomial models, and descriptive statistics.

SUMMARY – CONCLUSIONS:

Efficacy / clinical pharmacology results:

Co-primary endpoints:

For the co-primary efficacy endpoints of FEV_1 AUC_{0-3h} response at Day 85 and trough FEV_1 response at Day 85, both doses of olodaterol (5 µg and 10µg) showed a statistically significantly greater effect than placebo:

- For FEV_1 AUC_{0-3h} response at Day 85, both doses of olodaterol had estimated adjusted mean values that were statistically significantly greater than that of placebo (5 µg: 0.172 L difference [0.165 vs. -0.007 L, $p<0.0001$]; 10 µg: 0.176 L difference [0.169 vs. -0.007 L, $p<0.0001$]).

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Efficacy / clinical pharmacology results (continued):

- For trough FEV_1 response at Day 85, both doses of olodaterol had estimated adjusted mean values that were statistically significantly greater than that of placebo (5 µg: 0.091 L difference [0.050 vs. -0.041 L, p<0.0001]; 10 µg: 0.101 L difference [0.060 vs. -0.041 L, p<0.0001])

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 75% 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 (1222.11) and the replicate study 1222.12 is presented in a separate report (U10-3303-01 Study 1222.9992).

Secondary endpoints:

In the subset of patients that had 12-hour post-dose PFTs on Day 85, FEV_1 AUC_{0-12} response for both doses of olodaterol had estimated adjusted mean values that were statistically significantly greater than that of placebo (5 µg: 0.173 L difference [0.144 vs. -0.029 L, p<0.0001]; 10 µg: 0.169 L difference [0.139 vs. -0.029 L, p<0.0001].

Results for FEV_1 AUC_{0-3h} response and for trough FEV_1 response at individual test days over 48 weeks were similar to those at the primary endpoint visit (Day 85). FEV_1 $peak_{0-3h}$ responses were consistent over the 48 week treatment period.

On Day 1, the mean difference in FEV_1 compared to placebo at 5, 15, and 30 minutes post-dose was 0.115, 0.158, and 0.162 L for the olodaterol 5µg group, respectively, and 0.115, 0.155, and 0.160 L for the olodaterol 10 µg group, respectively.

FVC results were consistent with the FEV_1 results. Both olodaterol dose groups showed a statistically significant increase in FVC AUC_{0-3h} response, trough FVC response, and FVC $peak_{0-3h}$ response compared to placebo over 48 weeks (p<0.0001), as well as a statistically significant increase in FVC AUC_{0-12h} response compared to placebo at Day 85 (Week 12) (p<0.0001).

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Efficacy / clinical pharmacology results (continued):

Morning and evening PEFR results exhibited statistically significant bronchodilation in both treatment groups compared with placebo at all assessments. Over 48 weeks of treatment, the mean daily (24-hour) use, the mean daytime use, and the mean nighttime use of rescue medication was higher in the placebo group than in the olodaterol groups. The PGR after 6, 12, 24, and 48 weeks of treatment was significantly reduced (indicating an improvement in respiratory condition) in both olodaterol treatment groups at all time points compared to placebo.

Time to first COPD exacerbation, moderate COPD exacerbation, and COPD exacerbation leading to hospitalisation did not occur statistically significantly earlier in patients treated with placebo than in patients treated with olodaterol. The hazard ratios for mean time to first COPD exacerbation compared to placebo were 0.728 (p = 0.0658) for the olodaterol 5 µg treatment group and 0.799 (p=0.1701) for the olodaterol 10 µg treatment group. Mean number of COPD exacerbations, moderate COPD exacerbation, and COPD exacerbation leading to hospitalisation per patient/year were not statistically significantly higher in placebo treated patients than patients treated with olodaterol.

Clinical Pharmacology:

Overall, the geometric mean (gMean) plasma concentration 10 minutes after inhalation of olodaterol ($C_{0\ 167,ss}$) in the olodaterol 10 µg treatment group (6.62 pg/mL) was 1.6 fold higher than that of the olodaterol 5 µg treatment group (4.04 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 (N=183) than in the olodaterol 10 µg treatment group (N=40). As these data are omitted in the calculation of the descriptive statistics, the gMean value of the olodaterol 5 µg treatment group is more 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 inhalation of 5 and 10 µg olodaterol.

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Safety results:

Once daily treatment with olodaterol 5 µg or 10 µg for 48 weeks was generally safe and well tolerated; there were no safety concerns identified.

- There were 5 deaths during the treatment period (1 in the placebo treatment group, 3 in the olodaterol 5 µg treatment group, and 1 in the olodaterol 10 µg treatment group). There were 5 post-study deaths; 4 patients had discontinued the study, and their deaths were reported as a result of solicited vital status follow-up during the planned observation period, (planned 48 week treatment period + 2 week follow-up period) (2 in the placebo treatment group, 1 in the olodaterol 5 µg treatment group, and 1 in the olodaterol 10 µg treatment group) while 1 patient (olodaterol 5 µg treatment group) completed the study and the death was reported by the investigator outside of the vital status follow-up period (unsolicited).
- There were 116 patients who had at least one SAE (placebo: 34 [16.3%] patients, olodaterol 5 µg: 39 [18.8%] patients, olodaterol 10 µg: 43 [20.8%] patients). SAEs that occurred in more than 2 patients included COPD exacerbations (42 [6.7%]), pneumonia (8 [1.3%]), lobar pneumonia (3 [0.5%]), atrial fibrillation (3 [0.5%]), and fall (3 [0.5%]). There were no notable differences in SAEs between treatment groups.
- There was 1 patient with an SAE considered by the investigator to be related to the study drug (atrial fibrillation in the olodaterol 10 µg group).
- Fifty-one patients (8.2%) discontinued study drug due to AEs (9.6% in the placebo group, 7.2% in the olodaterol 5 µg group, and 7.7% in the olodaterol 10 µg group).
- Adverse events were reported in 72.6% and 70.5% of patients treated with olodaterol 5 µg and 10 µg, respectively, and in 74.2% of patients treated with placebo.
- The most frequently reported AEs were COPD exacerbation (30.1%), upper respiratory tract infection (7.9%), and nasopharyngitis (7.5%).
- The majority of AEs were mild to moderate in intensity, with severe AEs reported in 19.2% of patients. Forty-five (7.2%) patients had one or more related AE.

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Safety results (continued):

- Forty-one patients (6.6%) experienced a study-drug administration-related respiratory event indicative of bronchoconstriction, including 31 patients (5.0%) with a ≥15% decrease from pre-dose FEV_1, and 11 patients (1.8%) requiring rescue medication within 30 minutes of study drug inhalation at a clinic visit.
- There were no notable differences among the treatment groups in the occurrences of abnormalities in vital signs, laboratory parameters (except CPK), ECG results, Holter monitoring, and physical examination findings.
- Mean changes from baseline for CPK levels (last value on treatment) were -24 U/L, +8 U/L, and +59 U/L for the placebo, olodaterol 5 µg, and olodaterol 10 µg treatment groups, respectively. Using maximum on treatment values, upward shifts from baseline were noted for CPK; 11/172 patients (6.4%) in the placebo treatment group, 31/177 (17.5%) in the olodaterol 5 µg treatment group, and 38/183 patients (20.8%) in the olodaterol 10 µg treatment group. One patient in the olodaterol 10 µg treatment group discontinued study drug due to an adverse event of increased blood CPK.
- There were no statistically significant differences in blood potassium levels between the olodaterol groups and the placebo group.

Conclusions:

The primary objective of the present study was met with olodaterol 5 µg once daily and olodaterol 10 µg once daily showing statistically significant improvements compared to placebo for the co-primary endpoints of FEV_1 AUC_{0-3h} response at Day 85 and trough FEV_1 response at Day 85. Once daily treatment with olodaterol 5 µg or 10 µg for 48 weeks was generally safe and well tolerated; there were no safety concerns identified. An evaluation of the preferred dose of olodaterol 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} on test days 1, 15, 43, 85, 169, and 337	Table 15.2.1.1.2: 1
Trough FEV_1 on test days 15, 43, 85, 127, 169, 225, and 337	Table 15.2.1.1.3: 1
FEV_1 $peak_{0-3h}$ on test days 1, 15, 43, 85, 169, and 337	Table 15.2.1.1.4: 1
FEV_1 at all time points on days 1, 15, 43, 85, 127, 169, 225, 281, and 337	Table 15.2.1.1.1: 1
FVC AUC_{0-3h} on test days 1, 15, 43, 85, 169, and 337	Table 15.2.1.2.2: 1
Trough FVC on test days 15, 43, 85, 127, 169, 225, and 337	Table 15.2.1.2.3: 1
FVC $peak_{0-3h}$ on test days 1, 15, 43, 85, 169, and 337	Table 15.2.1.2.4: 1
FVC AUC_{0-12h} on test day 85	Table 15.2.1.2.2: 4
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				859
Not entered/randomsed				234
Entered/randomised				625
Not treated				1
Treated	209(100.00)	208(100.00)	207(100.00)	624(100.00)
Not prematurely discontinued from trial medication #	159(76.08)	173(83.17)	172(83.09)	504(80.77)
Prematurely discontinued from trial medication	50(23.92)	35(16.83)	35(16.91)	120(19.23)
Adverse event	21(10.05)	17(8.17)	16(7.73)	54(8.65)
AE study dis. worse	13(6.22)	7(3.37)	4(1.93)	24(3.85)
AE-oth. dis. worse	2(0.96)	0(0.00)	3(1.45)	5(0.80)
AE-other	6(2.87)	10(4.81)	9(4.35)	25(4.01)
Lack of efficacy	13(6.22)	4(1.92)	1(0.48)	18(2.88)
Non compl prot.	0(0.00)	3(1.44)	2(0.97)	5(0.80)
Lost to follow-up	2(0.96)	1(0.48)	2(0.97)	5(0.80)
Consent withdrawn	11(5.26)	8(3.85)	11(5.31)	30(4.81)
Other	3(1.44)	2(0.96)	3(1.45)	8(1.28)

NOTE: All percentages based on the numbers of patients treated.
One patient was randomized to study drug prior to review of the screening ECG. As the ECG was abnormal, the patient did not meet the screening criteria was not treated.

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	0.024 (0.014)			
	Olo 5ug	0.189 (0.014)	0.165 (0.019)	<.0001	(0.128, 0.201)
	Olo 10ug	0.199 (0.014)	0.175 (0.019)	<.0001	(0.139, 0.212)
15	Placebo	-0.000 (0.014)			
	Olo 5ug	0.180 (0.014)	0.181 (0.019)	<.0001	(0.144, 0.217)
	Olo 10ug	0.192 (0.014)	0.192 (0.019)	<.0001	(0.156, 0.229)
43	Placebo	-0.001 (0.014)			
	Olo 5ug	0.169 (0.014)	0.170 (0.019)	<.0001	(0.133, 0.207)
	Olo 10ug	0.165 (0.014)	0.167 (0.019)	<.0001	(0.130, 0.204)
85	Placebo	-0.007 (0.014)			
	Olo 5ug	0.165 (0.014)	0.172 (0.019)	<.0001	(0.135, 0.209)
	Olo 10ug	0.169 (0.014)	0.176 (0.019)	<.0001	(0.139, 0.214)
169	Placebo	-0.018 (0.014)			
	Olo 5ug	0.156 (0.014)	0.174 (0.019)	<.0001	(0.136, 0.212)
	Olo 10ug	0.143 (0.014)	0.161 (0.019)	<.0001	(0.123, 0.199)
337	Placebo	-0.043 (0.014)			
	Olo 5ug	0.130 (0.014)	0.173 (0.019)	<.0001	(0.134, 0.211)
	Olo 10ug	0.126 (0.014)	0.169 (0.020)	<.0001	(0.131, 0.208)

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 (208), Olo 5ug (206), Olo 10ug (206)
Common baseline mean (SE): 1.139 (0.019)

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	-0.019 (0.014)			
	Olo 5ug	0.076 (0.014)	0.095 (0.018)	<.0001	(0.059, 0.131)
	Olo 10ug	0.091 (0.014)	0.111 (0.018)	<.0001	(0.075, 0.147)
43	Placebo	-0.022 (0.014)			
	Olo 5ug	0.073 (0.014)	0.095 (0.019)	<.0001	(0.059, 0.131)
	Olo 10ug	0.069 (0.014)	0.091 (0.019)	<.0001	(0.054, 0.127)
85	Placebo	-0.041 (0.014)			
	Olo 5ug	0.050 (0.014)	0.091 (0.019)	<.0001	(0.054, 0.128)
	Olo 10ug	0.060 (0.014)	0.101 (0.019)	<.0001	(0.064, 0.137)
127	Placebo	-0.042 (0.014)			
	Olo 5ug	0.056 (0.014)	0.098 (0.019)	<.0001	(0.061, 0.135)
	Olo 10ug	0.059 (0.014)	0.101 (0.019)	<.0001	(0.064, 0.138)
169	Placebo	-0.050 (0.014)			
	Olo 5ug	0.036 (0.014)	0.086 (0.019)	<.0001	(0.049, 0.123)
	Olo 10ug	0.039 (0.014)	0.089 (0.019)	<.0001	(0.051, 0.126)
225	Placebo	-0.051 (0.014)			
	Olo 5ug	0.041 (0.014)	0.092 (0.019)	<.0001	(0.054, 0.130)
	Olo 10ug	0.034 (0.014)	0.085 (0.019)	<.0001	(0.048, 0.123)
281	Placebo	-0.061 (0.014)			
	Olo 5ug	0.046 (0.014)	0.107 (0.019)	<.0001	(0.069, 0.145)
	Olo 10ug	0.044 (0.014)	0.105 (0.019)	<.0001	(0.068, 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 (200), Olo 5ug (199), Olo 10ug (202)
Common baseline mean (SE): 1.139 (0.019)

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	-0.074 (0.014)			
	Olo 5ug	0.019 (0.014)	0.092 (0.019)	<.0001	(0.055, 0.130)
	Olo 10ug	0.017 (0.014)	0.091 (0.019)	<.0001	(0.053, 0.129)

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 (200), Olo 5ug (199), Olo 10ug (202)
Common baseline mean (SE): 1.139 (0.019)

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	0.104 (0.015)			
	Olo 5ug	0.259 (0.015)	0.155 (0.020)	<.0001	(0.115, 0.194)
	Olo 10ug	0.275 (0.015)	0.171 (0.020)	<.0001	(0.131, 0.211)
15	Placebo	0.077 (0.015)			
	Olo 5ug	0.254 (0.015)	0.177 (0.020)	<.0001	(0.137, 0.217)
	Olo 10ug	0.267 (0.015)	0.190 (0.020)	<.0001	(0.150, 0.230)
43	Placebo	0.066 (0.015)			
	Olo 5ug	0.238 (0.015)	0.172 (0.021)	<.0001	(0.132, 0.212)
	Olo 10ug	0.238 (0.015)	0.172 (0.021)	<.0001	(0.132, 0.212)
85	Placebo	0.071 (0.015)			
	Olo 5ug	0.235 (0.015)	0.164 (0.021)	<.0001	(0.123, 0.204)
	Olo 10ug	0.236 (0.015)	0.165 (0.021)	<.0001	(0.124, 0.206)
169	Placebo	0.055 (0.016)			
	Olo 5ug	0.230 (0.015)	0.175 (0.021)	<.0001	(0.134, 0.216)
	Olo 10ug	0.206 (0.015)	0.151 (0.021)	<.0001	(0.110, 0.192)
337	Placebo	0.029 (0.016)			
	Olo 5ug	0.198 (0.016)	0.169 (0.021)	<.0001	(0.128, 0.211)
	Olo 10ug	0.192 (0.016)	0.163 (0.021)	<.0001	(0.121, 0.205)

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 (208), Olo 5ug (206), Olo 10ug (206)
Common baseline mean (SE): 1.139 (0.019)

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

Table 15.2.1.1.1: 1 Adjusted mean (SE) FEV1 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	1.127 (0.019)			
		Olo 5ug	1.127 (0.019)			
		Olo 10ug	1.127 (0.019)			
	-0:10	Placebo	1.151 (0.019)			
		Olo 5ug	1.151 (0.019)			
		Olo 10ug	1.151 (0.019)			
	0:05	Placebo	1.152 (0.013)			
		Olo 5ug	1.267 (0.013)	0.115 (0.018)	<.0001	(0.080, 0.150)
		Olo 10ug	1.268 (0.013)	0.115 (0.018)	<.0001	(0.080, 0.150)
	0:15	Placebo	1.150 (0.014)			
		Olo 5ug	1.307 (0.014)	0.158 (0.019)	<.0001	(0.121, 0.195)
		Olo 10ug	1.305 (0.014)	0.155 (0.019)	<.0001	(0.118, 0.192)
	0:30	Placebo	1.160 (0.014)			
		Olo 5ug	1.322 (0.014)	0.162 (0.019)	<.0001	(0.124, 0.200)
		Olo 10ug	1.320 (0.014)	0.160 (0.019)	<.0001	(0.123, 0.198)
	1:00	Placebo	1.157 (0.014)			
		Olo 5ug	1.332 (0.014)	0.175 (0.019)	<.0001	(0.138, 0.212)
		Olo 10ug	1.339 (0.014)	0.183 (0.019)	<.0001	(0.145, 0.220)
	2:00	Placebo	1.179 (0.015)			
		Olo 5ug	1.350 (0.015)	0.171 (0.020)	<.0001	(0.132, 0.211)
		Olo 10ug	1.368 (0.015)	0.189 (0.020)	<.0001	(0.149, 0.229)

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 (208), Olo 5ug (206), Olo 10ug (206)
Common baseline mean (SE): 1.139 (0.019)

Source data: Appendix 16.1.9.2, Statdoc 6.1.1.1.1 ctr\pft-adjmean-mmrm-time.sas 10AUG2011

Table 15.2.1.1.1: 1 Adjusted mean (SE) FEV1 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	1.176 (0.015)			
		Olo 5ug	1.343 (0.015)	0.167 (0.020)	<.0001	(0.128, 0.205)
		Olo 10ug	1.361 (0.015)	0.185 (0.020)	<.0001	(0.146, 0.224)
15	-0:10	Placebo	1.123 (0.014)			
		Olo 5ug	1.218 (0.014)	0.095 (0.019)	<.0001	(0.058, 0.132)
		Olo 10ug	1.234 (0.014)	0.111 (0.019)	<.0001	(0.074, 0.147)
	0:05	Placebo	1.129 (0.013)			
		Olo 5ug	1.285 (0.013)	0.156 (0.018)	<.0001	(0.120, 0.191)
		Olo 10ug	1.298 (0.013)	0.168 (0.018)	<.0001	(0.133, 0.204)
	0:15	Placebo	1.140 (0.014)			
		Olo 5ug	1.304 (0.014)	0.163 (0.019)	<.0001	(0.126, 0.200)
		Olo 10ug	1.325 (0.014)	0.184 (0.019)	<.0001	(0.147, 0.222)
	0:30	Placebo	1.138 (0.014)			
		Olo 5ug	1.320 (0.014)	0.182 (0.019)	<.0001	(0.144, 0.220)
		Olo 10ug	1.335 (0.014)	0.197 (0.019)	<.0001	(0.159, 0.235)
	1:00	Placebo	1.138 (0.014)			
		Olo 5ug	1.328 (0.014)	0.190 (0.019)	<.0001	(0.152, 0.228)
		Olo 10ug	1.341 (0.014)	0.202 (0.019)	<.0001	(0.165, 0.240)
	2:00	Placebo	1.148 (0.015)			
		Olo 5ug	1.332 (0.015)	0.184 (0.020)	<.0001	(0.144, 0.224)
		Olo 10ug	1.341 (0.015)	0.193 (0.020)	<.0001	(0.153, 0.233)

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 (208), Olo 5ug (206), Olo 10ug (206)
Common baseline mean (SE): 1.139 (0.019)

Source data: Appendix 16.1.9.2, Statdoc 6.1.1.1.1 ctr\pft-adjmean-mmrm-time.sas 10AUG2011

Table 15.2.1.1.1: 1 Adjusted mean (SE) FEV1 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	1.148 (0.015)			
		Olo 5ug	1.330 (0.015)	0.182 (0.020)	<.0001	(0.143, 0.221)
		Olo 10ug	1.341 (0.015)	0.193 (0.020)	<.0001	(0.154, 0.232)
43	-1:00	Placebo	1.112 (0.013)			
		Olo 5ug	1.202 (0.013)	0.090 (0.017)	<.0001	(0.056, 0.124)
		Olo 10ug	1.200 (0.013)	0.088 (0.017)	<.0001	(0.054, 0.122)
	-0:10	Placebo	1.131 (0.014)			
		Olo 5ug	1.231 (0.014)	0.100 (0.019)	<.0001	(0.063, 0.137)
		Olo 10ug	1.220 (0.014)	0.090 (0.019)	<.0001	(0.053, 0.127)
	0:05	Placebo	1.122 (0.013)			
		Olo 5ug	1.276 (0.013)	0.154 (0.018)	<.0001	(0.118, 0.190)
		Olo 10ug	1.271 (0.013)	0.149 (0.018)	<.0001	(0.113, 0.184)
	0:15	Placebo	1.135 (0.014)			
		Olo 5ug	1.293 (0.014)	0.158 (0.019)	<.0001	(0.121, 0.196)
		Olo 10ug	1.292 (0.014)	0.157 (0.019)	<.0001	(0.119, 0.194)
	0:30	Placebo	1.135 (0.014)			
		Olo 5ug	1.315 (0.014)	0.180 (0.020)	<.0001	(0.141, 0.218)
		Olo 10ug	1.297 (0.014)	0.162 (0.020)	<.0001	(0.124, 0.200)
	1:00	Placebo	1.138 (0.014)			
		Olo 5ug	1.309 (0.014)	0.171 (0.019)	<.0001	(0.133, 0.209)
		Olo 10ug	1.310 (0.014)	0.172 (0.019)	<.0001	(0.134, 0.210)

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 (208), Olo 5ug (206), Olo 10ug (206)
Common baseline mean (SE): 1.139 (0.019)

Source data: Appendix 16.1.9.2, Statdoc 6.1.1.1.1 ctr\pft-adjmean-mmrm-time.sas 10AUG2011

Table 15.2.1.1.1: 1 Adjusted mean (SE) FEV1 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	1.147 (0.015)			
		Olo 5ug	1.325 (0.015)	0.178 (0.021)	<.0001	(0.138, 0.219)
		Olo 10ug	1.319 (0.015)	0.172 (0.021)	<.0001	(0.132, 0.213)
	3:00	Placebo	1.150 (0.015)			
		Olo 5ug	1.316 (0.015)	0.166 (0.020)	<.0001	(0.126, 0.205)
		Olo 10ug	1.320 (0.015)	0.170 (0.020)	<.0001	(0.131, 0.210)
85	-1:00	Placebo	1.090 (0.013)			
		Olo 5ug	1.184 (0.013)	0.095 (0.017)	<.0001	(0.061, 0.129)
		Olo 10ug	1.187 (0.013)	0.097 (0.017)	<.0001	(0.063, 0.131)
	-0:10	Placebo	1.114 (0.014)			
		Olo 5ug	1.202 (0.014)	0.087 (0.019)	<.0001	(0.050, 0.125)
		Olo 10ug	1.215 (0.014)	0.101 (0.019)	<.0001	(0.064, 0.138)
	0:05	Placebo	1.111 (0.014)			
		Olo 5ug	1.272 (0.013)	0.161 (0.018)	<.0001	(0.125, 0.197)
		Olo 10ug	1.272 (0.013)	0.160 (0.018)	<.0001	(0.124, 0.196)
	0:15	Placebo	1.118 (0.014)			
		Olo 5ug	1.285 (0.014)	0.168 (0.019)	<.0001	(0.130, 0.206)
		Olo 10ug	1.294 (0.014)	0.176 (0.019)	<.0001	(0.138, 0.214)
	0:30	Placebo	1.123 (0.015)			
		Olo 5ug	1.305 (0.014)	0.182 (0.020)	<.0001	(0.144, 0.221)
		Olo 10ug	1.302 (0.014)	0.179 (0.020)	<.0001	(0.141, 0.218)

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 (208), Olo 5ug (206), Olo 10ug (206)
Common baseline mean (SE): 1.139 (0.019)

Source data: Appendix 16.1.9.2, Statdoc 6.1.1.1.1 ctr\pft-adjmean-mmrm-time.sas 10AUG2011

Table 15.2.1.1.1: 1 Adjusted mean (SE) FEV1 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	1.125 (0.014)			
		Olo 5ug	1.307 (0.014)	0.182 (0.019)	<.0001	(0.144, 0.220)
		Olo 10ug	1.309 (0.014)	0.183 (0.019)	<.0001	(0.145, 0.222)
	2:00	Placebo	1.156 (0.015)			
		Olo 5ug	1.321 (0.015)	0.165 (0.021)	<.0001	(0.124, 0.206)
		Olo 10ug	1.331 (0.015)	0.175 (0.021)	<.0001	(0.134, 0.216)
	3:00	Placebo	1.138 (0.015)			
		Olo 5ug	1.313 (0.015)	0.175 (0.020)	<.0001	(0.135, 0.215)
		Olo 10ug	1.316 (0.015)	0.177 (0.020)	<.0001	(0.138, 0.217)
127	-0:10	Placebo	1.100 (0.014)			
		Olo 5ug	1.199 (0.014)	0.098 (0.019)	<.0001	(0.061, 0.136)
		Olo 10ug	1.202 (0.014)	0.101 (0.019)	<.0001	(0.064, 0.138)
169	-0:10	Placebo	1.092 (0.014)			
		Olo 5ug	1.179 (0.014)	0.086 (0.019)	<.0001	(0.049, 0.124)
		Olo 10ug	1.181 (0.014)	0.088 (0.019)	<.0001	(0.051, 0.126)
	0:05	Placebo	1.101 (0.014)			
		Olo 5ug	1.254 (0.014)	0.153 (0.019)	<.0001	(0.116, 0.189)
		Olo 10ug	1.245 (0.014)	0.144 (0.019)	<.0001	(0.107, 0.180)
	0:15	Placebo	1.113 (0.014)			
		Olo 5ug	1.288 (0.014)	0.175 (0.020)	<.0001	(0.136, 0.213)
		Olo 10ug	1.265 (0.014)	0.152 (0.020)	<.0001	(0.113, 0.190)

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 (208), Olo 5ug (206), Olo 10ug (206)
Common baseline mean (SE): 1.139 (0.019)

Source data: Appendix 16.1.9.2, Statdoc 6.1.1.1.1 ctr\pft-adjmean-mmrm-time.sas 10AUG2011

Table 15.2.1.1.1: 1 Adjusted mean (SE) FEV1 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	1.121 (0.015)			
		Olo 5ug	1.308 (0.015)	0.187 (0.020)	<.0001	(0.148, 0.226)
		Olo 10ug	1.279 (0.015)	0.157 (0.020)	<.0001	(0.118, 0.196)
	1:00	Placebo	1.119 (0.015)			
		Olo 5ug	1.301 (0.014)	0.182 (0.020)	<.0001	(0.144, 0.221)
		Olo 10ug	1.289 (0.014)	0.171 (0.020)	<.0001	(0.132, 0.209)
	2:00	Placebo	1.135 (0.016)			
		Olo 5ug	1.305 (0.015)	0.170 (0.021)	<.0001	(0.129, 0.211)
		Olo 10ug	1.298 (0.015)	0.162 (0.021)	<.0001	(0.121, 0.204)
	3:00	Placebo	1.132 (0.015)			
		Olo 5ug	1.299 (0.015)	0.166 (0.020)	<.0001	(0.126, 0.206)
		Olo 10ug	1.295 (0.015)	0.163 (0.021)	<.0001	(0.122, 0.203)
225	-0:10	Placebo	1.091 (0.014)			
		Olo 5ug	1.184 (0.014)	0.092 (0.019)	<.0001	(0.054, 0.130)
		Olo 10ug	1.176 (0.014)	0.085 (0.019)	<.0001	(0.047, 0.123)
281	-0:10	Placebo	1.081 (0.014)			
		Olo 5ug	1.188 (0.014)	0.107 (0.019)	<.0001	(0.069, 0.145)
		Olo 10ug	1.186 (0.014)	0.105 (0.019)	<.0001	(0.067, 0.143)
337	-0:10	Placebo	1.069 (0.014)			
		Olo 5ug	1.161 (0.014)	0.093 (0.019)	<.0001	(0.054, 0.131)
		Olo 10ug	1.159 (0.014)	0.091 (0.019)	<.0001	(0.053, 0.129)

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 (208), Olo 5ug (206), Olo 10ug (206)
Common baseline mean (SE): 1.139 (0.019)

Source data: Appendix 16.1.9.2, Statdoc 6.1.1.1.1 ctr\pft-adjmean-mmrm-time.sas 10AUG2011

Table 15.2.1.1.1: 1 Adjusted mean (SE) FEV1 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	1.091 (0.014)			
		Olo 5ug	1.229 (0.014)	0.137 (0.019)	<.0001	(0.100, 0.174)
		Olo 10ug	1.229 (0.014)	0.137 (0.019)	<.0001	(0.100, 0.174)
	0:15	Placebo	1.092 (0.015)			
		Olo 5ug	1.257 (0.015)	0.166 (0.020)	<.0001	(0.127, 0.205)
		Olo 10ug	1.254 (0.015)	0.162 (0.020)	<.0001	(0.123, 0.201)
	0:30	Placebo	1.097 (0.015)			
		Olo 5ug	1.261 (0.015)	0.164 (0.020)	<.0001	(0.125, 0.204)
		Olo 10ug	1.270 (0.015)	0.173 (0.020)	<.0001	(0.133, 0.212)
	1:00	Placebo	1.103 (0.015)			
		Olo 5ug	1.274 (0.015)	0.171 (0.020)	<.0001	(0.132, 0.210)
		Olo 10ug	1.263 (0.015)	0.160 (0.020)	<.0001	(0.121, 0.199)
	2:00	Placebo	1.113 (0.016)			
		Olo 5ug	1.288 (0.016)	0.175 (0.021)	<.0001	(0.133, 0.217)
		Olo 10ug	1.282 (0.016)	0.170 (0.021)	<.0001	(0.128, 0.212)
	3:00	Placebo	1.107 (0.015)			
		Olo 5ug	1.283 (0.015)	0.176 (0.021)	<.0001	(0.135, 0.216)
		Olo 10ug	1.279 (0.015)	0.172 (0.021)	<.0001	(0.131, 0.213)

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 (208), Olo 5ug (206), Olo 10ug (206)
Common baseline mean (SE): 1.139 (0.019)

Source data: Appendix 16.1.9.2, Statdoc 6.1.1.1.1 ctr\pft-adjmean-mmrm-time.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	0.063 (0.027)			
	Olo 5ug	0.350 (0.027)	0.288 (0.037)	<.0001	(0.216, 0.359)
	Olo 10ug	0.392 (0.027)	0.330 (0.037)	<.0001	(0.258, 0.401)
15	Placebo	0.026 (0.027)			
	Olo 5ug	0.323 (0.027)	0.296 (0.037)	<.0001	(0.224, 0.368)
	Olo 10ug	0.353 (0.027)	0.327 (0.037)	<.0001	(0.255, 0.399)
43	Placebo	0.022 (0.028)			
	Olo 5ug	0.276 (0.028)	0.254 (0.037)	<.0001	(0.181, 0.327)
	Olo 10ug	0.316 (0.027)	0.293 (0.037)	<.0001	(0.220, 0.366)
85	Placebo	0.003 (0.028)			
	Olo 5ug	0.277 (0.028)	0.275 (0.037)	<.0001	(0.201, 0.348)
	Olo 10ug	0.295 (0.028)	0.292 (0.037)	<.0001	(0.219, 0.366)
169	Placebo	0.026 (0.028)			
	Olo 5ug	0.261 (0.028)	0.235 (0.038)	<.0001	(0.161, 0.309)
	Olo 10ug	0.281 (0.028)	0.254 (0.038)	<.0001	(0.180, 0.329)
337	Placebo	-0.040 (0.028)			
	Olo 5ug	0.204 (0.028)	0.244 (0.038)	<.0001	(0.169, 0.319)
	Olo 10ug	0.231 (0.028)	0.271 (0.038)	<.0001	(0.196, 0.346)

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 (208), Olo 5ug (206), Olo 10ug (206)
Common baseline mean (SE): 2.602 (0.032)

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

Table 15.2.1.2.3: 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	-0.015 (0.027)			
	Olo 5ug	0.132 (0.027)	0.147 (0.036)	<.0001	(0.076, 0.218)
	Olo 10ug	0.169 (0.027)	0.184 (0.036)	<.0001	(0.113, 0.255)
43	Placebo	-0.005 (0.027)			
	Olo 5ug	0.125 (0.027)	0.131 (0.037)	0.0003	(0.059, 0.203)
	Olo 10ug	0.135 (0.027)	0.141 (0.036)	0.0001	(0.069, 0.213)
85	Placebo	-0.030 (0.027)			
	Olo 5ug	0.085 (0.027)	0.115 (0.037)	0.0019	(0.043, 0.187)
	Olo 10ug	0.130 (0.027)	0.160 (0.037)	<.0001	(0.088, 0.233)
127	Placebo	-0.028 (0.028)			
	Olo 5ug	0.102 (0.027)	0.130 (0.037)	0.0005	(0.057, 0.203)
	Olo 10ug	0.134 (0.027)	0.162 (0.037)	<.0001	(0.089, 0.235)
169	Placebo	-0.028 (0.028)			
	Olo 5ug	0.055 (0.027)	0.083 (0.037)	0.0261	(0.010, 0.156)
	Olo 10ug	0.096 (0.027)	0.123 (0.037)	0.0010	(0.050, 0.197)
225	Placebo	-0.026 (0.028)			
	Olo 5ug	0.065 (0.028)	0.091 (0.038)	0.0154	(0.018, 0.165)
	Olo 10ug	0.097 (0.027)	0.123 (0.038)	0.0011	(0.049, 0.197)
281	Placebo	-0.044 (0.028)			
	Olo 5ug	0.087 (0.028)	0.131 (0.038)	0.0006	(0.057, 0.205)
	Olo 10ug	0.111 (0.028)	0.154 (0.038)	<.0001	(0.080, 0.229)

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 (200), Olo 5ug (199), Olo 10ug (202)
Common baseline mean (SE): 2.595 (0.033)

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	-0.083 (0.028)			
	Olo 5ug	0.011 (0.028)	0.094 (0.038)	0.0134	(0.019, 0.168)
	Olo 10ug	0.032 (0.028)	0.115 (0.038)	0.0025	(0.040, 0.190)

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 (200), Olo 5ug (199), Olo 10ug (202)
Common baseline mean (SE): 2.595 (0.033)

Source data: Appendix 16.1.9.2, Statdoc 6.1.2.3.1 ctr\pft-adjmean-mmrm.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	0.245 (0.029)			
	Olo 5ug	0.509 (0.029)	0.263 (0.039)	<.0001	(0.187, 0.339)
	Olo 10ug	0.546 (0.029)	0.300 (0.039)	<.0001	(0.225, 0.376)
15	Placebo	0.207 (0.029)			
	Olo 5ug	0.471 (0.029)	0.264 (0.039)	<.0001	(0.188, 0.341)
	Olo 10ug	0.499 (0.029)	0.292 (0.039)	<.0001	(0.216, 0.368)
43	Placebo	0.180 (0.029)			
	Olo 5ug	0.430 (0.029)	0.251 (0.039)	<.0001	(0.174, 0.328)
	Olo 10ug	0.460 (0.029)	0.280 (0.039)	<.0001	(0.203, 0.358)
85	Placebo	0.169 (0.029)			
	Olo 5ug	0.421 (0.029)	0.251 (0.040)	<.0001	(0.174, 0.329)
	Olo 10ug	0.430 (0.029)	0.260 (0.040)	<.0001	(0.183, 0.338)
169	Placebo	0.188 (0.030)			
	Olo 5ug	0.419 (0.029)	0.232 (0.040)	<.0001	(0.153, 0.310)
	Olo 10ug	0.420 (0.030)	0.232 (0.040)	<.0001	(0.154, 0.311)
337	Placebo	0.109 (0.030)			
	Olo 5ug	0.356 (0.030)	0.247 (0.040)	<.0001	(0.168, 0.327)
	Olo 10ug	0.369 (0.030)	0.260 (0.041)	<.0001	(0.181, 0.340)

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 (208), Olo 5ug (206), Olo 10ug (206)
Common baseline mean (SE): 2.602 (0.032)

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

Table 15.2.1.2.2: 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	-0.019 (0.049)			
	Olo 5ug	0.283 (0.045)	0.302 (0.061)	<.0001	(0.181, 0.422)
	Olo 10ug	0.230 (0.044)	0.249 (0.061)	<.0001	(0.128, 0.370)

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 (71), Olo 5ug (85), Olo 10ug (85)
Common baseline mean (SE): 2.682 (0.052)

Source data: Appendix 16.1.9.2, Statdoc 6.1.2.2.3 ctr\pft-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
1	Placebo	191.843 (2.074)			
	Olo 5ug	207.444 (2.090)	15.600 (2.772)	<.0001	(10.157, 21.043)
	Olo 10ug	209.506 (2.075)	17.663 (2.768)	<.0001	(12.226, 23.100)
2	Placebo	191.918 (2.234)			
	Olo 5ug	204.075 (2.252)	12.157 (2.986)	<.0001	(6.294, 18.021)
	Olo 10ug	208.639 (2.236)	16.721 (2.982)	<.0001	(10.864, 22.578)
3	Placebo	189.346 (2.390)			
	Olo 5ug	206.262 (2.409)	16.916 (3.195)	<.0001	(10.642, 23.190)
	Olo 10ug	209.784 (2.392)	20.438 (3.191)	<.0001	(14.171, 26.705)
4	Placebo	187.601 (2.475)			
	Olo 5ug	204.493 (2.495)	16.892 (3.308)	<.0001	(10.394, 23.389)
	Olo 10ug	207.494 (2.477)	19.893 (3.305)	<.0001	(13.403, 26.383)
5	Placebo	186.100 (2.485)			
	Olo 5ug	203.940 (2.505)	17.840 (3.322)	<.0001	(11.317, 24.364)
	Olo 10ug	206.585 (2.487)	20.485 (3.318)	<.0001	(13.969, 27.002)
6	Placebo	187.369 (2.604)			
	Olo 5ug	203.201 (2.625)	15.832 (3.480)	<.0001	(8.998, 22.667)
	Olo 10ug	206.293 (2.606)	18.924 (3.476)	<.0001	(12.097, 25.751)
7	Placebo	186.795 (2.597)			
	Olo 5ug	201.865 (2.618)	15.071 (3.471)	<.0001	(8.255, 21.887)
	Olo 10ug	207.227 (2.599)	20.433 (3.467)	<.0001	(13.624, 27.241)
8	Placebo	186.324 (2.660)			
	Olo 5ug	202.978 (2.681)	16.654 (3.555)	<.0001	(9.673, 23.635)
	Olo 10ug	206.197 (2.662)	19.874 (3.551)	<.0001	(12.900, 26.847)

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 (204), Olo 5ug (202), Olo 10ug (203)
Common baseline mean (SE): 192.943 (3.728)

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	186.268 (2.758)			
	Olo 5ug	201.360 (2.780)	15.092 (3.686)	<.0001	(7.853, 22.332)
	Olo 10ug	205.301 (2.760)	19.033 (3.682)	<.0001	(11.801, 26.264)
10	Placebo	186.866 (2.712)			
	Olo 5ug	201.482 (2.734)	14.616 (3.625)	<.0001	(7.497, 21.734)
	Olo 10ug	205.084 (2.714)	18.218 (3.621)	<.0001	(11.107, 25.328)
11	Placebo	185.321 (2.711)			
	Olo 5ug	199.415 (2.733)	14.094 (3.624)	0.0001	(6.978, 21.211)
	Olo 10ug	204.299 (2.713)	18.978 (3.620)	<.0001	(11.869, 26.086)
12	Placebo	185.319 (2.717)			
	Olo 5ug	198.329 (2.739)	13.010 (3.632)	0.0004	(5.878, 20.142)
	Olo 10ug	204.753 (2.719)	19.434 (3.628)	<.0001	(12.309, 26.558)
13	Placebo	184.370 (2.848)			
	Olo 5ug	201.791 (2.870)	17.421 (3.806)	<.0001	(9.946, 24.895)
	Olo 10ug	206.350 (2.850)	21.980 (3.802)	<.0001	(14.513, 29.446)
14	Placebo	183.181 (2.792)			
	Olo 5ug	200.126 (2.814)	16.945 (3.731)	<.0001	(9.617, 24.272)
	Olo 10ug	202.729 (2.794)	19.548 (3.727)	<.0001	(12.228, 26.867)
15	Placebo	181.446 (2.890)			
	Olo 5ug	198.888 (2.913)	17.442 (3.862)	<.0001	(9.857, 25.027)
	Olo 10ug	204.148 (2.892)	22.702 (3.858)	<.0001	(15.125, 30.279)
16	Placebo	182.253 (2.897)			
	Olo 5ug	197.667 (2.920)	15.415 (3.872)	<.0001	(7.811, 23.019)
	Olo 10ug	203.159 (2.899)	20.907 (3.868)	<.0001	(13.311, 28.503)

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 (204), Olo 5ug (202), Olo 10ug (203)
Common baseline mean (SE): 192.943 (3.728)

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	182.233 (2.877)			
	Olo 5ug	198.060 (2.900)	15.826 (3.845)	<.0001	(8.275, 23.378)
	Olo 10ug	201.825 (2.879)	19.591 (3.841)	<.0001	(12.048, 27.135)
18	Placebo	181.106 (2.893)			
	Olo 5ug	197.947 (2.917)	16.841 (3.867)	<.0001	(9.246, 24.436)
	Olo 10ug	201.488 (2.896)	20.382 (3.863)	<.0001	(12.795, 27.968)
19	Placebo	182.136 (2.940)			
	Olo 5ug	197.915 (2.964)	15.779 (3.930)	<.0001	(8.061, 23.496)
	Olo 10ug	201.661 (2.942)	19.525 (3.925)	<.0001	(11.816, 27.234)
20	Placebo	181.665 (2.924)			
	Olo 5ug	197.486 (2.947)	15.821 (3.908)	<.0001	(8.146, 23.495)
	Olo 10ug	200.232 (2.926)	18.567 (3.903)	<.0001	(10.901, 26.233)
21	Placebo	182.577 (3.007)			
	Olo 5ug	197.215 (3.031)	14.638 (4.020)	0.0003	(6.744, 22.532)
	Olo 10ug	199.836 (3.010)	17.259 (4.015)	<.0001	(9.374, 25.145)
22	Placebo	182.017 (2.983)			
	Olo 5ug	197.431 (3.007)	15.415 (3.987)	0.0001	(7.584, 23.245)
	Olo 10ug	197.970 (2.985)	15.953 (3.983)	<.0001	(8.132, 23.775)
23	Placebo	182.084 (2.985)			
	Olo 5ug	196.566 (3.009)	14.483 (3.989)	0.0003	(6.648, 22.318)
	Olo 10ug	199.493 (2.987)	17.409 (3.985)	<.0001	(9.583, 25.236)
24	Placebo	181.933 (3.009)			
	Olo 5ug	196.623 (3.033)	14.690 (4.022)	0.0003	(6.792, 22.589)
	Olo 10ug	197.037 (3.011)	15.104 (4.017)	0.0002	(7.214, 22.994)

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 (204), Olo 5ug (202), Olo 10ug (203)
Common baseline mean (SE): 192.943 (3.728)

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	183.228 (3.015)			
	Olo 5ug	197.516 (3.040)	14.288 (4.030)	0.0004	(6.373, 22.203)
	Olo 10ug	197.601 (3.018)	14.373 (4.026)	0.0004	(6.467, 22.280)
26	Placebo	181.760 (3.077)			
	Olo 5ug	198.002 (3.102)	16.242 (4.113)	<.0001	(8.165, 24.319)
	Olo 10ug	199.051 (3.079)	17.292 (4.108)	<.0001	(9.224, 25.360)
27	Placebo	182.398 (3.086)			
	Olo 5ug	197.218 (3.110)	14.821 (4.124)	0.0004	(6.721, 22.920)
	Olo 10ug	198.372 (3.088)	15.975 (4.120)	0.0001	(7.884, 24.065)
28	Placebo	182.256 (3.054)			
	Olo 5ug	196.572 (3.079)	14.316 (4.082)	0.0005	(6.299, 22.333)
	Olo 10ug	197.354 (3.057)	15.097 (4.078)	0.0002	(7.089, 23.105)
29	Placebo	182.607 (3.017)			
	Olo 5ug	195.837 (3.041)	13.230 (4.032)	0.0011	(5.312, 21.148)
	Olo 10ug	196.697 (3.019)	14.090 (4.027)	0.0005	(6.181, 21.999)
30	Placebo	180.165 (3.084)			
	Olo 5ug	195.009 (3.109)	14.844 (4.122)	0.0003	(6.748, 22.939)
	Olo 10ug	197.322 (3.087)	17.156 (4.118)	<.0001	(9.069, 25.243)
31	Placebo	181.254 (3.002)			
	Olo 5ug	194.502 (3.026)	13.248 (4.012)	0.0010	(5.368, 21.128)
	Olo 10ug	195.913 (3.004)	14.659 (4.008)	0.0003	(6.788, 22.530)
32	Placebo	178.954 (3.072)			
	Olo 5ug	194.130 (3.097)	15.176 (4.106)	0.0002	(7.112, 23.240)
	Olo 10ug	196.361 (3.075)	17.407 (4.102)	<.0001	(9.352, 25.463)

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 (204), Olo 5ug (202), Olo 10ug (203)
Common baseline mean (SE): 192.943 (3.728)

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	180.296 (2.998)			
	Olo 5ug	194.814 (3.022)	14.518 (4.007)	0.0003	(6.649, 22.387)
	Olo 10ug	195.018 (3.000)	14.722 (4.003)	0.0003	(6.861, 22.583)
34	Placebo	179.510 (2.982)			
	Olo 5ug	195.479 (3.006)	15.969 (3.985)	<.0001	(8.143, 23.796)
	Olo 10ug	193.693 (2.984)	14.183 (3.981)	0.0004	(6.365, 22.001)
35	Placebo	181.885 (3.087)			
	Olo 5ug	194.873 (3.112)	12.988 (4.127)	0.0017	(4.884, 21.092)
	Olo 10ug	194.917 (3.090)	13.032 (4.122)	0.0016	(4.937, 21.127)
36	Placebo	180.052 (3.114)			
	Olo 5ug	195.144 (3.139)	15.092 (4.162)	0.0003	(6.918, 23.265)
	Olo 10ug	194.980 (3.116)	14.927 (4.157)	0.0004	(6.763, 23.092)
37	Placebo	179.696 (3.023)			
	Olo 5ug	195.897 (3.048)	16.201 (4.041)	<.0001	(8.265, 24.137)
	Olo 10ug	196.084 (3.026)	16.389 (4.037)	<.0001	(8.461, 24.316)
38	Placebo	180.393 (3.026)			
	Olo 5ug	195.751 (3.051)	15.358 (4.045)	0.0002	(7.415, 23.302)
	Olo 10ug	197.383 (3.029)	16.990 (4.040)	<.0001	(9.055, 24.925)
39	Placebo	180.227 (3.001)			
	Olo 5ug	196.366 (3.025)	16.139 (4.011)	<.0001	(8.262, 24.016)
	Olo 10ug	196.952 (3.003)	16.725 (4.006)	<.0001	(8.856, 24.593)
40	Placebo	179.994 (3.099)			
	Olo 5ug	196.728 (3.124)	16.735 (4.142)	<.0001	(8.601, 24.868)
	Olo 10ug	196.837 (3.101)	16.843 (4.137)	<.0001	(8.718, 24.968)

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 (204), Olo 5ug (202), Olo 10ug (203)
Common baseline mean (SE): 192.943 (3.728)

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	181.243 (3.056)			
	Olo 5ug	194.224 (3.081)	12.981 (4.085)	0.0016	(4.959, 21.003)
	Olo 10ug	195.582 (3.059)	14.339 (4.080)	0.0005	(6.326, 22.352)
42	Placebo	178.822 (3.083)			
	Olo 5ug	194.720 (3.108)	15.898 (4.121)	0.0001	(7.806, 23.990)
	Olo 10ug	195.271 (3.085)	16.449 (4.116)	<.0001	(8.366, 24.533)
43	Placebo	180.553 (3.136)			
	Olo 5ug	194.896 (3.161)	14.343 (4.191)	0.0007	(6.112, 22.573)
	Olo 10ug	196.308 (3.138)	15.755 (4.186)	0.0002	(7.534, 23.977)
44	Placebo	179.400 (3.190)			
	Olo 5ug	195.261 (3.216)	15.860 (4.264)	0.0002	(7.486, 24.234)
	Olo 10ug	195.360 (3.193)	15.959 (4.259)	0.0002	(7.595, 24.324)
45	Placebo	179.080 (3.217)			
	Olo 5ug	194.603 (3.242)	15.523 (4.299)	0.0003	(7.079, 23.966)
	Olo 10ug	196.015 (3.219)	16.935 (4.295)	<.0001	(8.501, 25.369)
46	Placebo	178.977 (3.218)			
	Olo 5ug	194.790 (3.244)	15.813 (4.301)	0.0003	(7.367, 24.260)
	Olo 10ug	195.890 (3.220)	16.913 (4.296)	<.0001	(8.476, 25.351)
47	Placebo	179.453 (3.181)			
	Olo 5ug	193.389 (3.207)	13.937 (4.252)	0.0011	(5.586, 22.287)
	Olo 10ug	194.821 (3.184)	15.368 (4.247)	0.0003	(7.027, 23.709)
48	Placebo	180.019 (3.182)			
	Olo 5ug	193.376 (3.207)	13.357 (4.253)	0.0018	(5.005, 21.709)
	Olo 10ug	195.475 (3.184)	15.457 (4.248)	0.0003	(7.114, 23.800)

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 (204), Olo 5ug (202), Olo 10ug (203)
Common baseline mean (SE): 192.943 (3.728)

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	204.717 (1.938)			
	Olo 5ug	225.360 (1.961)	20.643 (2.599)	<.0001	(15.538, 25.747)
	Olo 10ug	227.402 (1.939)	22.684 (2.588)	<.0001	(17.602, 27.766)
2	Placebo	202.843 (2.039)			
	Olo 5ug	221.717 (2.063)	18.875 (2.735)	<.0001	(13.504, 24.246)
	Olo 10ug	221.760 (2.040)	18.917 (2.723)	<.0001	(13.570, 24.265)
3	Placebo	202.648 (2.211)			
	Olo 5ug	223.125 (2.237)	20.477 (2.965)	<.0001	(14.654, 26.301)
	Olo 10ug	222.969 (2.211)	20.321 (2.952)	<.0001	(14.523, 26.119)
4	Placebo	199.309 (2.352)			
	Olo 5ug	221.637 (2.379)	22.328 (3.154)	<.0001	(16.133, 28.523)
	Olo 10ug	221.125 (2.353)	21.816 (3.140)	<.0001	(15.648, 27.983)
5	Placebo	198.971 (2.376)			
	Olo 5ug	219.125 (2.404)	20.154 (3.187)	<.0001	(13.895, 26.414)
	Olo 10ug	219.048 (2.377)	20.077 (3.173)	<.0001	(13.845, 26.308)
6	Placebo	199.426 (2.510)			
	Olo 5ug	218.783 (2.539)	19.357 (3.366)	<.0001	(12.746, 25.969)
	Olo 10ug	217.210 (2.511)	17.784 (3.352)	<.0001	(11.202, 24.367)
7	Placebo	200.088 (2.600)			
	Olo 5ug	219.229 (2.630)	19.142 (3.487)	<.0001	(12.293, 25.990)
	Olo 10ug	219.062 (2.601)	18.974 (3.472)	<.0001	(12.156, 25.792)
8	Placebo	199.551 (2.689)			
	Olo 5ug	217.338 (2.720)	17.787 (3.606)	<.0001	(10.704, 24.870)
	Olo 10ug	217.477 (2.690)	17.926 (3.591)	<.0001	(10.874, 24.977)

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 (203), Olo 5ug (199), Olo 10ug (203)
Common baseline mean (SE): 204.872 (3.902)

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	199.107 (2.614)			
	Olo 5ug	216.173 (2.645)	17.066 (3.507)	<.0001	(10.180, 23.953)
	Olo 10ug	217.252 (2.615)	18.146 (3.491)	<.0001	(11.290, 25.002)
10	Placebo	198.390 (2.555)			
	Olo 5ug	216.449 (2.584)	18.059 (3.426)	<.0001	(11.330, 24.787)
	Olo 10ug	214.878 (2.555)	16.487 (3.411)	<.0001	(9.788, 23.186)
11	Placebo	198.461 (2.683)			
	Olo 5ug	214.090 (2.714)	15.629 (3.598)	<.0001	(8.563, 22.695)
	Olo 10ug	216.149 (2.683)	17.687 (3.582)	<.0001	(10.652, 24.722)
12	Placebo	198.766 (2.684)			
	Olo 5ug	216.437 (2.715)	17.671 (3.600)	<.0001	(10.601, 24.741)
	Olo 10ug	214.103 (2.685)	15.337 (3.584)	<.0001	(8.298, 22.376)
13	Placebo	197.917 (2.711)			
	Olo 5ug	216.281 (2.742)	18.364 (3.635)	<.0001	(11.224, 25.504)
	Olo 10ug	216.621 (2.711)	18.704 (3.619)	<.0001	(11.596, 25.812)
14	Placebo	196.715 (2.799)			
	Olo 5ug	215.577 (2.831)	18.861 (3.754)	<.0001	(11.489, 26.234)
	Olo 10ug	214.149 (2.800)	17.434 (3.737)	<.0001	(10.094, 24.774)
15	Placebo	194.161 (2.749)			
	Olo 5ug	215.218 (2.781)	21.057 (3.687)	<.0001	(13.815, 28.299)
	Olo 10ug	214.822 (2.750)	20.661 (3.671)	<.0001	(13.451, 27.871)
16	Placebo	193.172 (2.773)			
	Olo 5ug	213.224 (2.805)	20.052 (3.719)	<.0001	(12.749, 27.356)
	Olo 10ug	214.528 (2.774)	21.356 (3.702)	<.0001	(14.084, 28.627)

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 (203), Olo 5ug (199), Olo 10ug (203)
Common baseline mean (SE): 204.872 (3.902)

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	195.446 (2.912)			
	Olo 5ug	213.068 (2.946)	17.622 (3.906)	<.0001	(9.951, 25.293)
	Olo 10ug	211.897 (2.913)	16.452 (3.889)	<.0001	(8.815, 24.089)
18	Placebo	192.798 (2.887)			
	Olo 5ug	213.706 (2.920)	20.909 (3.871)	<.0001	(13.305, 28.512)
	Olo 10ug	214.435 (2.887)	21.637 (3.854)	<.0001	(14.067, 29.207)
19	Placebo	195.241 (2.929)			
	Olo 5ug	213.203 (2.963)	17.962 (3.928)	<.0001	(10.247, 25.677)
	Olo 10ug	213.503 (2.930)	18.262 (3.911)	<.0001	(10.581, 25.944)
20	Placebo	195.237 (2.892)			
	Olo 5ug	212.346 (2.925)	17.109 (3.878)	<.0001	(9.492, 24.726)
	Olo 10ug	211.740 (2.893)	16.504 (3.861)	<.0001	(8.920, 24.087)
21	Placebo	194.673 (2.960)			
	Olo 5ug	211.552 (2.994)	16.879 (3.970)	<.0001	(9.083, 24.675)
	Olo 10ug	210.368 (2.961)	15.695 (3.952)	<.0001	(7.934, 23.457)
22	Placebo	193.410 (2.938)			
	Olo 5ug	211.562 (2.973)	18.152 (3.941)	<.0001	(10.412, 25.892)
	Olo 10ug	209.997 (2.939)	16.587 (3.924)	<.0001	(8.881, 24.293)
23	Placebo	193.963 (2.932)			
	Olo 5ug	211.753 (2.966)	17.791 (3.932)	<.0001	(10.068, 25.513)
	Olo 10ug	210.153 (2.933)	16.190 (3.915)	<.0001	(8.501, 23.878)
24	Placebo	194.592 (3.001)			
	Olo 5ug	210.880 (3.036)	16.288 (4.025)	<.0001	(8.384, 24.192)
	Olo 10ug	208.447 (3.002)	13.856 (4.007)	0.0006	(5.986, 21.725)

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 (203), Olo 5ug (199), Olo 10ug (203)
Common baseline mean (SE): 204.872 (3.902)

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	195.216 (2.903)			
	Olo 5ug	212.290 (2.937)	17.073 (3.894)	<.0001	(9.426, 24.721)
	Olo 10ug	208.593 (2.904)	13.376 (3.877)	0.0006	(5.762, 20.990)
26	Placebo	195.249 (2.977)			
	Olo 5ug	212.821 (3.011)	17.572 (3.992)	<.0001	(9.732, 25.412)
	Olo 10ug	209.989 (2.977)	14.740 (3.975)	0.0002	(6.934, 22.546)
27	Placebo	195.579 (2.923)			
	Olo 5ug	212.857 (2.957)	17.278 (3.921)	<.0001	(9.578, 24.978)
	Olo 10ug	209.303 (2.924)	13.724 (3.904)	0.0005	(6.058, 21.391)
28	Placebo	195.124 (2.996)			
	Olo 5ug	212.338 (3.030)	17.214 (4.018)	<.0001	(9.324, 25.105)
	Olo 10ug	206.674 (2.997)	11.550 (4.000)	0.0040	(3.695, 19.406)
29	Placebo	194.136 (2.978)			
	Olo 5ug	212.638 (3.012)	18.502 (3.993)	<.0001	(10.659, 26.345)
	Olo 10ug	208.469 (2.978)	14.334 (3.976)	0.0003	(6.525, 22.142)
30	Placebo	192.952 (2.933)			
	Olo 5ug	210.775 (2.967)	17.823 (3.933)	<.0001	(10.099, 25.547)
	Olo 10ug	207.714 (2.933)	14.762 (3.916)	0.0002	(7.072, 22.453)
31	Placebo	191.794 (2.923)			
	Olo 5ug	209.016 (2.957)	17.221 (3.920)	<.0001	(9.523, 24.920)
	Olo 10ug	207.079 (2.924)	15.285 (3.903)	0.0001	(7.621, 22.950)
32	Placebo	189.785 (3.038)			
	Olo 5ug	210.988 (3.073)	21.203 (4.074)	<.0001	(13.201, 29.205)
	Olo 10ug	206.710 (3.039)	16.925 (4.057)	<.0001	(8.959, 24.892)

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 (203), Olo 5ug (199), Olo 10ug (203)
Common baseline mean (SE): 204.872 (3.902)

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	191.468 (3.042)			
	Olo 5ug	210.006 (3.077)	18.538 (4.079)	<.0001	(10.527, 26.550)
	Olo 10ug	207.299 (3.042)	15.831 (4.061)	0.0001	(7.855, 23.807)
34	Placebo	194.307 (3.022)			
	Olo 5ug	211.501 (3.057)	17.194 (4.053)	<.0001	(9.234, 25.154)
	Olo 10ug	205.366 (3.023)	11.058 (4.035)	0.0063	(3.133, 18.984)
35	Placebo	194.737 (2.995)			
	Olo 5ug	209.558 (3.030)	14.821 (4.017)	0.0002	(6.932, 22.710)
	Olo 10ug	206.003 (2.996)	11.265 (3.999)	0.0050	(3.411, 19.120)
36	Placebo	192.769 (3.036)			
	Olo 5ug	211.417 (3.071)	18.648 (4.072)	<.0001	(10.651, 26.644)
	Olo 10ug	206.690 (3.037)	13.921 (4.054)	0.0006	(5.960, 21.882)
37	Placebo	190.280 (3.036)			
	Olo 5ug	211.223 (3.071)	20.943 (4.072)	<.0001	(12.946, 28.940)
	Olo 10ug	206.333 (3.037)	16.053 (4.054)	<.0001	(8.092, 24.015)
38	Placebo	191.860 (3.029)			
	Olo 5ug	209.490 (3.064)	17.630 (4.062)	<.0001	(9.652, 25.608)
	Olo 10ug	207.996 (3.030)	16.136 (4.044)	<.0001	(8.193, 24.079)
39	Placebo	192.697 (3.120)			
	Olo 5ug	211.314 (3.157)	18.616 (4.185)	<.0001	(10.398, 26.835)
	Olo 10ug	207.743 (3.121)	15.046 (4.167)	0.0003	(6.864, 23.229)
40	Placebo	192.432 (3.142)			
	Olo 5ug	211.274 (3.179)	18.842 (4.214)	<.0001	(10.565, 27.118)
	Olo 10ug	206.273 (3.143)	13.841 (4.196)	0.0010	(5.601, 22.081)

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 (203), Olo 5ug (199), Olo 10ug (203)
Common baseline mean (SE): 204.872 (3.902)

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	193.001 (3.125)			
	Olo 5ug	209.732 (3.161)	16.731 (4.191)	<.0001	(8.499, 24.963)
	Olo 10ug	206.088 (3.126)	13.087 (4.173)	0.0018	(4.891, 21.282)
42	Placebo	194.048 (3.091)			
	Olo 5ug	209.312 (3.127)	15.264 (4.145)	0.0003	(7.123, 23.406)
	Olo 10ug	204.554 (3.092)	10.506 (4.127)	0.0112	(2.400, 18.611)
43	Placebo	192.865 (3.194)			
	Olo 5ug	209.728 (3.231)	16.863 (4.284)	<.0001	(8.450, 25.276)
	Olo 10ug	206.699 (3.195)	13.834 (4.265)	0.0012	(5.458, 22.210)
44	Placebo	191.801 (3.178)			
	Olo 5ug	208.992 (3.215)	17.191 (4.263)	<.0001	(8.819, 25.563)
	Olo 10ug	204.806 (3.179)	13.005 (4.244)	0.0023	(4.670, 21.340)
45	Placebo	191.747 (3.169)			
	Olo 5ug	208.040 (3.206)	16.293 (4.251)	0.0001	(7.945, 24.641)
	Olo 10ug	204.475 (3.170)	12.728 (4.232)	0.0027	(4.417, 21.039)
46	Placebo	191.160 (3.196)			
	Olo 5ug	208.181 (3.233)	17.021 (4.286)	<.0001	(8.604, 25.438)
	Olo 10ug	204.491 (3.197)	13.331 (4.267)	0.0019	(4.951, 21.712)
47	Placebo	190.877 (3.177)			
	Olo 5ug	207.723 (3.214)	16.846 (4.262)	<.0001	(8.477, 25.216)
	Olo 10ug	204.940 (3.178)	14.063 (4.243)	0.0010	(5.731, 22.396)
48	Placebo	190.676 (3.165)			
	Olo 5ug	207.862 (3.202)	17.186 (4.245)	<.0001	(8.849, 25.523)
	Olo 10ug	205.236 (3.166)	14.560 (4.226)	0.0006	(6.259, 22.860)

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 (203), Olo 5ug (199), Olo 10ug (203)
Common baseline mean (SE): 204.872 (3.902)

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