Boehringer Ingelheim

Clinical Study Synopsis for Public Disclosure

This clinical study synopsis is provided in line with **Boehringer Ingelheim's *Policy on Transparency and Publication of Clinical Study Data***.

The synopsis - which is part of the clinical study report - had been prepared in accordance with best practice and applicable legal and regulatory requirements at the time of study completion.

The synopsis may include approved and non-approved uses, doses, formulations, treatment regimens and/or age groups; it has not necessarily been submitted to regulatory authorities.

A synopsis is not intended to provide a comprehensive analysis of all data currently available regarding a particular drug. More current information regarding a drug is available in the approved labeling information which may vary from country to country..

Additional information on this study and the drug concerned may be provided upon request based on **Boehringer Ingelheim's Policy on Transparency and Publication of Clinical Study Data**.

Name of company: Boehringer Ingelheim		**Tabulated Trial Report**	Boehringer Ingelheim
Name of finished product: Not applicable		**EudraCT No.:** 2008-001933-84	
Name of active ingredient: Olodaterol (BI 1744)		**Page:** 1 of 10	**Synopsis No.:**
Module:		**Volume:**	
Report date: 27 Jan 2012	**Trial No. / U No.:** 1222.13/ U10-3194-01	**Date of trial:** 03 Feb 2009 – 02 Dec 2010	**Date of revision:** Not applicable

Title of trial:	A randomised, double-blind, double-dummy, 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, and 48 weeks of twice daily Foradil® (12 µg) delivered by the Aerolizer® 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
Objectives:	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]) delivered via the Respimat® inhaler in patients with COPD
Methodology:	Randomised, double-blind, double-dummy, placebo-controlled, active-comparator, parallel group design

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No. of subjects:	
planned:	entered: 860 (215 per treatment group)
actual:	enrolled: 1212; entered/randomized: 906; treated: 904 Placebo: treated: 225 • analyzed for co-primary endpoint forced expiratory volume in 1 second (FEV_1) area under the curve (AUC) over 0 to 3 hours ($_{0\text{-}3h}$) response at Day 169: 217 • analyzed for co-primary endpoint trough FEV_1 response at Day 169: 205 olodaterol 5 µg: treated: 227 • analyzed for co-primary endpoint FEV_1 $AUC_{0\text{-}3h}$ response at Day 169: 222 • analyzed for co-primary endpoint trough FEV_1 response at Day 169: 220 olodaterol 10 µg: treated: 225 • analyzed for co-primary endpoint FEV_1 $AUC_{0\text{-}3h}$ response at Day 169: 223 • analyzed for co-primary endpoint trough FEV_1 response at Day 169: 219 Foradil® 12 µg bid: treated: 227 • analyzed for co-primary endpoint FEV_1 $AUC_{0\text{-}3h}$ response at Day 169: 223 • analyzed for co-primary endpoint trough FEV_1 response at Day 169: 215
Diagnosis and main criteria for inclusion:	Male or female outpatients, 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 5.0 µg]) once daily (calculated as free base)
mode of admin.:	Oral inhalation
batch no.:	2.5 µg/actuation: B082000026, B072000346 5.0 µg/actuation: B082000029, B072000356

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Reference therapy 1:	Placebo inhalation matching olodaterol
dose:	Not applicable (N/A)
mode of admin.:	Oral inhalation
batch no.:	B082000022, B082000136, B082000080, B102000047
Reference therapy 2:	Foradil® - Aerolizer®
dose:	12 µg twice daily
mode of admin.:	Oral inhalation
batch no.:	B082000081, B082000207, B082000271, B092000044, B092000081, B082000184, B092000063, B102000031, B082000260, B092000024
Reference therapy 3:	Placebo inhalation matching Foradil® - Aerolizer®
dose:	N/A
mode of admin.:	Oral inhalation
batch no.:	B082000046, B082000098, B082000281, B092000046, B102000028
Duration of treatment:	48 weeks
Criteria for evaluation:	
Efficacy / clinical pharmacology:	Efficacy parameters included: FEV_1 AUC_{0-3h} response; trough FEV_1 response; Mahler TDI; St. George's Respiratory Questionnaire (SGRQ); FEV_1 $peak_{0-3h}$ response; FVC AUC_{0-3h} response; trough FVC response; FVC $peak_{0-3h}$ response; FEV_1 and FVC at individual time points; morning and evening peak expiratory flow rate (PEFR); daytime, night time, 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. Pharmacokinetics (PK) was assessed by plasma concentrations of olodaterol. Systemic pharmacodynamics (PD) was assessed using blood values of potassium.

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Safety:	Adverse events (including physical examination), vital signs, laboratory evaluations, electrocardiogram (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:

Efficacy results presented in this report, based on analyses of the data from Study 1222.13 only, are restricted to lung function (FEV_1 and FVC) (comparisons to placebo), PEFR, rescue medication use, PGR and COPD exacerbations.

Efficacy results for the (i) Mahler TDI focal score (co-primary endpoint), (ii) SGRQ total score (key secondary endpoint), (iii) comparisons between olodaterol and Foradil® (FEV_1 AUC_{0-3h} response at Day 169, trough FEV_1 response at Day 169, Mahler TDI focal score) (key secondary endpoints), and (iv) Mahler Dyspnoea Indices component scores and SGRQ component scores over 48 weeks (other secondary endpoints), which are based on pre-specified analyses of the combined dataset from Study 1222.13 and the replicate Study 1222.14, are described in a separate report (Study 1222.9993).

Co-primary endpoints (lung function):

- Treatment with 5 µg and 10 µg olodaterol resulted in statistically significant improvement in FEV_1 AUC_{0-3h} response compared with placebo at Day 169 (Week 24): differences were 0.151 L (0.142 vs. -0.009 L) for 5 µg olodaterol and 0.165 L (0.156 vs. -0.009 L) for 10 µg olodaterol compared to placebo ($p<0.0001$ for both doses). A statistically significant increase was also observed for 12 µg Foradil® compared with placebo (0.177 L difference [0.168 vs. -0.009 L], $p<0.0001$).

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Efficacy/clinical pharmacology (cont'd):

- Treatment with 5 µg and 10 µg olodaterol resulted in statistically significant improvement in trough FEV_1 response compared with placebo at Day 169 (Week 24): differences were 0.078 L (0.021 vs. -0.056 L) for 5 µg olodaterol and 0.085 L (0.028 vs. -0.056 L) for 10 µg olodaterol compared to placebo ($p \leq 0.0002$ for both doses). A statistically significant increase was also observed for 12 µg Foradil® compared with placebo (0.054 L difference [-0.002 vs. -0.056 L], p=0.0088).

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% of 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 (1222.13) and the replicate study 1222.14 is presented in a separate report (Study 1222.9993).

Key secondary endpoints:

As described above, analyses of key secondary endpoints are described in a separate report (Study 1222.9993).

Other secondary endpoints:

Supportive analyses of lung function (FEV_1 and FVC) over the 48-week treatment period were generally consistent with the primary analyses for both olodaterol doses (5 µg and 10 µg). Statistically significant increases were observed in the active treatment groups (both olodaterol dose groups and 12 µg Foradil®) compared to placebo ($p<0.0001$ to p=0.0455) for the following secondary endpoints:

- FEV_1 $AUC_{0\text{-}3h}$ response and FEV_1 $peak_{0\text{-}3h}$ response (all three active treatment groups compared to placebo on all test days).

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Efficacy/clinical pharmacology (cont'd):

- Trough FEV_1 response (all three active treatment groups compared to placebo on all test days, with exception of Day 281 where none of the increases observed in the three active treatment groups compared to placebo achieved statistical significance).
- Adjusted mean FEV_1 for each individual time point (all three active treatment groups compared to placebo on all test days where PFTs were performed post-dose).
- FVC $AUC_{0\text{-}3h}$ response and FVC $peak_{0\text{-}3h}$ response (all three active treatment groups compared to placebo on all test days).
- Trough FVC response (variable test days in all three active treatment groups: 10 µg olodaterol [Days 15, 43, 85, and 169], 5 µg olodaterol [Days 43, 85, and 337], and 12 µg Foradil® [Days 15, 43, and 85]).
- Adjusted mean FVC for each individual time point (all three active treatment groups compared to placebo on all test days where PFTs were performed post-dose).

Consistent with primary and secondary analyses which demonstrate improvement in lung function up to 48 weeks, patients also demonstrated improved PEFR, reduced use of rescue medication, and improvement in overall respiratory condition (PGR) during the trial:

- Statistically significant improvement in morning PEFR compared to placebo was observed for the majority of all time points over 48 weeks in the 5 µg olodaterol group and all time points in 10 µg olodaterol and 12 µg Foradil® treatment groups. Statistically significant improvement was observed in evening PEFR for all time points over 48 weeks in all three active treatment groups.

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Efficacy/clinical pharmacology (cont'd):

- Treatment with 5 µg and 10 µg olodaterol resulted in a statistically significant reduction in mean daytime, night time, and daily (24-hour) use of rescue medication (open-label salbutamol) compared to placebo from Week 1 through Week 48. Although weekly mean daytime, night time, and daily (24-hour) rescue medication use in the 12 µg Foradil® treatment group was also reduced compared to placebo, the magnitude of the reduction was consistently less than the reduction observed in both olodaterol dose groups and statistically significant reductions were not observed at all time points.
- As rated on the PGR, improvement in respiratory condition was shown to be statistically significantly greater in both olodaterol dose groups compared to placebo up to 24 weeks (as assessed at Weeks 6, 12, and 24) but not after 48 weeks (as assessed at Week 48). Similar improvement was shown in the 12 µg Foradil® group (compared to placebo) up to 12 weeks.

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 either olodaterol or 12 µg Foradil®. The hazard ratios for mean time to first COPD exacerbation compared to placebo were 1.162 (p=0.3424) in the 5 µg olodaterol dose group, 1.186 (p=0.3023) in the 10 µg olodaterol dose group, and 0.854 (p=0.3589) in the 12 µg Foradil® group. There were no statistically significant differences between any of the three active treatment groups compared to placebo in the mean number of COPD exacerbations, moderate COPD exacerbations, and COPD exacerbations leading to hospitalization per patient year.

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Efficacy/clinical pharmacology (cont'd):	**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 (7.25 pg/mL) was 1.7-fold higher than that of the olodaterol 5 µg treatment group (4.18 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=176) than in the olodaterol 10 µg treatment group (N=43). 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. There was no evidence of a relationship between blood potassium levels and the olodaterol plasma concentrations achieved after daily inhalations of 5 or 10 µg olodaterol. Olodaterol plasma concentrations in Asians tended to be slightly higher than in Whites.
Safety results:	In this 48-week study, long-term administration of inhaled olodaterol was generally safe and well tolerated and no safety concerns were identified: The percentage of patients who experienced at least one AE was comparable in all four treatment groups: placebo (68.0%), 5 µg olodaterol (70.5%), 10 µg olodaterol (72.9%), and 12 µg Foradil® (65.6%). The most common AEs were COPD (reported terms: exacerbation, worsening, or deterioration of COPD) (30.3%), nasopharyngitis (9.4%), and upper respiratory tract infection (6.1%). The overall incidence of severe (10.3%) and drug-related (7.7%) AEs was low and generally comparable between the four treatment groups. A total of 26 deaths occurred during the study (25 patients in the treated set and 1 patient who was randomized but not treated). In the treated set, 17 patients experienced AEs that led to death during treatment (4 patients [placebo], 3 patients [5 µg olodaterol], 6 patients [10 µg olodaterol], and 4 patients [12 µg Foradil®]); 4 patients experienced AEs that led to death with onset during the post-treatment period (2 patients [5 µg olodaterol], 2 patients [12 µg Foradil®]); and 4 patients experienced AEs that led to death with onset

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Safety results (cont'd)

during the post-study period (all 4 patients had received placebo during the treatment period). Three of the 4 post-study fatal events were reported as a result of vital status follow up within the planned observation period. The fourth patient experienced a fatal SAE of myocardial infarction that was programmatically categorized as a post-study fatal event, although the event was later determined to have actually occurred while the patient was on treatment with placebo. Of the 26 patients who experienced fatal events, one patient (placebo group) experienced a fatal event (myocardial infarction, as above) that was considered by the Investigator to be related to trial medication.

A total of 123/904 patients (13.6%) reported at least one SAE during the study (placebo [31 patients, 13.8%], 5 µg olodaterol [33 patients, 14.5%], 10 µg olodaterol [26 patients, 11.6%], and 12 µg Foradil® [33 patients, 14.5%]). SAEs that occurred in more than 2 patients overall were COPD (41 patients, 4.5%), pneumonia (18 patients, 2.0%), gastroenteritis (4 patients, 0.4%), infective exacerbation of chronic obstructive airways (4 patients, 0.4%), atrial fibrillation (4 patients, 0.4%), and acute respiratory failure (4 patients, 0.4%).

A total of 8 patients had SAEs considered by the Investigator to be drug-related: 6 patients had SAEs considered related to trial medication (5 occurred on treatment and one was reported post-study) and 2 patients had SAEs considered exclusively related to study design procedures. SAEs considered by the Investigator to be related to trial medication included COPD (3 patients, 5 µg olodaterol), atrial fibrillation (1 patient, 12 µg Foradil®), and ECG QT prolonged, ECG T-wave inversion, and chest pain (all 3 events occurred in 1 patient, 12 µg Foradil®). The sixth patient experienced a fatal SAE of myocardial infarction that was programmatically categorized as a post-study fatal event and later determined to have occurred while on treatment (see summary of deaths above). SAEs considered related to study design procedures included pneumonia (1 patient, 5 µg olodaterol) and a single event of COPD (exacerbation) that was reported during screening (1 patient, 12 µg Foradil®).

Sixty-five patients (7.2%) discontinued study drug due to at least one treatment-emergent AE (placebo [7.1%], 5 µg olodaterol [6.6%], 10 µg olodaterol [6.7%], and 12 µg Foradil® [8.4%]). AEs that resulted in study drug discontinuation

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Safety results (cont'd)	reported in 3 or more patients were COPD (23 patients, 2.5%), pneumonia (3 patients, 0.3%), and dyspnoea (3 patients, 0.3%). The frequency of discontinuation due to AEs of COPD (exacerbation) was 2.2%, 4.0%, 1.8%, 2.2% in the placebo, 5 µg olodaterol, 10 µg olodaterol, and 12 µg Foradil® treatment groups, respectively. There were no notable differences among the treatment groups in the occurrences of abnormalities in vital signs, laboratory parameters, ECG results, Holter monitoring, and physical examination findings. Slightly lower mean potassium levels were observed on Days 43 and 85 (1 hour and 3 hours post dose) for all three active treatment groups compared with placebo (range: -0.035 mmol/L to -0.099 mmol/L), reaching statistical significance at 3 hours post dose on Day 85 for both olodaterol doses and 1 hour post dose for 12 µg Foradil®. The comprehensive analysis for ECG evaluations and the Holter monitoring data was based on data from this trial and the replicate trial (Study 1222.14). Results of the combined analysis are presented in the separate combined report (Study 1222.9993).
Conclusions:	With respect to lung function, 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_{0-3} response at Day 169 and trough FEV_1 response at Day 169. Conclusions regarding the assessment of symptomatic benefit are presented in a separate combined report (Study 1222.9993). 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 results of 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 $AUC_{0\text{-}3h}$ on test days 1, 15, 43, 85, 169, and 337	Table 15.2.1.1.2: 1
FEV_1 $peak_{0\text{-}3h}$ on test days 1, 15, 43, 85, 169, and 337	Table 15.2.1.1.4: 1
Trough FEV_1 on test days 15, 43, 85, 127, 169, 225, and 337	Table 15.2.1.1.3: 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 $AUC_{0\text{-}3h}$ on test days 1, 15, 43, 85, 169, and 337	Table 15.2.1.2.2: 2
FVC $peak_{0\text{-}3h}$ on test days 1, 15, 43, 85, 169, and 337	Table 15.2.1.2.4: 1
Trough FVC on test days 15, 43, 85, 127, 169, 225, and 337	Table 15.2.1.2.3: 1
FVC at all time points on days 1, 15, 43, 85, 127, 169, 225, 281, and 337	Table 15.2.1.2.1: 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	Form 12ug	Total
Enrolled					1212
Not entered/randomised					306
Entered/randomised					906
Not treated					2
Treated	225(100.00)	227(100.00)	225(100.00)	227(100.00)	904(100.00)
Not prematurely discontinued from trial medication #	168(74.67)	191(84.14)	186(82.67)	184(81.06)	729(80.64)
Prematurely discontinued from trial medication	57(25.33)	36(15.86)	39(17.33)	43(18.94)	175(19.36)
Adverse event	18(8.00)	16(7.05)	15(6.67)	20(8.81)	69(7.63)
AE study dis. worse	7(3.11)	11(4.85)	4(1.78)	4(1.76)	26(2.88)
AE-oth. dis. worse	0(0.00)	2(0.88)	0(0.00)	2(0.88)	4(0.44)
AE-other	11(4.89)	3(1.32)	11(4.89)	14(6.17)	39(4.31)
Lack of efficacy	9(4.00)	2(0.88)	1(0.44)	3(1.32)	15(1.66)
Non compl prot.	2(0.89)	3(1.32)	2(0.89)	3(1.32)	10(1.11)
Lost to follow-up	2(0.89)	2(0.88)	4(1.78)	0(0.00)	8(0.88)
Consent withdrawn	20(8.89)	9(3.96)	11(4.89)	14(6.17)	54(5.97)
Other	6(2.67)	4(1.76)	6(2.67)	3(1.32)	19(2.10)

Includes Patient [redacted] who withdrew consent prior to dosing and Patient [redacted] who was withdrawn due to inability to perform spirometry.

Source data: Appendix 16.2, Listing 1.1 ctr\eot-t20-disp.sas 11OCT2011

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	0.030 (0.015)			
	Olo 5ug	0.198 (0.015)	0.168 (0.020)	<.0001	(0.128, 0.208)
	Olo 10ug	0.198 (0.015)	0.168 (0.020)	<.0001	(0.129, 0.208)
	Form 12ug	0.207 (0.015)	0.177 (0.020)	<.0001	(0.138, 0.217)
15	Placebo	0.015 (0.015)			
	Olo 5ug	0.201 (0.015)	0.186 (0.020)	<.0001	(0.146, 0.226)
	Olo 10ug	0.181 (0.015)	0.166 (0.020)	<.0001	(0.126, 0.206)
	Form 12ug	0.221 (0.015)	0.206 (0.020)	<.0001	(0.166, 0.246)
43	Placebo	0.001 (0.015)			
	Olo 5ug	0.178 (0.015)	0.176 (0.021)	<.0001	(0.136, 0.217)
	Olo 10ug	0.161 (0.015)	0.160 (0.021)	<.0001	(0.119, 0.200)
	Form 12ug	0.194 (0.015)	0.192 (0.021)	<.0001	(0.152, 0.233)
85	Placebo	-0.003 (0.015)			
	Olo 5ug	0.176 (0.015)	0.178 (0.021)	<.0001	(0.137, 0.219)
	Olo 10ug	0.167 (0.015)	0.170 (0.021)	<.0001	(0.129, 0.211)
	Form 12ug	0.182 (0.015)	0.185 (0.021)	<.0001	(0.144, 0.226)
169	Placebo	-0.009 (0.016)			
	Olo 5ug	0.142 (0.015)	0.151 (0.021)	<.0001	(0.110, 0.193)
	Olo 10ug	0.156 (0.015)	0.165 (0.021)	<.0001	(0.124, 0.206)
	Form 12ug	0.168 (0.015)	0.177 (0.021)	<.0001	(0.136, 0.218)
337	Placebo	-0.023 (0.016)			
	Olo 5ug	0.122 (0.015)	0.145 (0.021)	<.0001	(0.103, 0.186)
	Olo 10ug	0.123 (0.015)	0.146 (0.021)	<.0001	(0.105, 0.188)
	Form 12ug	0.149 (0.015)	0.172 (0.021)	<.0001	(0.130, 0.214)

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 (217), Olo 5ug (222), Olo 10ug (223), Form 12ug (223)
Common baseline mean (SE): 1.204 (0.016)

Source data: Appendix 16.1.9.2, Statdoc 6.1.1.2.1 ctr\pft-adjmean-mmrm.sas 13OCT2011

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	0.110 (0.016)			
	Olo 5ug	0.273 (0.016)	0.163 (0.022)	<.0001	(0.121, 0.205)
	Olo 10ug	0.270 (0.016)	0.160 (0.021)	<.0001	(0.118, 0.202)
	Form 12ug	0.280 (0.016)	0.170 (0.021)	<.0001	(0.128, 0.212)
15	Placebo	0.100 (0.016)			
	Olo 5ug	0.277 (0.016)	0.177 (0.022)	<.0001	(0.135, 0.220)
	Olo 10ug	0.250 (0.016)	0.150 (0.022)	<.0001	(0.108, 0.193)
	Form 12ug	0.290 (0.016)	0.190 (0.022)	<.0001	(0.148, 0.233)
43	Placebo	0.081 (0.016)			
	Olo 5ug	0.248 (0.016)	0.166 (0.022)	<.0001	(0.124, 0.209)
	Olo 10ug	0.234 (0.016)	0.152 (0.022)	<.0001	(0.109, 0.195)
	Form 12ug	0.264 (0.016)	0.182 (0.022)	<.0001	(0.139, 0.226)
85	Placebo	0.082 (0.016)			
	Olo 5ug	0.247 (0.016)	0.165 (0.022)	<.0001	(0.122, 0.208)
	Olo 10ug	0.241 (0.016)	0.159 (0.022)	<.0001	(0.116, 0.203)
	Form 12ug	0.256 (0.016)	0.174 (0.022)	<.0001	(0.130, 0.218)
169	Placebo	0.068 (0.017)			
	Olo 5ug	0.216 (0.016)	0.148 (0.022)	<.0001	(0.104, 0.191)
	Olo 10ug	0.225 (0.016)	0.156 (0.022)	<.0001	(0.112, 0.200)
	Form 12ug	0.236 (0.016)	0.167 (0.022)	<.0001	(0.123, 0.211)
337	Placebo	0.053 (0.017)			
	Olo 5ug	0.192 (0.016)	0.139 (0.023)	<.0001	(0.095, 0.183)
	Olo 10ug	0.193 (0.016)	0.140 (0.023)	<.0001	(0.095, 0.184)
	Form 12ug	0.215 (0.016)	0.162 (0.023)	<.0001	(0.117, 0.206)

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 (217), Olo 5ug (222), Olo 10ug (223), Form 12ug (223)
Common baseline mean (SE): 1.204 (0.016)

Source data: Appendix 16.1.9.2, Statdoc 6.1.1.4.1 ctr\pft-adjmean-mmrm.sas 13OCT2011

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 (0.015)			
	Olo 5ug	0.068 (0.014)	0.087 (0.020)	<.0001	(0.048, 0.126)
	Olo 10ug	0.060 (0.014)	0.079 (0.020)	<.0001	(0.040, 0.118)
	Form 12ug	0.061 (0.014)	0.080 (0.020)	<.0001	(0.040, 0.119)
43	Placebo	-0.037 (0.015)			
	Olo 5ug	0.049 (0.014)	0.086 (0.020)	<.0001	(0.047, 0.125)
	Olo 10ug	0.041 (0.014)	0.078 (0.020)	0.0001	(0.038, 0.117)
	Form 12ug	0.042 (0.014)	0.079 (0.020)	<.0001	(0.039, 0.119)
85	Placebo	-0.027 (0.015)			
	Olo 5ug	0.056 (0.014)	0.083 (0.020)	<.0001	(0.043, 0.123)
	Olo 10ug	0.048 (0.014)	0.075 (0.020)	0.0002	(0.035, 0.114)
	Form 12ug	0.033 (0.015)	0.059 (0.020)	0.0037	(0.019, 0.100)
127	Placebo	-0.019 (0.015)			
	Olo 5ug	0.046 (0.014)	0.065 (0.020)	0.0016	(0.025, 0.105)
	Olo 10ug	0.026 (0.015)	0.045 (0.020)	0.0276	(0.005, 0.085)
	Form 12ug	0.023 (0.015)	0.042 (0.021)	0.0426	(0.001, 0.082)
169	Placebo	-0.056 (0.015)			
	Olo 5ug	0.021 (0.015)	0.078 (0.021)	0.0002	(0.037, 0.118)
	Olo 10ug	0.028 (0.015)	0.085 (0.021)	<.0001	(0.044, 0.125)
	Form 12ug	-0.002 (0.015)	0.054 (0.021)	0.0088	(0.014, 0.095)
225	Placebo	-0.023 (0.015)			
	Olo 5ug	0.023 (0.015)	0.047 (0.021)	0.0237	(0.006, 0.087)
	Olo 10ug	0.026 (0.015)	0.049 (0.021)	0.0175	(0.009, 0.090)
	Form 12ug	0.021 (0.015)	0.044 (0.021)	0.0339	(0.003, 0.085)

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 (220), Olo 10ug (219), Form 12ug (215)
Common baseline mean (SE): 1.204 (0.016)

Source data: Appendix 16.1.9.2, Statdoc 6.1.1.3.1 ctr\pft-adjmean-mmrm.sas 13OCT2011

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
281	Placebo	-0.020 (0.016)			
	Olo 5ug	0.020 (0.015)	0.040 (0.021)	0.0537	(-0.001, 0.081)
	Olo 10ug	0.017 (0.015)	0.037 (0.021)	0.0808	(-0.004, 0.078)
	Form 12ug	0.004 (0.015)	0.024 (0.021)	0.2579	(-0.017, 0.065)
337	Placebo	-0.065 (0.015)			
	Olo 5ug	0.003 (0.015)	0.068 (0.021)	0.0011	(0.027, 0.109)
	Olo 10ug	-0.009 (0.015)	0.057 (0.021)	0.0069	(0.016, 0.098)
	Form 12ug	-0.006 (0.015)	0.059 (0.021)	0.0047	(0.018, 0.101)

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 (220), Olo 10ug (219), Form 12ug (215)
Common baseline mean (SE): 1.204 (0.016)

Source data: Appendix 16.1.9.2, Statdoc 6.1.1.3.1 ctr\pft-adjmean-mmrm.sas 13OCT2011

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	1.195 (0.016)			
		Olo 5ug	1.195 (0.016)			
		Olo 10ug	1.195 (0.016)			
		Form 12ug	1.195 (0.016)			
	-0:10	Placebo	1.212 (0.016)			
		Olo 5ug	1.212 (0.016)			
		Olo 10ug	1.212 (0.016)			
		Form 12ug	1.212 (0.016)			
	0:05	Placebo	1.226 (0.014)			
		Olo 5ug	1.340 (0.014)	0.114 (0.019)	<.0001	(0.077, 0.152)
		Olo 10ug	1.337 (0.014)	0.111 (0.019)	<.0001	(0.074, 0.148)
		Form 12ug	1.357 (0.014)	0.131 (0.019)	<.0001	(0.094, 0.169)
	0:15	Placebo	1.235 (0.015)			
		Olo 5ug	1.380 (0.014)	0.145 (0.020)	<.0001	(0.106, 0.184)
		Olo 10ug	1.371 (0.014)	0.136 (0.020)	<.0001	(0.097, 0.175)
		Form 12ug	1.389 (0.014)	0.153 (0.020)	<.0001	(0.114, 0.192)
	0:30	Placebo	1.243 (0.015)			
		Olo 5ug	1.395 (0.015)	0.153 (0.020)	<.0001	(0.113, 0.193)
		Olo 10ug	1.391 (0.015)	0.149 (0.020)	<.0001	(0.109, 0.189)
		Form 12ug	1.402 (0.015)	0.160 (0.020)	<.0001	(0.120, 0.200)
	1:00	Placebo	1.227 (0.015)			
		Olo 5ug	1.406 (0.015)	0.178 (0.021)	<.0001	(0.137, 0.220)
		Olo 10ug	1.400 (0.015)	0.172 (0.021)	<.0001	(0.131, 0.214)
		Form 12ug	1.418 (0.015)	0.190 (0.021)	<.0001	(0.149, 0.232)

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 (217), Olo 5ug (222), Olo 10ug (223), Form 12ug (223)
Common baseline mean (SE): 1.204 (0.016)

Source data: Appendix 16.1.9.2, Statdoc 6.1.1.1.1 ctr\pft-adjmean-mmrm-time.sas 13OCT2011

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	2:00	Placebo	1.247 (0.016)			
		Olo 5ug	1.426 (0.015)	0.179 (0.021)	<.0001	(0.137, 0.221)
		Olo 10ug	1.433 (0.015)	0.186 (0.021)	<.0001	(0.144, 0.228)
		Form 12ug	1.440 (0.015)	0.192 (0.021)	<.0001	(0.151, 0.234)
	3:00	Placebo	1.254 (0.016)			
		Olo 5ug	1.434 (0.016)	0.180 (0.022)	<.0001	(0.138, 0.223)
		Olo 10ug	1.436 (0.016)	0.183 (0.022)	<.0001	(0.140, 0.225)
		Form 12ug	1.431 (0.016)	0.177 (0.022)	<.0001	(0.134, 0.220)
15	-0:10	Placebo	1.196 (0.015)			
		Olo 5ug	1.282 (0.014)	0.086 (0.020)	<.0001	(0.047, 0.126)
		Olo 10ug	1.275 (0.014)	0.079 (0.020)	0.0001	(0.039, 0.118)
		Form 12ug	1.276 (0.015)	0.080 (0.020)	<.0001	(0.040, 0.119)
	0:05	Placebo	1.212 (0.014)			
		Olo 5ug	1.353 (0.014)	0.141 (0.019)	<.0001	(0.104, 0.179)
		Olo 10ug	1.337 (0.014)	0.125 (0.019)	<.0001	(0.087, 0.163)
		Form 12ug	1.387 (0.014)	0.175 (0.019)	<.0001	(0.137, 0.213)
	0:15	Placebo	1.214 (0.015)			
		Olo 5ug	1.380 (0.014)	0.167 (0.020)	<.0001	(0.127, 0.206)
		Olo 10ug	1.364 (0.014)	0.150 (0.020)	<.0001	(0.111, 0.190)
		Form 12ug	1.413 (0.015)	0.199 (0.020)	<.0001	(0.160, 0.239)
	0:30	Placebo	1.225 (0.015)			
		Olo 5ug	1.399 (0.015)	0.174 (0.021)	<.0001	(0.134, 0.215)
		Olo 10ug	1.378 (0.015)	0.154 (0.021)	<.0001	(0.113, 0.194)
		Form 12ug	1.427 (0.015)	0.202 (0.021)	<.0001	(0.162, 0.243)

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 (217), Olo 5ug (222), Olo 10ug (223), Form 12ug (223)
Common baseline mean (SE): 1.204 (0.016)

Source data: Appendix 16.1.9.2, Statdoc 6.1.1.1.1 ctr\pft-adjmean-mmrm-time.sas 13OCT2011

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	1:00	Placebo	1.221 (0.016)			
		Olo 5ug	1.409 (0.015)	0.189 (0.021)	<.0001	(0.147, 0.230)
		Olo 10ug	1.395 (0.015)	0.175 (0.021)	<.0001	(0.133, 0.217)
		Form 12ug	1.445 (0.015)	0.224 (0.021)	<.0001	(0.183, 0.266)
	2:00	Placebo	1.236 (0.016)			
		Olo 5ug	1.433 (0.015)	0.197 (0.022)	<.0001	(0.155, 0.240)
		Olo 10ug	1.410 (0.016)	0.174 (0.022)	<.0001	(0.131, 0.216)
		Form 12ug	1.440 (0.016)	0.204 (0.022)	<.0001	(0.161, 0.246)
	3:00	Placebo	1.225 (0.016)			
		Olo 5ug	1.421 (0.016)	0.196 (0.022)	<.0001	(0.153, 0.239)
		Olo 10ug	1.403 (0.016)	0.178 (0.022)	<.0001	(0.135, 0.221)
		Form 12ug	1.432 (0.016)	0.207 (0.022)	<.0001	(0.164, 0.250)
43	-1:00	Placebo	1.170 (0.015)			
		Olo 5ug	1.248 (0.014)	0.077 (0.020)	<.0001	(0.039, 0.116)
		Olo 10ug	1.249 (0.014)	0.079 (0.020)	<.0001	(0.040, 0.117)
		Form 12ug	1.242 (0.014)	0.071 (0.020)	0.0003	(0.033, 0.110)
	-0:10	Placebo	1.181 (0.015)			
		Olo 5ug	1.277 (0.014)	0.096 (0.020)	<.0001	(0.056, 0.135)
		Olo 10ug	1.260 (0.014)	0.079 (0.020)	0.0001	(0.039, 0.118)
		Form 12ug	1.268 (0.015)	0.087 (0.020)	<.0001	(0.047, 0.127)
	0:05	Placebo	1.187 (0.014)			
		Olo 5ug	1.339 (0.014)	0.152 (0.019)	<.0001	(0.113, 0.190)
		Olo 10ug	1.320 (0.014)	0.133 (0.019)	<.0001	(0.095, 0.171)
		Form 12ug	1.367 (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 (217), Olo 5ug (222), Olo 10ug (223), Form 12ug (223)
Common baseline mean (SE): 1.204 (0.016)

Source data: Appendix 16.1.9.2, Statdoc 6.1.1.1.1 ctr\pft-adjmean-mmrm-time.sas 13OCT2011

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	0:15	Placebo	1.183 (0.015)			
		Olo 5ug	1.367 (0.014)	0.183 (0.020)	<.0001	(0.144, 0.223)
		Olo 10ug	1.341 (0.015)	0.157 (0.020)	<.0001	(0.117, 0.197)
		Form 12ug	1.387 (0.015)	0.203 (0.020)	<.0001	(0.163, 0.243)
	0:30	Placebo	1.198 (0.015)			
		Olo 5ug	1.380 (0.015)	0.182 (0.021)	<.0001	(0.141, 0.223)
		Olo 10ug	1.354 (0.015)	0.156 (0.021)	<.0001	(0.115, 0.197)
		Form 12ug	1.402 (0.015)	0.204 (0.021)	<.0001	(0.163, 0.245)
	1:00	Placebo	1.202 (0.016)			
		Olo 5ug	1.379 (0.015)	0.178 (0.021)	<.0001	(0.135, 0.220)
		Olo 10ug	1.362 (0.015)	0.161 (0.021)	<.0001	(0.119, 0.203)
		Form 12ug	1.407 (0.016)	0.205 (0.022)	<.0001	(0.163, 0.248)
	2:00	Placebo	1.232 (0.016)			
		Olo 5ug	1.418 (0.016)	0.186 (0.022)	<.0001	(0.143, 0.228)
		Olo 10ug	1.397 (0.016)	0.165 (0.022)	<.0001	(0.122, 0.207)
		Form 12ug	1.421 (0.016)	0.189 (0.022)	<.0001	(0.146, 0.232)
	3:00	Placebo	1.230 (0.016)			
		Olo 5ug	1.391 (0.016)	0.161 (0.022)	<.0001	(0.117, 0.204)
		Olo 10ug	1.382 (0.016)	0.152 (0.022)	<.0001	(0.108, 0.196)
		Form 12ug	1.396 (0.016)	0.165 (0.022)	<.0001	(0.121, 0.209)
85	-1:00	Placebo	1.176 (0.015)			
		Olo 5ug	1.255 (0.014)	0.079 (0.020)	<.0001	(0.040, 0.118)
		Olo 10ug	1.247 (0.014)	0.071 (0.020)	0.0004	(0.032, 0.110)
		Form 12ug	1.233 (0.014)	0.057 (0.020)	0.0045	(0.018, 0.096)

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 (217), Olo 5ug (222), Olo 10ug (223), Form 12ug (223)
Common baseline mean (SE): 1.204 (0.016)

Source data: Appendix 16.1.9.2, Statdoc 6.1.1.1.1 ctr\pft-adjmean-mmrm-time.sas 13OCT2011

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	-0:10	Placebo	1.194 (0.015)			
		Olo 5ug	1.284 (0.015)	0.089 (0.021)	<.0001	(0.049, 0.130)
		Olo 10ug	1.276 (0.015)	0.081 (0.021)	<.0001	(0.041, 0.122)
		Form 12ug	1.256 (0.015)	0.062 (0.021)	0.0027	(0.022, 0.103)
	0:05	Placebo	1.184 (0.015)			
		Olo 5ug	1.337 (0.014)	0.153 (0.020)	<.0001	(0.114, 0.192)
		Olo 10ug	1.336 (0.014)	0.152 (0.020)	<.0001	(0.113, 0.190)
		Form 12ug	1.364 (0.014)	0.180 (0.020)	<.0001	(0.141, 0.219)
	0:15	Placebo	1.190 (0.015)			
		Olo 5ug	1.361 (0.015)	0.171 (0.021)	<.0001	(0.130, 0.211)
		Olo 10ug	1.353 (0.015)	0.163 (0.021)	<.0001	(0.123, 0.204)
		Form 12ug	1.370 (0.015)	0.180 (0.021)	<.0001	(0.140, 0.221)
	0:30	Placebo	1.200 (0.016)			
		Olo 5ug	1.371 (0.015)	0.170 (0.021)	<.0001	(0.129, 0.212)
		Olo 10ug	1.367 (0.015)	0.167 (0.021)	<.0001	(0.126, 0.208)
		Form 12ug	1.392 (0.015)	0.192 (0.021)	<.0001	(0.150, 0.233)
	1:00	Placebo	1.192 (0.016)			
		Olo 5ug	1.385 (0.015)	0.192 (0.022)	<.0001	(0.150, 0.235)
		Olo 10ug	1.367 (0.016)	0.175 (0.022)	<.0001	(0.132, 0.218)
		Form 12ug	1.390 (0.016)	0.198 (0.022)	<.0001	(0.155, 0.241)
	2:00	Placebo	1.222 (0.016)			
		Olo 5ug	1.412 (0.016)	0.190 (0.022)	<.0001	(0.147, 0.234)
		Olo 10ug	1.401 (0.016)	0.179 (0.022)	<.0001	(0.136, 0.222)
		Form 12ug	1.406 (0.016)	0.184 (0.022)	<.0001	(0.141, 0.228)

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 (217), Olo 5ug (222), Olo 10ug (223), Form 12ug (223)
Common baseline mean (SE): 1.204 (0.016)

Source data: Appendix 16.1.9.2, Statdoc 6.1.1.1.1 ctr\pft-adjmean-mmrm-time.sas 13OCT2011

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	3:00	Placebo	1.226 (0.017)			
		Olo 5ug	1.399 (0.016)	0.173 (0.022)	<.0001	(0.128, 0.217)
		Olo 10ug	1.387 (0.016)	0.161 (0.022)	<.0001	(0.117, 0.205)
		Form 12ug	1.399 (0.016)	0.173 (0.023)	<.0001	(0.128, 0.217)
127	-0:10	Placebo	1.196 (0.015)			
		Olo 5ug	1.261 (0.015)	0.064 (0.021)	0.0019	(0.024, 0.105)
		Olo 10ug	1.241 (0.015)	0.045 (0.021)	0.0296	(0.004, 0.086)
		Form 12ug	1.238 (0.015)	0.042 (0.021)	0.0449	(0.001, 0.082)
169	-0:10	Placebo	1.159 (0.015)			
		Olo 5ug	1.236 (0.015)	0.077 (0.021)	0.0002	(0.036, 0.118)
		Olo 10ug	1.243 (0.015)	0.085 (0.021)	<.0001	(0.044, 0.126)
		Form 12ug	1.213 (0.015)	0.055 (0.021)	0.0093	(0.013, 0.096)
	0:05	Placebo	1.182 (0.015)			
		Olo 5ug	1.296 (0.014)	0.115 (0.020)	<.0001	(0.076, 0.154)
		Olo 10ug	1.310 (0.014)	0.129 (0.020)	<.0001	(0.089, 0.168)
		Form 12ug	1.337 (0.014)	0.155 (0.020)	<.0001	(0.116, 0.195)
	0:15	Placebo	1.182 (0.015)			
		Olo 5ug	1.316 (0.015)	0.134 (0.021)	<.0001	(0.093, 0.174)
		Olo 10ug	1.334 (0.015)	0.152 (0.021)	<.0001	(0.111, 0.192)
		Form 12ug	1.355 (0.015)	0.173 (0.021)	<.0001	(0.132, 0.214)
	0:30	Placebo	1.199 (0.016)			
		Olo 5ug	1.341 (0.015)	0.142 (0.021)	<.0001	(0.100, 0.183)
		Olo 10ug	1.354 (0.015)	0.155 (0.021)	<.0001	(0.113, 0.197)
		Form 12ug	1.381 (0.015)	0.182 (0.021)	<.0001	(0.140, 0.224)

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 (217), Olo 5ug (222), Olo 10ug (223), Form 12ug (223)
Common baseline mean (SE): 1.204 (0.016)

Source data: Appendix 16.1.9.2, Statdoc 6.1.1.1.1 ctr\pft-adjmean-mmrm-time.sas 13OCT2011

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	1:00	Placebo	1.202 (0.016)			
		Olo 5ug	1.358 (0.016)	0.156 (0.022)	<.0001	(0.113, 0.199)
		Olo 10ug	1.367 (0.016)	0.165 (0.022)	<.0001	(0.122, 0.208)
		Form 12ug	1.387 (0.016)	0.185 (0.022)	<.0001	(0.141, 0.228)
	2:00	Placebo	1.214 (0.017)			
		Olo 5ug	1.377 (0.016)	0.164 (0.022)	<.0001	(0.120, 0.208)
		Olo 10ug	1.383 (0.016)	0.169 (0.022)	<.0001	(0.125, 0.213)
		Form 12ug	1.394 (0.016)	0.180 (0.022)	<.0001	(0.136, 0.224)
	3:00	Placebo	1.203 (0.017)			
		Olo 5ug	1.371 (0.016)	0.167 (0.023)	<.0001	(0.123, 0.212)
		Olo 10ug	1.380 (0.016)	0.177 (0.023)	<.0001	(0.133, 0.222)
		Form 12ug	1.372 (0.016)	0.169 (0.023)	<.0001	(0.125, 0.214)
225	-0:10	Placebo	1.192 (0.015)			
		Olo 5ug	1.238 (0.015)	0.046 (0.021)	0.0269	(0.005, 0.087)
		Olo 10ug	1.241 (0.015)	0.049 (0.021)	0.0193	(0.008, 0.090)
		Form 12ug	1.236 (0.015)	0.044 (0.021)	0.0363	(0.003, 0.085)
281	-0:10	Placebo	1.195 (0.016)			
		Olo 5ug	1.235 (0.015)	0.040 (0.021)	0.0579	(-0.001, 0.081)
		Olo 10ug	1.231 (0.015)	0.036 (0.021)	0.0857	(-0.005, 0.078)
		Form 12ug	1.218 (0.015)	0.024 (0.021)	0.2664	(-0.018, 0.065)
337	-0:10	Placebo	1.150 (0.016)			
		Olo 5ug	1.217 (0.015)	0.068 (0.021)	0.0013	(0.026, 0.109)
		Olo 10ug	1.206 (0.015)	0.056 (0.021)	0.0080	(0.015, 0.097)
		Form 12ug	1.209 (0.015)	0.059 (0.021)	0.0052	(0.018, 0.101)

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 (217), Olo 5ug (222), Olo 10ug (223), Form 12ug (223)
Common baseline mean (SE): 1.204 (0.016)

Source data: Appendix 16.1.9.2, Statdoc 6.1.1.1.1 ctr\pft-adjmean-mmrm-time.sas 13OCT2011

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	1.160 (0.015)			
		Olo 5ug	1.292 (0.014)	0.133 (0.020)	<.0001	(0.093, 0.172)
		Olo 10ug	1.272 (0.014)	0.113 (0.020)	<.0001	(0.073, 0.153)
		Form 12ug	1.317 (0.014)	0.157 (0.020)	<.0001	(0.118, 0.197)
	0:15	Placebo	1.175 (0.016)			
		Olo 5ug	1.312 (0.015)	0.137 (0.021)	<.0001	(0.096, 0.178)
		Olo 10ug	1.293 (0.015)	0.118 (0.021)	<.0001	(0.077, 0.159)
		Form 12ug	1.337 (0.015)	0.163 (0.021)	<.0001	(0.121, 0.204)
	0:30	Placebo	1.173 (0.016)			
		Olo 5ug	1.325 (0.015)	0.152 (0.021)	<.0001	(0.110, 0.194)
		Olo 10ug	1.313 (0.015)	0.140 (0.022)	<.0001	(0.098, 0.183)
		Form 12ug	1.355 (0.015)	0.183 (0.022)	<.0001	(0.140, 0.225)
	1:00	Placebo	1.180 (0.016)			
		Olo 5ug	1.334 (0.016)	0.154 (0.022)	<.0001	(0.111, 0.198)
		Olo 10ug	1.329 (0.016)	0.149 (0.022)	<.0001	(0.106, 0.193)
		Form 12ug	1.363 (0.016)	0.183 (0.022)	<.0001	(0.139, 0.226)
	2:00	Placebo	1.204 (0.017)			
		Olo 5ug	1.353 (0.016)	0.149 (0.022)	<.0001	(0.105, 0.193)
		Olo 10ug	1.355 (0.016)	0.151 (0.023)	<.0001	(0.106, 0.195)
		Form 12ug	1.377 (0.016)	0.173 (0.023)	<.0001	(0.129, 0.218)
	3:00	Placebo	1.196 (0.017)			
		Olo 5ug	1.343 (0.016)	0.147 (0.023)	<.0001	(0.103, 0.192)
		Olo 10ug	1.359 (0.016)	0.163 (0.023)	<.0001	(0.118, 0.208)
		Form 12ug	1.356 (0.016)	0.160 (0.023)	<.0001	(0.115, 0.206)

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 (217), Olo 5ug (222), Olo 10ug (223), Form 12ug (223)
Common baseline mean (SE): 1.204 (0.016)

Source data: Appendix 16.1.9.2, Statdoc 6.1.1.1.1 ctr\pft-adjmean-mmrm-time.sas 13OCT2011

Table 15.2.1.2.2: 2 Adjusted mean (SE) FVC AUC (0-3) response active treatment comparisons over 48 weeks - analysis with imputation (FAS)

		Treatment difference		
Test day	Comparison	Mean (SE)	P-value	95% CI
1	Olo 10ug - Olo 5ug	0.017 (0.037)	0.6432	(-0.055, 0.090)
	Olo 10ug - Form 12ug	-0.021 (0.037)	0.5619	(-0.094, 0.051)
	Olo 5ug - Form 12ug	-0.039 (0.037)	0.2972	(-0.111, 0.034)
15	Olo 10ug - Olo 5ug	0.012 (0.037)	0.7490	(-0.061, 0.085)
	Olo 10ug - Form 12ug	-0.072 (0.037)	0.0519	(-0.145, 0.001)
	Olo 5ug - Form 12ug	-0.084 (0.037)	0.0237	(-0.157, -0.011)
43	Olo 10ug - Olo 5ug	0.014 (0.037)	0.7136	(-0.060, 0.087)
	Olo 10ug - Form 12ug	-0.060 (0.038)	0.1085	(-0.134, 0.013)
	Olo 5ug - Form 12ug	-0.074 (0.037)	0.0484	(-0.147, -0.001)
85	Olo 10ug - Olo 5ug	0.044 (0.038)	0.2408	(-0.030, 0.118)
	Olo 10ug - Form 12ug	-0.022 (0.038)	0.5612	(-0.096, 0.052)
	Olo 5ug - Form 12ug	-0.066 (0.038)	0.0804	(-0.140, 0.008)
169	Olo 10ug - Olo 5ug	0.033 (0.038)	0.3907	(-0.042, 0.107)
	Olo 10ug - Form 12ug	-0.027 (0.038)	0.4772	(-0.102, 0.048)
	Olo 5ug - Form 12ug	-0.060 (0.038)	0.1168	(-0.134, 0.015)
337	Olo 10ug - Olo 5ug	0.024 (0.038)	0.5373	(-0.051, 0.099)
	Olo 10ug - Form 12ug	-0.040 (0.039)	0.2947	(-0.116, 0.035)
	Olo 5ug - Form 12ug	-0.064 (0.038)	0.0950	(-0.139, 0.011)

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 (217), Olo 5ug (222), Olo 10ug (223), Form 12ug (223)

Source data: Appendix 16.1.9.2, Statdoc 6.1.2.2.1 ctr\pft-adjmean-mmrm.sas 13OCT2011

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	0.224 (0.029)			
	Olo 5ug	0.472 (0.028)	0.248 (0.039)	<.0001	(0.171, 0.325)
	Olo 10ug	0.500 (0.028)	0.276 (0.039)	<.0001	(0.199, 0.353)
	Form 12ug	0.503 (0.028)	0.279 (0.039)	<.0001	(0.202, 0.356)
15	Placebo	0.268 (0.029)			
	Olo 5ug	0.454 (0.028)	0.186 (0.040)	<.0001	(0.108, 0.264)
	Olo 10ug	0.474 (0.028)	0.206 (0.040)	<.0001	(0.128, 0.284)
	Form 12ug	0.551 (0.029)	0.283 (0.040)	<.0001	(0.205, 0.361)
43	Placebo	0.202 (0.029)			
	Olo 5ug	0.411 (0.028)	0.209 (0.040)	<.0001	(0.131, 0.288)
	Olo 10ug	0.433 (0.029)	0.231 (0.040)	<.0001	(0.153, 0.310)
	Form 12ug	0.467 (0.029)	0.265 (0.040)	<.0001	(0.187, 0.344)
85	Placebo	0.194 (0.030)			
	Olo 5ug	0.382 (0.029)	0.188 (0.040)	<.0001	(0.108, 0.267)
	Olo 10ug	0.432 (0.029)	0.238 (0.041)	<.0001	(0.159, 0.318)
	Form 12ug	0.450 (0.029)	0.256 (0.041)	<.0001	(0.177, 0.336)
169	Placebo	0.207 (0.030)			
	Olo 5ug	0.379 (0.029)	0.173 (0.041)	<.0001	(0.092, 0.253)
	Olo 10ug	0.414 (0.029)	0.207 (0.041)	<.0001	(0.127, 0.288)
	Form 12ug	0.424 (0.029)	0.217 (0.041)	<.0001	(0.137, 0.298)
337	Placebo	0.193 (0.031)			
	Olo 5ug	0.344 (0.029)	0.150 (0.041)	0.0003	(0.070, 0.231)
	Olo 10ug	0.371 (0.030)	0.178 (0.041)	<.0001	(0.096, 0.259)
	Form 12ug	0.416 (0.030)	0.223 (0.042)	<.0001	(0.141, 0.304)

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 (217), Olo 5ug (222), Olo 10ug (223), Form 12ug (223)
Common baseline mean (SE): 2.766 (0.028)

Source data: Appendix 16.1.9.2, Statdoc 6.1.2.4.1 ctr\pft-adjmean-mmrm.sas 13OCT2011

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	0.042 (0.028)			
	Olo 5ug	0.110 (0.027)	0.068 (0.038)	0.0781	(-0.008, 0.143)
	Olo 10ug	0.119 (0.028)	0.077 (0.039)	0.0455	(0.002, 0.153)
	Form 12ug	0.126 (0.028)	0.085 (0.039)	0.0290	(0.009, 0.160)
43	Placebo	-0.046 (0.029)			
	Olo 5ug	0.065 (0.027)	0.110 (0.039)	0.0043	(0.035, 0.186)
	Olo 10ug	0.085 (0.028)	0.131 (0.039)	0.0007	(0.055, 0.207)
	Form 12ug	0.090 (0.028)	0.136 (0.039)	0.0005	(0.060, 0.212)
85	Placebo	-0.018 (0.029)			
	Olo 5ug	0.079 (0.028)	0.097 (0.039)	0.0136	(0.020, 0.173)
	Olo 10ug	0.087 (0.028)	0.105 (0.039)	0.0076	(0.028, 0.182)
	Form 12ug	0.068 (0.028)	0.086 (0.039)	0.0294	(0.009, 0.163)
127	Placebo	0.060 (0.029)			
	Olo 5ug	0.066 (0.028)	0.007 (0.039)	0.8674	(-0.071, 0.084)
	Olo 10ug	0.078 (0.028)	0.018 (0.040)	0.6487	(-0.060, 0.096)
	Form 12ug	0.063 (0.028)	0.004 (0.040)	0.9267	(-0.074, 0.081)
169	Placebo	-0.018 (0.029)			
	Olo 5ug	0.038 (0.028)	0.056 (0.040)	0.1603	(-0.022, 0.134)
	Olo 10ug	0.064 (0.028)	0.082 (0.040)	0.0399	(0.004, 0.160)
	Form 12ug	0.001 (0.029)	0.019 (0.040)	0.6328	(-0.059, 0.098)
225	Placebo	0.019 (0.030)			
	Olo 5ug	0.080 (0.028)	0.061 (0.040)	0.1270	(-0.017, 0.139)
	Olo 10ug	0.084 (0.028)	0.064 (0.040)	0.1076	(-0.014, 0.143)
	Form 12ug	0.077 (0.029)	0.058 (0.040)	0.1492	(-0.021, 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.

Number of patients contributing to models: Placebo (205), Olo 5ug (220), Olo 10ug (219), Form 12ug (215)
Common baseline mean (SE): 2.766 (0.028)

Source data: Appendix 16.1.9.2, Statdoc 6.1.2.3.1 ctr\pft-adjmean-mmrm.sas 13OCT2011

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
281	Placebo	0.028 (0.030)			
	Olo 5ug	0.087 (0.028)	0.059 (0.040)	0.1394	(-0.019, 0.138)
	Olo 10ug	0.086 (0.029)	0.058 (0.040)	0.1532	(-0.022, 0.137)
	Form 12ug	0.052 (0.029)	0.024 (0.041)	0.5511	(-0.055, 0.104)
337	Placebo	-0.061 (0.030)			
	Olo 5ug	0.022 (0.028)	0.083 (0.040)	0.0385	(0.004, 0.162)
	Olo 10ug	-0.002 (0.029)	0.059 (0.040)	0.1420	(-0.020, 0.138)
	Form 12ug	0.006 (0.029)	0.067 (0.040)	0.0965	(-0.012, 0.147)

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 (220), Olo 10ug (219), Form 12ug (215)
Common baseline mean (SE): 2.766 (0.028)

Source data: Appendix 16.1.9.2, Statdoc 6.1.2.3.1 ctr\pft-adjmean-mmrm.sas 13OCT2011

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	2.757 (0.028)			
		Olo 5ug	2.757 (0.028)			
		Olo 10ug	2.757 (0.028)			
		Form 12ug	2.757 (0.028)			
	-0:10	Placebo	2.774 (0.028)			
		Olo 5ug	2.774 (0.028)			
		Olo 10ug	2.774 (0.028)			
		Form 12ug	2.774 (0.028)			
	0:05	Placebo	2.785 (0.027)			
		Olo 5ug	3.000 (0.027)	0.214 (0.038)	<.0001	(0.141, 0.288)
		Olo 10ug	3.008 (0.027)	0.222 (0.037)	<.0001	(0.149, 0.296)
		Form 12ug	3.051 (0.027)	0.266 (0.037)	<.0001	(0.192, 0.339)
	0:15	Placebo	2.787 (0.028)			
		Olo 5ug	3.050 (0.028)	0.263 (0.039)	<.0001	(0.187, 0.339)
		Olo 10ug	3.046 (0.028)	0.258 (0.039)	<.0001	(0.183, 0.334)
		Form 12ug	3.087 (0.028)	0.300 (0.039)	<.0001	(0.224, 0.375)
	0:30	Placebo	2.832 (0.029)			
		Olo 5ug	3.074 (0.029)	0.242 (0.040)	<.0001	(0.164, 0.319)
		Olo 10ug	3.067 (0.028)	0.234 (0.039)	<.0001	(0.157, 0.312)
		Form 12ug	3.110 (0.029)	0.277 (0.039)	<.0001	(0.200, 0.355)
	1:00	Placebo	2.791 (0.029)			
		Olo 5ug	3.069 (0.028)	0.278 (0.039)	<.0001	(0.201, 0.356)
		Olo 10ug	3.077 (0.028)	0.286 (0.039)	<.0001	(0.209, 0.364)
		Form 12ug	3.134 (0.029)	0.343 (0.039)	<.0001	(0.266, 0.421)

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 (217), Olo 5ug (222), Olo 10ug (223), Form 12ug (223)
Common baseline mean (SE): 2.766 (0.028)

Source data: Appendix 16.1.9.2, Statdoc 6.1.2.1.1 ctr\pft-adjmean-mmrm-time.sas 13OCT2011

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	2:00	Placebo	2.836 (0.029)			
		Olo 5ug	3.108 (0.028)	0.272 (0.039)	<.0001	(0.195, 0.349)
		Olo 10ug	3.146 (0.028)	0.309 (0.039)	<.0001	(0.232, 0.386)
		Form 12ug	3.143 (0.028)	0.306 (0.039)	<.0001	(0.229, 0.383)
	3:00	Placebo	2.850 (0.029)			
		Olo 5ug	3.128 (0.029)	0.278 (0.040)	<.0001	(0.199, 0.356)
		Olo 10ug	3.149 (0.029)	0.299 (0.040)	<.0001	(0.221, 0.377)
		Form 12ug	3.138 (0.029)	0.287 (0.040)	<.0001	(0.209, 0.365)
15	-0:10	Placebo	2.830 (0.029)			
		Olo 5ug	2.897 (0.028)	0.067 (0.039)	0.0844	(-0.009, 0.144)
		Olo 10ug	2.906 (0.028)	0.076 (0.039)	0.0516	(-0.001, 0.153)
		Form 12ug	2.915 (0.028)	0.085 (0.039)	0.0308	(0.008, 0.162)
	0:05	Placebo	2.830 (0.028)			
		Olo 5ug	3.025 (0.027)	0.195 (0.038)	<.0001	(0.120, 0.269)
		Olo 10ug	3.016 (0.027)	0.186 (0.038)	<.0001	(0.111, 0.261)
		Form 12ug	3.116 (0.027)	0.286 (0.038)	<.0001	(0.212, 0.361)
	0:15	Placebo	2.834 (0.029)			
		Olo 5ug	3.021 (0.028)	0.187 (0.039)	<.0001	(0.110, 0.263)
		Olo 10ug	3.043 (0.028)	0.208 (0.039)	<.0001	(0.132, 0.285)
		Form 12ug	3.143 (0.028)	0.309 (0.039)	<.0001	(0.232, 0.386)
	0:30	Placebo	2.857 (0.029)			
		Olo 5ug	3.053 (0.029)	0.196 (0.040)	<.0001	(0.118, 0.274)
		Olo 10ug	3.078 (0.029)	0.221 (0.040)	<.0001	(0.143, 0.299)
		Form 12ug	3.157 (0.029)	0.300 (0.040)	<.0001	(0.221, 0.379)

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 (217), Olo 5ug (222), Olo 10ug (223), Form 12ug (223)
Common baseline mean (SE): 2.766 (0.028)

Source data: Appendix 16.1.9.2, Statdoc 6.1.2.1.1 ctr\pft-adjmean-mmrm-time.sas 13OCT2011

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	1:00	Placebo	2.858 (0.029)			
		Olo 5ug	3.067 (0.029)	0.209 (0.040)	<.0001	(0.131, 0.287)
		Olo 10ug	3.106 (0.029)	0.248 (0.040)	<.0001	(0.170, 0.326)
		Form 12ug	3.184 (0.029)	0.326 (0.040)	<.0001	(0.248, 0.405)
	2:00	Placebo	2.854 (0.029)			
		Olo 5ug	3.112 (0.028)	0.258 (0.040)	<.0001	(0.180, 0.336)
		Olo 10ug	3.112 (0.028)	0.258 (0.040)	<.0001	(0.180, 0.336)
		Form 12ug	3.165 (0.029)	0.312 (0.040)	<.0001	(0.234, 0.390)
	3:00	Placebo	2.861 (0.030)			
		Olo 5ug	3.092 (0.029)	0.231 (0.040)	<.0001	(0.152, 0.310)
		Olo 10ug	3.094 (0.029)	0.233 (0.040)	<.0001	(0.154, 0.312)
		Form 12ug	3.159 (0.029)	0.298 (0.040)	<.0001	(0.219, 0.377)
43	-1:00	Placebo	2.739 (0.028)			
		Olo 5ug	2.832 (0.027)	0.092 (0.038)	0.0144	(0.018, 0.166)
		Olo 10ug	2.850 (0.027)	0.111 (0.038)	0.0034	(0.037, 0.185)
		Form 12ug	2.848 (0.028)	0.109 (0.038)	0.0044	(0.034, 0.183)
	-0:10	Placebo	2.736 (0.029)			
		Olo 5ug	2.863 (0.028)	0.127 (0.039)	0.0012	(0.050, 0.204)
		Olo 10ug	2.885 (0.028)	0.149 (0.039)	0.0002	(0.072, 0.226)
		Form 12ug	2.894 (0.028)	0.158 (0.039)	<.0001	(0.081, 0.236)
	0:05	Placebo	2.742 (0.028)			
		Olo 5ug	2.965 (0.027)	0.222 (0.038)	<.0001	(0.147, 0.298)
		Olo 10ug	2.973 (0.027)	0.230 (0.038)	<.0001	(0.155, 0.306)
		Form 12ug	3.054 (0.028)	0.311 (0.039)	<.0001	(0.236, 0.387)

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 (217), Olo 5ug (222), Olo 10ug (223), Form 12ug (223)
Common baseline mean (SE): 2.766 (0.028)

Source data: Appendix 16.1.9.2, Statdoc 6.1.2.1.1 ctr\pft-adjmean-mmrm-time.sas 13OCT2011

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	0:15	Placebo	2.748 (0.029)			
		Olo 5ug	2.994 (0.028)	0.246 (0.039)	<.0001	(0.169, 0.323)
		Olo 10ug	2.977 (0.028)	0.229 (0.039)	<.0001	(0.152, 0.306)
		Form 12ug	3.071 (0.028)	0.323 (0.040)	<.0001	(0.245, 0.400)
	0:30	Placebo	2.774 (0.030)			
		Olo 5ug	3.019 (0.029)	0.245 (0.040)	<.0001	(0.166, 0.324)
		Olo 10ug	3.013 (0.029)	0.239 (0.040)	<.0001	(0.160, 0.319)
		Form 12ug	3.085 (0.029)	0.311 (0.041)	<.0001	(0.232, 0.391)
	1:00	Placebo	2.791 (0.030)			
		Olo 5ug	3.011 (0.029)	0.220 (0.040)	<.0001	(0.141, 0.299)
		Olo 10ug	3.017 (0.029)	0.226 (0.040)	<.0001	(0.147, 0.305)
		Form 12ug	3.104 (0.029)	0.313 (0.040)	<.0001	(0.234, 0.393)
	2:00	Placebo	2.817 (0.029)			
		Olo 5ug	3.073 (0.029)	0.257 (0.040)	<.0001	(0.178, 0.335)
		Olo 10ug	3.089 (0.029)	0.273 (0.040)	<.0001	(0.194, 0.351)
		Form 12ug	3.133 (0.029)	0.316 (0.040)	<.0001	(0.237, 0.395)
	3:00	Placebo	2.824 (0.030)			
		Olo 5ug	3.040 (0.029)	0.216 (0.041)	<.0001	(0.136, 0.295)
		Olo 10ug	3.066 (0.029)	0.242 (0.041)	<.0001	(0.162, 0.322)
		Form 12ug	3.094 (0.029)	0.270 (0.041)	<.0001	(0.190, 0.350)
85	-1:00	Placebo	2.749 (0.028)			
		Olo 5ug	2.843 (0.027)	0.094 (0.038)	0.0143	(0.019, 0.169)
		Olo 10ug	2.856 (0.027)	0.107 (0.038)	0.0054	(0.032, 0.182)
		Form 12ug	2.834 (0.028)	0.085 (0.039)	0.0271	(0.010, 0.161)

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 (217), Olo 5ug (222), Olo 10ug (223), Form 12ug (223)
Common baseline mean (SE): 2.766 (0.028)

Source data: Appendix 16.1.9.2, Statdoc 6.1.2.1.1 ctr\pft-adjmean-mmrm-time.sas 13OCT2011

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	-0:10	Placebo	2.780 (0.029)			
		Olo 5ug	2.880 (0.028)	0.100 (0.040)	0.0118	(0.022, 0.178)
		Olo 10ug	2.884 (0.028)	0.104 (0.040)	0.0092	(0.026, 0.182)
		Form 12ug	2.864 (0.029)	0.084 (0.040)	0.0362	(0.005, 0.162)
	0:05	Placebo	2.737 (0.029)			
		Olo 5ug	2.944 (0.028)	0.207 (0.039)	<.0001	(0.131, 0.283)
		Olo 10ug	3.001 (0.028)	0.264 (0.039)	<.0001	(0.188, 0.340)
		Form 12ug	3.045 (0.028)	0.308 (0.039)	<.0001	(0.232, 0.385)
	0:15	Placebo	2.748 (0.029)			
		Olo 5ug	2.969 (0.028)	0.222 (0.040)	<.0001	(0.144, 0.300)
		Olo 10ug	3.009 (0.028)	0.261 (0.040)	<.0001	(0.183, 0.339)
		Form 12ug	3.028 (0.029)	0.281 (0.040)	<.0001	(0.202, 0.359)
	0:30	Placebo	2.785 (0.030)			
		Olo 5ug	2.999 (0.029)	0.214 (0.041)	<.0001	(0.134, 0.294)
		Olo 10ug	3.045 (0.029)	0.260 (0.041)	<.0001	(0.180, 0.340)
		Form 12ug	3.067 (0.029)	0.282 (0.041)	<.0001	(0.202, 0.363)
	1:00	Placebo	2.788 (0.030)			
		Olo 5ug	3.009 (0.029)	0.221 (0.041)	<.0001	(0.141, 0.301)
		Olo 10ug	3.041 (0.029)	0.252 (0.041)	<.0001	(0.172, 0.332)
		Form 12ug	3.080 (0.029)	0.292 (0.041)	<.0001	(0.211, 0.372)
	2:00	Placebo	2.822 (0.030)			
		Olo 5ug	3.038 (0.029)	0.216 (0.041)	<.0001	(0.136, 0.295)
		Olo 10ug	3.088 (0.029)	0.266 (0.041)	<.0001	(0.186, 0.346)
		Form 12ug	3.098 (0.029)	0.276 (0.041)	<.0001	(0.196, 0.356)

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 (217), Olo 5ug (222), Olo 10ug (223), Form 12ug (223)
Common baseline mean (SE): 2.766 (0.028)

Source data: Appendix 16.1.9.2, Statdoc 6.1.2.1.1 ctr\pft-adjmean-mmrm-time.sas 13OCT2011

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	3:00	Placebo	2.830 (0.030)			
		Olo 5ug	3.045 (0.029)	0.215 (0.041)	<.0001	(0.134, 0.296)
		Olo 10ug	3.062 (0.029)	0.232 (0.041)	<.0001	(0.152, 0.313)
		Form 12ug	3.084 (0.030)	0.254 (0.041)	<.0001	(0.173, 0.335)
127	-0:10	Placebo	2.848 (0.030)			
		Olo 5ug	2.854 (0.028)	0.006 (0.040)	0.8731	(-0.072, 0.085)
		Olo 10ug	2.866 (0.029)	0.018 (0.040)	0.6606	(-0.061, 0.096)
		Form 12ug	2.851 (0.029)	0.003 (0.040)	0.9384	(-0.076, 0.082)
169	-0:10	Placebo	2.770 (0.030)			
		Olo 5ug	2.826 (0.028)	0.056 (0.040)	0.1672	(-0.023, 0.135)
		Olo 10ug	2.852 (0.029)	0.082 (0.040)	0.0433	(0.002, 0.161)
		Form 12ug	2.789 (0.029)	0.019 (0.041)	0.6427	(-0.061, 0.099)
	0:05	Placebo	2.755 (0.029)			
		Olo 5ug	2.929 (0.028)	0.174 (0.039)	<.0001	(0.098, 0.251)
		Olo 10ug	2.950 (0.028)	0.195 (0.039)	<.0001	(0.118, 0.272)
		Form 12ug	3.017 (0.028)	0.262 (0.039)	<.0001	(0.185, 0.339)
	0:15	Placebo	2.764 (0.030)			
		Olo 5ug	2.935 (0.028)	0.171 (0.040)	<.0001	(0.092, 0.250)
		Olo 10ug	2.984 (0.029)	0.220 (0.040)	<.0001	(0.141, 0.299)
		Form 12ug	3.033 (0.029)	0.269 (0.040)	<.0001	(0.190, 0.348)
	0:30	Placebo	2.814 (0.030)			
		Olo 5ug	2.978 (0.029)	0.164 (0.041)	<.0001	(0.084, 0.245)
		Olo 10ug	3.024 (0.029)	0.210 (0.041)	<.0001	(0.129, 0.291)
		Form 12ug	3.057 (0.030)	0.243 (0.041)	<.0001	(0.162, 0.324)

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 (217), Olo 5ug (222), Olo 10ug (223), Form 12ug (223)
Common baseline mean (SE): 2.766 (0.028)

Source data: Appendix 16.1.9.2, Statdoc 6.1.2.1.1 ctr\pft-adjmean-mmrm-time.sas 13OCT2011

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	1:00	Placebo	2.821 (0.030)			
		Olo 5ug	3.005 (0.029)	0.185 (0.041)	<.0001	(0.104, 0.265)
		Olo 10ug	3.032 (0.029)	0.212 (0.041)	<.0001	(0.131, 0.293)
		Form 12ug	3.051 (0.030)	0.230 (0.041)	<.0001	(0.149, 0.312)
	2:00	Placebo	2.833 (0.030)			
		Olo 5ug	3.041 (0.029)	0.208 (0.041)	<.0001	(0.128, 0.288)
		Olo 10ug	3.048 (0.029)	0.215 (0.041)	<.0001	(0.134, 0.295)
		Form 12ug	3.085 (0.029)	0.251 (0.041)	<.0001	(0.170, 0.332)
	3:00	Placebo	2.824 (0.031)			
		Olo 5ug	3.016 (0.029)	0.192 (0.041)	<.0001	(0.111, 0.274)
		Olo 10ug	3.046 (0.030)	0.223 (0.042)	<.0001	(0.141, 0.304)
		Form 12ug	3.058 (0.030)	0.234 (0.042)	<.0001	(0.152, 0.316)
225	-0:10	Placebo	2.808 (0.030)			
		Olo 5ug	2.868 (0.028)	0.060 (0.040)	0.1372	(-0.019, 0.139)
		Olo 10ug	2.872 (0.029)	0.064 (0.041)	0.1146	(-0.016, 0.144)
		Form 12ug	2.864 (0.029)	0.057 (0.041)	0.1655	(-0.023, 0.136)
281	-0:10	Placebo	2.816 (0.030)			
		Olo 5ug	2.875 (0.028)	0.059 (0.041)	0.1478	(-0.021, 0.139)
		Olo 10ug	2.873 (0.029)	0.057 (0.041)	0.1625	(-0.023, 0.138)
		Form 12ug	2.839 (0.029)	0.023 (0.041)	0.5750	(-0.058, 0.104)
337	-0:10	Placebo	2.727 (0.030)			
		Olo 5ug	2.810 (0.029)	0.083 (0.041)	0.0425	(0.003, 0.162)
		Olo 10ug	2.786 (0.029)	0.059 (0.041)	0.1521	(-0.022, 0.139)
		Form 12ug	2.793 (0.029)	0.066 (0.041)	0.1082	(-0.015, 0.147)

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 (217), Olo 5ug (222), Olo 10ug (223), Form 12ug (223)
Common baseline mean (SE): 2.766 (0.028)

Source data: Appendix 16.1.9.2, Statdoc 6.1.2.1.1 ctr\pft-adjmean-mmrm-time.sas 13OCT2011

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	2.730 (0.029)			
		Olo 5ug	2.912 (0.028)	0.183 (0.040)	<.0001	(0.105, 0.260)
		Olo 10ug	2.922 (0.028)	0.192 (0.040)	<.0001	(0.114, 0.270)
		Form 12ug	2.982 (0.028)	0.252 (0.040)	<.0001	(0.174, 0.330)
	0:15	Placebo	2.736 (0.030)			
		Olo 5ug	2.939 (0.029)	0.203 (0.041)	<.0001	(0.123, 0.282)
		Olo 10ug	2.923 (0.029)	0.186 (0.041)	<.0001	(0.106, 0.266)
		Form 12ug	3.002 (0.029)	0.266 (0.041)	<.0001	(0.186, 0.346)
	0:30	Placebo	2.780 (0.031)			
		Olo 5ug	2.963 (0.029)	0.183 (0.041)	<.0001	(0.101, 0.264)
		Olo 10ug	2.978 (0.030)	0.198 (0.042)	<.0001	(0.116, 0.280)
		Form 12ug	3.039 (0.030)	0.259 (0.042)	<.0001	(0.177, 0.341)
	1:00	Placebo	2.771 (0.031)			
		Olo 5ug	2.977 (0.029)	0.206 (0.041)	<.0001	(0.125, 0.287)
		Olo 10ug	2.977 (0.030)	0.206 (0.042)	<.0001	(0.124, 0.288)
		Form 12ug	3.048 (0.030)	0.276 (0.042)	<.0001	(0.194, 0.358)
	2:00	Placebo	2.825 (0.031)			
		Olo 5ug	3.005 (0.029)	0.180 (0.041)	<.0001	(0.098, 0.261)
		Olo 10ug	3.040 (0.030)	0.215 (0.042)	<.0001	(0.134, 0.297)
		Form 12ug	3.053 (0.030)	0.228 (0.042)	<.0001	(0.146, 0.310)
	3:00	Placebo	2.827 (0.031)			
		Olo 5ug	2.996 (0.029)	0.170 (0.042)	<.0001	(0.088, 0.252)
		Olo 10ug	3.018 (0.030)	0.191 (0.042)	<.0001	(0.109, 0.274)
		Form 12ug	3.037 (0.030)	0.210 (0.042)	<.0001	(0.127, 0.293)

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 (217), Olo 5ug (222), Olo 10ug (223), Form 12ug (223)
Common baseline mean (SE): 2.766 (0.028)

Source data: Appendix 16.1.9.2, Statdoc 6.1.2.1.1 ctr\pft-adjmean-mmrm-time.sas 13OCT2011

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	200.530 (2.199)			
	Olo 5ug	221.146 (2.217)	20.616 (3.008)	<.0001	(14.713, 26.519)
	Olo 10ug	220.260 (2.190)	19.730 (2.989)	<.0001	(13.863, 25.598)
	Form 12ug	219.126 (2.187)	18.596 (2.983)	<.0001	(12.740, 24.451)
2	Placebo	198.385 (2.362)			
	Olo 5ug	220.797 (2.381)	22.413 (3.231)	<.0001	(16.072, 28.753)
	Olo 10ug	217.507 (2.353)	19.122 (3.211)	<.0001	(12.820, 25.425)
	Form 12ug	216.680 (2.349)	18.295 (3.204)	<.0001	(12.006, 24.584)
3	Placebo	198.993 (2.536)			
	Olo 5ug	218.411 (2.557)	19.417 (3.469)	<.0001	(12.609, 26.226)
	Olo 10ug	221.936 (2.526)	22.943 (3.448)	<.0001	(16.176, 29.710)
	Form 12ug	216.924 (2.522)	17.930 (3.441)	<.0001	(11.177, 24.683)
4	Placebo	198.976 (2.612)			
	Olo 5ug	215.555 (2.633)	16.580 (3.572)	<.0001	(9.568, 23.591)
	Olo 10ug	219.802 (2.602)	20.826 (3.551)	<.0001	(13.857, 27.795)
	Form 12ug	218.730 (2.597)	19.754 (3.543)	<.0001	(12.799, 26.708)
5	Placebo	199.281 (2.772)			
	Olo 5ug	215.571 (2.794)	16.291 (3.791)	<.0001	(8.850, 23.731)
	Olo 10ug	218.466 (2.761)	19.185 (3.768)	<.0001	(11.790, 26.580)
	Form 12ug	218.219 (2.756)	18.938 (3.760)	<.0001	(11.558, 26.318)
6	Placebo	199.141 (2.829)			
	Olo 5ug	215.611 (2.852)	16.470 (3.869)	<.0001	(8.876, 24.065)
	Olo 10ug	215.763 (2.818)	16.622 (3.846)	<.0001	(9.074, 24.171)
	Form 12ug	215.736 (2.813)	16.595 (3.838)	<.0001	(9.062, 24.128)

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 (214), Olo 5ug (212), Olo 10ug (216), Form 12ug (218)
Common baseline mean (SE): 204.178 (3.135)

Source data: Appendix 16.1.9.2, Statdoc 6.2.2.1 ctr\diary-adjmean-ancova.sas 11OCT2011

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
7	Placebo	199.523 (2.956)			
	Olo 5ug	214.126 (2.980)	14.603 (4.042)	0.0003	(6.669, 22.537)
	Olo 10ug	216.579 (2.944)	17.056 (4.018)	<.0001	(9.170, 24.942)
	Form 12ug	217.054 (2.939)	17.531 (4.010)	<.0001	(9.661, 25.401)
8	Placebo	198.166 (2.946)			
	Olo 5ug	213.572 (2.970)	15.406 (4.029)	0.0001	(7.499, 23.313)
	Olo 10ug	215.483 (2.934)	17.318 (4.004)	<.0001	(9.458, 25.177)
	Form 12ug	216.618 (2.929)	18.452 (3.996)	<.0001	(10.609, 26.295)
9	Placebo	198.488 (3.019)			
	Olo 5ug	212.558 (3.044)	14.070 (4.129)	0.0007	(5.966, 22.173)
	Olo 10ug	216.332 (3.007)	17.844 (4.104)	<.0001	(9.789, 25.898)
	Form 12ug	217.487 (3.002)	18.999 (4.095)	<.0001	(10.961, 27.037)
10	Placebo	199.026 (3.128)			
	Olo 5ug	212.673 (3.153)	13.646 (4.277)	0.0015	(5.251, 22.042)
	Olo 10ug	215.786 (3.115)	16.760 (4.251)	<.0001	(8.416, 25.105)
	Form 12ug	216.296 (3.110)	17.270 (4.243)	<.0001	(8.943, 25.597)
11	Placebo	198.345 (3.158)			
	Olo 5ug	212.212 (3.183)	13.866 (4.318)	0.0014	(5.390, 22.343)
	Olo 10ug	214.291 (3.145)	15.945 (4.292)	0.0002	(7.521, 24.370)
	Form 12ug	214.184 (3.140)	15.839 (4.283)	0.0002	(7.432, 24.246)
12	Placebo	197.946 (3.246)			
	Olo 5ug	213.358 (3.272)	15.412 (4.439)	0.0005	(6.700, 24.124)
	Olo 10ug	215.497 (3.233)	17.551 (4.412)	<.0001	(8.891, 26.210)
	Form 12ug	216.479 (3.227)	18.533 (4.403)	<.0001	(9.891, 27.174)

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 (214), Olo 5ug (212), Olo 10ug (216), Form 12ug (218)
Common baseline mean (SE): 204.178 (3.135)

Source data: Appendix 16.1.9.2, Statdoc 6.2.2.1 ctr\diary-adjmean-ancova.sas 11OCT2011

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
13	Placebo	199.034 (3.181)			
	Olo 5ug	214.776 (3.207)	15.742 (4.350)	0.0003	(7.203, 24.280)
	Olo 10ug	216.511 (3.168)	17.477 (4.324)	<.0001	(8.990, 25.963)
	Form 12ug	217.617 (3.163)	18.583 (4.315)	<.0001	(10.114, 27.052)
14	Placebo	198.312 (3.306)			
	Olo 5ug	215.527 (3.333)	17.215 (4.521)	0.0002	(8.341, 26.089)
	Olo 10ug	215.127 (3.293)	16.815 (4.494)	0.0002	(7.995, 25.636)
	Form 12ug	215.676 (3.287)	17.364 (4.485)	0.0001	(8.562, 26.166)
15	Placebo	198.858 (3.345)			
	Olo 5ug	215.004 (3.372)	16.146 (4.574)	0.0004	(7.167, 25.124)
	Olo 10ug	212.488 (3.331)	13.630 (4.547)	0.0028	(4.706, 22.554)
	Form 12ug	215.437 (3.326)	16.579 (4.537)	0.0003	(7.673, 25.484)
16	Placebo	198.650 (3.357)			
	Olo 5ug	214.145 (3.384)	15.495 (4.591)	0.0008	(6.485, 24.506)
	Olo 10ug	213.212 (3.343)	14.563 (4.563)	0.0015	(5.607, 23.518)
	Form 12ug	215.736 (3.338)	17.086 (4.553)	0.0002	(8.149, 26.024)
17	Placebo	198.991 (3.411)			
	Olo 5ug	213.229 (3.438)	14.238 (4.664)	0.0023	(5.083, 23.393)
	Olo 10ug	214.282 (3.397)	15.292 (4.636)	0.0010	(6.192, 24.391)
	Form 12ug	214.122 (3.391)	15.131 (4.626)	0.0011	(6.051, 24.212)
18	Placebo	198.046 (3.381)			
	Olo 5ug	212.609 (3.408)	14.563 (4.623)	0.0017	(5.489, 23.638)
	Olo 10ug	211.412 (3.367)	13.366 (4.595)	0.0037	(4.347, 22.386)
	Form 12ug	213.919 (3.362)	15.873 (4.586)	0.0006	(6.872, 24.874)

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 (214), Olo 5ug (212), Olo 10ug (216), Form 12ug (218)
Common baseline mean (SE): 204.178 (3.135)

Source data: Appendix 16.1.9.2, Statdoc 6.2.2.1 ctr\diary-adjmean-ancova.sas 11OCT2011

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
19	Placebo	198.124 (3.369)			
	Olo 5ug	212.784 (3.397)	14.660 (4.608)	0.0015	(5.616, 23.703)
	Olo 10ug	212.285 (3.356)	14.161 (4.580)	0.0021	(5.172, 23.150)
	Form 12ug	215.364 (3.350)	17.240 (4.570)	0.0002	(8.269, 26.210)
20	Placebo	198.506 (3.321)			
	Olo 5ug	213.746 (3.348)	15.240 (4.541)	0.0008	(6.327, 24.153)
	Olo 10ug	213.647 (3.307)	15.142 (4.514)	0.0008	(6.282, 24.001)
	Form 12ug	216.017 (3.302)	17.512 (4.504)	0.0001	(8.671, 26.352)
21	Placebo	196.851 (3.396)			
	Olo 5ug	213.406 (3.424)	16.554 (4.645)	0.0004	(7.438, 25.671)
	Olo 10ug	211.582 (3.383)	14.731 (4.616)	0.0015	(5.670, 23.792)
	Form 12ug	214.547 (3.377)	17.695 (4.607)	0.0001	(8.653, 26.737)
22	Placebo	198.169 (3.379)			
	Olo 5ug	213.402 (3.406)	15.233 (4.620)	0.0010	(6.165, 24.302)
	Olo 10ug	210.525 (3.365)	12.356 (4.592)	0.0073	(3.342, 21.369)
	Form 12ug	213.699 (3.359)	15.530 (4.583)	0.0007	(6.535, 24.525)
23	Placebo	196.875 (3.381)			
	Olo 5ug	212.900 (3.408)	16.024 (4.623)	0.0006	(6.950, 25.099)
	Olo 10ug	208.972 (3.367)	12.096 (4.595)	0.0086	(3.077, 21.116)
	Form 12ug	213.929 (3.362)	17.053 (4.586)	0.0002	(8.052, 26.054)
24	Placebo	196.429 (3.392)			
	Olo 5ug	211.496 (3.420)	15.067 (4.639)	0.0012	(5.962, 24.173)
	Olo 10ug	211.428 (3.379)	14.999 (4.611)	0.0012	(5.949, 24.049)
	Form 12ug	214.070 (3.373)	17.642 (4.601)	0.0001	(8.610, 26.673)

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 (214), Olo 5ug (212), Olo 10ug (216), Form 12ug (218)
Common baseline mean (SE): 204.178 (3.135)

Source data: Appendix 16.1.9.2, Statdoc 6.2.2.1 ctr\diary-adjmean-ancova.sas 11OCT2011

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	195.672 (3.382)			
	Olo 5ug	212.881 (3.410)	17.209 (4.626)	0.0002	(8.130, 26.288)
	Olo 10ug	211.402 (3.369)	15.731 (4.597)	0.0007	(6.707, 24.754)
	Form 12ug	217.696 (3.363)	22.025 (4.588)	<.0001	(13.020, 31.030)
26	Placebo	197.483 (3.338)			
	Olo 5ug	211.922 (3.365)	14.439 (4.564)	0.0016	(5.480, 23.397)
	Olo 10ug	211.994 (3.324)	14.511 (4.537)	0.0014	(5.606, 23.416)
	Form 12ug	217.259 (3.319)	19.776 (4.527)	<.0001	(10.890, 28.662)
27	Placebo	196.408 (3.423)			
	Olo 5ug	211.906 (3.451)	15.498 (4.682)	0.0010	(6.309, 24.687)
	Olo 10ug	211.329 (3.409)	14.921 (4.653)	0.0014	(5.788, 24.054)
	Form 12ug	217.196 (3.404)	20.789 (4.644)	<.0001	(11.675, 29.903)
28	Placebo	197.784 (3.459)			
	Olo 5ug	210.600 (3.487)	12.817 (4.730)	0.0069	(3.532, 22.101)
	Olo 10ug	208.856 (3.445)	11.072 (4.702)	0.0188	(1.844, 20.301)
	Form 12ug	215.074 (3.440)	17.290 (4.692)	0.0002	(8.081, 26.500)
29	Placebo	195.255 (3.444)			
	Olo 5ug	210.333 (3.471)	15.078 (4.709)	0.0014	(5.835, 24.321)
	Olo 10ug	208.750 (3.430)	13.494 (4.681)	0.0040	(4.308, 22.681)
	Form 12ug	215.530 (3.424)	20.274 (4.671)	<.0001	(11.106, 29.442)
30	Placebo	195.326 (3.470)			
	Olo 5ug	209.728 (3.498)	14.403 (4.746)	0.0025	(5.089, 23.717)
	Olo 10ug	210.036 (3.456)	14.710 (4.717)	0.0019	(5.453, 23.968)
	Form 12ug	213.581 (3.451)	18.255 (4.707)	0.0001	(9.017, 27.494)

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 (214), Olo 5ug (212), Olo 10ug (216), Form 12ug (218)
Common baseline mean (SE): 204.178 (3.135)

Source data: Appendix 16.1.9.2, Statdoc 6.2.2.1 ctr\diary-adjmean-ancova.sas 11OCT2011

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
31	Placebo	196.124 (3.505)			
	Olo 5ug	208.883 (3.533)	12.759 (4.793)	0.0079	(3.352, 22.166)
	Olo 10ug	209.376 (3.491)	13.252 (4.764)	0.0055	(3.902, 22.603)
	Form 12ug	214.208 (3.485)	18.084 (4.754)	0.0002	(8.753, 27.415)
32	Placebo	196.381 (3.536)			
	Olo 5ug	208.434 (3.565)	12.052 (4.836)	0.0129	(2.561, 21.543)
	Olo 10ug	208.786 (3.522)	12.404 (4.806)	0.0100	(2.970, 21.838)
	Form 12ug	216.078 (3.516)	19.696 (4.796)	<.0001	(10.282, 29.110)
33	Placebo	197.315 (3.566)			
	Olo 5ug	207.938 (3.595)	10.623 (4.877)	0.0297	(1.050, 20.195)
	Olo 10ug	210.032 (3.552)	12.716 (4.847)	0.0089	(3.202, 22.230)
	Form 12ug	216.014 (3.546)	18.699 (4.837)	0.0001	(9.204, 28.193)
34	Placebo	196.364 (3.573)			
	Olo 5ug	208.271 (3.602)	11.908 (4.886)	0.0150	(2.318, 21.497)
	Olo 10ug	210.711 (3.558)	14.348 (4.856)	0.0032	(4.817, 23.879)
	Form 12ug	215.961 (3.552)	19.598 (4.846)	<.0001	(10.086, 29.109)
35	Placebo	196.766 (3.617)			
	Olo 5ug	207.960 (3.646)	11.194 (4.946)	0.0239	(1.486, 20.903)
	Olo 10ug	210.838 (3.602)	14.072 (4.916)	0.0043	(4.423, 23.722)
	Form 12ug	216.116 (3.597)	19.350 (4.906)	<.0001	(9.720, 28.979)
36	Placebo	198.606 (3.645)			
	Olo 5ug	206.726 (3.675)	8.120 (4.985)	0.1037	(-1.665, 17.905)
	Olo 10ug	212.058 (3.631)	13.451 (4.955)	0.0068	(3.726, 23.177)
	Form 12ug	213.987 (3.625)	15.380 (4.945)	0.0019	(5.675, 25.086)

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 (214), Olo 5ug (212), Olo 10ug (216), Form 12ug (218)
Common baseline mean (SE): 204.178 (3.135)

Source data: Appendix 16.1.9.2, Statdoc 6.2.2.1 ctr\diary-adjmean-ancova.sas 11OCT2011

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
37	Placebo	197.961 (3.582)			
	Olo 5ug	209.014 (3.611)	11.053 (4.898)	0.0243	(1.439, 20.667)
	Olo 10ug	211.120 (3.567)	13.159 (4.869)	0.0070	(3.604, 22.715)
	Form 12ug	213.336 (3.562)	15.375 (4.858)	0.0016	(5.839, 24.911)
38	Placebo	197.222 (3.632)			
	Olo 5ug	208.484 (3.661)	11.262 (4.966)	0.0236	(1.514, 21.009)
	Olo 10ug	211.335 (3.617)	14.113 (4.936)	0.0044	(4.425, 23.801)
	Form 12ug	214.920 (3.611)	17.698 (4.926)	0.0003	(8.030, 27.366)
39	Placebo	198.256 (3.683)			
	Olo 5ug	207.440 (3.713)	9.184 (5.037)	0.0686	(-0.702, 19.070)
	Olo 10ug	210.265 (3.668)	12.009 (5.006)	0.0167	(2.183, 21.835)
	Form 12ug	215.834 (3.662)	17.579 (4.996)	0.0005	(7.773, 27.384)
40	Placebo	198.504 (3.711)			
	Olo 5ug	206.840 (3.741)	8.335 (5.075)	0.1009	(-1.625, 18.296)
	Olo 10ug	210.307 (3.696)	11.802 (5.044)	0.0195	(1.902, 21.702)
	Form 12ug	215.943 (3.690)	17.439 (5.034)	0.0006	(7.559, 27.319)
41	Placebo	197.439 (3.730)			
	Olo 5ug	207.357 (3.760)	9.918 (5.101)	0.0522	(-0.093, 19.929)
	Olo 10ug	210.699 (3.715)	13.260 (5.070)	0.0091	(3.309, 23.210)
	Form 12ug	215.834 (3.709)	18.395 (5.059)	0.0003	(8.465, 28.325)
42	Placebo	197.256 (3.717)			
	Olo 5ug	208.446 (3.747)	11.190 (5.083)	0.0280	(1.213, 21.166)
	Olo 10ug	210.427 (3.702)	13.171 (5.052)	0.0093	(3.255, 23.087)
	Form 12ug	216.970 (3.696)	19.714 (5.042)	<.0001	(9.818, 29.610)

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 (214), Olo 5ug (212), Olo 10ug (216), Form 12ug (218)
Common baseline mean (SE): 204.178 (3.135)

Source data: Appendix 16.1.9.2, Statdoc 6.2.2.1 ctr\diary-adjmean-ancova.sas 11OCT2011

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
43	Placebo	196.656 (3.726)			
	Olo 5ug	208.998 (3.756)	12.341 (5.096)	0.0156	(2.340, 22.343)
	Olo 10ug	210.822 (3.711)	14.166 (5.065)	0.0053	(4.225, 24.107)
	Form 12ug	217.951 (3.705)	21.295 (5.054)	<.0001	(11.375, 31.215)
44	Placebo	195.277 (3.734)			
	Olo 5ug	208.861 (3.764)	13.584 (5.106)	0.0079	(3.563, 23.606)
	Olo 10ug	209.158 (3.718)	13.881 (5.075)	0.0064	(3.920, 23.841)
	Form 12ug	218.027 (3.713)	22.750 (5.064)	<.0001	(12.810, 32.690)
45	Placebo	194.414 (3.734)			
	Olo 5ug	208.432 (3.764)	14.017 (5.107)	0.0062	(3.994, 24.040)
	Olo 10ug	209.907 (3.719)	15.493 (5.076)	0.0023	(5.531, 25.455)
	Form 12ug	216.238 (3.713)	21.823 (5.065)	<.0001	(11.882, 31.765)
46	Placebo	195.910 (3.798)			
	Olo 5ug	209.069 (3.829)	13.159 (5.194)	0.0115	(2.965, 23.353)
	Olo 10ug	210.234 (3.783)	14.324 (5.162)	0.0056	(4.192, 24.457)
	Form 12ug	216.711 (3.777)	20.801 (5.152)	<.0001	(10.690, 30.913)
47	Placebo	195.993 (3.770)			
	Olo 5ug	208.840 (3.800)	12.847 (5.155)	0.0129	(2.728, 22.965)
	Olo 10ug	210.826 (3.754)	14.833 (5.124)	0.0039	(4.776, 24.890)
	Form 12ug	214.543 (3.749)	18.550 (5.114)	0.0003	(8.514, 28.587)
48	Placebo	195.828 (3.836)			
	Olo 5ug	209.079 (3.867)	13.251 (5.246)	0.0117	(2.955, 23.546)
	Olo 10ug	210.268 (3.820)	14.440 (5.214)	0.0057	(4.206, 24.673)
	Form 12ug	215.871 (3.814)	20.043 (5.203)	0.0001	(9.831, 30.255)

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 (214), Olo 5ug (212), Olo 10ug (216), Form 12ug (218)
Common baseline mean (SE): 204.178 (3.135)

Source data: Appendix 16.1.9.2, Statdoc 6.2.2.1 ctr\diary-adjmean-ancova.sas 11OCT2011

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	211.688 (2.211)			
	Olo 5ug	235.160 (2.241)	23.472 (3.029)	<.0001	(17.527, 29.418)
	Olo 10ug	234.659 (2.210)	22.971 (3.011)	<.0001	(17.061, 28.881)
	Form 12ug	227.101 (2.191)	15.413 (2.991)	<.0001	(9.543, 21.283)
2	Placebo	210.043 (2.265)			
	Olo 5ug	230.376 (2.296)	20.333 (3.102)	<.0001	(14.244, 26.422)
	Olo 10ug	232.087 (2.263)	22.045 (3.084)	<.0001	(15.991, 28.098)
	Form 12ug	225.769 (2.244)	15.726 (3.063)	<.0001	(9.714, 21.738)
3	Placebo	208.763 (2.469)			
	Olo 5ug	227.315 (2.502)	18.553 (3.382)	<.0001	(11.916, 25.190)
	Olo 10ug	232.531 (2.467)	23.768 (3.361)	<.0001	(17.171, 30.366)
	Form 12ug	225.831 (2.446)	17.069 (3.339)	<.0001	(10.516, 23.621)
4	Placebo	206.715 (2.559)			
	Olo 5ug	226.797 (2.593)	20.082 (3.505)	<.0001	(13.203, 26.961)
	Olo 10ug	229.780 (2.557)	23.065 (3.484)	<.0001	(16.227, 29.903)
	Form 12ug	224.257 (2.535)	17.542 (3.460)	<.0001	(10.751, 24.334)
5	Placebo	208.186 (2.806)			
	Olo 5ug	225.881 (2.844)	17.695 (3.844)	<.0001	(10.150, 25.240)
	Olo 10ug	230.395 (2.804)	22.209 (3.821)	<.0001	(14.708, 29.709)
	Form 12ug	224.391 (2.781)	16.205 (3.795)	<.0001	(8.756, 23.654)
6	Placebo	207.950 (2.769)			
	Olo 5ug	226.201 (2.807)	18.251 (3.794)	<.0001	(10.805, 25.697)
	Olo 10ug	225.738 (2.767)	17.788 (3.771)	<.0001	(10.386, 25.190)
	Form 12ug	222.378 (2.744)	14.428 (3.746)	0.0001	(7.076, 21.779)

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 (215), Olo 5ug (211), Olo 10ug (215), Form 12ug (221)
Common baseline mean (SE): 214.204 (3.285)

Source data: Appendix 16.1.9.2, Statdoc 6.2.1.3 ctr\diary-adjmean-ancova.sas 11OCT2011

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
7	Placebo	206.800 (2.848)			
	Olo 5ug	224.019 (2.887)	17.219 (3.902)	<.0001	(9.561, 24.877)
	Olo 10ug	226.520 (2.846)	19.720 (3.879)	<.0001	(12.107, 27.333)
	Form 12ug	224.526 (2.823)	17.725 (3.852)	<.0001	(10.164, 25.286)
8	Placebo	207.092 (2.811)			
	Olo 5ug	222.434 (2.849)	15.342 (3.850)	<.0001	(7.785, 22.898)
	Olo 10ug	226.891 (2.809)	19.799 (3.827)	<.0001	(12.287, 27.311)
	Form 12ug	224.118 (2.785)	17.026 (3.801)	<.0001	(9.565, 24.486)
9	Placebo	205.276 (2.951)			
	Olo 5ug	223.976 (2.991)	18.700 (4.043)	<.0001	(10.766, 26.635)
	Olo 10ug	227.302 (2.949)	22.027 (4.019)	<.0001	(14.139, 29.914)
	Form 12ug	224.823 (2.925)	19.548 (3.991)	<.0001	(11.714, 27.382)
10	Placebo	205.997 (2.997)			
	Olo 5ug	221.837 (3.038)	15.840 (4.105)	0.0001	(7.783, 23.898)
	Olo 10ug	225.127 (2.995)	19.131 (4.081)	<.0001	(11.121, 27.140)
	Form 12ug	222.638 (2.970)	16.641 (4.053)	<.0001	(8.686, 24.596)
11	Placebo	205.112 (3.003)			
	Olo 5ug	221.802 (3.044)	16.690 (4.113)	<.0001	(8.616, 24.764)
	Olo 10ug	223.414 (3.001)	18.303 (4.089)	<.0001	(10.277, 26.329)
	Form 12ug	221.480 (2.976)	16.369 (4.061)	<.0001	(8.398, 24.340)
12	Placebo	204.580 (3.089)			
	Olo 5ug	223.986 (3.131)	19.405 (4.232)	<.0001	(11.099, 27.712)
	Olo 10ug	224.806 (3.087)	20.226 (4.207)	<.0001	(11.969, 28.483)
	Form 12ug	220.917 (3.062)	16.337 (4.178)	<.0001	(8.136, 24.537)

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 (215), Olo 5ug (211), Olo 10ug (215), Form 12ug (221)
Common baseline mean (SE): 214.204 (3.285)

Source data: Appendix 16.1.9.2, Statdoc 6.2.1.3 ctr\diary-adjmean-ancova.sas 11OCT2011

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
13	Placebo	205.659 (3.096)			
	Olo 5ug	223.977 (3.138)	18.318 (4.241)	<.0001	(9.994, 26.642)
	Olo 10ug	226.500 (3.094)	20.841 (4.216)	<.0001	(12.566, 29.116)
	Form 12ug	223.624 (3.068)	17.965 (4.187)	<.0001	(9.747, 26.184)
14	Placebo	205.021 (3.165)			
	Olo 5ug	224.071 (3.208)	19.051 (4.336)	<.0001	(10.541, 27.560)
	Olo 10ug	224.735 (3.163)	19.715 (4.310)	<.0001	(11.255, 28.174)
	Form 12ug	222.122 (3.136)	17.101 (4.280)	<.0001	(8.700, 25.503)
15	Placebo	206.166 (3.193)			
	Olo 5ug	225.023 (3.236)	18.857 (4.373)	<.0001	(10.273, 27.441)
	Olo 10ug	223.205 (3.190)	17.040 (4.348)	<.0001	(8.507, 25.573)
	Form 12ug	221.148 (3.164)	14.982 (4.318)	0.0005	(6.508, 23.457)
16	Placebo	206.313 (3.173)			
	Olo 5ug	221.573 (3.216)	15.260 (4.347)	0.0005	(6.728, 23.792)
	Olo 10ug	224.619 (3.171)	18.306 (4.321)	<.0001	(9.825, 26.787)
	Form 12ug	219.627 (3.145)	13.314 (4.292)	0.0020	(4.891, 21.737)
17	Placebo	206.063 (3.266)			
	Olo 5ug	219.500 (3.310)	13.437 (4.474)	0.0027	(4.656, 22.218)
	Olo 10ug	221.801 (3.264)	15.738 (4.447)	0.0004	(7.009, 24.467)
	Form 12ug	218.265 (3.237)	12.202 (4.417)	0.0059	(3.532, 20.871)
18	Placebo	204.913 (3.284)			
	Olo 5ug	220.386 (3.329)	15.473 (4.499)	0.0006	(6.642, 24.303)
	Olo 10ug	223.386 (3.282)	18.473 (4.472)	<.0001	(9.695, 27.251)
	Form 12ug	220.500 (3.255)	15.587 (4.442)	0.0005	(6.869, 24.305)

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 (215), Olo 5ug (211), Olo 10ug (215), Form 12ug (221)
Common baseline mean (SE): 214.204 (3.285)

Source data: Appendix 16.1.9.2, Statdoc 6.2.1.3 ctr\diary-adjmean-ancova.sas 11OCT2011

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
19	Placebo	206.285 (3.292)			
	Olo 5ug	222.036 (3.337)	15.751 (4.510)	0.0005	(6.899, 24.603)
	Olo 10ug	224.916 (3.290)	18.631 (4.483)	<.0001	(9.831, 27.430)
	Form 12ug	221.936 (3.263)	15.651 (4.453)	0.0005	(6.912, 24.391)
20	Placebo	204.809 (3.286)			
	Olo 5ug	222.320 (3.330)	17.511 (4.501)	0.0001	(8.678, 26.345)
	Olo 10ug	224.718 (3.283)	19.909 (4.474)	<.0001	(11.127, 28.690)
	Form 12ug	221.721 (3.256)	16.912 (4.444)	0.0002	(8.190, 25.633)
21	Placebo	203.150 (3.324)			
	Olo 5ug	220.724 (3.369)	17.574 (4.553)	0.0001	(8.638, 26.510)
	Olo 10ug	222.083 (3.321)	18.934 (4.526)	<.0001	(10.051, 27.817)
	Form 12ug	221.138 (3.294)	17.989 (4.495)	<.0001	(9.166, 26.811)
22	Placebo	204.557 (3.297)			
	Olo 5ug	223.293 (3.342)	18.736 (4.517)	<.0001	(9.870, 27.601)
	Olo 10ug	220.718 (3.295)	16.160 (4.490)	0.0003	(7.347, 24.973)
	Form 12ug	218.436 (3.268)	13.879 (4.460)	0.0019	(5.126, 22.631)
23	Placebo	203.914 (3.378)			
	Olo 5ug	221.242 (3.424)	17.329 (4.628)	0.0002	(8.245, 26.412)
	Olo 10ug	219.707 (3.376)	15.793 (4.600)	0.0006	(6.764, 24.823)
	Form 12ug	218.718 (3.348)	14.804 (4.569)	0.0012	(5.837, 23.772)
24	Placebo	202.256 (3.363)			
	Olo 5ug	219.977 (3.408)	17.721 (4.606)	0.0001	(8.680, 26.762)
	Olo 10ug	220.727 (3.360)	18.471 (4.579)	<.0001	(9.484, 27.458)
	Form 12ug	220.129 (3.332)	17.873 (4.548)	<.0001	(8.947, 26.799)

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 (215), Olo 5ug (211), Olo 10ug (215), Form 12ug (221)
Common baseline mean (SE): 214.204 (3.285)

Source data: Appendix 16.1.9.2, Statdoc 6.2.1.3 ctr\diary-adjmean-ancova.sas 11OCT2011

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	203.513 (3.327)			
	Olo 5ug	219.766 (3.372)	16.253 (4.558)	0.0004	(7.307, 25.199)
	Olo 10ug	222.573 (3.325)	19.060 (4.531)	<.0001	(10.167, 27.953)
	Form 12ug	220.766 (3.297)	17.253 (4.500)	0.0001	(8.421, 26.086)
26	Placebo	203.625 (3.355)			
	Olo 5ug	220.637 (3.401)	17.012 (4.596)	0.0002	(7.991, 26.032)
	Olo 10ug	221.928 (3.353)	18.303 (4.569)	<.0001	(9.336, 27.270)
	Form 12ug	220.351 (3.325)	16.726 (4.537)	0.0002	(7.820, 25.632)
27	Placebo	202.319 (3.410)			
	Olo 5ug	221.773 (3.456)	19.454 (4.671)	<.0001	(10.286, 28.622)
	Olo 10ug	220.599 (3.408)	18.280 (4.643)	<.0001	(9.166, 27.394)
	Form 12ug	221.863 (3.379)	19.544 (4.612)	<.0001	(10.492, 28.595)
28	Placebo	202.377 (3.409)			
	Olo 5ug	220.494 (3.456)	18.117 (4.670)	0.0001	(8.950, 27.283)
	Olo 10ug	220.596 (3.407)	18.219 (4.643)	<.0001	(9.107, 27.331)
	Form 12ug	220.320 (3.379)	17.942 (4.611)	0.0001	(8.892, 26.992)
29	Placebo	201.357 (3.461)			
	Olo 5ug	219.523 (3.508)	18.166 (4.740)	0.0001	(8.862, 27.471)
	Olo 10ug	218.845 (3.458)	17.488 (4.712)	0.0002	(8.239, 26.737)
	Form 12ug	221.874 (3.429)	20.517 (4.680)	<.0001	(11.331, 29.703)
30	Placebo	200.317 (3.481)			
	Olo 5ug	220.738 (3.529)	20.421 (4.769)	<.0001	(11.061, 29.781)
	Olo 10ug	219.332 (3.479)	19.015 (4.741)	<.0001	(9.711, 28.320)
	Form 12ug	221.178 (3.450)	20.861 (4.708)	<.0001	(11.620, 30.102)

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 (215), Olo 5ug (211), Olo 10ug (215), Form 12ug (221)
Common baseline mean (SE): 214.204 (3.285)

Source data: Appendix 16.1.9.2, Statdoc 6.2.1.3 ctr\diary-adjmean-ancova.sas 11OCT2011

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
31	Placebo	199.890 (3.486)			
	Olo 5ug	219.879 (3.533)	19.988 (4.775)	<.0001	(10.616, 29.361)
	Olo 10ug	218.908 (3.483)	19.017 (4.747)	<.0001	(9.700, 28.334)
	Form 12ug	219.970 (3.455)	20.080 (4.715)	<.0001	(10.826, 29.333)
32	Placebo	202.871 (3.493)			
	Olo 5ug	218.606 (3.540)	15.735 (4.784)	0.0010	(6.345, 25.126)
	Olo 10ug	219.491 (3.490)	16.620 (4.756)	0.0005	(7.285, 25.955)
	Form 12ug	218.842 (3.461)	15.971 (4.724)	0.0008	(6.699, 25.242)
33	Placebo	201.738 (3.512)			
	Olo 5ug	219.152 (3.560)	17.415 (4.811)	0.0003	(7.972, 26.857)
	Olo 10ug	219.579 (3.509)	17.841 (4.782)	0.0002	(8.455, 27.227)
	Form 12ug	220.791 (3.480)	19.053 (4.750)	<.0001	(9.731, 28.376)
34	Placebo	200.891 (3.574)			
	Olo 5ug	218.442 (3.623)	17.551 (4.896)	0.0004	(7.941, 27.161)
	Olo 10ug	219.640 (3.572)	18.750 (4.867)	0.0001	(9.197, 28.302)
	Form 12ug	219.920 (3.542)	19.030 (4.834)	<.0001	(9.542, 28.517)
35	Placebo	201.693 (3.581)			
	Olo 5ug	217.122 (3.630)	15.429 (4.906)	0.0017	(5.800, 25.058)
	Olo 10ug	220.899 (3.579)	19.206 (4.877)	<.0001	(9.635, 28.778)
	Form 12ug	220.480 (3.549)	18.787 (4.843)	0.0001	(9.281, 28.294)
36	Placebo	202.213 (3.555)			
	Olo 5ug	216.664 (3.603)	14.451 (4.870)	0.0031	(4.893, 24.010)
	Olo 10ug	219.942 (3.553)	17.729 (4.841)	0.0003	(8.227, 27.231)
	Form 12ug	219.218 (3.523)	17.005 (4.808)	0.0004	(7.568, 26.442)

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 (215), Olo 5ug (211), Olo 10ug (215), Form 12ug (221)
Common baseline mean (SE): 214.204 (3.285)

Source data: Appendix 16.1.9.2, Statdoc 6.2.1.3 ctr\diary-adjmean-ancova.sas 11OCT2011

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
37	Placebo	203.175 (3.576)			
	Olo 5ug	219.253 (3.624)	16.078 (4.898)	0.0011	(6.465, 25.692)
	Olo 10ug	219.268 (3.573)	16.093 (4.869)	0.0010	(6.537, 25.650)
	Form 12ug	219.174 (3.543)	15.999 (4.836)	0.0010	(6.507, 25.490)
38	Placebo	203.856 (3.596)			
	Olo 5ug	218.269 (3.645)	14.413 (4.927)	0.0035	(4.744, 24.083)
	Olo 10ug	220.172 (3.594)	16.316 (4.897)	0.0009	(6.703, 25.928)
	Form 12ug	219.080 (3.564)	15.223 (4.864)	0.0018	(5.677, 24.770)
39	Placebo	202.562 (3.631)			
	Olo 5ug	217.327 (3.680)	14.766 (4.974)	0.0031	(5.004, 24.527)
	Olo 10ug	219.539 (3.628)	16.977 (4.944)	0.0006	(7.273, 26.681)
	Form 12ug	219.601 (3.598)	17.039 (4.910)	0.0005	(7.402, 26.677)
40	Placebo	204.435 (3.614)			
	Olo 5ug	214.520 (3.663)	10.085 (4.951)	0.0420	(0.367, 19.802)
	Olo 10ug	219.614 (3.612)	15.179 (4.922)	0.0021	(5.518, 24.839)
	Form 12ug	219.816 (3.582)	15.381 (4.888)	0.0017	(5.787, 24.975)
41	Placebo	203.322 (3.664)			
	Olo 5ug	216.408 (3.714)	13.087 (5.019)	0.0093	(3.236, 22.938)
	Olo 10ug	220.022 (3.661)	16.700 (4.989)	0.0009	(6.907, 26.492)
	Form 12ug	219.863 (3.631)	16.541 (4.955)	0.0009	(6.815, 26.267)
42	Placebo	202.483 (3.680)			
	Olo 5ug	217.596 (3.730)	15.113 (5.042)	0.0028	(5.218, 25.008)
	Olo 10ug	218.920 (3.678)	16.436 (5.012)	0.0011	(6.600, 26.273)
	Form 12ug	221.174 (3.647)	18.691 (4.977)	0.0002	(8.921, 28.460)

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 (215), Olo 5ug (211), Olo 10ug (215), Form 12ug (221)
Common baseline mean (SE): 214.204 (3.285)

Source data: Appendix 16.1.9.2, Statdoc 6.2.1.3 ctr\diary-adjmean-ancova.sas 11OCT2011

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
43	Placebo	202.157 (3.651)			
	Olo 5ug	219.302 (3.700)	17.144 (5.001)	0.0006	(7.329, 26.959)
	Olo 10ug	220.576 (3.648)	18.418 (4.971)	0.0002	(8.661, 28.175)
	Form 12ug	220.809 (3.618)	18.651 (4.937)	0.0002	(8.961, 28.342)
44	Placebo	201.677 (3.674)			
	Olo 5ug	219.154 (3.724)	17.477 (5.033)	0.0005	(7.598, 27.356)
	Olo 10ug	218.081 (3.672)	16.404 (5.004)	0.0011	(6.583, 26.225)
	Form 12ug	220.254 (3.641)	18.577 (4.969)	0.0002	(8.823, 28.331)
45	Placebo	200.402 (3.695)			
	Olo 5ug	217.695 (3.745)	17.293 (5.062)	0.0007	(7.357, 27.228)
	Olo 10ug	217.615 (3.693)	17.213 (5.032)	0.0007	(7.337, 27.090)
	Form 12ug	220.921 (3.662)	20.519 (4.998)	<.0001	(10.710, 30.328)
46	Placebo	201.729 (3.722)			
	Olo 5ug	215.948 (3.772)	14.219 (5.098)	0.0054	(4.213, 24.226)
	Olo 10ug	220.300 (3.719)	18.570 (5.068)	0.0003	(8.623, 28.518)
	Form 12ug	219.518 (3.688)	17.789 (5.033)	0.0004	(7.910, 27.668)
47	Placebo	201.120 (3.692)			
	Olo 5ug	216.893 (3.742)	15.773 (5.057)	0.0019	(5.847, 25.698)
	Olo 10ug	218.687 (3.689)	17.567 (5.027)	0.0005	(7.700, 27.434)
	Form 12ug	219.819 (3.658)	18.698 (4.993)	0.0002	(8.899, 28.498)
48	Placebo	201.194 (3.721)			
	Olo 5ug	216.672 (3.771)	15.478 (5.097)	0.0025	(5.474, 25.482)
	Olo 10ug	218.354 (3.718)	17.160 (5.067)	0.0007	(7.215, 27.105)
	Form 12ug	219.198 (3.687)	18.005 (5.032)	0.0004	(8.128, 27.881)

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 (215), Olo 5ug (211), Olo 10ug (215), Form 12ug (221)
Common baseline mean (SE): 214.204 (3.285)

Source data: Appendix 16.1.9.2, Statdoc 6.2.1.3 ctr\diary-adjmean-ancova.sas 11OCT2011