

Clinical Study Synopsis for Public Disclosure

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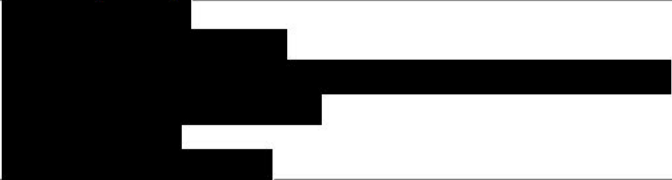
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| Name of company: Boehringer Ingelheim | | Tabulated Trial Report | |  Boehringer Ingelheim Synopsis No.: |
| Name of finished product: Not applicable | | EudraCT No.: 2008-001934-28 | | |
| Name of active ingredient: Olodaterol (BI 1744) | | Page: 1 of 9 | | |
| Module: | | Volume: | | |
| Report date: 31 January 2012 | Trial No. / U No.: 1222.14 / U10-3195-01 | Date of trial: 27 Jan 2009 – 08 Dec 2010 | Date of revision: Not applicable | |
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| 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 [g] and 10 [g [2 actuations of 5 [g]) 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: |  | | | |
| Trial sites: | Multicentre Study, c.f. 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. | | | |
| No. of subjects: | | | | |
| planned: | entered: 860 (215 per group) | | | |
| actual: | Enrolled: 1257; entered/randomized: 937; treated: 934 <u>Placebo:</u> treated: 235 <ul style="list-style-type: none"> analyzed for co-primary endpoint forced expiratory volume in 1 second (FEV₁) area under the curve (AUC) over 0 to 3 hours (0-3h) response at Day 169: 233 analyzed for co-primary endpoint trough FEV₁ response at Day 169: 232 | | | |


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| <p><u>olodaterol 5 µg</u>: treated: 232</p> <ul style="list-style-type: none"> • analyzed for co-primary endpoint FEV₁ AUC_{0-3h} response at Day 169: 230 • analyzed for co-primary endpoint trough FEV₁ response at Day 169: 229 <p><u>olodaterol 10 µg</u>: treated: 234</p> <ul style="list-style-type: none"> • analyzed for co-primary endpoint FEV₁ AUC_{0-3h} response at Day 169: 233 • analyzed for co-primary endpoint trough FEV₁ response at Day 169: 228 <p><u>Foradil® 12 µg bid</u>: treated: 233</p> <ul style="list-style-type: none"> • analyzed for co-primary endpoint FEV₁ AUC_{0-3h} response at Day 169: 232 • analyzed for co-primary endpoint trough FEV₁ response at Day 169: 229 | | | | |
| 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 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 | | | |
| Reference therapy 1: | Placebo inhalation matching olodaterol | | | |
| dose: | Not applicable | | | |
| mode of admin.: | Oral inhalation | | | |
| batch no.: | B082000022, B082000136, B082000101 | | | |
| Reference therapy 2: | Foradil® - Aerolizer® | | | |
| dose: | 12 µg twice daily | | | |
| mode of admin.: | Oral inhalation | | | |
| batch no.: | B082000081, B082000184, B082000207, B082000060, B082000271, B092000024, B092000044, B092000063, B092000044, B092000081 | | | |


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| Reference therapy 3: Placebo inhalation matching Foradil® - Aerolizer® dose: N/A mode of admin.: Oral inhalation batch no.: B082000046, B082000098, B082000080, B082000281, B092000046, B102000047, 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. 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 results: Efficacy results presented in this report, based on analyses of the data from Study 1222.14 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) | | | | |


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| Module: | | Volume: | | |
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| <p>SGRQ total score (key secondary endpoint), (iii) comparisons between olodaterol and Foradil® (FEV₁ AUC_{0-3h} response at Day 169, trough FEV₁ 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 1222.14 and the replicate Study 1222.13, are described in a separate report (Study 1222.9993).</p> <p>Co-primary endpoints (lung function):</p> <ul style="list-style-type: none"> • Treatment with olodaterol 5 µg and 10 µg resulted in statistically significant improvement in FEV₁ AUC_{0-3h} response compared with placebo at Day 169 (Week 24): differences were 0.129 L (0.116 vs. -0.013 L) for olodaterol 5 µg and 0.154 L (0.140 vs. -0.013 L) for olodaterol 10 µg compared to placebo (p<0.0001 for both doses). A statistically significant increase was also observed for Foradil® 12 µg compared with placebo (0.150 L difference [0.137 vs. -0.013 L], p<0.0001). • Treatment with olodaterol 5 µg and 10 µg resulted in statistically significant improvement in trough FEV₁ response compared with placebo at Day 169 (Week 24): differences were 0.053 L (-0.003 vs. -0.055 L) for olodaterol 5 µg and 0.069 L (0.014 vs. -0.055 L) for olodaterol 10 µg compared to placebo (p≤0.0055 for both doses). A statistically significant increase was also observed for Foradil® 12 µg compared with placebo (0.042 L difference [-0.013 vs. -0.055 L], p=0.0270). <p>Since patients taking tiotropium at screening continued with tiotropium as concomitant therapy throughout the trial, randomisation was stratified by concomitant tiotropium use, and tiotropium use stratum was included as a covariate in the model for the primary analyses. The results were dominated by the subgroup of patients who did not concomitantly use tiotropium (about 75% patients). The patients who used tiotropium concomitantly also showed improvement with olodaterol; however, due to the smaller sample size, the results were imprecise and not always statistically significant.</p> <p>An analysis by tiotropium stratum based on the combined dataset from this study (1222.14) and the replicate study 1222.13 is presented in a separate report (Study 1222.9993).</p> | | | | |

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| Module: | | Volume: | | |
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| <p>Key secondary endpoints:</p> <p>As described above, analyses of key secondary endpoints are described in a separate report (Study 1222.9993).</p> <p>Other secondary endpoints:</p> <p>Supportive analyses of lung function (FEV₁ 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 Foradil® 12 µg) compared to placebo (p<0.0001 to p=0.0270) for the following secondary endpoints:</p> <ul style="list-style-type: none"> • FEV₁ AUC_{0-3h} response and FEV₁ peak_{0-3h} response (all three active treatment groups compared to placebo on all test days). • Trough FEV₁ response [all three active treatment groups compared to placebo on all test days with the exception of Day 337 for the Foradil® 12 µg group (p=0.0664)]. • Adjusted mean FEV₁ response 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_{0-3h} response and FVC peak_{0-3h} response (all three active treatment groups compared to placebo on all test days). • FVC trough response: there were statistically significant increases observed for both olodaterol dose groups, compared with placebo, on all test days except day 169 (p=0.0718 for olodaterol 5 µg; p=0.0863 for olodaterol 10 µg) and day 225 for the olodaterol 10 µg group (p=0.0601). There was a statistically significant increase in FVC trough response observed for the olodaterol 5 µg group on Day 225. Statistically significant increases were observed for the Foradil 12® µg group on all test days except days 169 (p=0.2982), 225 (p=0.2573), 281 (p=0.1598), and 337 (p=0.3147). • 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). | | | | |

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| <p>Consistent with the primary and secondary analyses which demonstrated 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:</p> <ul style="list-style-type: none"> • There was statistically significant improvement in morning and evening PEFR observed for both olodaterol 5 µg and 10 µg and for Foradil® 12 µg compared with placebo at all assessments over 48 weeks. • There was a reduced need for daytime, nighttime, and daily (24-hour) rescue medication use for patients receiving olodaterol 5 µg or 10 µg or Foradil® 12 µg compared with placebo. Statistically significant reductions were observed for most weeks for mean daytime rescue medication use and for all weeks for mean nighttime and daily (24-hour) use for the olodaterol 10 µg group compared with placebo. Although weekly mean daytime, nighttime, and daily (24-hour) rescue medication use was also reduced in the olodaterol 5 µg and the Foradil® 12 µg treatment groups compared to placebo, the magnitude of the reductions was consistently less than the reduction observed in the olodaterol 10 µg group and statistically significant reductions were not observed at all time points. • As rated on the PGR, significant improvement in respiratory condition was observed on test days 43, 85, and 169 for the olodaterol 10 µg and the Foradil® 12 µg treatment groups, and on test days 43 and 85 for the olodaterol 5 µg treatment group, compared with placebo. <p>Time to first COPD exacerbation, moderate COPD exacerbation, and COPD exacerbation leading to hospitalisation was not statistically significantly earlier in patients treated with placebo compared with patients treated with olodaterol 5 µg, olodaterol 10 µg, or Foradil® 12 µg. The hazard ratios for mean time to first COPD exacerbation compared to placebo were 0.802 (p=0.1946) for the olodaterol 5 µg group, 0.872 (p=0.141) for the olodaterol 10 µg group, and 0.922 (p=0.6404) for the Foradil® 12 µg 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.</p> | | | | |

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| Name of active ingredient: Olodaterol (BI 1744) | | Page: 7 of 9 | | |
| Module: | | Volume: | | |
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| <p>Clinical Pharmacology:</p> <p>Overall, the geometric mean (gMean) $C_{0.167,ss}$ value of the olodaterol 10 µg treatment group (6.98 pg/mL) was 1.8-fold higher than that of the olodaterol 5 µg treatment group (3.92 pg/mL). The reason for this slightly less than dose-proportional increase is the higher incidence of plasma concentrations below the limit of quantification in the olodaterol 5 µg treatment group (BLQ, NOP: N=187) than in the olodaterol 10 µg treatment group (BLQ, NOP: N=39). As these data are omitted in the calculation of the descriptive statistics, the gMean value of the olodaterol 5 µg treatment group is more pronouncedly prone to certain overestimation than the gMean value of the olodaterol 10 µg treatment group.</p> <p>Olodaterol plasma concentrations at 10 min post dose and potassium concentrations at 3 hours post dose on day 85, but not on day 43, appeared to be inversely correlated. Olodaterol plasma concentrations in Asians tended to be slightly higher than in Whites.</p> | | | | |
| <p>Safety results:</p> <p>In this 48-week study, long-term administration of inhaled olodaterol 5 µg and 10 µg was generally safe and well tolerated and no safety concerns were identified:</p> <p>The percentage of patients reported with at least one AE was comparable in all four treatment groups: placebo (73.6%), olodaterol 5 µg (72.8%), olodaterol 10 µg (72.2%), and Foradil® 12 µg (72.5%). The most common treatment-emergent AEs were COPD (reported terms: exacerbation, worsening, or deterioration of COPD) (27.5%), nasopharyngitis (11.8%), upper respiratory tract infection (7.4%), and cough (5.1%). Nasopharyngitis was reported more frequently in both olodaterol treatment groups than in the placebo treatment group: placebo, 9.4%; olodaterol 5 µg, 15.9%; olodaterol 10 µg, 12.0%; Foradil® 12 µg, 9.9%. The incidence of the remaining most common AEs was comparable between the four treatment groups. The overall incidence of severe (12.3%) and drug related (8.1%) AEs was low; fewer patients in the olodaterol dose groups (5.2%-5.6%) were reported with investigator defined drug-related AEs compared to the placebo (10.6%) and Foradil® 12 µg (11.2%) groups.</p> <p>Overall, there were 31 deaths reported for patients randomized in the trial. 25 deaths were a result of AEs that occurred during the treatment period (6 placebo, 7 olodaterol 5 µg, 6 olodaterol 10 µg, 6 Foradil® 12 µg. There were 3 deaths due</p> | | | | |

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| <p>to AEs that occurred during the post-treatment period (2 placebo, 1 olodaterol 10 µg). There were 4 deaths that were a result of post-study AEs (1 placebo, 1 olodaterol 5 µg, 1 Foradil® 12 µg). One patient (in the olodaterol 5 µg group) died due to AEs that occurred both during the treatment period and in the post study period, however, this death is counted only once in the overall total number of deaths for the study. There were three deaths that were reported for patients who were in the screening period and who were never randomized. None of the deaths were considered to be related to study drug; one death, reported for a patient receiving placebo, was considered by the investigator as related to study design. COPD was the most common AE that led to death (7 patients).</p> <p>A total of 159 patients (17.0%) reported at least one SAE during the study: placebo (20.4%), olodaterol 5 µg (14.7%), olodaterol 10 µg (17.5%), and Foradil® 12 µg (15.5%). The most commonly reported treatment-emergent SAEs, overall, were COPD (67 patients, 7.2%); pneumonia (15 patients, 1.6%); dyspnoea (5 patients, 0.5%); atrial fibrillation, pulmonary embolism, and respiratory failure (4 patients each, 0.4%); pneumothorax, intervertebral disc protrusion, acute myocardial infarction, acute coronary syndrome, and death (3 patients each, 0.3%). No other SAE was reported for more than 2 patients.</p> <p>There were no patients receiving olodaterol 5 µg reported with treatment-emergent SAEs that were considered related to study drug by the investigator; there was one patient receiving olodaterol 10 µg, four patients receiving placebo and five patients receiving Foradil® 12 µg reported with study-related SAEs: five patients (one receiving olodaterol 10 µg, three receiving placebo and one receiving Foradil® 12 µg) had SAEs considered related to trial medication and four patients (all receiving Foradil® 12 µg) were reported with SAEs (COPD) considered related to study design procedures. One patient in the olodaterol 10 µg group, was reported with dizziness during the post-treatment period (>12 days after treatment stop date) that was considered related to study drug.</p> <p>There were 67 patients (7.2%) reported with at least one treatment-emergent AE that led to discontinuation of study drug: placebo (8.1%), olodaterol 5 µg (6.5%), olodaterol 10 µg (6.8%) and Foradil® 12 µg (7.3%). The most common treatment-emergent AEs that led to study drug discontinuation were COPD (22 patients, 2.4%); dyspnoea (4 patients, 0.4%), death (3 patients, 0.3%); pneumonia, bladder cancer, lung neoplasm malignant, acute myocardial</p> | | | | |

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| <p>infarction, atrial fibrillation, ventricular extrasystoles, respiratory failure, renal failure acute, chest pain were reported for 2 patients each (0.2%). The frequency of discontinuation due to AEs of COPD (exacerbation) was 1.7% in the placebo group, 2.2% in the olodaterol 5 µg group, 2.6% in the olodaterol 10 µg group and 3.0% in the Foradil® 12 µg group.</p> <p>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.</p> <p>There were no statistically significant decreases of mean blood potassium levels compared to placebo for any of the active treatment groups (olodaterol 5 µg, olodaterol 10 µg, and Foradil® 12 µg).</p> <p>The comprehensive analysis for ECG evaluations and the Holter monitoring data was based on data from this trial and the replicate trial (Study 1222.13). The results of the combined analysis are presented in the separate combined report (Study 1222.9993).</p> | | | | |
| <p>Conclusions: With respect to lung function, the primary objective of the present study was met, with olodaterol 5 µg once daily and olodaterol 10µg once daily showing statistically significant improvements compared to placebo for the co-primary endpoints of FEV₁ AUC₀₋₃ response at Day 169 and trough FEV₁ response at Day 169. Conclusions regarding the assessment of symptomatic benefit are presented in a separate report. 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.</p> | | | | |

Trial Synopsis - Appendix

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

| Results for | presented in |
|--|---------------------|
| Patient disposition | Table 15.1.1: 1 |
| FEV ₁ AUC _{0-3h} on test days 1, 15, 43, 85, 169, and 337 | Table 15.2.1.1.2: 1 |
| FEV ₁ peak _{0-3h} 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 _{0-3h} on test days 1, 15, 43, 85, 169, and 337 | Table 15.2.1.2.2: 2 |
| FVC peak _{0-3h} 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 PEF, Weeks 1 to 48 | Table 15.2.2.1: 1 |
| Evening Weekly PEF, 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 | | | | | 1257 |
| Not entered/randomised | | | | | 320 |
| Entered/randomised | | | | | 937 |
| Not treated | | | | | 3 |
| Treated | 235 (100.00) | 232 (100.00) | 234 (100.00) | 233 (100.00) | 934 (100.00) |
| Not prematurely discontinued from trial medication # | 184 (78.30) | 195 (84.05) | 198 (84.62) | 193 (82.83) | 770 (82.44) |
| Prematurely discontinued from trial medication | 51 (21.70) | 37 (15.95) | 36 (15.38) | 40 (17.17) | 164 (17.56) |
| Adverse event | 19 (8.09) | 16 (6.90) | 16 (6.84) | 16 (6.87) | 67 (7.17) |
| AE study dis. worse | 5 (2.13) | 6 (2.59) | 4 (1.71) | 9 (3.86) | 24 (2.57) |
| AE-oth. dis. worse | 2 (0.85) | 1 (0.43) | 3 (1.28) | 1 (0.43) | 7 (0.75) |
| AE-other | 12 (5.11) | 9 (3.88) | 9 (3.85) | 6 (2.58) | 36 (3.85) |
| Lack of efficacy | 8 (3.40) | 1 (0.43) | 3 (1.28) | 2 (0.86) | 14 (1.50) |
| Non compl prot. | 2 (0.85) | 2 (0.86) | 0 (0.00) | 2 (0.86) | 6 (0.64) |
| Lost to follow-up | 2 (0.85) | 1 (0.43) | 2 (0.85) | 3 (1.29) | 8 (0.86) |
| Consent withdrawn | 16 (6.81) | 8 (3.45) | 8 (3.42) | 13 (5.58) | 45 (4.82) |
| Other | 4 (1.70) | 9 (3.88) | 7 (2.99) | 4 (1.72) | 24 (2.57) |

Patient [REDACTED] and Patient [REDACTED] were randomized and withdrew consent prior to receiving study medication. Patient [REDACTED] was withdrawn prior to receiving study medication due to findings on pre-dose ECG.

Boehringer Ingelheim
BI Trial No.: 1222.14
1. - 15. CTR Main Part

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)

| Test day | Treatment | Treatment mean (SE) | Difference from Placebo | | |
|----------|-----------|---------------------|-------------------------|---------|-----------------|
| | | | Mean (SE) | P-value | 95% CI |
| 1 | Placebo | 0.033 (0.013) | | | |
| | Olo 5ug | 0.182 (0.014) | 0.149 (0.019) | <.0001 | (0.113, 0.186) |
| | Olo 10ug | 0.203 (0.013) | 0.171 (0.018) | <.0001 | (0.134, 0.207) |
| | Form 12ug | 0.185 (0.014) | 0.152 (0.019) | <.0001 | (0.115, 0.188) |
| 15 | Placebo | 0.021 (0.013) | | | |
| | Olo 5ug | 0.181 (0.014) | 0.160 (0.019) | <.0001 | (0.123, 0.196) |
| | Olo 10ug | 0.214 (0.013) | 0.193 (0.019) | <.0001 | (0.157, 0.229) |
| | Form 12ug | 0.183 (0.014) | 0.162 (0.019) | <.0001 | (0.126, 0.199) |
| 43 | Placebo | -0.010 (0.014) | | | |
| | Olo 5ug | 0.162 (0.014) | 0.172 (0.019) | <.0001 | (0.136, 0.209) |
| | Olo 10ug | 0.181 (0.014) | 0.192 (0.019) | <.0001 | (0.155, 0.228) |
| | Form 12ug | 0.174 (0.014) | 0.184 (0.019) | <.0001 | (0.148, 0.221) |
| 85 | Placebo | -0.008 (0.014) | | | |
| | Olo 5ug | 0.138 (0.014) | 0.145 (0.019) | <.0001 | (0.108, 0.182) |
| | Olo 10ug | 0.167 (0.014) | 0.175 (0.019) | <.0001 | (0.138, 0.212) |
| | Form 12ug | 0.163 (0.014) | 0.170 (0.019) | <.0001 | (0.133, 0.208) |
| 169 | Placebo | -0.013 (0.014) | | | |
| | Olo 5ug | 0.116 (0.014) | 0.129 (0.019) | <.0001 | (0.091, 0.167) |
| | Olo 10ug | 0.140 (0.014) | 0.154 (0.019) | <.0001 | (0.116, 0.191) |
| | Form 12ug | 0.137 (0.014) | 0.150 (0.019) | <.0001 | (0.112, 0.188) |
| 337 | Placebo | -0.025 (0.014) | | | |
| | Olo 5ug | 0.093 (0.014) | 0.118 (0.020) | <.0001 | (0.080, 0.156) |
| | Olo 10ug | 0.116 (0.014) | 0.141 (0.020) | <.0001 | (0.103, 0.180) |
| | Form 12ug | 0.104 (0.014) | 0.129 (0.020) | <.0001 | (0.091, 0.168) |

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 (233), Olo 5ug (230), Olo 10ug (233), Form 12ug (232)
Common baseline mean (SE): 1.211 (0.015)

Source data: Appendix 16.1.9.2, Statdoc 6.1.1.2.1

ctr\pft-adjmean-mmrm.sas 13OCT2011

Boehringer Ingelheim
BI Trial No.: 1222.14
1. - 15. CTR Main Part

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)

| Test day | Treatment | Treatment mean (SE) | Difference from Placebo | | | |
|----------|-----------|---------------------|-------------------------|---------|----------|--------|
| | | | Mean (SE) | P-value | 95% CI | |
| 1 | Placebo | 0.105 (0.014) | | | | |
| | Olo 5ug | 0.254 (0.014) | 0.149 (0.019) | <.0001 | (0.111, | 0.187) |
| | Olo 10ug | 0.277 (0.014) | 0.171 (0.019) | <.0001 | (0.133, | 0.209) |
| | Form 12ug | 0.255 (0.014) | 0.149 (0.019) | <.0001 | (0.111, | 0.187) |
| 15 | Placebo | 0.099 (0.014) | | | | |
| | Olo 5ug | 0.260 (0.014) | 0.161 (0.019) | <.0001 | (0.122, | 0.199) |
| | Olo 10ug | 0.278 (0.014) | 0.178 (0.019) | <.0001 | (0.140, | 0.216) |
| | Form 12ug | 0.253 (0.014) | 0.153 (0.019) | <.0001 | (0.115, | 0.191) |
| 43 | Placebo | 0.066 (0.014) | | | | |
| | Olo 5ug | 0.235 (0.014) | 0.168 (0.020) | <.0001 | (0.130, | 0.207) |
| | Olo 10ug | 0.248 (0.014) | 0.181 (0.020) | <.0001 | (0.143, | 0.220) |
| | Form 12ug | 0.242 (0.014) | 0.176 (0.020) | <.0001 | (0.137, | 0.214) |
| 85 | Placebo | 0.064 (0.014) | | | | |
| | Olo 5ug | 0.206 (0.014) | 0.141 (0.020) | <.0001 | (0.103, | 0.180) |
| | Olo 10ug | 0.232 (0.014) | 0.168 (0.020) | <.0001 | (0.129, | 0.207) |
| | Form 12ug | 0.228 (0.014) | 0.164 (0.020) | <.0001 | (0.125, | 0.203) |
| 169 | Placebo | 0.060 (0.015) | | | | |
| | Olo 5ug | 0.183 (0.014) | 0.123 (0.020) | <.0001 | (0.084, | 0.163) |
| | Olo 10ug | 0.211 (0.014) | 0.151 (0.020) | <.0001 | (0.112, | 0.191) |
| | Form 12ug | 0.203 (0.015) | 0.143 (0.020) | <.0001 | (0.104, | 0.183) |
| 337 | Placebo | 0.052 (0.015) | | | | |
| | Olo 5ug | 0.163 (0.015) | 0.112 (0.020) | <.0001 | (0.071, | 0.152) |
| | Olo 10ug | 0.178 (0.015) | 0.126 (0.020) | <.0001 | (0.086, | 0.166) |
| | Form 12ug | 0.170 (0.015) | 0.118 (0.020) | <.0001 | (0.078, | 0.158) |

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 (233), Olo 5ug (230), Olo 10ug (233), Form 12ug (232)
Common baseline mean (SE): 1.211 (0.015)

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)

| Test day | Treatment | Treatment mean (SE) | Difference from Placebo | | |
|----------|-----------|---------------------|-------------------------|---------|-----------------|
| | | | Mean (SE) | P-value | 95% CI |
| 15 | Placebo | -0.016 (0.013) | | | |
| | Olo 5ug | 0.053 (0.013) | 0.069 (0.018) | 0.0002 | (0.033, 0.105) |
| | Olo 10ug | 0.103 (0.013) | 0.119 (0.018) | <.0001 | (0.083, 0.155) |
| | Form 12ug | 0.033 (0.013) | 0.049 (0.018) | 0.0071 | (0.013, 0.085) |
| 43 | Placebo | -0.036 (0.013) | | | |
| | Olo 5ug | 0.047 (0.013) | 0.084 (0.018) | <.0001 | (0.048, 0.120) |
| | Olo 10ug | 0.068 (0.013) | 0.104 (0.018) | <.0001 | (0.068, 0.141) |
| | Form 12ug | 0.034 (0.013) | 0.070 (0.018) | 0.0001 | (0.034, 0.106) |
| 85 | Placebo | -0.041 (0.014) | | | |
| | Olo 5ug | 0.018 (0.013) | 0.059 (0.019) | 0.0017 | (0.022, 0.095) |
| | Olo 10ug | 0.052 (0.013) | 0.093 (0.019) | <.0001 | (0.057, 0.130) |
| | Form 12ug | 0.024 (0.014) | 0.065 (0.019) | 0.0005 | (0.028, 0.101) |
| 127 | Placebo | -0.036 (0.014) | | | |
| | Olo 5ug | 0.013 (0.014) | 0.050 (0.019) | 0.0085 | (0.013, 0.087) |
| | Olo 10ug | 0.049 (0.013) | 0.086 (0.019) | <.0001 | (0.049, 0.122) |
| | Form 12ug | 0.015 (0.014) | 0.051 (0.019) | 0.0067 | (0.014, 0.088) |
| 169 | Placebo | -0.055 (0.014) | | | |
| | Olo 5ug | -0.003 (0.014) | 0.053 (0.019) | 0.0055 | (0.015, 0.090) |
| | Olo 10ug | 0.014 (0.014) | 0.069 (0.019) | 0.0003 | (0.032, 0.106) |
| | Form 12ug | -0.013 (0.014) | 0.042 (0.019) | 0.0270 | (0.005, 0.080) |
| 225 | Placebo | -0.039 (0.014) | | | |
| | Olo 5ug | 0.023 (0.014) | 0.062 (0.019) | 0.0012 | (0.025, 0.100) |
| | Olo 10ug | 0.034 (0.014) | 0.073 (0.019) | 0.0002 | (0.035, 0.110) |
| | Form 12ug | 0.009 (0.014) | 0.048 (0.019) | 0.0117 | (0.011, 0.086) |

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 (232), Olo 5ug (229), Olo 10ug (228), Form 12ug (229)
Common baseline mean (SE): 1.213 (0.015)

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)

| Test day | Treatment | Treatment mean (SE) | Difference from Placebo | | | |
|----------|-----------|---------------------|-------------------------|---------|-----------|--------|
| | | | Mean (SE) | P-value | 95% CI | |
| 281 | Placebo | -0.043 (0.014) | | | | |
| | Olo 5ug | 0.019 (0.014) | 0.062 (0.019) | 0.0014 | (0.024, | 0.099) |
| | Olo 10ug | 0.041 (0.014) | 0.084 (0.019) | <.0001 | (0.047, | 0.122) |
| | Form 12ug | 0.013 (0.014) | 0.056 (0.019) | 0.0035 | (0.019, | 0.094) |
| 337 | Placebo | -0.060 (0.014) | | | | |
| | Olo 5ug | -0.016 (0.014) | 0.044 (0.019) | 0.0228 | (0.006, | 0.082) |
| | Olo 10ug | -0.001 (0.014) | 0.059 (0.019) | 0.0024 | (0.021, | 0.097) |
| | Form 12ug | -0.024 (0.014) | 0.036 (0.019) | 0.0664 | (-0.002, | 0.074) |

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 (232), Olo 5ug (229), Olo 10ug (228), Form 12ug (229)
Common baseline mean (SE): 1.213 (0.015)

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 | 1.200 (0.015) | | | |
| | | Olo 5ug | 1.200 (0.015) | | | |
| | | Olo 10ug | 1.200 (0.015) | | | |
| | | Form 12ug | 1.200 (0.015) | | | |
| | -0:10 | Placebo | 1.223 (0.015) | | | |
| | | Olo 5ug | 1.223 (0.015) | | | |
| | | Olo 10ug | 1.223 (0.015) | | | |
| | | Form 12ug | 1.223 (0.015) | | | |
| | 0:05 | Placebo | 1.229 (0.013) | | | |
| | | Olo 5ug | 1.332 (0.013) | 0.102 (0.018) | <.0001 | (0.068, 0.137) |
| | | Olo 10ug | 1.342 (0.013) | 0.113 (0.017) | <.0001 | (0.079, 0.147) |
| | | Form 12ug | 1.357 (0.013) | 0.128 (0.018) | <.0001 | (0.093, 0.162) |
| | 0:15 | Placebo | 1.229 (0.013) | | | |
| | | Olo 5ug | 1.365 (0.013) | 0.136 (0.018) | <.0001 | (0.101, 0.172) |
| | | Olo 10ug | 1.377 (0.013) | 0.149 (0.018) | <.0001 | (0.113, 0.184) |
| | | Form 12ug | 1.384 (0.013) | 0.155 (0.018) | <.0001 | (0.120, 0.191) |
| | 0:30 | Placebo | 1.243 (0.014) | | | |
| | | Olo 5ug | 1.378 (0.014) | 0.135 (0.019) | <.0001 | (0.098, 0.172) |
| | | Olo 10ug | 1.397 (0.014) | 0.154 (0.019) | <.0001 | (0.117, 0.191) |
| | | Form 12ug | 1.397 (0.014) | 0.154 (0.019) | <.0001 | (0.117, 0.191) |
| | 1:00 | Placebo | 1.235 (0.014) | | | |
| | | Olo 5ug | 1.392 (0.014) | 0.157 (0.019) | <.0001 | (0.119, 0.194) |
| | | Olo 10ug | 1.413 (0.014) | 0.178 (0.019) | <.0001 | (0.141, 0.215) |
| | | Form 12ug | 1.394 (0.014) | 0.159 (0.019) | <.0001 | (0.122, 0.197) |

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 (233), Olo 5ug (230), Olo 10ug (233), Form 12ug (232)
Common baseline mean (SE): 1.211 (0.015)

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 | 1.263 (0.014) | | | | |
| | | Olo 5ug | 1.421 (0.014) | 0.158 (0.020) | <.0001 | (0.120, | 0.197) |
| | | Olo 10ug | 1.446 (0.014) | 0.183 (0.020) | <.0001 | (0.144, | 0.222) |
| | | Form 12ug | 1.418 (0.014) | 0.155 (0.020) | <.0001 | (0.116, | 0.194) |
| | 3:00 | Placebo | 1.258 (0.014) | | | | |
| | | Olo 5ug | 1.419 (0.014) | 0.161 (0.020) | <.0001 | (0.122, | 0.199) |
| | | Olo 10ug | 1.442 (0.014) | 0.184 (0.020) | <.0001 | (0.146, | 0.223) |
| | | Form 12ug | 1.408 (0.014) | 0.150 (0.020) | <.0001 | (0.111, | 0.188) |
| 15 | -0:10 | Placebo | 1.201 (0.013) | | | | |
| | | Olo 5ug | 1.270 (0.013) | 0.069 (0.018) | 0.0002 | (0.033, | 0.105) |
| | | Olo 10ug | 1.320 (0.013) | 0.119 (0.018) | <.0001 | (0.083, | 0.156) |
| | | Form 12ug | 1.251 (0.013) | 0.050 (0.018) | 0.0071 | (0.014, | 0.086) |
| | 0:05 | Placebo | 1.216 (0.013) | | | | |
| | | Olo 5ug | 1.347 (0.013) | 0.131 (0.018) | <.0001 | (0.096, | 0.165) |
| | | Olo 10ug | 1.380 (0.013) | 0.164 (0.018) | <.0001 | (0.129, | 0.198) |
| | | Form 12ug | 1.364 (0.013) | 0.149 (0.018) | <.0001 | (0.114, | 0.183) |
| | 0:15 | Placebo | 1.223 (0.013) | | | | |
| | | Olo 5ug | 1.376 (0.013) | 0.153 (0.018) | <.0001 | (0.118, | 0.189) |
| | | Olo 10ug | 1.412 (0.013) | 0.189 (0.018) | <.0001 | (0.154, | 0.225) |
| | | Form 12ug | 1.386 (0.013) | 0.163 (0.018) | <.0001 | (0.127, | 0.198) |
| | 0:30 | Placebo | 1.229 (0.014) | | | | |
| | | Olo 5ug | 1.381 (0.014) | 0.153 (0.019) | <.0001 | (0.116, | 0.190) |
| | | Olo 10ug | 1.419 (0.014) | 0.190 (0.019) | <.0001 | (0.154, | 0.227) |
| | | Form 12ug | 1.392 (0.014) | 0.164 (0.019) | <.0001 | (0.127, | 0.201) |

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 (233), Olo 5ug (230), Olo 10ug (233), Form 12ug (232)
Common baseline mean (SE): 1.211 (0.015)

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 | 1.233 (0.014) | | | | |
| | | Olo 5ug | 1.393 (0.014) | 0.160 (0.019) | <.0001 | (0.122, | 0.197) |
| | | Olo 10ug | 1.429 (0.014) | 0.196 (0.019) | <.0001 | (0.159, | 0.233) |
| | | Form 12ug | 1.409 (0.014) | 0.175 (0.019) | <.0001 | (0.138, | 0.213) |
| | 2:00 | Placebo | 1.245 (0.014) | | | | |
| | | Olo 5ug | 1.415 (0.014) | 0.170 (0.020) | <.0001 | (0.131, | 0.209) |
| | | Olo 10ug | 1.444 (0.014) | 0.200 (0.020) | <.0001 | (0.161, | 0.239) |
| | | Form 12ug | 1.408 (0.014) | 0.163 (0.020) | <.0001 | (0.125, | 0.202) |
| | 3:00 | Placebo | 1.249 (0.014) | | | | |
| | | Olo 5ug | 1.405 (0.014) | 0.156 (0.020) | <.0001 | (0.117, | 0.195) |
| | | Olo 10ug | 1.433 (0.014) | 0.184 (0.020) | <.0001 | (0.145, | 0.223) |
| | | Form 12ug | 1.394 (0.014) | 0.145 (0.020) | <.0001 | (0.106, | 0.184) |
| 43 | -1:00 | Placebo | 1.170 (0.013) | | | | |
| | | Olo 5ug | 1.253 (0.013) | 0.083 (0.017) | <.0001 | (0.049, | 0.117) |
| | | Olo 10ug | 1.272 (0.013) | 0.103 (0.017) | <.0001 | (0.069, | 0.137) |
| | | Form 12ug | 1.234 (0.013) | 0.064 (0.017) | 0.0002 | (0.030, | 0.099) |
| | -0:10 | Placebo | 1.188 (0.013) | | | | |
| | | Olo 5ug | 1.271 (0.013) | 0.083 (0.019) | <.0001 | (0.047, | 0.120) |
| | | Olo 10ug | 1.294 (0.013) | 0.106 (0.019) | <.0001 | (0.070, | 0.142) |
| | | Form 12ug | 1.264 (0.014) | 0.076 (0.019) | <.0001 | (0.040, | 0.113) |
| | 0:05 | Placebo | 1.188 (0.013) | | | | |
| | | Olo 5ug | 1.327 (0.013) | 0.139 (0.018) | <.0001 | (0.104, | 0.174) |
| | | Olo 10ug | 1.357 (0.013) | 0.169 (0.018) | <.0001 | (0.134, | 0.204) |
| | | Form 12ug | 1.359 (0.013) | 0.171 (0.018) | <.0001 | (0.136, | 0.205) |

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

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 (233), Olo 5ug (230), Olo 10ug (233), Form 12ug (232)
Common baseline mean (SE): 1.211 (0.015)

Source data: Appendix 16.1.9.2, Statdoc 6.1.1.1.1

ctr\pft-adjmean-mmrm-time.sas 13OCT2011

Boehringer Ingelheim
BI Trial No.: 1222.14
1. - 15. CTR Main PartTable 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 | 1.193 (0.013) | | | | |
| | | Olo 5ug | 1.351 (0.013) | 0.158 (0.018) | <.0001 | (0.122, | 0.194) |
| | | Olo 10ug | 1.368 (0.013) | 0.176 (0.018) | <.0001 | (0.140, | 0.212) |
| | | Form 12ug | 1.369 (0.013) | 0.177 (0.018) | <.0001 | (0.140, | 0.213) |
| | 0:30 | Placebo | 1.196 (0.014) | | | | |
| | | Olo 5ug | 1.363 (0.014) | 0.168 (0.019) | <.0001 | (0.130, | 0.205) |
| | | Olo 10ug | 1.384 (0.014) | 0.188 (0.019) | <.0001 | (0.151, | 0.226) |
| | | Form 12ug | 1.388 (0.014) | 0.192 (0.019) | <.0001 | (0.155, | 0.230) |
| | 1:00 | Placebo | 1.191 (0.014) | | | | |
| | | Olo 5ug | 1.373 (0.014) | 0.182 (0.019) | <.0001 | (0.144, | 0.220) |
| | | Olo 10ug | 1.387 (0.014) | 0.195 (0.019) | <.0001 | (0.158, | 0.233) |
| | | Form 12ug | 1.385 (0.014) | 0.194 (0.019) | <.0001 | (0.156, | 0.231) |
| | 2:00 | Placebo | 1.216 (0.015) | | | | |
| | | Olo 5ug | 1.394 (0.015) | 0.178 (0.020) | <.0001 | (0.139, | 0.217) |
| | | Olo 10ug | 1.419 (0.014) | 0.203 (0.020) | <.0001 | (0.164, | 0.242) |
| | | Form 12ug | 1.405 (0.015) | 0.189 (0.020) | <.0001 | (0.149, | 0.228) |
| | 3:00 | Placebo | 1.221 (0.014) | | | | |
| | | Olo 5ug | 1.394 (0.014) | 0.173 (0.020) | <.0001 | (0.134, | 0.212) |
| | | Olo 10ug | 1.405 (0.014) | 0.185 (0.020) | <.0001 | (0.146, | 0.224) |
| | | Form 12ug | 1.395 (0.015) | 0.174 (0.020) | <.0001 | (0.135, | 0.213) |
| 85 | -1:00 | Placebo | 1.164 (0.013) | | | | |
| | | Olo 5ug | 1.216 (0.013) | 0.052 (0.018) | 0.0030 | (0.018, | 0.087) |
| | | Olo 10ug | 1.254 (0.013) | 0.090 (0.018) | <.0001 | (0.055, | 0.124) |
| | | Form 12ug | 1.230 (0.013) | 0.066 (0.018) | 0.0002 | (0.032, | 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 (233), Olo 5ug (230), Olo 10ug (233), Form 12ug (232)
Common baseline mean (SE): 1.211 (0.015)

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 | 1.184 (0.014) | | | | |
| | | Olo 5ug | 1.249 (0.014) | 0.065 (0.019) | 0.0006 | (0.028, | 0.102) |
| | | Olo 10ug | 1.282 (0.014) | 0.098 (0.019) | <.0001 | (0.061, | 0.135) |
| | | Form 12ug | 1.249 (0.014) | 0.065 (0.019) | 0.0006 | (0.028, | 0.102) |
| | 0:05 | Placebo | 1.185 (0.013) | | | | |
| | | Olo 5ug | 1.316 (0.013) | 0.131 (0.018) | <.0001 | (0.096, | 0.167) |
| | | Olo 10ug | 1.334 (0.013) | 0.149 (0.018) | <.0001 | (0.113, | 0.184) |
| | | Form 12ug | 1.350 (0.013) | 0.164 (0.018) | <.0001 | (0.129, | 0.200) |
| | 0:15 | Placebo | 1.197 (0.014) | | | | |
| | | Olo 5ug | 1.330 (0.013) | 0.134 (0.019) | <.0001 | (0.097, | 0.170) |
| | | Olo 10ug | 1.354 (0.013) | 0.157 (0.019) | <.0001 | (0.121, | 0.194) |
| | | Form 12ug | 1.365 (0.013) | 0.168 (0.019) | <.0001 | (0.132, | 0.205) |
| | 0:30 | Placebo | 1.200 (0.014) | | | | |
| | | Olo 5ug | 1.337 (0.014) | 0.136 (0.019) | <.0001 | (0.099, | 0.174) |
| | | Olo 10ug | 1.381 (0.014) | 0.181 (0.019) | <.0001 | (0.143, | 0.218) |
| | | Form 12ug | 1.378 (0.014) | 0.178 (0.019) | <.0001 | (0.140, | 0.216) |
| | 1:00 | Placebo | 1.206 (0.014) | | | | |
| | | Olo 5ug | 1.344 (0.014) | 0.138 (0.019) | <.0001 | (0.100, | 0.176) |
| | | Olo 10ug | 1.371 (0.014) | 0.166 (0.019) | <.0001 | (0.127, | 0.204) |
| | | Form 12ug | 1.371 (0.014) | 0.165 (0.020) | <.0001 | (0.126, | 0.203) |
| | 2:00 | Placebo | 1.211 (0.015) | | | | |
| | | Olo 5ug | 1.375 (0.015) | 0.164 (0.020) | <.0001 | (0.125, | 0.204) |
| | | Olo 10ug | 1.404 (0.015) | 0.193 (0.020) | <.0001 | (0.153, | 0.233) |
| | | Form 12ug | 1.394 (0.015) | 0.183 (0.020) | <.0001 | (0.143, | 0.223) |

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 (233), Olo 5ug (230), Olo 10ug (233), Form 12ug (232)
Common baseline mean (SE): 1.211 (0.015)

Source data: Appendix 16.1.9.2, Statdoc 6.1.1.1.1

ctr\pft-adjmean-mmrm-time.sas 13OCT2011

Boehringer Ingelheim
BI Trial No.: 1222.14
1. - 15. CTR Main PartTable 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 | 1.219 (0.015) | | | | |
| | | Olo 5ug | 1.361 (0.015) | 0.142 (0.020) | <.0001 | (0.103, | 0.182) |
| | | Olo 10ug | 1.391 (0.015) | 0.172 (0.020) | <.0001 | (0.132, | 0.211) |
| | | Form 12ug | 1.380 (0.015) | 0.161 (0.020) | <.0001 | (0.121, | 0.200) |
| 127 | -0:10 | Placebo | 1.182 (0.014) | | | | |
| | | Olo 5ug | 1.231 (0.014) | 0.050 (0.019) | 0.0090 | (0.012, | 0.087) |
| | | Olo 10ug | 1.267 (0.014) | 0.085 (0.019) | <.0001 | (0.048, | 0.123) |
| | | Form 12ug | 1.232 (0.014) | 0.051 (0.019) | 0.0077 | (0.013, | 0.088) |
| 169 | -0:10 | Placebo | 1.163 (0.014) | | | | |
| | | Olo 5ug | 1.215 (0.014) | 0.053 (0.019) | 0.0061 | (0.015, | 0.090) |
| | | Olo 10ug | 1.232 (0.014) | 0.069 (0.019) | 0.0003 | (0.031, | 0.106) |
| | | Form 12ug | 1.204 (0.014) | 0.042 (0.019) | 0.0303 | (0.004, | 0.079) |
| | 0:05 | Placebo | 1.180 (0.013) | | | | |
| | | Olo 5ug | 1.288 (0.013) | 0.108 (0.018) | <.0001 | (0.072, | 0.144) |
| | | Olo 10ug | 1.308 (0.013) | 0.128 (0.018) | <.0001 | (0.092, | 0.164) |
| | | Form 12ug | 1.313 (0.013) | 0.133 (0.018) | <.0001 | (0.097, | 0.169) |
| | 0:15 | Placebo | 1.192 (0.014) | | | | |
| | | Olo 5ug | 1.310 (0.014) | 0.118 (0.019) | <.0001 | (0.081, | 0.155) |
| | | Olo 10ug | 1.334 (0.014) | 0.142 (0.019) | <.0001 | (0.105, | 0.179) |
| | | Form 12ug | 1.335 (0.014) | 0.143 (0.019) | <.0001 | (0.106, | 0.180) |
| | 0:30 | Placebo | 1.190 (0.014) | | | | |
| | | Olo 5ug | 1.324 (0.014) | 0.133 (0.020) | <.0001 | (0.095, | 0.172) |
| | | Olo 10ug | 1.347 (0.014) | 0.157 (0.020) | <.0001 | (0.119, | 0.195) |
| | | Form 12ug | 1.348 (0.014) | 0.158 (0.020) | <.0001 | (0.119, | 0.196) |

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 (233), Olo 5ug (230), Olo 10ug (233), Form 12ug (232)
Common baseline mean (SE): 1.211 (0.015)

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 | 1.188 (0.014) | | | | |
| | | Olo 5ug | 1.322 (0.014) | 0.135 (0.020) | <.0001 | (0.096, | 0.173) |
| | | Olo 10ug | 1.342 (0.014) | 0.155 (0.020) | <.0001 | (0.116, | 0.193) |
| | | Form 12ug | 1.352 (0.014) | 0.164 (0.020) | <.0001 | (0.125, | 0.203) |
| | 2:00 | Placebo | 1.218 (0.015) | | | | |
| | | Olo 5ug | 1.352 (0.015) | 0.134 (0.021) | <.0001 | (0.094, | 0.174) |
| | | Olo 10ug | 1.376 (0.015) | 0.158 (0.021) | <.0001 | (0.118, | 0.198) |
| | | Form 12ug | 1.368 (0.015) | 0.150 (0.021) | <.0001 | (0.110, | 0.191) |
| | 3:00 | Placebo | 1.212 (0.015) | | | | |
| | | Olo 5ug | 1.340 (0.015) | 0.128 (0.021) | <.0001 | (0.087, | 0.168) |
| | | Olo 10ug | 1.372 (0.015) | 0.160 (0.020) | <.0001 | (0.120, | 0.200) |
| | | Form 12ug | 1.354 (0.015) | 0.141 (0.021) | <.0001 | (0.101, | 0.182) |
| 225 | -0:10 | Placebo | 1.179 (0.014) | | | | |
| | | Olo 5ug | 1.241 (0.014) | 0.062 (0.019) | 0.0013 | (0.024, | 0.100) |
| | | Olo 10ug | 1.251 (0.014) | 0.073 (0.019) | 0.0002 | (0.035, | 0.111) |
| | | Form 12ug | 1.227 (0.014) | 0.048 (0.019) | 0.0132 | (0.010, | 0.086) |
| 281 | -0:10 | Placebo | 1.175 (0.014) | | | | |
| | | Olo 5ug | 1.236 (0.014) | 0.061 (0.019) | 0.0016 | (0.023, | 0.100) |
| | | Olo 10ug | 1.259 (0.014) | 0.084 (0.019) | <.0001 | (0.046, | 0.122) |
| | | Form 12ug | 1.231 (0.014) | 0.056 (0.019) | 0.0040 | (0.018, | 0.094) |
| 337 | -0:10 | Placebo | 1.158 (0.014) | | | | |
| | | Olo 5ug | 1.202 (0.014) | 0.044 (0.020) | 0.0246 | (0.006, | 0.082) |
| | | Olo 10ug | 1.217 (0.014) | 0.059 (0.020) | 0.0027 | (0.020, | 0.097) |
| | | Form 12ug | 1.194 (0.014) | 0.036 (0.020) | 0.0700 | (-0.003, | 0.074) |

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 (233), Olo 5ug (230), Olo 10ug (233), Form 12ug (232)
Common baseline mean (SE): 1.211 (0.015)

Source data: Appendix 16.1.9.2, Statdoc 6.1.1.1.1

ctr\pft-adjmean-mmrm-time.sas 13OCT2011

Boehringer Ingelheim
BI Trial No.: 1222.14
1. - 15. CTR Main Part

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 | 1.172 (0.014) | | | | |
| | | Olo 5ug | 1.261 (0.013) | 0.089 (0.019) | <.0001 | (0.053, | 0.126) |
| | | Olo 10ug | 1.287 (0.013) | 0.115 (0.019) | <.0001 | (0.078, | 0.151) |
| | | Form 12ug | 1.286 (0.013) | 0.114 (0.019) | <.0001 | (0.077, | 0.150) |
| | 0:15 | Placebo | 1.186 (0.014) | | | | |
| | | Olo 5ug | 1.285 (0.014) | 0.099 (0.019) | <.0001 | (0.061, | 0.137) |
| | | Olo 10ug | 1.311 (0.014) | 0.125 (0.019) | <.0001 | (0.087, | 0.163) |
| | | Form 12ug | 1.306 (0.014) | 0.120 (0.019) | <.0001 | (0.082, | 0.158) |
| | 0:30 | Placebo | 1.190 (0.014) | | | | |
| | | Olo 5ug | 1.301 (0.014) | 0.111 (0.020) | <.0001 | (0.072, | 0.150) |
| | | Olo 10ug | 1.321 (0.014) | 0.132 (0.020) | <.0001 | (0.093, | 0.171) |
| | | Form 12ug | 1.319 (0.014) | 0.129 (0.020) | <.0001 | (0.090, | 0.168) |
| | 1:00 | Placebo | 1.184 (0.015) | | | | |
| | | Olo 5ug | 1.307 (0.014) | 0.123 (0.020) | <.0001 | (0.084, | 0.163) |
| | | Olo 10ug | 1.327 (0.014) | 0.143 (0.020) | <.0001 | (0.103, | 0.182) |
| | | Form 12ug | 1.316 (0.014) | 0.132 (0.020) | <.0001 | (0.092, | 0.171) |
| | 2:00 | Placebo | 1.196 (0.015) | | | | |
| | | Olo 5ug | 1.320 (0.015) | 0.123 (0.021) | <.0001 | (0.082, | 0.164) |
| | | Olo 10ug | 1.348 (0.015) | 0.152 (0.021) | <.0001 | (0.111, | 0.193) |
| | | Form 12ug | 1.335 (0.015) | 0.139 (0.021) | <.0001 | (0.098, | 0.180) |
| | 3:00 | Placebo | 1.198 (0.015) | | | | |
| | | Olo 5ug | 1.323 (0.015) | 0.125 (0.021) | <.0001 | (0.084, | 0.166) |
| | | Olo 10ug | 1.342 (0.015) | 0.144 (0.021) | <.0001 | (0.103, | 0.185) |
| | | Form 12ug | 1.320 (0.015) | 0.122 (0.021) | <.0001 | (0.081, | 0.163) |

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 (233), Olo 5ug (230), Olo 10ug (233), Form 12ug (232)
Common baseline mean (SE): 1.211 (0.015)

Source data: Appendix 16.1.9.2, Statdoc 6.1.1.1.1

ctr\pft-adjmean-mmrm-time.sas 13OCT2011

Boehringer Ingelheim
BI Trial No.: 1222.14
1. - 15. CTR Main Part

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)

| Test day | Comparison | Treatment difference | | | |
|----------|----------------------|----------------------|---------|-----------|--------|
| | | Mean (SE) | P-value | 95% CI | |
| 1 | Olo 10ug - Olo 5ug | -0.015 (0.035) | 0.6746 | (-0.083, | 0.054) |
| | Olo 10ug - Form 12ug | -0.017 (0.035) | 0.6313 | (-0.085, | 0.052) |
| | Olo 5ug - Form 12ug | -0.002 (0.035) | 0.9530 | (-0.071, | 0.066) |
| 15 | Olo 10ug - Olo 5ug | 0.019 (0.035) | 0.5852 | (-0.049, | 0.088) |
| | Olo 10ug - Form 12ug | -0.016 (0.035) | 0.6432 | (-0.085, | 0.052) |
| | Olo 5ug - Form 12ug | -0.035 (0.035) | 0.3143 | (-0.104, | 0.033) |
| 43 | Olo 10ug - Olo 5ug | -0.002 (0.035) | 0.9582 | (-0.071, | 0.067) |
| | Olo 10ug - Form 12ug | -0.032 (0.035) | 0.3647 | (-0.101, | 0.037) |
| | Olo 5ug - Form 12ug | -0.030 (0.035) | 0.3947 | (-0.099, | 0.039) |
| 85 | Olo 10ug - Olo 5ug | 0.018 (0.035) | 0.6115 | (-0.051, | 0.087) |
| | Olo 10ug - Form 12ug | -0.028 (0.035) | 0.4333 | (-0.097, | 0.042) |
| | Olo 5ug - Form 12ug | -0.046 (0.035) | 0.1976 | (-0.115, | 0.024) |
| 169 | Olo 10ug - Olo 5ug | 0.014 (0.036) | 0.7028 | (-0.056, | 0.084) |
| | Olo 10ug - Form 12ug | -0.028 (0.036) | 0.4309 | (-0.098, | 0.042) |
| | Olo 5ug - Form 12ug | -0.042 (0.036) | 0.2440 | (-0.112, | 0.029) |
| 337 | Olo 10ug - Olo 5ug | 0.019 (0.036) | 0.5954 | (-0.052, | 0.091) |
| | Olo 10ug - Form 12ug | 0.017 (0.036) | 0.6379 | (-0.054, | 0.088) |
| | Olo 5ug - Form 12ug | -0.002 (0.036) | 0.9515 | (-0.074, | 0.069) |

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 (233), Olo 5ug (230), Olo 10ug (233), Form 12ug (232)

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)

| Test day | Treatment | Treatment mean (SE) | Difference from Placebo | | |
|----------|-----------|---------------------|-------------------------|---------|-----------------|
| | | | Mean (SE) | P-value | 95% CI |
| 1 | Placebo | 0.226 (0.027) | | | |
| | Olo 5ug | 0.501 (0.027) | 0.274 (0.037) | <.0001 | (0.201, 0.347) |
| | Olo 10ug | 0.469 (0.027) | 0.243 (0.037) | <.0001 | (0.170, 0.315) |
| | Form 12ug | 0.497 (0.027) | 0.271 (0.037) | <.0001 | (0.198, 0.343) |
| 15 | Placebo | 0.247 (0.027) | | | |
| | Olo 5ug | 0.480 (0.027) | 0.233 (0.037) | <.0001 | (0.160, 0.306) |
| | Olo 10ug | 0.476 (0.027) | 0.229 (0.037) | <.0001 | (0.156, 0.302) |
| | Form 12ug | 0.495 (0.027) | 0.248 (0.037) | <.0001 | (0.175, 0.321) |
| 43 | Placebo | 0.196 (0.027) | | | |
| | Olo 5ug | 0.443 (0.027) | 0.247 (0.038) | <.0001 | (0.174, 0.321) |
| | Olo 10ug | 0.417 (0.027) | 0.221 (0.037) | <.0001 | (0.148, 0.295) |
| | Form 12ug | 0.450 (0.027) | 0.254 (0.038) | <.0001 | (0.180, 0.328) |
| 85 | Placebo | 0.171 (0.028) | | | |
| | Olo 5ug | 0.386 (0.027) | 0.215 (0.038) | <.0001 | (0.141, 0.289) |
| | Olo 10ug | 0.396 (0.027) | 0.226 (0.038) | <.0001 | (0.151, 0.300) |
| | Form 12ug | 0.436 (0.028) | 0.265 (0.038) | <.0001 | (0.191, 0.340) |
| 169 | Placebo | 0.189 (0.028) | | | |
| | Olo 5ug | 0.371 (0.028) | 0.182 (0.039) | <.0001 | (0.106, 0.258) |
| | Olo 10ug | 0.369 (0.028) | 0.180 (0.038) | <.0001 | (0.105, 0.256) |
| | Form 12ug | 0.397 (0.028) | 0.207 (0.039) | <.0001 | (0.132, 0.283) |
| 337 | Placebo | 0.137 (0.029) | | | |
| | Olo 5ug | 0.325 (0.028) | 0.188 (0.039) | <.0001 | (0.111, 0.265) |
| | Olo 10ug | 0.352 (0.028) | 0.214 (0.039) | <.0001 | (0.138, 0.291) |
| | Form 12ug | 0.329 (0.028) | 0.192 (0.039) | <.0001 | (0.115, 0.269) |

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 (233), Olo 5ug (230), Olo 10ug (233), Form 12ug (232)
Common baseline mean (SE): 2.678 (0.026)

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)

| Test day | Treatment | Treatment mean (SE) | Difference from Placebo | | | |
|----------|-----------|---------------------|-------------------------|---------|-----------|--------|
| | | | Mean (SE) | P-value | 95% CI | |
| 15 | Placebo | 0.030 (0.026) | | | | |
| | Olo 5ug | 0.118 (0.026) | 0.088 (0.035) | 0.0133 | (0.018, | 0.157) |
| | Olo 10ug | 0.173 (0.026) | 0.143 (0.035) | <.0001 | (0.073, | 0.212) |
| | Form 12ug | 0.111 (0.026) | 0.082 (0.035) | 0.0212 | (0.012, | 0.151) |
| 43 | Placebo | -0.014 (0.026) | | | | |
| | Olo 5ug | 0.113 (0.026) | 0.127 (0.036) | 0.0004 | (0.057, | 0.197) |
| | Olo 10ug | 0.101 (0.026) | 0.115 (0.036) | 0.0012 | (0.045, | 0.185) |
| | Form 12ug | 0.085 (0.026) | 0.099 (0.036) | 0.0056 | (0.029, | 0.169) |
| 85 | Placebo | -0.041 (0.026) | | | | |
| | Olo 5ug | 0.062 (0.026) | 0.103 (0.036) | 0.0045 | (0.032, | 0.173) |
| | Olo 10ug | 0.062 (0.026) | 0.102 (0.036) | 0.0046 | (0.032, | 0.173) |
| | Form 12ug | 0.070 (0.026) | 0.110 (0.036) | 0.0023 | (0.039, | 0.181) |
| 127 | Placebo | -0.014 (0.027) | | | | |
| | Olo 5ug | 0.084 (0.026) | 0.097 (0.037) | 0.0077 | (0.026, | 0.169) |
| | Olo 10ug | 0.107 (0.026) | 0.121 (0.036) | 0.0009 | (0.050, | 0.193) |
| | Form 12ug | 0.064 (0.026) | 0.078 (0.037) | 0.0339 | (0.006, | 0.149) |
| 169 | Placebo | -0.044 (0.027) | | | | |
| | Olo 5ug | 0.023 (0.026) | 0.066 (0.037) | 0.0718 | (-0.006, | 0.139) |
| | Olo 10ug | 0.019 (0.026) | 0.063 (0.037) | 0.0863 | (-0.009, | 0.135) |
| | Form 12ug | -0.005 (0.027) | 0.038 (0.037) | 0.2982 | (-0.034, | 0.111) |
| 225 | Placebo | -0.007 (0.027) | | | | |
| | Olo 5ug | 0.081 (0.027) | 0.087 (0.037) | 0.0190 | (0.014, | 0.160) |
| | Olo 10ug | 0.063 (0.027) | 0.070 (0.037) | 0.0601 | (-0.003, | 0.143) |
| | Form 12ug | 0.036 (0.027) | 0.042 (0.037) | 0.2573 | (-0.031, | 0.115) |

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 (232), Olo 5ug (229), Olo 10ug (228), Form 12ug (229)
Common baseline mean (SE): 2.682 (0.026)

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)

| Test day | Treatment | Treatment mean (SE) | Difference from Placebo | | | |
|----------|-----------|---------------------|-------------------------|---------|-----------|--------|
| | | | Mean (SE) | P-value | 95% CI | |
| 281 | Placebo | -0.016 (0.027) | | | | |
| | Olo 5ug | 0.071 (0.027) | 0.087 (0.037) | 0.0200 | (0.014, | 0.160) |
| | Olo 10ug | 0.105 (0.027) | 0.121 (0.037) | 0.0013 | (0.047, | 0.194) |
| | Form 12ug | 0.037 (0.027) | 0.053 (0.037) | 0.1598 | (-0.021, | 0.126) |
| 337 | Placebo | -0.069 (0.027) | | | | |
| | Olo 5ug | 0.012 (0.027) | 0.081 (0.038) | 0.0307 | (0.008, | 0.155) |
| | Olo 10ug | 0.032 (0.027) | 0.101 (0.038) | 0.0073 | (0.027, | 0.175) |
| | Form 12ug | -0.031 (0.027) | 0.038 (0.038) | 0.3147 | (-0.036, | 0.112) |

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 (232), Olo 5ug (229), Olo 10ug (228), Form 12ug (229)
Common baseline mean (SE): 2.682 (0.026)

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 | 2.658 (0.027) | | | |
| | | Olo 5ug | 2.658 (0.027) | | | |
| | | Olo 10ug | 2.658 (0.027) | | | |
| | | Form 12ug | 2.658 (0.027) | | | |
| | -0:10 | Placebo | 2.699 (0.026) | | | |
| | | Olo 5ug | 2.699 (0.026) | | | |
| | | Olo 10ug | 2.699 (0.026) | | | |
| | | Form 12ug | 2.699 (0.026) | | | |
| | 0:05 | Placebo | 2.711 (0.025) | | | |
| | | Olo 5ug | 2.910 (0.025) | 0.199 (0.034) | <.0001 | (0.132, 0.267) |
| | | Olo 10ug | 2.931 (0.025) | 0.220 (0.034) | <.0001 | (0.153, 0.287) |
| | | Form 12ug | 2.968 (0.025) | 0.257 (0.034) | <.0001 | (0.189, 0.324) |
| | 0:15 | Placebo | 2.716 (0.026) | | | |
| | | Olo 5ug | 2.972 (0.026) | 0.255 (0.035) | <.0001 | (0.186, 0.325) |
| | | Olo 10ug | 2.957 (0.026) | 0.240 (0.035) | <.0001 | (0.171, 0.309) |
| | | Form 12ug | 3.001 (0.026) | 0.285 (0.035) | <.0001 | (0.216, 0.354) |
| | 0:30 | Placebo | 2.748 (0.026) | | | |
| | | Olo 5ug | 2.997 (0.027) | 0.249 (0.037) | <.0001 | (0.177, 0.321) |
| | | Olo 10ug | 2.993 (0.027) | 0.245 (0.037) | <.0001 | (0.173, 0.316) |
| | | Form 12ug | 3.028 (0.027) | 0.280 (0.037) | <.0001 | (0.208, 0.351) |
| | 1:00 | Placebo | 2.741 (0.026) | | | |
| | | Olo 5ug | 3.010 (0.027) | 0.269 (0.036) | <.0001 | (0.197, 0.340) |
| | | Olo 10ug | 3.000 (0.026) | 0.260 (0.036) | <.0001 | (0.188, 0.331) |
| | | Form 12ug | 3.018 (0.026) | 0.277 (0.036) | <.0001 | (0.206, 0.349) |

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 (233), Olo 5ug (230), Olo 10ug (233), Form 12ug (232)
Common baseline mean (SE): 2.678 (0.026)

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 | 2.799 (0.027) | | | |
| | | Olo 5ug | 3.060 (0.027) | 0.262 (0.037) | <.0001 | (0.188, 0.335) |
| | | Olo 10ug | 3.037 (0.027) | 0.239 (0.037) | <.0001 | (0.166, 0.312) |
| | | Form 12ug | 3.051 (0.027) | 0.252 (0.037) | <.0001 | (0.179, 0.326) |
| | 3:00 | Placebo | 2.789 (0.027) | | | |
| | | Olo 5ug | 3.066 (0.027) | 0.277 (0.037) | <.0001 | (0.204, 0.350) |
| | | Olo 10ug | 3.042 (0.027) | 0.253 (0.037) | <.0001 | (0.180, 0.326) |
| | | Form 12ug | 3.034 (0.027) | 0.245 (0.037) | <.0001 | (0.172, 0.318) |
| 15 | -0:10 | Placebo | 2.726 (0.026) | | | |
| | | Olo 5ug | 2.815 (0.026) | 0.088 (0.036) | 0.0137 | (0.018, 0.158) |
| | | Olo 10ug | 2.870 (0.026) | 0.144 (0.036) | <.0001 | (0.073, 0.214) |
| | | Form 12ug | 2.809 (0.026) | 0.083 (0.036) | 0.0204 | (0.013, 0.153) |
| | 0:05 | Placebo | 2.736 (0.025) | | | |
| | | Olo 5ug | 2.924 (0.025) | 0.188 (0.034) | <.0001 | (0.120, 0.255) |
| | | Olo 10ug | 2.955 (0.025) | 0.219 (0.034) | <.0001 | (0.152, 0.286) |
| | | Form 12ug | 2.989 (0.025) | 0.253 (0.034) | <.0001 | (0.186, 0.321) |
| | 0:15 | Placebo | 2.739 (0.026) | | | |
| | | Olo 5ug | 2.957 (0.026) | 0.218 (0.035) | <.0001 | (0.148, 0.287) |
| | | Olo 10ug | 2.980 (0.026) | 0.241 (0.035) | <.0001 | (0.171, 0.310) |
| | | Form 12ug | 3.017 (0.026) | 0.278 (0.035) | <.0001 | (0.208, 0.347) |
| | 0:30 | Placebo | 2.770 (0.027) | | | |
| | | Olo 5ug | 2.973 (0.027) | 0.203 (0.037) | <.0001 | (0.131, 0.275) |
| | | Olo 10ug | 3.003 (0.027) | 0.233 (0.037) | <.0001 | (0.161, 0.305) |
| | | Form 12ug | 3.035 (0.027) | 0.265 (0.037) | <.0001 | (0.193, 0.337) |

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 (233), Olo 5ug (230), Olo 10ug (233), Form 12ug (232)
Common baseline mean (SE): 2.678 (0.026)

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 | 2.776 (0.026) | | | |
| | | Olo 5ug | 3.011 (0.027) | 0.235 (0.037) | <.0001 | (0.163, 0.307) |
| | | Olo 10ug | 3.028 (0.027) | 0.252 (0.036) | <.0001 | (0.181, 0.324) |
| | | Form 12ug | 3.064 (0.027) | 0.288 (0.036) | <.0001 | (0.216, 0.360) |
| | 2:00 | Placebo | 2.783 (0.027) | | | |
| | | Olo 5ug | 3.027 (0.027) | 0.244 (0.038) | <.0001 | (0.170, 0.318) |
| | | Olo 10ug | 3.042 (0.027) | 0.259 (0.037) | <.0001 | (0.186, 0.333) |
| | | Form 12ug | 3.050 (0.027) | 0.267 (0.037) | <.0001 | (0.194, 0.341) |
| | 3:00 | Placebo | 2.795 (0.027) | | | |
| | | Olo 5ug | 3.020 (0.027) | 0.225 (0.037) | <.0001 | (0.152, 0.299) |
| | | Olo 10ug | 3.032 (0.027) | 0.237 (0.037) | <.0001 | (0.164, 0.310) |
| | | Form 12ug | 3.018 (0.027) | 0.223 (0.037) | <.0001 | (0.150, 0.296) |
| 43 | -1:00 | Placebo | 2.660 (0.024) | | | |
| | | Olo 5ug | 2.795 (0.024) | 0.135 (0.034) | <.0001 | (0.069, 0.201) |
| | | Olo 10ug | 2.765 (0.024) | 0.106 (0.033) | 0.0016 | (0.040, 0.171) |
| | | Form 12ug | 2.762 (0.024) | 0.102 (0.034) | 0.0023 | (0.037, 0.168) |
| | -0:10 | Placebo | 2.694 (0.026) | | | |
| | | Olo 5ug | 2.810 (0.026) | 0.117 (0.036) | 0.0012 | (0.046, 0.188) |
| | | Olo 10ug | 2.818 (0.026) | 0.125 (0.036) | 0.0005 | (0.054, 0.195) |
| | | Form 12ug | 2.789 (0.026) | 0.096 (0.036) | 0.0078 | (0.025, 0.166) |
| | 0:05 | Placebo | 2.674 (0.025) | | | |
| | | Olo 5ug | 2.913 (0.025) | 0.240 (0.035) | <.0001 | (0.172, 0.308) |
| | | Olo 10ug | 2.909 (0.025) | 0.235 (0.035) | <.0001 | (0.167, 0.303) |
| | | Form 12ug | 2.964 (0.025) | 0.290 (0.035) | <.0001 | (0.222, 0.358) |

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 (233), Olo 5ug (230), Olo 10ug (233), Form 12ug (232)
Common baseline mean (SE): 2.678 (0.026)

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 | 2.686 (0.026) | | | |
| | | Olo 5ug | 2.940 (0.026) | 0.254 (0.036) | <.0001 | (0.184, 0.324) |
| | | Olo 10ug | 2.922 (0.026) | 0.236 (0.036) | <.0001 | (0.166, 0.306) |
| | | Form 12ug | 2.976 (0.026) | 0.291 (0.036) | <.0001 | (0.221, 0.361) |
| | 0:30 | Placebo | 2.692 (0.027) | | | |
| | | Olo 5ug | 2.954 (0.027) | 0.262 (0.037) | <.0001 | (0.189, 0.335) |
| | | Olo 10ug | 2.945 (0.027) | 0.254 (0.037) | <.0001 | (0.181, 0.326) |
| | | Form 12ug | 3.012 (0.027) | 0.320 (0.037) | <.0001 | (0.248, 0.393) |
| | 1:00 | Placebo | 2.697 (0.027) | | | |
| | | Olo 5ug | 2.953 (0.027) | 0.256 (0.037) | <.0001 | (0.183, 0.328) |
| | | Olo 10ug | 2.946 (0.027) | 0.249 (0.037) | <.0001 | (0.177, 0.321) |
| | | Form 12ug | 2.987 (0.027) | 0.290 (0.037) | <.0001 | (0.217, 0.362) |
| | 2:00 | Placebo | 2.739 (0.027) | | | |
| | | Olo 5ug | 2.989 (0.027) | 0.250 (0.038) | <.0001 | (0.175, 0.324) |
| | | Olo 10ug | 2.999 (0.027) | 0.260 (0.038) | <.0001 | (0.186, 0.334) |
| | | Form 12ug | 3.020 (0.028) | 0.281 (0.038) | <.0001 | (0.207, 0.355) |
| | 3:00 | Placebo | 2.745 (0.027) | | | |
| | | Olo 5ug | 2.996 (0.027) | 0.251 (0.038) | <.0001 | (0.177, 0.325) |
| | | Olo 10ug | 2.988 (0.027) | 0.243 (0.038) | <.0001 | (0.169, 0.317) |
| | | Form 12ug | 2.994 (0.027) | 0.249 (0.038) | <.0001 | (0.175, 0.323) |
| 85 | -1:00 | Placebo | 2.641 (0.025) | | | |
| | | Olo 5ug | 2.738 (0.025) | 0.096 (0.034) | 0.0045 | (0.030, 0.163) |
| | | Olo 10ug | 2.733 (0.025) | 0.092 (0.034) | 0.0068 | (0.025, 0.158) |
| | | Form 12ug | 2.758 (0.025) | 0.117 (0.034) | 0.0006 | (0.050, 0.183) |

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 (233), Olo 5ug (230), Olo 10ug (233), Form 12ug (232)
Common baseline mean (SE): 2.678 (0.026)

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 | 2.658 (0.026) | | | | |
| | | Olo 5ug | 2.767 (0.026) | 0.109 (0.036) | 0.0028 | (0.038, | 0.180) |
| | | Olo 10ug | 2.773 (0.026) | 0.114 (0.036) | 0.0017 | (0.043, | 0.186) |
| | | Form 12ug | 2.764 (0.026) | 0.105 (0.037) | 0.0040 | (0.034, | 0.177) |
| | 0:05 | Placebo | 2.663 (0.025) | | | | |
| | | Olo 5ug | 2.871 (0.025) | 0.208 (0.035) | <.0001 | (0.139, | 0.277) |
| | | Olo 10ug | 2.874 (0.025) | 0.211 (0.035) | <.0001 | (0.143, | 0.280) |
| | | Form 12ug | 2.945 (0.025) | 0.282 (0.035) | <.0001 | (0.214, | 0.351) |
| | 0:15 | Placebo | 2.667 (0.026) | | | | |
| | | Olo 5ug | 2.883 (0.026) | 0.217 (0.036) | <.0001 | (0.146, | 0.288) |
| | | Olo 10ug | 2.894 (0.026) | 0.228 (0.036) | <.0001 | (0.157, | 0.298) |
| | | Form 12ug | 2.954 (0.026) | 0.288 (0.036) | <.0001 | (0.217, | 0.359) |
| | 0:30 | Placebo | 2.684 (0.027) | | | | |
| | | Olo 5ug | 2.906 (0.027) | 0.223 (0.037) | <.0001 | (0.149, | 0.296) |
| | | Olo 10ug | 2.932 (0.027) | 0.249 (0.037) | <.0001 | (0.175, | 0.322) |
| | | Form 12ug | 2.976 (0.027) | 0.292 (0.037) | <.0001 | (0.219, | 0.366) |
| | 1:00 | Placebo | 2.688 (0.027) | | | | |
| | | Olo 5ug | 2.903 (0.027) | 0.215 (0.037) | <.0001 | (0.142, | 0.288) |
| | | Olo 10ug | 2.927 (0.027) | 0.239 (0.037) | <.0001 | (0.166, | 0.312) |
| | | Form 12ug | 2.954 (0.027) | 0.266 (0.037) | <.0001 | (0.193, | 0.339) |
| | 2:00 | Placebo | 2.703 (0.028) | | | | |
| | | Olo 5ug | 2.964 (0.028) | 0.261 (0.038) | <.0001 | (0.186, | 0.336) |
| | | Olo 10ug | 2.972 (0.028) | 0.268 (0.038) | <.0001 | (0.194, | 0.343) |
| | | Form 12ug | 2.993 (0.028) | 0.290 (0.038) | <.0001 | (0.215, | 0.365) |

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 (233), Olo 5ug (230), Olo 10ug (233), Form 12ug (232)
Common baseline mean (SE): 2.678 (0.026)

Source data: Appendix 16.1.9.2, Statdoc 6.1.2.1.1

ctr\pft-adjmean-mmrm-time.sas 13OCT2011

Boehringer Ingelheim
BI Trial No.: 1222.14
1. - 15. CTR Main Part

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 | 2.722 (0.028) | | | | |
| | | Olo 5ug | 2.938 (0.027) | 0.216 (0.038) | <.0001 | (0.141, | 0.290) |
| | | Olo 10ug | 2.967 (0.027) | 0.245 (0.038) | <.0001 | (0.170, | 0.320) |
| | | Form 12ug | 2.978 (0.028) | 0.255 (0.038) | <.0001 | (0.181, | 0.330) |
| 127 | -0:10 | Placebo | 2.684 (0.027) | | | | |
| | | Olo 5ug | 2.782 (0.026) | 0.098 (0.037) | 0.0081 | (0.025, | 0.170) |
| | | Olo 10ug | 2.805 (0.026) | 0.121 (0.037) | 0.0010 | (0.049, | 0.193) |
| | | Form 12ug | 2.761 (0.027) | 0.078 (0.037) | 0.0359 | (0.005, | 0.150) |
| 169 | -0:10 | Placebo | 2.655 (0.027) | | | | |
| | | Olo 5ug | 2.721 (0.027) | 0.066 (0.037) | 0.0764 | (-0.007, | 0.139) |
| | | Olo 10ug | 2.717 (0.027) | 0.062 (0.037) | 0.0936 | (-0.011, | 0.135) |
| | | Form 12ug | 2.692 (0.027) | 0.038 (0.037) | 0.3097 | (-0.035, | 0.111) |
| | 0:05 | Placebo | 2.663 (0.026) | | | | |
| | | Olo 5ug | 2.860 (0.026) | 0.197 (0.036) | <.0001 | (0.127, | 0.267) |
| | | Olo 10ug | 2.854 (0.026) | 0.191 (0.036) | <.0001 | (0.122, | 0.261) |
| | | Form 12ug | 2.891 (0.026) | 0.228 (0.036) | <.0001 | (0.158, | 0.298) |
| | 0:15 | Placebo | 2.678 (0.027) | | | | |
| | | Olo 5ug | 2.883 (0.026) | 0.205 (0.037) | <.0001 | (0.133, | 0.277) |
| | | Olo 10ug | 2.876 (0.026) | 0.198 (0.037) | <.0001 | (0.126, | 0.270) |
| | | Form 12ug | 2.918 (0.026) | 0.240 (0.037) | <.0001 | (0.168, | 0.312) |
| | 0:30 | Placebo | 2.694 (0.028) | | | | |
| | | Olo 5ug | 2.892 (0.027) | 0.198 (0.038) | <.0001 | (0.123, | 0.273) |
| | | Olo 10ug | 2.901 (0.027) | 0.207 (0.038) | <.0001 | (0.132, | 0.281) |
| | | Form 12ug | 2.951 (0.027) | 0.257 (0.038) | <.0001 | (0.183, | 0.332) |

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 (233), Olo 5ug (230), Olo 10ug (233), Form 12ug (232)
Common baseline mean (SE): 2.678 (0.026)

Source data: Appendix 16.1.9.2, Statdoc 6.1.2.1.1

ctr\pft-adjmean-mmrm-time.sas 13OCT2011

Boehringer Ingelheim
BI Trial No.: 1222.14
1. - 15. CTR Main Part

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 | 2.678 (0.028) | | | |
| | | Olo 5ug | 2.881 (0.027) | 0.203 (0.038) | <.0001 | (0.129, 0.277) |
| | | Olo 10ug | 2.895 (0.027) | 0.217 (0.038) | <.0001 | (0.143, 0.291) |
| | | Form 12ug | 2.954 (0.027) | 0.276 (0.038) | <.0001 | (0.202, 0.351) |
| | 2:00 | Placebo | 2.725 (0.028) | | | |
| | | Olo 5ug | 2.932 (0.028) | 0.208 (0.039) | <.0001 | (0.131, 0.284) |
| | | Olo 10ug | 2.959 (0.028) | 0.234 (0.039) | <.0001 | (0.158, 0.310) |
| | | Form 12ug | 2.965 (0.028) | 0.240 (0.039) | <.0001 | (0.164, 0.316) |
| | 3:00 | Placebo | 2.726 (0.028) | | | |
| | | Olo 5ug | 2.921 (0.028) | 0.195 (0.039) | <.0001 | (0.119, 0.271) |
| | | Olo 10ug | 2.920 (0.028) | 0.194 (0.039) | <.0001 | (0.119, 0.270) |
| | | Form 12ug | 2.930 (0.028) | 0.204 (0.039) | <.0001 | (0.128, 0.280) |
| 225 | -0:10 | Placebo | 2.691 (0.027) | | | |
| | | Olo 5ug | 2.778 (0.027) | 0.087 (0.038) | 0.0206 | (0.013, 0.161) |
| | | Olo 10ug | 2.761 (0.027) | 0.070 (0.038) | 0.0636 | (-0.004, 0.143) |
| | | Form 12ug | 2.733 (0.027) | 0.042 (0.038) | 0.2647 | (-0.032, 0.116) |
| 281 | -0:10 | Placebo | 2.683 (0.028) | | | |
| | | Olo 5ug | 2.769 (0.027) | 0.086 (0.038) | 0.0222 | (0.012, 0.160) |
| | | Olo 10ug | 2.803 (0.027) | 0.120 (0.038) | 0.0015 | (0.046, 0.194) |
| | | Form 12ug | 2.735 (0.027) | 0.052 (0.038) | 0.1677 | (-0.022, 0.126) |
| 337 | -0:10 | Placebo | 2.629 (0.028) | | | |
| | | Olo 5ug | 2.710 (0.027) | 0.081 (0.038) | 0.0332 | (0.006, 0.155) |
| | | Olo 10ug | 2.729 (0.027) | 0.100 (0.038) | 0.0084 | (0.026, 0.175) |
| | | Form 12ug | 2.666 (0.027) | 0.038 (0.038) | 0.3239 | (-0.037, 0.112) |

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 (233), Olo 5ug (230), Olo 10ug (233), Form 12ug (232)
Common baseline mean (SE): 2.678 (0.026)

Source data: Appendix 16.1.9.2, Statdoc 6.1.2.1.1

ctr\pft-adjmean-mmrm-time.sas 13OCT2011

Boehringer Ingelheim
BI Trial No.: 1222.14
1. - 15. CTR Main Part

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 | 2.623 (0.026) | | | |
| | | Olo 5ug | 2.793 (0.026) | 0.169 (0.036) | <.0001 | (0.098, 0.241) |
| | | Olo 10ug | 2.829 (0.026) | 0.206 (0.036) | <.0001 | (0.135, 0.277) |
| | | Form 12ug | 2.838 (0.026) | 0.214 (0.036) | <.0001 | (0.143, 0.285) |
| | 0:15 | Placebo | 2.634 (0.027) | | | |
| | | Olo 5ug | 2.833 (0.027) | 0.199 (0.037) | <.0001 | (0.126, 0.273) |
| | | Olo 10ug | 2.859 (0.027) | 0.226 (0.037) | <.0001 | (0.153, 0.299) |
| | | Form 12ug | 2.860 (0.027) | 0.226 (0.037) | <.0001 | (0.153, 0.299) |
| | 0:30 | Placebo | 2.649 (0.028) | | | |
| | | Olo 5ug | 2.858 (0.028) | 0.209 (0.039) | <.0001 | (0.133, 0.285) |
| | | Olo 10ug | 2.877 (0.028) | 0.229 (0.039) | <.0001 | (0.153, 0.305) |
| | | Form 12ug | 2.885 (0.028) | 0.236 (0.039) | <.0001 | (0.160, 0.312) |
| | 1:00 | Placebo | 2.643 (0.028) | | | |
| | | Olo 5ug | 2.872 (0.028) | 0.229 (0.038) | <.0001 | (0.154, 0.305) |
| | | Olo 10ug | 2.874 (0.028) | 0.231 (0.038) | <.0001 | (0.156, 0.306) |
| | | Form 12ug | 2.863 (0.028) | 0.221 (0.038) | <.0001 | (0.145, 0.296) |
| | 2:00 | Placebo | 2.662 (0.029) | | | |
| | | Olo 5ug | 2.890 (0.028) | 0.228 (0.040) | <.0001 | (0.150, 0.305) |
| | | Olo 10ug | 2.924 (0.028) | 0.262 (0.039) | <.0001 | (0.185, 0.339) |
| | | Form 12ug | 2.895 (0.028) | 0.233 (0.039) | <.0001 | (0.155, 0.310) |
| | 3:00 | Placebo | 2.680 (0.029) | | | |
| | | Olo 5ug | 2.895 (0.028) | 0.215 (0.039) | <.0001 | (0.138, 0.293) |
| | | Olo 10ug | 2.905 (0.028) | 0.225 (0.039) | <.0001 | (0.148, 0.303) |
| | | Form 12ug | 2.878 (0.028) | 0.198 (0.039) | <.0001 | (0.121, 0.276) |

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 (233), Olo 5ug (230), Olo 10ug (233), Form 12ug (232)
Common baseline mean (SE): 2.678 (0.026)

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)

| Week | Treatment | Treatment mean (SE) | Difference from Placebo | | |
|------|-----------|---------------------|-------------------------|---------|-------------------|
| | | | Mean (SE) | P-value | 95% CI |
| 1 | Placebo | 202.692 (2.074) | | | |
| | Olo 5ug | 214.002 (2.064) | 11.311 (2.813) | <.0001 | (5.789, 16.832) |
| | Olo 10ug | 227.930 (2.077) | 25.238 (2.816) | <.0001 | (19.710, 30.766) |
| | Form 12ug | 218.852 (2.093) | 16.160 (2.826) | <.0001 | (10.614, 21.706) |
| 2 | Placebo | 199.614 (2.326) | | | |
| | Olo 5ug | 211.521 (2.314) | 11.908 (3.155) | 0.0002 | (5.716, 18.099) |
| | Olo 10ug | 228.314 (2.329) | 28.701 (3.158) | <.0001 | (22.503, 34.899) |
| | Form 12ug | 215.610 (2.347) | 15.997 (3.169) | <.0001 | (9.778, 22.216) |
| 3 | Placebo | 199.329 (2.600) | | | |
| | Olo 5ug | 214.327 (2.586) | 14.998 (3.526) | <.0001 | (8.078, 21.917) |
| | Olo 10ug | 228.146 (2.603) | 28.817 (3.530) | <.0001 | (21.889, 35.744) |
| | Form 12ug | 216.370 (2.623) | 17.041 (3.541) | <.0001 | (10.090, 23.991) |
| 4 | Placebo | 198.389 (2.654) | | | |
| | Olo 5ug | 211.564 (2.641) | 13.175 (3.600) | 0.0003 | (6.110, 20.240) |
| | Olo 10ug | 227.796 (2.658) | 29.407 (3.604) | <.0001 | (22.335, 36.480) |
| | Form 12ug | 217.365 (2.678) | 18.976 (3.616) | <.0001 | (11.880, 26.072) |
| 5 | Placebo | 198.628 (2.871) | | | |
| | Olo 5ug | 211.920 (2.856) | 13.292 (3.894) | 0.0007 | (5.650, 20.933) |
| | Olo 10ug | 227.520 (2.875) | 28.892 (3.898) | <.0001 | (21.242, 36.541) |
| | Form 12ug | 215.668 (2.897) | 17.040 (3.911) | <.0001 | (9.365, 24.715) |
| 6 | Placebo | 199.257 (2.841) | | | |
| | Olo 5ug | 209.564 (2.827) | 10.308 (3.853) | 0.0076 | (2.746, 17.870) |
| | Olo 10ug | 224.306 (2.845) | 25.050 (3.857) | <.0001 | (17.479, 32.620) |
| | Form 12ug | 212.886 (2.867) | 13.630 (3.870) | 0.0005 | (6.034, 21.225) |

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 (225), Olo 5ug (227), Olo 10ug (226), Form 12ug (224)
Common baseline mean (SE): 201.790 (3.052)

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)

| Week | Treatment | Treatment mean (SE) | Difference from Placebo | | |
|------|-----------|---------------------|-------------------------|---------|-------------------|
| | | | Mean (SE) | P-value | 95% CI |
| 7 | Placebo | 198.535 (2.848) | | | |
| | Olo 5ug | 210.289 (2.834) | 11.754 (3.863) | 0.0024 | (4.172, 19.336) |
| | Olo 10ug | 224.301 (2.852) | 25.766 (3.867) | <.0001 | (18.175, 33.356) |
| | Form 12ug | 212.024 (2.874) | 13.489 (3.880) | 0.0005 | (5.873, 21.104) |
| 8 | Placebo | 198.380 (2.865) | | | |
| | Olo 5ug | 211.789 (2.850) | 13.410 (3.886) | 0.0006 | (5.784, 21.036) |
| | Olo 10ug | 223.782 (2.869) | 25.403 (3.890) | <.0001 | (17.769, 33.037) |
| | Form 12ug | 213.667 (2.891) | 15.288 (3.903) | <.0001 | (7.628, 22.947) |
| 9 | Placebo | 200.892 (3.041) | | | |
| | Olo 5ug | 212.319 (3.025) | 11.427 (4.124) | 0.0057 | (3.333, 19.521) |
| | Olo 10ug | 224.540 (3.045) | 23.648 (4.129) | <.0001 | (15.545, 31.751) |
| | Form 12ug | 214.125 (3.068) | 13.233 (4.142) | 0.0015 | (5.103, 21.363) |
| 10 | Placebo | 201.574 (3.048) | | | |
| | Olo 5ug | 210.870 (3.033) | 9.296 (4.134) | 0.0248 | (1.183, 17.409) |
| | Olo 10ug | 222.593 (3.052) | 21.019 (4.138) | <.0001 | (12.897, 29.141) |
| | Form 12ug | 212.888 (3.075) | 11.314 (4.152) | 0.0066 | (3.165, 19.463) |
| 11 | Placebo | 199.406 (2.977) | | | |
| | Olo 5ug | 210.894 (2.962) | 11.488 (4.038) | 0.0045 | (3.563, 19.412) |
| | Olo 10ug | 220.758 (2.981) | 21.353 (4.042) | <.0001 | (13.419, 29.286) |
| | Form 12ug | 211.097 (3.004) | 11.691 (4.056) | 0.0040 | (3.732, 19.651) |
| 12 | Placebo | 199.112 (3.041) | | | |
| | Olo 5ug | 210.885 (3.026) | 11.772 (4.124) | 0.0044 | (3.678, 19.867) |
| | Olo 10ug | 221.240 (3.045) | 22.128 (4.129) | <.0001 | (14.024, 30.231) |
| | Form 12ug | 213.236 (3.068) | 14.124 (4.143) | 0.0007 | (5.993, 22.254) |

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 (225), Olo 5ug (227), Olo 10ug (226), Form 12ug (224)
Common baseline mean (SE): 201.790 (3.052)

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)

| Week | Treatment | Treatment mean (SE) | Difference from Placebo | | |
|------|-----------|---------------------|-------------------------|---------|-------------------|
| | | | Mean (SE) | P-value | 95% CI |
| 13 | Placebo | 199.579 (3.067) | | | |
| | Olo 5ug | 212.305 (3.052) | 12.725 (4.160) | 0.0023 | (4.560, 20.890) |
| | Olo 10ug | 220.873 (3.072) | 21.294 (4.165) | <.0001 | (13.120, 29.467) |
| | Form 12ug | 214.296 (3.095) | 14.717 (4.179) | 0.0005 | (6.516, 22.918) |
| 14 | Placebo | 198.604 (3.163) | | | |
| | Olo 5ug | 210.994 (3.147) | 12.391 (4.290) | 0.0040 | (3.971, 20.811) |
| | Olo 10ug | 220.147 (3.168) | 21.543 (4.295) | <.0001 | (13.114, 29.972) |
| | Form 12ug | 213.301 (3.192) | 14.698 (4.309) | 0.0007 | (6.240, 23.155) |
| 15 | Placebo | 198.557 (3.144) | | | |
| | Olo 5ug | 210.824 (3.128) | 12.268 (4.264) | 0.0041 | (3.899, 20.636) |
| | Olo 10ug | 219.525 (3.148) | 20.968 (4.269) | <.0001 | (12.590, 29.346) |
| | Form 12ug | 210.938 (3.172) | 12.381 (4.283) | 0.0039 | (3.975, 20.787) |
| 16 | Placebo | 197.434 (3.164) | | | |
| | Olo 5ug | 211.580 (3.148) | 14.147 (4.291) | 0.0010 | (5.725, 22.568) |
| | Olo 10ug | 218.145 (3.168) | 20.711 (4.296) | <.0001 | (12.280, 29.142) |
| | Form 12ug | 208.968 (3.192) | 11.534 (4.310) | 0.0076 | (3.075, 19.993) |
| 17 | Placebo | 199.456 (3.166) | | | |
| | Olo 5ug | 208.902 (3.150) | 9.447 (4.293) | 0.0280 | (1.020, 17.873) |
| | Olo 10ug | 218.847 (3.170) | 19.392 (4.298) | <.0001 | (10.956, 27.827) |
| | Form 12ug | 211.744 (3.194) | 12.288 (4.312) | 0.0045 | (3.825, 20.752) |
| 18 | Placebo | 199.255 (3.251) | | | |
| | Olo 5ug | 209.951 (3.235) | 10.697 (4.409) | 0.0155 | (2.043, 19.351) |
| | Olo 10ug | 219.210 (3.256) | 19.955 (4.414) | <.0001 | (11.292, 28.619) |
| | Form 12ug | 210.957 (3.280) | 11.702 (4.429) | 0.0084 | (3.010, 20.395) |

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 (225), Olo 5ug (227), Olo 10ug (226), Form 12ug (224)
Common baseline mean (SE): 201.790 (3.052)

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)

| Week | Treatment | Treatment mean (SE) | Difference from Placebo | | |
|------|-----------|---------------------|-------------------------|---------|-------------------|
| | | | Mean (SE) | P-value | 95% CI |
| 19 | Placebo | 199.993 (3.252) | | | |
| | Olo 5ug | 210.727 (3.236) | 10.733 (4.411) | 0.0152 | (2.076, 19.390) |
| | Olo 10ug | 221.123 (3.257) | 21.130 (4.416) | <.0001 | (12.463, 29.796) |
| | Form 12ug | 211.101 (3.282) | 11.108 (4.430) | 0.0123 | (2.412, 19.803) |
| 20 | Placebo | 196.931 (3.190) | | | |
| | Olo 5ug | 211.001 (3.174) | 14.069 (4.327) | 0.0012 | (5.577, 22.562) |
| | Olo 10ug | 221.110 (3.195) | 24.178 (4.332) | <.0001 | (15.676, 32.680) |
| | Form 12ug | 210.617 (3.219) | 13.685 (4.346) | 0.0017 | (5.155, 22.216) |
| 21 | Placebo | 198.329 (3.264) | | | |
| | Olo 5ug | 211.186 (3.248) | 12.857 (4.427) | 0.0038 | (4.168, 21.546) |
| | Olo 10ug | 218.421 (3.269) | 20.092 (4.432) | <.0001 | (11.393, 28.791) |
| | Form 12ug | 209.688 (3.294) | 11.359 (4.447) | 0.0108 | (2.632, 20.087) |
| 22 | Placebo | 197.084 (3.246) | | | |
| | Olo 5ug | 209.963 (3.229) | 12.879 (4.402) | 0.0035 | (4.240, 21.519) |
| | Olo 10ug | 218.374 (3.250) | 21.291 (4.407) | <.0001 | (12.642, 29.940) |
| | Form 12ug | 207.867 (3.275) | 10.784 (4.422) | 0.0149 | (2.106, 19.462) |
| 23 | Placebo | 196.876 (3.195) | | | |
| | Olo 5ug | 211.110 (3.179) | 14.234 (4.333) | 0.0011 | (5.730, 22.739) |
| | Olo 10ug | 217.520 (3.199) | 20.644 (4.338) | <.0001 | (12.130, 29.158) |
| | Form 12ug | 209.248 (3.224) | 12.372 (4.352) | 0.0046 | (3.830, 20.914) |
| 24 | Placebo | 196.789 (3.270) | | | |
| | Olo 5ug | 210.496 (3.253) | 13.707 (4.435) | 0.0021 | (5.004, 22.411) |
| | Olo 10ug | 217.660 (3.274) | 20.871 (4.440) | <.0001 | (12.158, 29.584) |
| | Form 12ug | 211.038 (3.299) | 14.249 (4.454) | 0.0014 | (5.506, 22.991) |

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 (225), Olo 5ug (227), Olo 10ug (226), Form 12ug (224)
Common baseline mean (SE): 201.790 (3.052)

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)

| Week | Treatment | Treatment mean (SE) | Difference from Placebo | | |
|------|-----------|---------------------|-------------------------|---------|-------------------|
| | | | Mean (SE) | P-value | 95% CI |
| 25 | Placebo | 198.221 (3.270) | | | |
| | Olo 5ug | 212.354 (3.254) | 14.132 (4.435) | 0.0015 | (5.428, 22.837) |
| | Olo 10ug | 219.302 (3.275) | 21.081 (4.440) | <.0001 | (12.366, 29.795) |
| | Form 12ug | 209.384 (3.300) | 11.162 (4.455) | 0.0124 | (2.419, 19.906) |
| 26 | Placebo | 196.356 (3.302) | | | |
| | Olo 5ug | 210.376 (3.285) | 14.020 (4.478) | 0.0018 | (5.231, 22.809) |
| | Olo 10ug | 219.487 (3.306) | 23.131 (4.483) | <.0001 | (14.333, 31.929) |
| | Form 12ug | 210.291 (3.332) | 13.934 (4.498) | 0.0020 | (5.107, 22.762) |
| 27 | Placebo | 196.234 (3.332) | | | |
| | Olo 5ug | 210.288 (3.315) | 14.054 (4.519) | 0.0019 | (5.184, 22.924) |
| | Olo 10ug | 218.998 (3.337) | 22.764 (4.524) | <.0001 | (13.885, 31.644) |
| | Form 12ug | 209.974 (3.362) | 13.740 (4.539) | 0.0025 | (4.831, 22.649) |
| 28 | Placebo | 196.000 (3.342) | | | |
| | Olo 5ug | 210.825 (3.326) | 14.825 (4.533) | 0.0011 | (5.928, 23.723) |
| | Olo 10ug | 219.827 (3.347) | 23.827 (4.538) | <.0001 | (14.920, 32.734) |
| | Form 12ug | 209.642 (3.373) | 13.642 (4.553) | 0.0028 | (4.705, 22.579) |
| 29 | Placebo | 195.572 (3.282) | | | |
| | Olo 5ug | 207.796 (3.265) | 12.224 (4.451) | 0.0062 | (3.488, 20.960) |
| | Olo 10ug | 218.420 (3.286) | 22.848 (4.456) | <.0001 | (14.102, 31.594) |
| | Form 12ug | 208.846 (3.312) | 13.274 (4.471) | 0.0031 | (4.499, 22.049) |
| 30 | Placebo | 194.857 (3.282) | | | |
| | Olo 5ug | 208.005 (3.265) | 13.148 (4.451) | 0.0032 | (4.413, 21.883) |
| | Olo 10ug | 217.957 (3.286) | 23.101 (4.456) | <.0001 | (14.356, 31.845) |
| | Form 12ug | 209.031 (3.311) | 14.175 (4.470) | 0.0016 | (5.401, 22.948) |

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 (225), Olo 5ug (227), Olo 10ug (226), Form 12ug (224)
Common baseline mean (SE): 201.790 (3.052)

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)

| Week | Treatment | Treatment mean (SE) | Difference from Placebo | | |
|------|-----------|---------------------|-------------------------|---------|-------------------|
| | | | Mean (SE) | P-value | 95% CI |
| 31 | Placebo | 195.053 (3.314) | | | |
| | Olo 5ug | 208.083 (3.298) | 13.030 (4.495) | 0.0038 | (4.208, 21.853) |
| | Olo 10ug | 217.253 (3.319) | 22.200 (4.500) | <.0001 | (13.368, 31.032) |
| | Form 12ug | 208.388 (3.344) | 13.335 (4.515) | 0.0032 | (4.474, 22.197) |
| 32 | Placebo | 194.222 (3.341) | | | |
| | Olo 5ug | 208.142 (3.324) | 13.920 (4.531) | 0.0022 | (5.027, 22.812) |
| | Olo 10ug | 216.690 (3.345) | 22.468 (4.536) | <.0001 | (13.566, 31.370) |
| | Form 12ug | 208.847 (3.371) | 14.625 (4.551) | 0.0014 | (5.693, 23.557) |
| 33 | Placebo | 195.930 (3.416) | | | |
| | Olo 5ug | 208.049 (3.398) | 12.119 (4.633) | 0.0090 | (3.027, 21.212) |
| | Olo 10ug | 217.574 (3.420) | 21.644 (4.638) | <.0001 | (12.541, 30.746) |
| | Form 12ug | 208.125 (3.447) | 12.195 (4.653) | 0.0089 | (3.062, 21.327) |
| 34 | Placebo | 193.507 (3.358) | | | |
| | Olo 5ug | 207.809 (3.341) | 14.302 (4.554) | 0.0017 | (5.364, 23.240) |
| | Olo 10ug | 216.577 (3.362) | 23.070 (4.559) | <.0001 | (14.122, 32.018) |
| | Form 12ug | 207.993 (3.388) | 14.486 (4.574) | 0.0016 | (5.508, 23.463) |
| 35 | Placebo | 192.459 (3.422) | | | |
| | Olo 5ug | 205.559 (3.405) | 13.100 (4.642) | 0.0049 | (3.990, 22.210) |
| | Olo 10ug | 217.459 (3.427) | 25.000 (4.647) | <.0001 | (15.880, 34.119) |
| | Form 12ug | 208.636 (3.453) | 16.177 (4.662) | 0.0005 | (7.027, 25.327) |
| 36 | Placebo | 193.953 (3.448) | | | |
| | Olo 5ug | 206.434 (3.431) | 12.481 (4.676) | 0.0077 | (3.303, 21.659) |
| | Olo 10ug | 217.586 (3.453) | 23.633 (4.682) | <.0001 | (14.445, 32.821) |
| | Form 12ug | 204.652 (3.479) | 10.699 (4.697) | 0.0230 | (1.481, 19.918) |

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 (225), Olo 5ug (227), Olo 10ug (226), Form 12ug (224)
Common baseline mean (SE): 201.790 (3.052)

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)

| Week | Treatment | Treatment mean (SE) | Difference from Placebo | | |
|------|-----------|---------------------|-------------------------|---------|-------------------|
| | | | Mean (SE) | P-value | 95% CI |
| 37 | Placebo | 193.175 (3.474) | | | |
| | Olo 5ug | 207.477 (3.457) | 14.302 (4.712) | 0.0025 | (5.054, 23.551) |
| | Olo 10ug | 218.764 (3.479) | 25.589 (4.717) | <.0001 | (16.331, 34.848) |
| | Form 12ug | 208.767 (3.506) | 15.592 (4.733) | 0.0010 | (6.303, 24.882) |
| 38 | Placebo | 194.608 (3.415) | | | |
| | Olo 5ug | 206.899 (3.398) | 12.291 (4.632) | 0.0081 | (3.201, 21.382) |
| | Olo 10ug | 219.866 (3.420) | 25.258 (4.637) | <.0001 | (16.158, 34.359) |
| | Form 12ug | 208.666 (3.446) | 14.058 (4.652) | 0.0026 | (4.927, 23.189) |
| 39 | Placebo | 192.523 (3.448) | | | |
| | Olo 5ug | 206.709 (3.431) | 14.186 (4.677) | 0.0025 | (5.008, 23.364) |
| | Olo 10ug | 218.908 (3.453) | 26.384 (4.682) | <.0001 | (17.196, 35.572) |
| | Form 12ug | 208.507 (3.479) | 15.984 (4.697) | 0.0007 | (6.765, 25.202) |
| 40 | Placebo | 194.307 (3.368) | | | |
| | Olo 5ug | 207.185 (3.351) | 12.878 (4.568) | 0.0049 | (3.913, 21.843) |
| | Olo 10ug | 219.939 (3.373) | 25.631 (4.573) | <.0001 | (16.656, 34.607) |
| | Form 12ug | 208.676 (3.399) | 14.369 (4.588) | 0.0018 | (5.364, 23.374) |
| 41 | Placebo | 194.481 (3.431) | | | |
| | Olo 5ug | 208.293 (3.414) | 13.812 (4.654) | 0.0031 | (4.679, 22.946) |
| | Olo 10ug | 220.910 (3.436) | 26.429 (4.659) | <.0001 | (17.286, 35.573) |
| | Form 12ug | 209.561 (3.462) | 15.080 (4.674) | 0.0013 | (5.906, 24.254) |
| 42 | Placebo | 192.220 (3.401) | | | |
| | Olo 5ug | 208.552 (3.384) | 16.333 (4.612) | 0.0004 | (7.280, 25.385) |
| | Olo 10ug | 216.578 (3.405) | 24.358 (4.617) | <.0001 | (15.296, 33.420) |
| | Form 12ug | 206.945 (3.431) | 14.726 (4.633) | 0.0015 | (5.633, 23.818) |

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 (225), Olo 5ug (227), Olo 10ug (226), Form 12ug (224)
Common baseline mean (SE): 201.790 (3.052)

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)

| Week | Treatment | Treatment mean (SE) | Difference from Placebo | | |
|------|-----------|---------------------|-------------------------|---------|-------------------|
| | | | Mean (SE) | P-value | 95% CI |
| 43 | Placebo | 194.308 (3.450) | | | |
| | Olo 5ug | 209.352 (3.433) | 15.043 (4.680) | 0.0014 | (5.859, 24.227) |
| | Olo 10ug | 217.016 (3.455) | 22.708 (4.685) | <.0001 | (13.514, 31.902) |
| | Form 12ug | 208.058 (3.481) | 13.750 (4.700) | 0.0035 | (4.525, 22.975) |
| 44 | Placebo | 192.961 (3.471) | | | |
| | Olo 5ug | 208.118 (3.454) | 15.157 (4.708) | 0.0013 | (5.917, 24.397) |
| | Olo 10ug | 217.419 (3.476) | 24.457 (4.713) | <.0001 | (15.208, 33.707) |
| | Form 12ug | 208.442 (3.503) | 15.481 (4.729) | 0.0011 | (6.200, 24.762) |
| 45 | Placebo | 192.924 (3.464) | | | |
| | Olo 5ug | 206.048 (3.446) | 13.124 (4.698) | 0.0053 | (3.904, 22.344) |
| | Olo 10ug | 217.292 (3.468) | 24.368 (4.703) | <.0001 | (15.138, 33.597) |
| | Form 12ug | 207.869 (3.495) | 14.945 (4.718) | 0.0016 | (5.685, 24.206) |
| 46 | Placebo | 193.302 (3.505) | | | |
| | Olo 5ug | 206.763 (3.487) | 13.462 (4.754) | 0.0047 | (4.132, 22.791) |
| | Olo 10ug | 217.971 (3.510) | 24.669 (4.759) | <.0001 | (15.329, 34.009) |
| | Form 12ug | 208.065 (3.537) | 14.763 (4.775) | 0.0021 | (5.392, 24.134) |
| 47 | Placebo | 192.996 (3.532) | | | |
| | Olo 5ug | 209.612 (3.514) | 16.617 (4.790) | 0.0005 | (7.216, 26.017) |
| | Olo 10ug | 218.096 (3.536) | 25.101 (4.795) | <.0001 | (15.690, 34.512) |
| | Form 12ug | 208.526 (3.564) | 15.530 (4.811) | 0.0013 | (6.088, 24.973) |
| 48 | Placebo | 194.820 (3.472) | | | |
| | Olo 5ug | 210.004 (3.455) | 15.183 (4.709) | 0.0013 | (5.941, 24.426) |
| | Olo 10ug | 216.976 (3.477) | 22.155 (4.715) | <.0001 | (12.902, 31.408) |
| | Form 12ug | 207.994 (3.504) | 13.174 (4.730) | 0.0055 | (3.890, 22.457) |

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 (225), Olo 5ug (227), Olo 10ug (226), Form 12ug (224)
Common baseline mean (SE): 201.790 (3.052)

Source data: Appendix 16.1.9.2, Statdoc 6.2.2.1

ctr\diary-adjmean-ancova.sas 11OCT2011

Boehringer Ingelheim
BI Trial No.: 1222.14
1. - 15. CTR Main Part

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

| Week | Treatment | Treatment mean (SE) | Difference from Placebo | | |
|------|-----------|---------------------|-------------------------|---------|-------------------|
| | | | Mean (SE) | P-value | 95% CI |
| 1 | Placebo | 211.336 (2.107) | | | |
| | Olo 5ug | 227.002 (2.112) | 15.665 (2.866) | <.0001 | (10.040, 21.290) |
| | Olo 10ug | 241.877 (2.107) | 30.541 (2.854) | <.0001 | (24.940, 36.141) |
| | Form 12ug | 226.585 (2.132) | 15.249 (2.874) | <.0001 | (9.608, 20.889) |
| 2 | Placebo | 207.455 (2.389) | | | |
| | Olo 5ug | 225.103 (2.395) | 17.647 (3.250) | <.0001 | (11.270, 24.025) |
| | Olo 10ug | 239.013 (2.389) | 31.558 (3.235) | <.0001 | (25.208, 37.908) |
| | Form 12ug | 223.406 (2.418) | 15.951 (3.258) | <.0001 | (9.556, 22.346) |
| 3 | Placebo | 207.108 (2.535) | | | |
| | Olo 5ug | 224.994 (2.541) | 17.886 (3.448) | <.0001 | (11.119, 24.653) |
| | Olo 10ug | 238.278 (2.534) | 31.170 (3.433) | <.0001 | (24.433, 37.908) |
| | Form 12ug | 223.238 (2.565) | 16.130 (3.457) | <.0001 | (9.344, 22.916) |
| 4 | Placebo | 206.344 (2.592) | | | |
| | Olo 5ug | 223.709 (2.598) | 17.365 (3.526) | <.0001 | (10.445, 24.284) |
| | Olo 10ug | 237.962 (2.592) | 31.618 (3.510) | <.0001 | (24.729, 38.508) |
| | Form 12ug | 225.288 (2.623) | 18.944 (3.535) | <.0001 | (12.005, 25.882) |
| 5 | Placebo | 208.252 (2.763) | | | |
| | Olo 5ug | 220.907 (2.770) | 12.655 (3.759) | 0.0008 | (5.278, 20.033) |
| | Olo 10ug | 234.754 (2.763) | 26.502 (3.743) | <.0001 | (19.157, 33.848) |
| | Form 12ug | 221.934 (2.797) | 13.682 (3.769) | 0.0003 | (6.284, 21.079) |
| 6 | Placebo | 207.748 (2.785) | | | |
| | Olo 5ug | 219.307 (2.792) | 11.559 (3.789) | 0.0023 | (4.124, 18.994) |
| | Olo 10ug | 233.245 (2.785) | 25.497 (3.772) | <.0001 | (18.094, 32.900) |
| | Form 12ug | 219.076 (2.819) | 11.327 (3.799) | 0.0029 | (3.872, 18.783) |

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 (224), Olo 5ug (223), Olo 10ug (227), Form 12ug (222)
Common baseline mean (SE): 212.571 (3.151)

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)

| Week | Treatment | Treatment mean (SE) | Difference from Placebo | | |
|------|-----------|---------------------|-------------------------|---------|-------------------|
| | | | Mean (SE) | P-value | 95% CI |
| 7 | Placebo | 205.133 (2.861) | | | |
| | Olo 5ug | 220.237 (2.869) | 15.103 (3.892) | 0.0001 | (7.464, 22.742) |
| | Olo 10ug | 233.226 (2.861) | 28.092 (3.875) | <.0001 | (20.486, 35.699) |
| | Form 12ug | 219.931 (2.896) | 14.798 (3.903) | 0.0002 | (7.137, 22.458) |
| 8 | Placebo | 206.585 (2.858) | | | |
| | Olo 5ug | 222.719 (2.866) | 16.134 (3.889) | <.0001 | (8.502, 23.765) |
| | Olo 10ug | 233.895 (2.858) | 27.310 (3.872) | <.0001 | (19.711, 34.908) |
| | Form 12ug | 220.400 (2.893) | 13.815 (3.899) | 0.0004 | (6.162, 21.467) |
| 9 | Placebo | 207.177 (2.896) | | | |
| | Olo 5ug | 223.090 (2.904) | 15.912 (3.940) | <.0001 | (8.179, 23.646) |
| | Olo 10ug | 232.931 (2.896) | 25.754 (3.923) | <.0001 | (18.055, 33.454) |
| | Form 12ug | 219.501 (2.932) | 12.323 (3.951) | 0.0019 | (4.569, 20.078) |
| 10 | Placebo | 207.679 (3.000) | | | |
| | Olo 5ug | 221.732 (3.008) | 14.053 (4.082) | 0.0006 | (6.041, 22.064) |
| | Olo 10ug | 231.351 (3.000) | 23.672 (4.064) | <.0001 | (15.695, 31.648) |
| | Form 12ug | 218.643 (3.037) | 10.963 (4.093) | 0.0075 | (2.930, 18.997) |
| 11 | Placebo | 207.098 (3.002) | | | |
| | Olo 5ug | 222.639 (3.009) | 15.541 (4.083) | 0.0002 | (7.526, 23.555) |
| | Olo 10ug | 230.142 (3.002) | 23.044 (4.066) | <.0001 | (15.064, 31.023) |
| | Form 12ug | 219.777 (3.038) | 12.679 (4.095) | 0.0020 | (4.643, 20.715) |
| 12 | Placebo | 206.319 (3.006) | | | |
| | Olo 5ug | 221.376 (3.014) | 15.057 (4.089) | 0.0002 | (7.031, 23.083) |
| | Olo 10ug | 231.328 (3.006) | 25.009 (4.072) | <.0001 | (17.018, 32.999) |
| | Form 12ug | 221.121 (3.043) | 14.801 (4.101) | 0.0003 | (6.754, 22.849) |

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 (224), Olo 5ug (223), Olo 10ug (227), Form 12ug (222)
Common baseline mean (SE): 212.571 (3.151)

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)

| Week | Treatment | Treatment mean (SE) | Difference from Placebo | | |
|------|-----------|---------------------|-------------------------|---------|-------------------|
| | | | Mean (SE) | P-value | 95% CI |
| 13 | Placebo | 206.886 (3.018) | | | |
| | Olo 5ug | 222.534 (3.026) | 15.648 (4.106) | 0.0001 | (7.590, 23.706) |
| | Olo 10ug | 230.033 (3.018) | 23.147 (4.088) | <.0001 | (15.124, 31.169) |
| | Form 12ug | 221.033 (3.055) | 14.146 (4.117) | 0.0006 | (6.066, 22.226) |
| 14 | Placebo | 205.257 (3.124) | | | |
| | Olo 5ug | 222.549 (3.132) | 17.292 (4.250) | <.0001 | (8.951, 25.634) |
| | Olo 10ug | 230.353 (3.124) | 25.096 (4.232) | <.0001 | (16.791, 33.402) |
| | Form 12ug | 219.737 (3.162) | 14.480 (4.262) | 0.0007 | (6.115, 22.844) |
| 15 | Placebo | 203.622 (3.068) | | | |
| | Olo 5ug | 221.321 (3.076) | 17.699 (4.174) | <.0001 | (9.507, 25.891) |
| | Olo 10ug | 228.977 (3.068) | 25.354 (4.156) | <.0001 | (17.198, 33.511) |
| | Form 12ug | 217.784 (3.106) | 14.162 (4.185) | 0.0007 | (5.947, 22.377) |
| 16 | Placebo | 202.514 (3.169) | | | |
| | Olo 5ug | 220.665 (3.178) | 18.151 (4.312) | <.0001 | (9.689, 26.613) |
| | Olo 10ug | 228.410 (3.169) | 25.895 (4.293) | <.0001 | (17.470, 34.321) |
| | Form 12ug | 216.122 (3.208) | 13.607 (4.323) | 0.0017 | (5.122, 22.093) |
| 17 | Placebo | 203.180 (3.126) | | | |
| | Olo 5ug | 219.156 (3.134) | 15.976 (4.253) | 0.0002 | (7.629, 24.323) |
| | Olo 10ug | 228.433 (3.126) | 25.254 (4.235) | <.0001 | (16.943, 33.565) |
| | Form 12ug | 217.406 (3.164) | 14.226 (4.265) | 0.0009 | (5.856, 22.597) |
| 18 | Placebo | 204.356 (3.214) | | | |
| | Olo 5ug | 219.025 (3.222) | 14.669 (4.372) | 0.0008 | (6.088, 23.250) |
| | Olo 10ug | 229.240 (3.214) | 24.884 (4.353) | <.0001 | (16.340, 33.427) |
| | Form 12ug | 217.620 (3.253) | 13.264 (4.384) | 0.0026 | (4.659, 21.868) |

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 (224), Olo 5ug (223), Olo 10ug (227), Form 12ug (222)
Common baseline mean (SE): 212.571 (3.151)

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)

| Week | Treatment | Treatment mean (SE) | Difference from Placebo | | |
|------|-----------|---------------------|-------------------------|---------|-------------------|
| | | | Mean (SE) | P-value | 95% CI |
| 19 | Placebo | 205.285 (3.171) | | | |
| | Olo 5ug | 222.517 (3.179) | 17.233 (4.314) | <.0001 | (8.767, 25.699) |
| | Olo 10ug | 228.068 (3.171) | 22.783 (4.295) | <.0001 | (14.354, 31.213) |
| | Form 12ug | 218.645 (3.209) | 13.360 (4.325) | 0.0021 | (4.871, 21.849) |
| 20 | Placebo | 203.127 (3.248) | | | |
| | Olo 5ug | 221.273 (3.256) | 18.147 (4.418) | <.0001 | (9.475, 26.818) |
| | Olo 10ug | 228.839 (3.248) | 25.712 (4.399) | <.0001 | (17.078, 34.345) |
| | Form 12ug | 218.215 (3.287) | 15.088 (4.430) | 0.0007 | (6.393, 23.783) |
| 21 | Placebo | 203.203 (3.249) | | | |
| | Olo 5ug | 221.823 (3.258) | 18.620 (4.421) | <.0001 | (9.944, 27.295) |
| | Olo 10ug | 225.891 (3.249) | 22.687 (4.401) | <.0001 | (14.049, 31.325) |
| | Form 12ug | 216.763 (3.289) | 13.559 (4.433) | 0.0023 | (4.860, 22.259) |
| 22 | Placebo | 203.110 (3.284) | | | |
| | Olo 5ug | 221.119 (3.293) | 18.009 (4.468) | <.0001 | (9.240, 26.778) |
| | Olo 10ug | 227.313 (3.284) | 24.203 (4.449) | <.0001 | (15.472, 32.933) |
| | Form 12ug | 216.781 (3.324) | 13.671 (4.480) | 0.0023 | (4.878, 22.464) |
| 23 | Placebo | 200.525 (3.284) | | | |
| | Olo 5ug | 219.856 (3.293) | 19.331 (4.468) | <.0001 | (10.562, 28.100) |
| | Olo 10ug | 224.526 (3.284) | 24.002 (4.448) | <.0001 | (15.271, 32.732) |
| | Form 12ug | 216.645 (3.324) | 16.120 (4.480) | 0.0003 | (7.328, 24.913) |
| 24 | Placebo | 202.505 (3.281) | | | |
| | Olo 5ug | 219.905 (3.289) | 17.400 (4.463) | 0.0001 | (8.640, 26.160) |
| | Olo 10ug | 225.380 (3.281) | 22.875 (4.444) | <.0001 | (14.153, 31.596) |
| | Form 12ug | 218.321 (3.321) | 15.816 (4.475) | 0.0004 | (7.032, 24.599) |

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 (224), Olo 5ug (223), Olo 10ug (227), Form 12ug (222)
Common baseline mean (SE): 212.571 (3.151)

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)

| Week | Treatment | Treatment mean (SE) | Difference from Placebo | | |
|------|-----------|---------------------|-------------------------|---------|-------------------|
| | | | Mean (SE) | P-value | 95% CI |
| 25 | Placebo | 202.921 (3.337) | | | |
| | Olo 5ug | 220.987 (3.346) | 18.066 (4.540) | <.0001 | (9.155, 26.977) |
| | Olo 10ug | 227.165 (3.337) | 24.244 (4.521) | <.0001 | (15.372, 33.116) |
| | Form 12ug | 217.271 (3.378) | 14.349 (4.553) | 0.0017 | (5.414, 23.285) |
| 26 | Placebo | 200.578 (3.346) | | | |
| | Olo 5ug | 219.983 (3.355) | 19.405 (4.552) | <.0001 | (10.471, 28.338) |
| | Olo 10ug | 228.544 (3.346) | 27.967 (4.532) | <.0001 | (19.072, 36.861) |
| | Form 12ug | 216.541 (3.387) | 15.963 (4.564) | 0.0005 | (7.005, 24.922) |
| 27 | Placebo | 199.686 (3.386) | | | |
| | Olo 5ug | 218.944 (3.395) | 19.258 (4.606) | <.0001 | (10.217, 28.299) |
| | Olo 10ug | 227.014 (3.386) | 27.328 (4.586) | <.0001 | (18.327, 36.329) |
| | Form 12ug | 217.513 (3.427) | 17.826 (4.619) | 0.0001 | (8.761, 26.892) |
| 28 | Placebo | 200.135 (3.447) | | | |
| | Olo 5ug | 218.128 (3.456) | 17.993 (4.690) | 0.0001 | (8.788, 27.197) |
| | Olo 10ug | 226.990 (3.447) | 26.855 (4.669) | <.0001 | (17.690, 36.019) |
| | Form 12ug | 216.879 (3.489) | 16.744 (4.703) | 0.0004 | (7.515, 25.974) |
| 29 | Placebo | 200.711 (3.387) | | | |
| | Olo 5ug | 215.933 (3.396) | 15.223 (4.608) | 0.0010 | (6.179, 24.267) |
| | Olo 10ug | 226.001 (3.387) | 25.290 (4.588) | <.0001 | (16.285, 34.295) |
| | Form 12ug | 216.889 (3.429) | 16.179 (4.621) | 0.0005 | (7.110, 25.248) |
| 30 | Placebo | 199.405 (3.358) | | | |
| | Olo 5ug | 216.915 (3.367) | 17.510 (4.568) | 0.0001 | (8.544, 26.476) |
| | Olo 10ug | 224.670 (3.358) | 25.265 (4.548) | <.0001 | (16.338, 34.192) |
| | Form 12ug | 216.500 (3.399) | 17.095 (4.581) | 0.0002 | (8.104, 26.085) |

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 (224), Olo 5ug (223), Olo 10ug (227), Form 12ug (222)
Common baseline mean (SE): 212.571 (3.151)

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)

| Week | Treatment | Treatment mean (SE) | Difference from Placebo | | |
|------|-----------|---------------------|-------------------------|---------|-------------------|
| | | | Mean (SE) | P-value | 95% CI |
| 31 | Placebo | 199.415 (3.375) | | | |
| | Olo 5ug | 217.894 (3.384) | 18.479 (4.592) | <.0001 | (9.467, 27.491) |
| | Olo 10ug | 223.948 (3.375) | 24.533 (4.572) | <.0001 | (15.561, 33.505) |
| | Form 12ug | 216.690 (3.416) | 17.275 (4.604) | 0.0002 | (8.239, 26.311) |
| 32 | Placebo | 198.601 (3.442) | | | |
| | Olo 5ug | 217.244 (3.451) | 18.643 (4.683) | <.0001 | (9.452, 27.834) |
| | Olo 10ug | 223.113 (3.442) | 24.512 (4.663) | <.0001 | (15.361, 33.663) |
| | Form 12ug | 217.257 (3.484) | 18.656 (4.696) | <.0001 | (9.440, 27.873) |
| 33 | Placebo | 199.246 (3.521) | | | |
| | Olo 5ug | 217.910 (3.531) | 18.664 (4.791) | 0.0001 | (9.262, 28.067) |
| | Olo 10ug | 222.045 (3.521) | 22.799 (4.770) | <.0001 | (13.437, 32.160) |
| | Form 12ug | 217.210 (3.564) | 17.964 (4.804) | 0.0002 | (8.536, 27.392) |
| 34 | Placebo | 198.814 (3.513) | | | |
| | Olo 5ug | 216.869 (3.522) | 18.055 (4.779) | 0.0002 | (8.675, 27.435) |
| | Olo 10ug | 222.251 (3.513) | 23.437 (4.758) | <.0001 | (14.098, 32.776) |
| | Form 12ug | 215.697 (3.556) | 16.883 (4.792) | 0.0004 | (7.477, 26.288) |
| 35 | Placebo | 196.433 (3.519) | | | |
| | Olo 5ug | 215.373 (3.528) | 18.940 (4.787) | <.0001 | (9.544, 28.336) |
| | Olo 10ug | 223.316 (3.519) | 26.883 (4.767) | <.0001 | (17.528, 36.238) |
| | Form 12ug | 213.995 (3.562) | 17.562 (4.801) | 0.0003 | (8.140, 26.983) |
| 36 | Placebo | 197.016 (3.520) | | | |
| | Olo 5ug | 216.167 (3.529) | 19.151 (4.789) | <.0001 | (9.752, 28.550) |
| | Olo 10ug | 223.257 (3.520) | 26.241 (4.768) | <.0001 | (16.883, 35.599) |
| | Form 12ug | 213.083 (3.563) | 16.067 (4.802) | 0.0009 | (6.642, 25.491) |

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 (224), Olo 5ug (223), Olo 10ug (227), Form 12ug (222)
Common baseline mean (SE): 212.571 (3.151)

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)

| Week | Treatment | Treatment mean (SE) | Difference from Placebo | | |
|------|-----------|---------------------|-------------------------|---------|-------------------|
| | | | Mean (SE) | P-value | 95% CI |
| 37 | Placebo | 198.957 (3.506) | | | |
| | Olo 5ug | 217.072 (3.515) | 18.115 (4.770) | 0.0002 | (8.754, 27.476) |
| | Olo 10ug | 224.629 (3.506) | 25.672 (4.749) | <.0001 | (16.351, 34.992) |
| | Form 12ug | 215.709 (3.549) | 16.752 (4.783) | 0.0005 | (7.365, 26.138) |
| 38 | Placebo | 197.542 (3.517) | | | |
| | Olo 5ug | 215.454 (3.526) | 17.912 (4.785) | 0.0002 | (8.521, 27.303) |
| | Olo 10ug | 224.973 (3.517) | 27.431 (4.764) | <.0001 | (18.081, 36.782) |
| | Form 12ug | 215.889 (3.560) | 18.348 (4.798) | 0.0001 | (8.931, 27.765) |
| 39 | Placebo | 196.457 (3.488) | | | |
| | Olo 5ug | 216.217 (3.497) | 19.761 (4.745) | <.0001 | (10.448, 29.073) |
| | Olo 10ug | 225.166 (3.488) | 28.709 (4.724) | <.0001 | (19.437, 37.981) |
| | Form 12ug | 215.521 (3.530) | 19.064 (4.758) | <.0001 | (9.726, 28.402) |
| 40 | Placebo | 197.220 (3.451) | | | |
| | Olo 5ug | 216.117 (3.460) | 18.897 (4.694) | <.0001 | (9.683, 28.110) |
| | Olo 10ug | 224.887 (3.451) | 27.667 (4.674) | <.0001 | (18.494, 36.840) |
| | Form 12ug | 214.627 (3.493) | 17.406 (4.707) | 0.0002 | (8.168, 26.645) |
| 41 | Placebo | 198.734 (3.450) | | | |
| | Olo 5ug | 215.956 (3.459) | 17.222 (4.694) | 0.0003 | (8.010, 26.434) |
| | Olo 10ug | 224.450 (3.450) | 25.717 (4.673) | <.0001 | (16.545, 34.888) |
| | Form 12ug | 215.625 (3.492) | 16.891 (4.706) | 0.0004 | (7.654, 26.128) |
| 42 | Placebo | 198.257 (3.439) | | | |
| | Olo 5ug | 217.683 (3.448) | 19.426 (4.679) | <.0001 | (10.242, 28.609) |
| | Olo 10ug | 222.760 (3.439) | 24.503 (4.659) | <.0001 | (15.360, 33.647) |
| | Form 12ug | 214.300 (3.481) | 16.043 (4.692) | 0.0007 | (6.835, 25.252) |

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 (224), Olo 5ug (223), Olo 10ug (227), Form 12ug (222)
Common baseline mean (SE): 212.571 (3.151)

Source data: Appendix 16.1.9.2, Statdoc 6.2.1.3

ctr\diary-adjmean-ancova.sas 11OCT2011

Boehringer Ingelheim
BI Trial No.: 1222.14
1. - 15. CTR Main Part

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

| Week | Treatment | Treatment mean (SE) | Difference from Placebo | | |
|------|-----------|---------------------|-------------------------|---------|-------------------|
| | | | Mean (SE) | P-value | 95% CI |
| 43 | Placebo | 195.875 (3.482) | | | |
| | Olo 5ug | 217.909 (3.491) | 22.033 (4.738) | <.0001 | (12.735, 31.332) |
| | Olo 10ug | 222.993 (3.482) | 27.118 (4.717) | <.0001 | (17.860, 36.376) |
| | Form 12ug | 214.770 (3.525) | 18.895 (4.751) | <.0001 | (9.571, 28.218) |
| 44 | Placebo | 195.979 (3.511) | | | |
| | Olo 5ug | 217.934 (3.520) | 21.956 (4.777) | <.0001 | (12.580, 31.331) |
| | Olo 10ug | 223.623 (3.511) | 27.644 (4.756) | <.0001 | (18.310, 36.979) |
| | Form 12ug | 214.777 (3.554) | 18.798 (4.790) | <.0001 | (9.397, 28.199) |
| 45 | Placebo | 196.098 (3.550) | | | |
| | Olo 5ug | 215.397 (3.560) | 19.299 (4.830) | <.0001 | (9.819, 28.778) |
| | Olo 10ug | 223.276 (3.550) | 27.178 (4.809) | <.0001 | (17.739, 36.616) |
| | Form 12ug | 214.737 (3.594) | 18.639 (4.843) | 0.0001 | (9.133, 28.144) |
| 46 | Placebo | 197.067 (3.576) | | | |
| | Olo 5ug | 215.409 (3.585) | 18.342 (4.865) | 0.0002 | (8.794, 27.890) |
| | Olo 10ug | 223.217 (3.576) | 26.150 (4.844) | <.0001 | (16.644, 35.656) |
| | Form 12ug | 213.884 (3.620) | 16.817 (4.878) | 0.0006 | (7.243, 26.391) |
| 47 | Placebo | 197.374 (3.513) | | | |
| | Olo 5ug | 215.793 (3.522) | 18.419 (4.779) | 0.0001 | (9.040, 27.799) |
| | Olo 10ug | 222.857 (3.513) | 25.483 (4.758) | <.0001 | (16.145, 34.822) |
| | Form 12ug | 213.820 (3.556) | 16.446 (4.792) | 0.0006 | (7.041, 25.851) |
| 48 | Placebo | 197.876 (3.535) | | | |
| | Olo 5ug | 214.669 (3.544) | 16.793 (4.809) | 0.0005 | (7.356, 26.231) |
| | Olo 10ug | 223.523 (3.535) | 25.647 (4.788) | <.0001 | (16.251, 35.043) |
| | Form 12ug | 212.548 (3.578) | 14.672 (4.822) | 0.0024 | (5.209, 24.136) |

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 (224), Olo 5ug (223), Olo 10ug (227), Form 12ug (222)
Common baseline mean (SE): 212.571 (3.151)

Source data: Appendix 16.1.9.2, Statdoc 6.2.1.3

ctr\diary-adjmean-ancova.sas 11OCT2011