Boehringer Ingelheim

Clinical Study Synopsis for Public Disclosure

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

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

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

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

Name of company: Boehringer Ingelheim		Tabulated Trial Report	Boehringer Ingelheim
Name of finished product: Not applicable		**EudraCT No.:** 2009-014880-38	
Name of active ingredient: Olodaterol (BI 1744) solution for inhalation - Respimat® Tiotropium solution for inhalation - Respimat®		**Page:** 1 of 9	**Synopsis No.:**
Module:		**Volume:** {hyperlink }	
Report date: 22 FEB 2012	**Trial No. / U No.:** 1237.18/ U11-1790-01	**Dates of trial:** 15 FEB 2010 – 03 FEB 2011	**Date of revision:** Not applicable

Title of trial:	A randomised, double-blind, 8 treatment, 4 period, incomplete crossover study to determine the optimal free dose combination of olodaterol and tiotropium (both delivered by the Respimat® Inhaler) after 4 weeks once daily treatment in patients with COPD
Coordinating Investigator:	[redacted]
Trial sites:	Multicentre (34 centres), multinational study conducted in Canada, Germany, The Netherlands, and Sweden
Publication (reference):	Data of this study have not been published
Clinical phase:	IIb
Objectives:	The primary objective of this study was to determine the optimum once daily dose of olodaterol (5.0 µg, 10.0 µg) and tiotropium (1.25 µg, 2.5 µg and 5.0 µg) in free dose combination (delivered by the Respimat® Inhaler) after 4 weeks of treatment in patients with chronic obstructive pulmonary disease (COPD). The selection of the optimum dose combination was to be based on bronchodilator efficacy and safety evaluations.
Methodology:	This was a randomised, double-blind, 8-treatment, 4-period, incomplete crossover study to determine the optimal free dose combination of olodaterol and tiotropium (both delivered using the Respimat® Inhaler). The trial compared the effects of different free dose combinations of olodaterol with tiotropium vs. each other, and vs. olodaterol alone; patients were randomised to receive 4 of the 8 free dose combinations of olodaterol (5.0 µg or 10.0 µg) and tiotropium (1.25 µg, 2.5 µg or 5.0 µg) or placebo inhalation solution. The study was to comprise: 2 weeks of run in, four 4-week treatment periods each separated by a 3-week washout period, and 3 weeks of follow up.

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No. of patients:	
planned:	randomised: 224 completed the study: 199
actual:	entered: 233 treated: 232 5.0 µg olodaterol: entered: 116 treated: 108 analysed (for primary endpoint): 107 1.25 µg/5.0 µg tiotropium/olodaterol: entered: 115 treated: 109 analysed (for primary endpoint): 107 2.5 µg/5.0 µg tiotropium/olodaterol: entered: 118 treated: 113 analysed (for primary endpoint): 109 5.0 µg/5.0 µg tiotropium/olodaterol: entered: 117 treated: 109 analysed (for primary endpoint): 104 10.0 µg olodaterol: entered: 117 treated: 109 analysed (for primary endpoint): 108 1.25 µg/10.0 µg tiotropium/olodaterol: entered: 115 treated: 110 analysed (for primary endpoint): 105 2.5 µg/10.0 µg tiotropium/olodaterol: entered: 117 treated: 110 analysed (for primary endpoint): 107 5.0 µg/10.0 µg tiotropium/olodaterol: entered: 117 treated: 111 analysed (for primary endpoint): 107
Diagnosis and main criteria for inclusion:	The study population comprised male and female patients, aged 40 years or older, who were current or ex-smokers with a diagnosis of COPD. Patients were to have relatively stable airway obstruction with a post-bronchodilator forced expiratory volume in 1 second (FEV_1) of ≥30% of predicted normal and <80% of predicted normal and a post-bronchodilator FEV_1/forced vital capacity (FVC) of <70% at Screening.

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Test product:	Olodaterol (BI 1744) solution for inhalation
dose:	2.5 µg per actuation, 5.0 µg per actuation (2 puffs in the morning)
mode of admin.:	Oral inhalation using the Respimat® Inhaler
batch nos.:	B072000346, B072000356
Test product:	Tiotropium solution for inhalation
dose:	0.625 µg per actuation, 1.25 µg per actuation, 2.5 µg per actuation (2 puffs in the morning)
mode of admin.:	Oral inhalation using the Respimat® Inhaler
batch nos.:	B092000113, B092000111, B092000103
Reference therapy:	Placebo matching tiotropium solution for inhalation
dose:	Not applicable (2 puffs in the morning)
mode of admin.:	Oral inhalation using the Respimat® Inhaler
batch no.:	B092000018
Duration of treatment:	The study was to comprise: 2 weeks of run in, four 4-week treatment periods each separated by a 3-week washout period, and 3 weeks of follow up. The duration of the treatment and washout periods of the trial was to be about 25 weeks.

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Criteria for evaluation:

Efficacy: Efficacy was assessed in terms of the primary efficacy variable of the trough FEV_1 response (change from baseline) after 4 weeks of treatment. Secondary endpoints assessed during the study comprised: trough FVC response after 4 weeks of treatment; FEV_1, FVC and peak expiratory flow (PEF) area under the curve from 0 to 3 hours (AUC_{0-3h}), AUC_{0-6h}, and $peak_{0-3h}$ responses after 4 weeks of treatment; FEV_1, FVC, and PEF AUC_{0-3h} and $peak_{0-3h}$ response after the first dose; individual FEV_1, FVC and PEF measurements at each timepoint; the weekly mean number of puffs of rescue medication used per day; the physician's global evaluation; and the patient's global rating.

Safety: Safety was assessed in terms of the incidence and intensity of adverse events (AEs) and vital signs (pulse rate and blood pressure).

Statistical methods: Treatment comparisons were assessed in an exploratory manner using a mixed effect repeated measures model, with treatment and period as fixed effects, patient as a random effect, and study baseline as a covariate. Other study data were presented using descriptive statistics.

SUMMARY – CONCLUSIONS:

Efficacy results: Overall, 232 patients with COPD (GOLD Stage II, III) were randomised and received at least 1 dose of trial medication (treated set); 133 patients (57.3%) were male, 222 patients (95.7%) were white, the mean age was 63.3 years (SD 8.2 years), and the post-bronchodilator FEV_1 was 1.55 L (SD 0.50 L; 55.0% of the predicted value). A total of 222 patients were included in the full analysis set.

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Efficacy results (continued):

For the primary efficacy endpoint of trough FEV_1 response [L] after 4 weeks of treatment, there were small numerical differences between 5.0 µg olodaterol and 10.0 µg olodaterol doses, when comparing both the monotherapy (12 mL difference) and the combination regimens with 1.25 µg tiotropium (9 mL difference), 2.5 µg tiotropium (30 mL difference) and 5.0 µg tiotropium (8 mL difference).

There was a statistically significant ($p<0.05$) increase of 54 mL in trough FEV_1 response when 1.25 µg tiotropium was added to 5.0 µg olodaterol as shown in Table 1; further stepwise increases in tiotropium dose (to 2.5 µg, and 5.0 µg) were associated with modest incremental increases in trough FEV_1 response (of 11 mL and 19 mL respectively). There was a statistically significant increase in trough FEV_1 response of 51 mL when 1.25 µg tiotropium was added to 10.0 µg olodaterol as shown in Table 2; increasing the tiotropium dose (to 2.5 µg, and 5.0 µg) resulted in an incremental increase in trough FEV_1 response (of 32 mL and -3 mL respectively).

Table 1

		Adjusted mean (SE) [L]	Difference vs. olodaterol 5 µg Mean (SE) [L]	95% CI
Olodaterol 5 µg		0.071 (0.018)		
Tiotropium	1.25/5 µg	0.125 (0.018)	0.054 (0.019)	(0.016, 0.092)
+	2.5/5 µg	0.136 (0.018)	0.065 (0.019)	(0.027, 0.103)
olodaterol	5/5 µg	0.155 (0.018)	0.084 (0.020)	(0.046, 0.122)

Table 2

		Adjusted mean (SE) [L]	Difference vs. olodaterol 10 µg Mean (SE) [L]	95% CI
Olodaterol 10 µg		0.083 (0.018)		
Tiotropium	1.25/10 µg	0.134 (0.018)	0.051 (0.019)	(0.013, 0.089)
+	2.5/10 µg	0.166 (0.018)	0.083 (0.019)	(0.045, 0.122)
olodaterol	5/10 µg	0.163 (0.018)	0.080 (0.020)	(0.042, 0.119)

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Efficacy results (continued):

When considering FEV_1 AUC_{0-6} response [L] after 4 weeks of treatment, there were modest numerical differences between the 5.0 µg olodaterol and 10.0 µg olodaterol doses, when comparing both the monotherapy (10 mL difference) and the combination regimens with 1.25 µg tiotropium (29 mL difference), 2.5 µg tiotropium (33 mL difference) and 5.0 µg tiotropium (35 mL difference).

There was a statistically significant increase of 78 mL in FEV_1 AUC_{0-6} response when 1.25 µg tiotropium was added to 5.0 µg olodaterol as shown in Table 3; further stepwise increases in tiotropium dose (to 2.5 µg and 5.0 µg) were associated with modest incremental increases in FEV_1 AUC_{0-6} response (of 21 mL and 19 mL respectively). There was a statistically significant increase of 98 mL in FEV_1 AUC_{0-6} response when 1.25 µg tiotropium was added to 10.0 µg olodaterol as shown in Table 4; further stepwise increases in tiotropium dose (to 2.5 µg and 5.0 µg) were associated with modest incremental increases in FEV_1 AUC_{0-6} response (of 23 mL and 23 mL respectively).

Table 3

		Adjusted mean (SE) [L]	Difference vs. olodaterol 5 µg	
			Mean (SE) [L]	95% CI
Olodaterol 5 µg		0.188 (0.020)		
Tiotropium	1.25/5 µg	0.267 (0.020)	0.078 (0.020)	(0.040, 0.117)
+	2.5/5 µg	0.287 (0.020)	0.099 (0.019)	(0.060, 0.137)
olodaterol	5/5 µg	0.307 (0.020)	0.118 (0.020)	(0.080, 0.157)

Table 4

		Adjusted mean (SE) [L]	Difference vs. olodaterol 10 µg	
			Mean (SE) [L]	95% CI
Olodaterol 10 µg		0.198 (0.020)		
Tiotropium	1.25/10 µg	0.296 (0.020)	0.098 (0.020)	(0.060, 0.136)
+	2.5/10 µg	0.320 (0.020)	0.121 (0.020)	(0.083, 0.159)
olodaterol	5/10 µg	0.342 (0.020)	0.144 (0.020)	(0.105, 0.182)

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Efficacy results (continued):

The FVC findings were supportive of the FEV_1 results, with statistically significant increases seen for all tiotropium/olodaterol treatment arms compared with olodaterol monotherapy; however, in contrast to FEV_1, there was not a clear separation between tiotropium doses for either trough FVC or FVC AUC_{0-6}.The PEF findings (with peak flow measured during spirometry manoeuvres) were also supportive of the FEV_1 results with statistically significant increases seen for all tiotropium/olodaterol treatment arms compared with olodaterol monotherapy; PEF showed clear evidence of dose ordering between tiotropium doses.

For the secondary efficacy endpoints of rescue medication use and physician's global evaluation, 4 weeks of treatment resulted in improvements for all treatment arms compared with pre-treatment baseline values with no notable differences across treatment arms. For the patient's global rating, patients generally rated their health (respiratory condition) as "a little better" after 4 weeks of treatment, with no notable differences across treatment arms (score range: 2.88 to 3.36).

Safety results:

Adverse events were reported in 42 patients (38.5%), 38 patients (33.6%) and 35 patients (32.1%) respectively during treatment with 1.25/5.0 µg, 2.5/5.0 µg and 5.0/5.0 µg tiotropium/olodaterol, compared with 35 patients (32.4%) during treatment with 5.0 µg olodaterol. AEs were reported in 32 patients (29.1%), 37 patients (33.6%) and 39 patients (35.1%) respectively during treatment with 1.25/10.0 µg, 2.5/10.0 µg and 5.0/10.0 µg tiotropium/olodaterol, compared with 36 patients (33.0%) during treatment with 10.0 µg olodaterol. The most common AEs were nasopharyngitis and COPD exacerbation. Most AEs seen during the study were mild or moderate in intensity; the incidence of severe AEs was comparable across treatment arms.

Two patients died during the study. In both cases, the cause of death was myocardial infarction that occurred during the washout phase after treatment with 10.0 µg olodaterol; onset of the event occurred 13 days after the last dose of olodaterol in 1 patient, and 5 days after the last dose of olodaterol in the other patient. Neither event was considered to be related to study medication.

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Safety results (continued):

Serious adverse events (SAEs) were reported in 1 patient (0.9%), 3 patients (2.7%) and 1 patient (0.9%) respectively during treatment with 1.25/5.0 µg, 2.5/5.0 µg and 5.0/5.0 µg tiotropium/olodaterol, compared with 4 patients (3.7%) during treatment with 5.0 µg olodaterol. SAEs were reported in 1 patient (0.9%), 5 patients (4.5%) and 0 patients (0.0%) respectively during treatment with 1.25/10.0 µg, 2.5/10.0 µg and 5.0/10.0 µg tiotropium/olodaterol, compared with 2 patients (1.8%) during treatment with 10.0 µg olodaterol. None of the SAEs reported during the study were considered related to the study medication. The majority of the SAEs were classified as such due to the requirement for hospitalisation (15 of 17).

Adverse events considered by the Investigator to be related to study medication were reported in 4 patients (3.7%), 1 patient (0.9%) and 4 patients (3.7%) respectively during treatment with 1.25/5.0 µg, 2.5/5.0 µg and 5.0/5.0 µg tiotropium/olodaterol, compared with 2 patients (1.9%) during treatment with 5.0 µg olodaterol. Adverse events considered by the Investigator to be related to study medication were reported in 1 patient (0.9%), 2 patients (1.8%) and 5 patients (4.5%) respectively during treatment with 1.25/10.0 µg, 2.5/10.0 µg and 5.0/10.0 µg tiotropium/olodaterol, compared with 2 patients (1.8%) during treatment with 10.0 µg olodaterol.

Adverse events leading to discontinuation of study medication occurred in 2 patients (1.8%), 2 patients (1.8%) and 2 patients (1.8%) respectively during treatment with 1.25/5.0 µg, 2.5/5.0 µg and 5.0/5.0 µg tiotropium/olodaterol, compared with 1 patient (0.9%) during treatment with 5.0 µg olodaterol. Adverse events leading to discontinuation of study medication occurred in 1 patient (0.9%), 0 patients (0.0%) and 1 patient (0.9%) respectively during treatment with 1.25/10.0 µg, 2.5/10.0 µg and 5.0/10.0 µg tiotropium/olodaterol, compared with 0 patients (0.0%) during treatment with 10.0 µg olodaterol.

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Conclusions:

Four weeks of once daily treatment with tiotropium/olodaterol (1.25 µg/5.0 µg, 2.5 µg/5.0 µg, 5.0 µg/5.0 µg) free combination and tiotropium/olodaterol (1.25 µg/10.0 µg, 2.5 µg/10.0 µg, 5.0 µg/10.0 µg) free combination was well tolerated in patients with COPD (GOLD Stage II, III), with no safety concerns being identified.

Small numerical differences in FEV_1 trough response and modest numerical differences in FEV_1 AUC_{0-6} response were seen when comparing dosing with 5.0 µg olodaterol and 10.0 µg olodaterol (both as monotherapy and in combination with tiotropium). Tiotropium at 1.25 µg increased bronchodilator efficacy when added to 5.0 µg olodaterol and 10.0 µg olodaterol. Clear dose ordering was seen with further increases in the tiotropium dose (to 2.5 µg and 5.0 µg), which achieved modest incremental increases in bronchodilator efficacy (FEV_1 response) of approximately 20 mL for each dose step. Determination of the optimal combination dose for tiotropium/olodaterol will need to consider the modest incremental benefit in bronchodilator efficacy per dose step in relation to the safety profile of the component doses.

Trial Synopsis - Appendix

The result tables on the following pages supplement the trial results presented in the Trial Synopsis. The appended tables provide the specific data results for patient disposition, adverse events and for the primary and several secondary endpoints. The number of secondary endpoints defined for this trial was too large to allow meaningful presentation in this format; therefore, results for at least 10 secondary endpoints are provided in the Trial Synopsis and the following tables.

Results for	**presented in**
Patient Disposition	Table 15.1.1: 1
Trough FEV_1 response after 4 weeks of treatment (Primary EP)	Table 15.2.1.1.1: 1 Table 15.2.1.1.1: 2
FEV_1 AUC_{0-3h} response after first dose of treatment (Secondary EP) FEV_1 AUC_{0-3h} response after 4 weeks of treatment (Secondary EP) FEV_1 AUC_{0-6h} response after 4 weeks of treatment (Secondary EP) FEV_1 $Peak_{0-3h}$ response after first dose of treatment (Secondary EP) FEV_1 $Peak_{0-3h}$ response after 4 weeks of treatment (Secondary EP)	Table 15.2.1.1.2: 1 Table 15.2.1.1.2: 2
Trough FVC response after 4 weeks of treatment (Secondary EP) FVC AUC_{0-3h} response after first dose of treatment (Secondary EP) FVC AUC_{0-3h} response after 4 weeks of treatment (Secondary EP) FVC AUC_{0-6h} response after 4 weeks of treatment (Secondary EP) FVC $Peak_{0-3h}$ response after first dose of treatment (Secondary EP) FVC $Peak_{0-3h}$ response after 4 weeks of treatment (Secondary EP)	Table 15.2.1.2.1: 1 Table 15.2.1.2.1: 2
PEF AUC_{0-3h} response after first dose of treatment (Secondary EP) PEF AUC_{0-3h} response after 4 weeks of treatment (Secondary EP) PEF AUC_{0-6h} response after 4 weeks of treatment (Secondary EP) PEF $Peak_{0-3h}$ response after first dose of treatment (Secondary EP) PEF $Peak_{0-3h}$ response after 4 weeks of treatment (Secondary EP)	Table 15.2.1.3.1: 1 Table 15.2.1.3.1: 2

Table 15.1.1: 1 Disposition of patients - enrolled patients

Disposition	Olo 5ug	T+O 1.25/5	T+O 2.5/5	T+O 5/5	Olo 10ug
Enrolled					
Not entered/randomised					
Entered/randomised	116	115	118	117	117
Not treated	8	6	5	8	8
Treated	108 (100.0)	109 (100.0)	113 (100.0)	109 (100.0)	109 (100.0)
NOT prematurely discontinued from trial medication	106 (98.1)	105 (96.3)	111 (98.2)	106 (97.2)	109 (100.0)
Prematurely discontinued from trial medication	2 (1.9)	4 (3.7)	2 (1.8)	3 (2.8)	0 (0.0)
Adverse events	1 (0.9)	2 (1.8)	2 (1.8)	2 (1.8)	0 (0.0)
Worsening of disease under study	1 (0.9)	0 (0.0)	1 (0.9)	2 (1.8)	0 (0.0)
Worsening of other pre-existing disease	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Other adverse event	0 (0.0)	2 (1.8)	1 (0.9)	0 (0.0)	0 (0.0)
Non compliant with protocol	0 (0.0)	1 (0.9)	0 (0.0)	0 (0.0)	0 (0.0)
Lost to follow-up	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Refused to continue taking trial medication	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Other	1 (0.9)	1 (0.9)	0 (0.0)	1 (0.9)	0 (0.0)

Table 15.1.1: 1 Disposition of patients - enrolled patients

Disposition	T+O 1.25/10	T+O 2.5/10	T+O 5/10	Total
Enrolled				283
Not entered/randomised				50
Entered/randomised	115	117	117	233
Not treated	5	7	6	1
Treated	110 (100.0)	110 (100.0)	111 (100.0)	232 (100.0)
NOT prematurely discontinued from trial medication	106 (96.4)	110 (100.0)	107 (96.4)	213 (91.8)
Prematurely discontinued from trial medication	4 (3.6)	0 (0.0)	4 (3.6)	19 (8.2)
Adverse events	1 (0.9)	0 (0.0)	2 (1.8)	10 (4.3)
Worsening of disease under study	0 (0.0)	0 (0.0)	0 (0.0)	4 (1.7)
Worsening of other pre-existing disease	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Other adverse event	1 (0.9)	0 (0.0)	2 (1.8)	6 (2.6)
Non compliant with protocol	1 (0.9)	0 (0.0)	0 (0.0)	2 (0.9)
Lost to follow-up	0 (0.0)	0 (0.0)	1 (0.9)	1 (0.4)
Refused to continue taking trial medication	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Other	2 (1.8)	0 (0.0)	1 (0.9)	6 (2.6)

Table 15.2.1.1.1: 1 Trough FEV1 response [L] - MMRM results (adjusted means (SE)) - FAS

Endpoint statistic		BI 1744 (Olodaterol) dose 5 ug	BI 1744 (Olodaterol) dose 10ug
Trough (pre-dose)	Tiotropium dose		
	0 ug	0.071 (0.018)	0.083 (0.018)
	1.25 ug	0.125 (0.018)	0.134 (0.018)
	2.5 ug	0.136 (0.018)	0.166 (0.018)
	5 ug	0.155 (0.018)	0.163 (0.018)

* adjusted for treatment, period, patient and study baseline.
Baseline mean(sd) at visit 2 = 1.353 (0.485)
Source data: Appendix 16.1.9.2, Statdoc 6.1.1.1.1

Table 15.2.1.1.1: 2 Trough FEV1 response [L] - MMRM results (treatment differences) - FAS

Endpoint statistic	Treatment Comparison	Difference Adjusted* mean (SE)	95% CI
Trough (pre-dose)	T+O 1.25/5 - Olo 5ug	0.054 (0.019)	(0.016, 0.092)
	T+O 2.5/5 - Olo 5ug	0.065 (0.019)	(0.027, 0.103)
	T+O 5/5 - Olo 5ug	0.084 (0.020)	(0.046, 0.122)
	T+O 2.5/5 - T+O 1.25/5	0.011 (0.019)	(-0.027, 0.049)
	T+O 5/5 - T+O 1.25/5	0.030 (0.020)	(-0.008, 0.069)
	T+O 5/5 - T+O 2.5/5	0.019 (0.019)	(-0.019, 0.058)
	T+O 1.25/10 - Olo 10ug	0.051 (0.019)	(0.013, 0.089)
	T+O 2.5/10 - Olo 10ug	0.083 (0.019)	(0.045, 0.122)
	T+O 5/10 - Olo 10ug	0.080 (0.020)	(0.042, 0.119)
	T+O 2.5/10 - T+O 1.25/10	0.033 (0.020)	(-0.006, 0.071)
	T+O 5/10 - T+O 1.25/10	0.030 (0.019)	(-0.009, 0.068)
	T+O 5/10 - T+O 2.5/10	-0.003 (0.019)	(-0.041, 0.035)

* adjusted for treatment, period, patient and study baseline.
Baseline mean(sd) at visit 2 = 1.353 (0.485)
Source data: Appendix 16.1.9.2, Statdoc 6.1.1.1.1

Table 15.2.1.1.2: 1 FEV1 AUC (0-3h) response [L], AUC (0-6h) response [L], peak (0-3h) response [L]
- MMRM results (adjusted means (SE)) - FAS

Endpoint statistic		BI 1744 (Olodaterol) dose 5 ug	BI 1744 (Olodaterol) dose 10ug
Peak (0-3h)	Tiotropium dose		
	0 ug	0.264 (0.023)	0.267 (0.023)
	1.25 ug	0.353 (0.023)	0.374 (0.023)
	2.5 ug	0.355 (0.022)	0.399 (0.023)
	5 ug	0.379 (0.023)	0.412 (0.023)
AUC (0-3h)	Tiotropium dose		
	0 ug	0.183 (0.020)	0.191 (0.020)
	1.25 ug	0.258 (0.020)	0.288 (0.020)
	2.5 ug	0.280 (0.020)	0.319 (0.020)
	5 ug	0.302 (0.020)	0.334 (0.020)
AUC (0-6h)	Tiotropium dose		
	0 ug	0.188 (0.020)	0.198 (0.020)
	1.25 ug	0.267 (0.020)	0.296 (0.020)
	2.5 ug	0.287 (0.020)	0.320 (0.020)
	5 ug	0.307 (0.020)	0.342 (0.020)
Peak (0-3h) first	Tiotropium dose		
	0 ug	0.287 (0.019)	0.270 (0.019)
	1.25 ug	0.267 (0.019)	0.324 (0.019)
	2.5 ug	0.300 (0.019)	0.315 (0.019)
	5 ug	0.298 (0.019)	0.317 (0.019)
AUC (0-3h) first	Tiotropium dose		
	0 ug	0.204 (0.017)	0.188 (0.017)
	1.25 ug	0.181 (0.017)	0.227 (0.017)
	2.5 ug	0.209 (0.017)	0.219 (0.017)
	5 ug	0.205 (0.017)	0.230 (0.017)

* adjusted for treatment, period, patient and study baseline.
Baseline mean(sd) at visit 2 = 1.353 (0.485)
Source data: Appendix 16.1.9.2, Statdoc 6.1.1.2.1

Table 15.2.1.1.2: 2 FEV1 AUC (0-3h) response [L], AUC (0-6h) response [L], peak (0-3h) response [L] - MMRM results (treatment comparisons) - FAS

Endpoint statistic	Treatment Comparison	Difference: Adjusted* mean (SE)	Difference: 95% CI
Peak (0-3h)	T+O 1.25/5 - Olo 5ug	0.089 (0.025)	(0.041, 0.138)
	T+O 2.5/5 - Olo 5ug	0.091 (0.024)	(0.043, 0.139)
	T+O 5/5 - Olo 5ug	0.115 (0.025)	(0.066, 0.164)
	T+O 2.5/5 - T+O 1.25/5	0.002 (0.025)	(-0.046, 0.050)
	T+O 5/5 - T+O 1.25/5	0.026 (0.025)	(-0.023, 0.074)
	T+O 5/5 - T+O 2.5/5	0.024 (0.025)	(-0.025, 0.072)
	T+O 1.25/10 - Olo 10ug	0.107 (0.025)	(0.059, 0.156)
	T+O 2.5/10 - Olo 10ug	0.132 (0.025)	(0.084, 0.181)
	T+O 5/10 - Olo 10ug	0.145 (0.025)	(0.096, 0.193)
	T+O 2.5/10 - T+O 1.25/10	0.025 (0.025)	(-0.024, 0.074)
	T+O 5/10 - T+O 1.25/10	0.038 (0.025)	(-0.010, 0.086)
	T+O 5/10 - T+O 2.5/10	0.013 (0.025)	(-0.036, 0.061)
AUC (0-3h)	T+O 1.25/5 - Olo 5ug	0.075 (0.020)	(0.035, 0.114)
	T+O 2.5/5 - Olo 5ug	0.097 (0.020)	(0.057, 0.137)
	T+O 5/5 - Olo 5ug	0.119 (0.020)	(0.079, 0.159)
	T+O 2.5/5 - T+O 1.25/5	0.022 (0.020)	(-0.017, 0.062)
	T+O 5/5 - T+O 1.25/5	0.045 (0.021)	(0.004, 0.085)
	T+O 5/5 - T+O 2.5/5	0.022 (0.020)	(-0.018, 0.062)
	T+O 1.25/10 - Olo 10ug	0.097 (0.020)	(0.057, 0.137)
	T+O 2.5/10 - Olo 10ug	0.128 (0.020)	(0.088, 0.168)
	T+O 5/10 - Olo 10ug	0.143 (0.020)	(0.103, 0.183)
	T+O 2.5/10 - T+O 1.25/10	0.031 (0.020)	(-0.009, 0.071)
	T+O 5/10 - T+O 1.25/10	0.046 (0.020)	(0.006, 0.086)
	T+O 5/10 - T+O 2.5/10	0.015 (0.020)	(-0.025, 0.055)

* adjusted for treatment, period, patient and study baseline.
Baseline mean(sd) at visit 2 = 1.353 (0.485)
Source data: Appendix 16.1.9.2, Statdoc 6.1.1.2.1

Table 15.2.1.1.2: 2 FEV1 AUC (0-3h) response [L], AUC (0-6h) response [L], peak (0-3h) response [L] - MMRM results (treatment comparisons) - FAS

Endpoint statistic	Treatment Comparison	Difference: Adjusted* mean (SE)	Difference: 95% CI
AUC (0-6h)	T+O 1.25/5 - Olo 5ug	0.078 (0.020)	(0.040, 0.117)
	T+O 2.5/5 - Olo 5ug	0.099 (0.019)	(0.060, 0.137)
	T+O 5/5 - Olo 5ug	0.118 (0.020)	(0.080, 0.157)
	T+O 2.5/5 - T+O 1.25/5	0.020 (0.019)	(-0.018, 0.058)
	T+O 5/5 - T+O 1.25/5	0.040 (0.020)	(0.001, 0.079)
	T+O 5/5 - T+O 2.5/5	0.020 (0.020)	(-0.019, 0.058)
	T+O 1.25/10 - Olo 10ug	0.098 (0.020)	(0.060, 0.136)
	T+O 2.5/10 - Olo 10ug	0.121 (0.020)	(0.083, 0.159)
	T+O 5/10 - Olo 10ug	0.144 (0.020)	(0.105, 0.182)
	T+O 2.5/10 - T+O 1.25/10	0.023 (0.020)	(-0.016, 0.062)
	T+O 5/10 - T+O 1.25/10	0.046 (0.019)	(0.007, 0.084)
	T+O 5/10 - T+O 2.5/10	0.023 (0.020)	(-0.016, 0.061)
Peak (0-3h) first	T+O 1.25/5 - Olo 5ug	-0.019 (0.020)	(-0.059, 0.020)
	T+O 2.5/5 - Olo 5ug	0.014 (0.020)	(-0.026, 0.053)
	T+O 5/5 - Olo 5ug	0.012 (0.020)	(-0.028, 0.051)
	T+O 2.5/5 - T+O 1.25/5	0.033 (0.020)	(-0.006, 0.072)
	T+O 5/5 - T+O 1.25/5	0.031 (0.020)	(-0.009, 0.071)
	T+O 5/5 - T+O 2.5/5	-0.002 (0.020)	(-0.041, 0.037)
	T+O 1.25/10 - Olo 10ug	0.054 (0.020)	(0.015, 0.093)
	T+O 2.5/10 - Olo 10ug	0.045 (0.020)	(0.006, 0.084)
	T+O 5/10 - Olo 10ug	0.047 (0.020)	(0.008, 0.087)
	T+O 2.5/10 - T+O 1.25/10	-0.009 (0.020)	(-0.049, 0.031)
	T+O 5/10 - T+O 1.25/10	-0.007 (0.020)	(-0.046, 0.033)
	T+O 5/10 - T+O 2.5/10	0.002 (0.020)	(-0.037, 0.042)

* adjusted for treatment, period, patient and study baseline.
Baseline mean(sd) at visit 2 = 1.353 (0.485)
Source data: Appendix 16.1.9.2, Statdoc 6.1.1.2.1

Table 15.2.1.1.2: 2 FEV1 AUC (0-3h) response [L], AUC (0-6h) response [L], peak (0-3h) response [L]
- MMRM results (treatment comparisons) - FAS

Endpoint statistic	Treatment Comparison	Difference: Adjusted* mean (SE)	Difference: 95% CI
AUC (0-3h) first	T+O 1.25/5 - Olo 5ug	-0.023 (0.018)	(-0.058, 0.012)
	T+O 2.5/5 - Olo 5ug	0.005 (0.018)	(-0.029, 0.040)
	T+O 5/5 - Olo 5ug	0.001 (0.018)	(-0.034, 0.036)
	T+O 2.5/5 - T+O 1.25/5	0.028 (0.018)	(-0.006, 0.063)
	T+O 5/5 - T+O 1.25/5	0.024 (0.018)	(-0.011, 0.059)
	T+O 5/5 - T+O 2.5/5	-0.004 (0.018)	(-0.039, 0.031)
	T+O 1.25/10 - Olo 10ug	0.039 (0.018)	(0.004, 0.073)
	T+O 2.5/10 - Olo 10ug	0.031 (0.018)	(-0.004, 0.066)
	T+O 5/10 - Olo 10ug	0.041 (0.018)	(0.006, 0.076)
	T+O 2.5/10 - T+O 1.25/10	-0.008 (0.018)	(-0.043, 0.027)
	T+O 5/10 - T+O 1.25/10	0.003 (0.018)	(-0.032, 0.037)
	T+O 5/10 - T+O 2.5/10	0.010 (0.018)	(-0.025, 0.045)

* adjusted for treatment, period, patient and study baseline.
Baseline mean(sd) at visit 2 = 1.353 (0.485)
Source data: Appendix 16.1.9.2, Statdoc 6.1.1.2.1

Table 15.2.1.2.1: 1 Trough FVC response [L], FVC AUC (0-3h) response [L], AUC (0-6h) response [L], peak (0-3h) response [L] - MMRM results (adjusted means (SE)) - FAS

Endpoint statistic		BI 1744 (Olodaterol) dose 5 ug	BI 1744 (Olodaterol) dose 10ug
Trough (pre-dose)	Tiotropium dose		
	0 ug	0.114 (0.029)	0.122 (0.029)
	1.25 ug	0.214 (0.029)	0.253 (0.029)
	2.5 ug	0.234 (0.029)	0.253 (0.029)
	5 ug	0.215 (0.029)	0.249 (0.029)
Peak (0-3h)	Tiotropium dose		
	0 ug	0.415 (0.035)	0.411 (0.035)
	1.25 ug	0.570 (0.035)	0.585 (0.035)
	2.5 ug	0.563 (0.035)	0.593 (0.035)
	5 ug	0.542 (0.035)	0.615 (0.035)
AUC (0-3h)	Tiotropium dose		
	0 ug	0.278 (0.032)	0.279 (0.032)
	1.25 ug	0.422 (0.032)	0.455 (0.032)
	2.5 ug	0.429 (0.032)	0.454 (0.032)
	5 ug	0.410 (0.032)	0.479 (0.032)
AUC (0-6h)	Tiotropium dose		
	0 ug	0.282 (0.032)	0.277 (0.032)
	1.25 ug	0.421 (0.032)	0.466 (0.032)
	2.5 ug	0.432 (0.032)	0.456 (0.032)
	5 ug	0.414 (0.032)	0.490 (0.032)

* adjusted for treatment, period, patient and study baseline.
Baseline mean(sd) at visit 2 = 2.773 (0.890)
Source data: Appendix 16.1.9.2, Statdoc 6.1.2.1

Table 15.2.1.2.1: 1 Trough FVC response [L], FVC AUC (0-3h) response [L], AUC (0-6h) response [L], peak (0-3h) response [L] - MMRM results (adjusted means (SE)) - FAS

Endpoint statistic		BI 1744 (Olodaterol) dose 5 ug	BI 1744 (Olodaterol) dose 10ug
Peak (0-3h) first	Tiotropium dose		
	0 ug	0.473 (0.031)	0.436 (0.031)
	1.25 ug	0.423 (0.031)	0.547 (0.032)
	2.5 ug	0.481 (0.031)	0.517 (0.031)
	5 ug	0.462 (0.032)	0.505 (0.031)
AUC (0-3h) first	Tiotropium dose		
	0 ug	0.333 (0.029)	0.303 (0.029)
	1.25 ug	0.285 (0.029)	0.393 (0.030)
	2.5 ug	0.326 (0.029)	0.363 (0.029)
	5 ug	0.319 (0.030)	0.359 (0.029)

* adjusted for treatment, period, patient and study baseline.
Baseline mean(sd) at visit 2 = 2.773 (0.890)
Source data: Appendix 16.1.9.2, Statdoc 6.1.2.1

Table 15.2.1.2.1: 2 Trough FVC response [L], FVC AUC (0-3h) response [L], AUC (0-6h) response [L], peak (0-3h) response [L] - MMRM results (treatment comparisons) - FAS

Endpoint statistic	Treatment Comparison	Difference: Adjusted* mean (SE)	Difference: 95% CI
Trough (pre-dose)	T+O 1.25/5 - Olo 5ug	0.099 (0.030)	(0.040, 0.159)
	T+O 2.5/5 - Olo 5ug	0.120 (0.030)	(0.061, 0.179)
	T+O 5/5 - Olo 5ug	0.100 (0.030)	(0.041, 0.160)
	T+O 2.5/5 - T+O 1.25/5	0.020 (0.030)	(-0.039, 0.079)
	T+O 5/5 - T+O 1.25/5	0.001 (0.031)	(-0.059, 0.061)
	T+O 5/5 - T+O 2.5/5	-0.019 (0.030)	(-0.079, 0.040)
	T+O 1.25/10 - Olo 10ug	0.131 (0.030)	(0.071, 0.190)
	T+O 2.5/10 - Olo 10ug	0.131 (0.030)	(0.072, 0.191)
	T+O 5/10 - Olo 10ug	0.127 (0.030)	(0.067, 0.187)
	T+O 2.5/10 - T+O 1.25/10	0.001 (0.031)	(-0.059, 0.061)
	T+O 5/10 - T+O 1.25/10	-0.004 (0.030)	(-0.063, 0.056)
	T+O 5/10 - T+O 2.5/10	-0.004 (0.030)	(-0.064, 0.055)
Peak (0-3h)	T+O 1.25/5 - Olo 5ug	0.155 (0.035)	(0.087, 0.223)
	T+O 2.5/5 - Olo 5ug	0.147 (0.035)	(0.079, 0.215)
	T+O 5/5 - Olo 5ug	0.127 (0.035)	(0.058, 0.195)
	T+O 2.5/5 - T+O 1.25/5	-0.008 (0.035)	(-0.075, 0.060)
	T+O 5/5 - T+O 1.25/5	-0.028 (0.035)	(-0.097, 0.041)
	T+O 5/5 - T+O 2.5/5	-0.020 (0.035)	(-0.089, 0.048)
	T+O 1.25/10 - Olo 10ug	0.174 (0.035)	(0.106, 0.242)
	T+O 2.5/10 - Olo 10ug	0.182 (0.035)	(0.113, 0.250)
	T+O 5/10 - Olo 10ug	0.204 (0.035)	(0.135, 0.272)
	T+O 2.5/10 - T+O 1.25/10	0.008 (0.035)	(-0.061, 0.076)
	T+O 5/10 - T+O 1.25/10	0.030 (0.035)	(-0.038, 0.098)
	T+O 5/10 - T+O 2.5/10	0.022 (0.035)	(-0.046, 0.090)

* adjusted for treatment, period, patient and study baseline.
Baseline mean(sd) at visit 2 = 2.773 (0.890)
Source data: Appendix 16.1.9.2, Statdoc 6.1.2.1

Table 15.2.1.2.1: 2 Trough FVC response [L], FVC AUC (0-3h) response [L], AUC (0-6h) response [L], peak (0-3h) response [L] - MMRM results (treatment comparisons) - FAS

Endpoint statistic	Treatment Comparison	Difference: Adjusted* mean (SE)	95% CI
AUC (0-3h)	T+O 1.25/5 - Olo 5ug	0.143 (0.030)	(0.084, 0.202)
	T+O 2.5/5 - Olo 5ug	0.151 (0.030)	(0.092, 0.210)
	T+O 5/5 - Olo 5ug	0.131 (0.030)	(0.072, 0.191)
	T+O 2.5/5 - T+O 1.25/5	0.008 (0.030)	(-0.051, 0.066)
	T+O 5/5 - T+O 1.25/5	-0.012 (0.030)	(-0.071, 0.048)
	T+O 5/5 - T+O 2.5/5	-0.020 (0.030)	(-0.079, 0.039)
	T+O 1.25/10 - Olo 10ug	0.175 (0.030)	(0.116, 0.234)
	T+O 2.5/10 - Olo 10ug	0.175 (0.030)	(0.116, 0.234)
	T+O 5/10 - Olo 10ug	0.200 (0.030)	(0.140, 0.259)
	T+O 2.5/10 - T+O 1.25/10	-0.000 (0.030)	(-0.060, 0.059)
	T+O 5/10 - T+O 1.25/10	0.024 (0.030)	(-0.035, 0.083)
	T+O 5/10 - T+O 2.5/10	0.024 (0.030)	(-0.035, 0.083)
AUC (0-6h)	T+O 1.25/5 - Olo 5ug	0.139 (0.029)	(0.081, 0.197)
	T+O 2.5/5 - Olo 5ug	0.150 (0.029)	(0.092, 0.207)
	T+O 5/5 - Olo 5ug	0.131 (0.029)	(0.073, 0.189)
	T+O 2.5/5 - T+O 1.25/5	0.011 (0.029)	(-0.047, 0.068)
	T+O 5/5 - T+O 1.25/5	-0.008 (0.030)	(-0.066, 0.051)
	T+O 5/5 - T+O 2.5/5	-0.018 (0.029)	(-0.076, 0.039)
	T+O 1.25/10 - Olo 10ug	0.189 (0.029)	(0.131, 0.247)
	T+O 2.5/10 - Olo 10ug	0.179 (0.029)	(0.121, 0.236)
	T+O 5/10 - Olo 10ug	0.213 (0.029)	(0.155, 0.271)
	T+O 2.5/10 - T+O 1.25/10	-0.010 (0.030)	(-0.069, 0.048)
	T+O 5/10 - T+O 1.25/10	0.024 (0.029)	(-0.033, 0.082)
	T+O 5/10 - T+O 2.5/10	0.035 (0.029)	(-0.023, 0.092)

* adjusted for treatment, period, patient and study baseline.
Baseline mean(sd) at visit 2 = 2.773 (0.890)
Source data: Appendix 16.1.9.2, Statdoc 6.1.2.1

Table 15.2.1.2.1: 2 Trough FVC response [L], FVC AUC (0-3h) response [L], AUC (0-6h) response [L], peak (0-3h) response [L] - MMRM results (treatment comparisons) - FAS

Endpoint statistic	Treatment Comparison	Difference: Adjusted* mean (SE)	Difference: 95% CI
Peak (0-3h) first	T+O 1.25/5 - Olo 5ug	-0.051 (0.032)	(-0.114, 0.013)
	T+O 2.5/5 - Olo 5ug	0.008 (0.032)	(-0.055, 0.071)
	T+O 5/5 - Olo 5ug	-0.011 (0.032)	(-0.074, 0.053)
	T+O 2.5/5 - T+O 1.25/5	0.059 (0.032)	(-0.004, 0.122)
	T+O 5/5 - T+O 1.25/5	0.040 (0.033)	(-0.024, 0.104)
	T+O 5/5 - T+O 2.5/5	-0.019 (0.032)	(-0.082, 0.045)
	T+O 1.25/10 - Olo 10ug	0.111 (0.032)	(0.047, 0.174)
	T+O 2.5/10 - Olo 10ug	0.081 (0.032)	(0.017, 0.144)
	T+O 5/10 - Olo 10ug	0.069 (0.032)	(0.005, 0.132)
	T+O 2.5/10 - T+O 1.25/10	-0.030 (0.033)	(-0.094, 0.034)
	T+O 5/10 - T+O 1.25/10	-0.042 (0.032)	(-0.105, 0.021)
	T+O 5/10 - T+O 2.5/10	-0.012 (0.032)	(-0.075, 0.052)
AUC (0-3h) first	T+O 1.25/5 - Olo 5ug	-0.048 (0.029)	(-0.106, 0.010)
	T+O 2.5/5 - Olo 5ug	-0.007 (0.029)	(-0.065, 0.051)
	T+O 5/5 - Olo 5ug	-0.014 (0.030)	(-0.072, 0.044)
	T+O 2.5/5 - T+O 1.25/5	0.041 (0.029)	(-0.017, 0.099)
	T+O 5/5 - T+O 1.25/5	0.034 (0.030)	(-0.024, 0.093)
	T+O 5/5 - T+O 2.5/5	-0.007 (0.030)	(-0.065, 0.051)
	T+O 1.25/10 - Olo 10ug	0.090 (0.030)	(0.032, 0.148)
	T+O 2.5/10 - Olo 10ug	0.059 (0.030)	(0.001, 0.118)
	T+O 5/10 - Olo 10ug	0.056 (0.030)	(-0.002, 0.114)
	T+O 2.5/10 - T+O 1.25/10	-0.031 (0.030)	(-0.089, 0.028)
	T+O 5/10 - T+O 1.25/10	-0.034 (0.030)	(-0.092, 0.024)
	T+O 5/10 - T+O 2.5/10	-0.003 (0.030)	(-0.062, 0.055)

* adjusted for treatment, period, patient and study baseline.
Baseline mean(sd) at visit 2 = 2.773 (0.890)
Source data: Appendix 16.1.9.2, Statdoc 6.1.2.1

Table 15.2.1.3.1: 1 PEF AUC (0-3h) response [L/min], AUC (0-6h) response [L/min], peak (0-3h) response [L/min]
- MMRM results (adjusted means (SE)) - FAS

Endpoint statistic		BI 1744 (Olodaterol) dose 5 ug	BI 1744 (Olodaterol) dose 10ug
Peak (0-3h)	Tiotropium dose		
	0 ug	46.010 (4.566)	49.025 (4.557)
	1.25 ug	64.693 (4.581)	66.767 (4.600)
	2.5 ug	69.610 (4.538)	73.140 (4.569)
	5 ug	76.108 (4.620)	74.120 (4.584)
AUC (0-3h)	Tiotropium dose		
	0 ug	25.542 (4.190)	29.713 (4.183)
	1.25 ug	44.301 (4.202)	48.032 (4.218)
	2.5 ug	50.698 (4.167)	53.224 (4.192)
	5 ug	55.346 (4.234)	52.531 (4.205)
AUC (0-6h)	Tiotropium dose		
	0 ug	28.071 (4.125)	31.831 (4.119)
	1.25 ug	46.822 (4.136)	51.485 (4.151)
	2.5 ug	54.081 (4.104)	54.593 (4.127)
	5 ug	57.418 (4.166)	57.367 (4.139)
Peak (0-3h) first	Tiotropium dose		
	0 ug	52.129 (4.363)	51.980 (4.355)
	1.25 ug	53.298 (4.366)	54.966 (4.400)
	2.5 ug	56.565 (4.335)	56.896 (4.367)
	5 ug	57.318 (4.406)	59.412 (4.370)

* adjusted for treatment, period, patient and study baseline.
Baseline mean(sd) at visit 2 = 238.331 (95.932)
Source data: Appendix 16.1.9.2, Statdoc 6.1.3.1

Table 15.2.1.3.1: 1 PEF AUC (0-3h) response [L/min], AUC (0-6h) response [L/min], peak (0-3h) response [L/min]
- MMRM results (adjusted means (SE)) - FAS

Endpoint statistic		BI 1744 (Olodaterol) dose 5 ug	10ug
AUC (0-3h) first	Tiotropium dose		
	0 ug	30.575 (4.047)	31.724 (4.040)
	1.25 ug	32.891 (4.050)	33.213 (4.079)
	2.5 ug	35.053 (4.022)	34.987 (4.051)
	5 ug	35.243 (4.084)	38.846 (4.065)

* adjusted for treatment, period, patient and study baseline.
Baseline mean(sd) at visit 2 = 238.331 (95.932)
Source data: Appendix 16.1.9.2, Statdoc 6.1.3.1

Table 15.2.1.3.1: 2 PEF AUC (0-3h) response [L/min], AUC (0-6h) response [L/min], peak (0-3h) response [L/min] - MMRM results (treatment comparisons) - FAS

Endpoint statistic	Treatment Comparison	Difference: Adjusted* mean (SE)	Difference: 95% CI
Peak (0-3h)	T+O 1.25/5 - Olo 5ug	18.682 (4.849)	(9.161, 28.204)
	T+O 2.5/5 - Olo 5ug	23.599 (4.830)	(14.116, 33.083)
	T+O 5/5 - Olo 5ug	30.097 (4.879)	(20.517, 39.677)
	T+O 2.5/5 - T+O 1.25/5	4.917 (4.830)	(-4.568, 14.402)
	T+O 5/5 - T+O 1.25/5	11.415 (4.907)	(1.780, 21.050)
	T+O 5/5 - T+O 2.5/5	6.498 (4.866)	(-3.057, 16.053)
	T+O 1.25/10 - Olo 10ug	17.742 (4.862)	(8.194, 27.290)
	T+O 2.5/10 - Olo 10ug	24.115 (4.856)	(14.580, 33.651)
	T+O 5/10 - Olo 10ug	25.095 (4.876)	(15.520, 34.670)
	T+O 2.5/10 - T+O 1.25/10	6.373 (4.896)	(-3.240, 15.986)
	T+O 5/10 - T+O 1.25/10	7.353 (4.845)	(-2.161, 16.866)
	T+O 5/10 - T+O 2.5/10	0.980 (4.861)	(-8.566, 10.525)
AUC (0-3h)	T+O 1.25/5 - Olo 5ug	18.759 (4.189)	(10.533, 26.985)
	T+O 2.5/5 - Olo 5ug	25.157 (4.173)	(16.962, 33.351)
	T+O 5/5 - Olo 5ug	29.804 (4.216)	(21.526, 38.082)
	T+O 2.5/5 - T+O 1.25/5	6.398 (4.173)	(-1.796, 14.592)
	T+O 5/5 - T+O 1.25/5	11.046 (4.239)	(2.721, 19.370)
	T+O 5/5 - T+O 2.5/5	4.648 (4.204)	(-3.608, 12.903)
	T+O 1.25/10 - Olo 10ug	18.318 (4.201)	(10.068, 26.568)
	T+O 2.5/10 - Olo 10ug	23.511 (4.197)	(15.270, 31.752)
	T+O 5/10 - Olo 10ug	22.817 (4.214)	(14.543, 31.092)
	T+O 2.5/10 - T+O 1.25/10	5.193 (4.230)	(-3.115, 13.500)
	T+O 5/10 - T+O 1.25/10	4.499 (4.185)	(-3.719, 12.717)
	T+O 5/10 - T+O 2.5/10	-0.694 (4.200)	(-8.941, 7.554)

* adjusted for treatment, period, patient and study baseline.
Baseline mean(sd) at visit 2 = 238.331 (95.932)
Source data: Appendix 16.1.9.2, Statdoc 6.1.3.1

Table 15.2.1.3.1: 2 PEF AUC (0-3h) response [L/min], AUC (0-6h) response [L/min], peak (0-3h) response [L/min] - MMRM results (treatment comparisons) - FAS

Endpoint statistic	Treatment Comparison	Difference: Adjusted* mean (SE)	Difference: 95% CI
AUC (0-6h)	T+O 1.25/5 - Olo 5ug	18.751 (4.013)	(10.870, 26.632)
	T+O 2.5/5 - Olo 5ug	26.009 (3.998)	(18.158, 33.860)
	T+O 5/5 - Olo 5ug	29.347 (4.039)	(21.416, 37.278)
	T+O 2.5/5 - T+O 1.25/5	7.259 (3.998)	(-0.592, 15.109)
	T+O 5/5 - T+O 1.25/5	10.596 (4.061)	(2.621, 18.571)
	T+O 5/5 - T+O 2.5/5	3.337 (4.028)	(-4.572, 11.247)
	T+O 1.25/10 - Olo 10ug	19.654 (4.025)	(11.750, 27.558)
	T+O 2.5/10 - Olo 10ug	22.762 (4.021)	(14.866, 30.659)
	T+O 5/10 - Olo 10ug	25.536 (4.038)	(17.607, 33.464)
	T+O 2.5/10 - T+O 1.25/10	3.108 (4.053)	(-4.852, 11.067)
	T+O 5/10 - T+O 1.25/10	5.881 (4.009)	(-1.991, 13.754)
	T+O 5/10 - T+O 2.5/10	2.773 (4.024)	(-5.129, 10.675)
Peak (0-3h) first	T+O 1.25/5 - Olo 5ug	1.170 (4.853)	(-8.360, 10.699)
	T+O 2.5/5 - Olo 5ug	4.436 (4.843)	(-5.073, 13.945)
	T+O 5/5 - Olo 5ug	5.189 (4.887)	(-4.407, 14.785)
	T+O 2.5/5 - T+O 1.25/5	3.267 (4.828)	(-6.214, 12.747)
	T+O 5/5 - T+O 1.25/5	4.020 (4.904)	(-5.610, 13.650)
	T+O 5/5 - T+O 2.5/5	0.753 (4.873)	(-8.816, 10.322)
	T+O 1.25/10 - Olo 10ug	2.986 (4.876)	(-6.589, 12.561)
	T+O 2.5/10 - Olo 10ug	4.916 (4.868)	(-4.643, 14.475)
	T+O 5/10 - Olo 10ug	7.432 (4.882)	(-2.154, 17.019)
	T+O 2.5/10 - T+O 1.25/10	1.930 (4.909)	(-7.708, 11.568)
	T+O 5/10 - T+O 1.25/10	4.446 (4.854)	(-5.085, 13.978)
	T+O 5/10 - T+O 2.5/10	2.517 (4.870)	(-7.046, 12.079)

* adjusted for treatment, period, patient and study baseline.
Baseline mean(sd) at visit 2 = 238.331 (95.932)
Source data: Appendix 16.1.9.2, Statdoc 6.1.3.1

Table 15.2.1.3.1: 2 PEF AUC (0-3h) response [L/min], AUC (0-6h) response [L/min], peak (0-3h) response [L/min] - MMRM results (treatment comparisons) - FAS

		Difference	
Endpoint statistic	Treatment Comparison	Adjusted* mean (SE)	95% CI
AUC (0-3h) first	T+O 1.25/5 - Olo 5ug	2.316 (4.371)	(-6.268, 10.900)
	T+O 2.5/5 - Olo 5ug	4.478 (4.362)	(-4.088, 13.044)
	T+O 5/5 - Olo 5ug	4.668 (4.403)	(-3.978, 13.314)
	T+O 2.5/5 - T+O 1.25/5	2.162 (4.349)	(-6.379, 10.702)
	T+O 5/5 - T+O 1.25/5	2.352 (4.419)	(-6.326, 11.029)
	T+O 5/5 - T+O 2.5/5	0.190 (4.390)	(-8.430, 8.810)
	T+O 1.25/10 - Olo 10ug	1.488 (4.392)	(-7.136, 10.113)
	T+O 2.5/10 - Olo 10ug	3.262 (4.386)	(-5.350, 11.875)
	T+O 5/10 - Olo 10ug	7.121 (4.408)	(-1.535, 15.778)
	T+O 2.5/10 - T+O 1.25/10	1.774 (4.423)	(-6.910, 10.458)
	T+O 5/10 - T+O 1.25/10	5.633 (4.381)	(-2.970, 14.236)
	T+O 5/10 - T+O 2.5/10	3.859 (4.403)	(-4.786, 12.504)

* adjusted for treatment, period, patient and study baseline.
Baseline mean(sd) at visit 2 = 238.331 (95.932)
Source data: Appendix 16.1.9.2, Statdoc 6.1.3.1