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: Spiriva® Respimat® inhaler		**EudraCT No.:** 2005-005616-25	
Name of active ingredient: Tiotropium bromide		**Page:** 1 of 6	**Synopsis No.:**
Module:		**Volume:**	
Report date: 14 AUG 2009	**Trial No. / U No.:** 205.342 / U09-1701-01	**Dates of trial:** 17 JUL 2006 – 10 SEP 2008	**Date of revision:** Not applicable

Title of trial:	A 16-week randomised, placebo-controlled, double-blind, double-dummy, parallel-group study comparing the efficacy and safety of tiotropium inhalation solution delivered by the Respimat® inhaler (2 puffs of 2.5 µg once daily) with that of salmeterol from the hydrofluoroalkane metered dose inhaler (2 puffs of 25 µg twice daily) in moderate persistent asthma patients homozygous for B16-Arg/Arg
Coordinating Investigator:	[redacted]
Trial sites:	Multinational study; 113 centres in 14 countries (Austria, Belgium, Denmark, Finland, France, Germany, Greece, Italy, Russia, Slovakia, South Africa, Spain, Turkey, and the United Kingdom)
Publication (reference):	Data of this study have not been published
Clinical phase:	IIa
Objective:	To compare the efficacy and safety of tiotropium inhalation solution (5 µg [2 puffs of 2.5 µg] once daily [q.d.], p m.) delivered by the Respimat® inhaler A5.2 with that of salmeterol metered dose inhaler (MDI) (50 µg [2 puffs of 25 µg] twice daily [b.i.d.]) in moderate persistent asthmatic patients homozygous for B16-Arg/Arg. The primary objective was to show non-inferiority of tiotropium versus salmeterol after 16 weeks of treatment. Superiority of tiotropium over placebo was also to be demonstrated.
Methodology:	Randomised (1:1:1), placebo-controlled, double-blind, double-dummy, parallel design comparison of 3 groups over a 16-week treatment period following a minimum 4-week open-label run-in period, and with a 4-week open-label follow-up period, both on stable dose of inhaled steroid (ICS) and salmeterol 50 µg b.i.d.

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Module:		**Volume:**	
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No. of subjects:	
planned:	entered: 360 (120 for each treatment group)
actual:	enrolled: 530 entered: 388 5 µg Tiotropium q.d. (p.m.) from the Respimat® inhaler A5.2: treated: 128; analysed (for primary endpoint): 128 50 µg Salmeterol MDI b.i.d.: treated: 134; analysed (for primary endpoint): 134 Placebo: treated: 126; analysed (for primary endpoint): 125
Diagnosis and main criteria for inclusion:	Male or female asthmatic outpatients homozygous for B16-Arg/Arg, age 18 - 65 years, smoking history of ≤10 pack-years, pre-bronchodilator forced expiratory volume in 1 second (FEV_1) ≤80% predicted (patients not on long-acting β_2-agonists [LABAs] within the last year) or pre-dose FEV_1 ≤90% predicted (patients on LABAs within the last 3 months), FEV_1 increase ≥12% and ≥200 mL on reversibility testing, treatment with inhaled corticosteroids within the last three months with a total daily dose of 400 - 1000 µg budesonide or equivalent (stable within the last 3 weeks). B16-Arg/Arg asthmatic patients were selected for this trial because it had been suggested that such patients might not benefit from treatment with short-acting β_2-agonists or LABAs. Recent evidence, however, suggests that such pharmacogenetic variation does not have a significant influence on the therapeutic response to LABA plus inhaled steroids in asthma patients.
Test product:	Tiotropium inhalation solution from the Respimat® inhaler A5.2
dose:	5 µg (2 puffs of 2.5 µg) q.d. (in the evening)
mode of admin.:	Oral inhalation from the Respimat® inhaler A5.2
batch no.:	B052000510
Reference therapy:	Salmeterol hydrofluoroalkane 134a MDI
dose:	50 µg (2 puffs of 25 µg) b.i.d. (morning and evening)

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Name of active ingredient: Tiotropium bromide		**Page:** 3 of 6	**Synopsis No.:**
Module:		**Volume:**	
Report date: 14 AUG 2009	**Trial No. / U No.:** 205.342 / U09-1701-01	**Dates of trial:** 17 JUL 2006 – 10 SEP 2008	**Date of revision:** Not applicable

mode of admin.:	Oral inhalation from the MDI
batch no.:	B062000131, B062000649, B072000162
Reference therapy:	Placebo
dose:	Not applicable
mode of admin.:	Oral inhalation from the Respimat® inhaler A5.2
batch no.:	B052000504
Reference therapy:	Placebo
dose:	Not applicable
mode of admin.:	Oral inhalation from the MDI
batch no.:	B062000130, B062000640, B062000501
Duration of treatment:	16 weeks double-blind, double-dummy treatment In addition, during the 4 week run-in period and 4-week follow-up period patients inhaled 50 µg salmeterol (two puffs of 25 µg b.i.d.) from the open-label salmeterol MDI.
Criteria for evaluation:	
Efficacy / clinical pharmacology:	Asthma monitor® AM2+: daily morning and evening pre-dose peak expiratory flow (PEF), daily morning and evening pre-dose FEV_1, use of rescue medication, questionnaire on asthma control, peak flow variability. Morning pre-dose FEV_1 and forced vital capacity (FVC) (by spirometry) and Mini-Asthma Quality of Life Questionnaire (Mini-AQLQ) at study visits; exacerbations of asthma The primary endpoint was the change in mean weekly morning pre-dose PEF from the last week prior to the randomisation visit to the last week of treatment.
Safety:	Monitoring of adverse events (AEs) throughout the study; vital signs (pulse and blood pressure) at study visits; electrocardiogram (ECG) and physical examination at Visit 1 and end of study.

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Name of active ingredient: Tiotropium bromide		**Page:** 4 of 6	**Synopsis No.:**
Module:		**Volume:**	
Report date: 14 AUG 2009	**Trial No. / U No.:** 205.342 / U09-1701-01	**Dates of trial:** 17 JUL 2006 – 10 SEP 2008	**Date of revision:** Not applicable

Statistical methods: Descriptive statistics; for efficacy, analysis of covariance with terms for centre, treatment, LABA pre-treatment and baseline.

SUMMARY – CONCLUSIONS:

Efficacy / clinical pharmacology results: There was no marked difference in demographic and other baseline characteristics across the 3 randomised treatment groups.

The change in mean weekly morning pre-dose PEF from the last week of the run-in period (open-label salmeterol 50 µg b.i.d.) prior to randomisation visit to the last week of treatment was similar in both active treatment groups in the full analysis set (FAS) with adjusted means (standard error) of -3.93 (4.873) and -3.15 (4.640) L/min for the tiotropium and salmeterol groups, respectively compared to -24.63 (4.835) L/min in the placebo group. Both active treatments (tiotropium and salmeterol) were statistically superior to placebo ($p<0.05$) and tiotropium was non inferior to salmeterol ($p<0.05$). The findings of the full analysis set were supported by the per protocol analysis of the primary endpoint and by the analysis of secondary endpoints (morning and evening mean weekly pre-dose PEF, and morning and evening mean weekly pre-dose FEV_1), which demonstrated the superiority of tiotropium over placebo and the non-inferiority of tiotropium to salmeterol.

Safety results: Mean (standard deviation) duration of double-blind exposure to trial medication was 109.6 (21.3) days (placebo), 110.9 (16.2) days (tiotropium), and 111.8 (16.8) days (salmeterol).

During the double-blind treatment and follow-up periods, the overall incidence of AEs was similar in the active treatment and placebo groups: 52 (41.3%) placebo patients; 51 (39.8%) tiotropium patients; 56 (41.8%) salmeterol patients. Few AEs were considered drug-related and the incidences of such AEs were also similar across groups: 4 (3.2%) placebo patients, 6 (4.7%) tiotropium patients, and 3 (2.2%) salmeterol patients. The most common AEs by preferred term were asthma exacerbation (including preferred term asthma) and nasopharyngitis. The incidence of asthma exacerbations was 13.5% for patients treated with placebo and was similar in the tiotropium (12.5%) and salmeterol (12.7%) groups. The incidence of nasopharyngitis was higher on placebo (7.1%) than on tiotropium (3.9%) or salmeterol (2.2%). All other individual AEs were reported by fewer than 5% of patients in any treatment group. Differences in individual preferred terms in the infections and infestations system organ class (SOC) at low numbers

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Name of finished product: Spiriva® Respimat® inhaler		**EudraCT No.:** 2005-005616-25	
Name of active ingredient: Tiotropium bromide		**Page:** 5 of 6	**Synopsis No.:**
Module:		**Volume:**	
Report date: 14 AUG 2009	**Trial No. / U No.:** 205.342 / U09-1701-01	**Dates of trial:** 17 JUL 2006 – 10 SEP 2008	**Date of revision:** Not applicable

appear compensated by related terms, i.e. nasopharyngitis was reported for 9, 5 or 3 patients, bronchitis (1, 4 or 5 patients), respiratory tract infection (2, 4, or 2 patients) and upper respiratory tract infection (3, 2 or 4 patients) in the placebo, tiotropium or salmeterol groups, respectively. These terms are unlikely to reflect differences between the treatments, as the incidence in the SOC was balanced across the treatment groups.

There were no deaths or immediately life-threatening AEs. The incidence of SAEs overall was low: 1 (0.8%) placebo patient, 2 (1.6%) tiotropium patients, compared to 7 (5.2%) salmeterol patients. All these SAEs were considered serious because the patients were hospitalised. The most common SAE was asthma exacerbation, reported for 4 salmeterol patients, 1 placebo patient, and no tiotropium patients. All other SAEs were different events, each reported for one patient in total: meningitis, pilonidal cyst (tiotropium), headache/nausea/joint injury, ligament injury, gastroenteritis (salmeterol). No SAEs were considered to be drug-related.

Nine patients discontinued study medication due to AEs and the incidence was higher for the tiotropium group than for placebo or salmeterol groups: 2 (1.6%) placebo patients, 5 (3.9%) tiotropium patients, and 2 (1.5%) salmeterol patients. The AEs leading to discontinuation for placebo patients were lichenoid keratosis (drug-related) and chest discomfort. For the tiotropium group, the AEs were bronchitis, sleep disorder (drug-related), hypertension (drug-related), asthma exacerbation (2 patients; one drug-related). For the salmeterol group, the AEs were chest pain (drug-related) and asthma exacerbation (the only AE that was both serious and led to discontinuation of trial drug).

There were no clinically meaningful changes in vitals signs from baseline.

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Name of active ingredient: Tiotropium bromide		**Page:** 6 of 6	**Synopsis No.:**
Module:		**Volume:**	
Report date: 14 AUG 2009	**Trial No. / U No.:** 205.342 / U09-1701-01	**Dates of trial:** 17 JUL 2006 – 10 SEP 2008	**Date of revision:** Not applicable

Conclusions:

The primary endpoint of this study, the change in mean weekly morning pre-dose PEF from baseline to the last week of treatment based on weekly means of electronic peak-flow meter recordings measured at home, demonstrated the statistical non-inferiority of tiotropium versus salmeterol and the superiority of both tiotropium and salmeterol versus placebo. Tiotropium was as effective as salmeterol in the treatment of patients homozygous for arginine at the 16th amino acid position of the β_2-adrenergic receptor (B16-Arg/Arg) with moderate persistent asthma (GINA step 3).

All active treatments showed a good safety profile generally balanced across the treatment groups. Serious asthma exacerbations leading to hospitalisation were recorded for 1, 0 or 4 patients, and discontinuations for asthma exacerbations for 0, 2 or 1 patients in the placebo, tiotropium or salmeterol groups, respectively.

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 the 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 additional secondary endpoints (some are composite) are provided in the Trial Synopsis and the following tables.

Results for	**presented in**
Disposition of patients	Table 15.1.1: 1
Weekly treatment means of Morning PEF Evening PEF Morning FEV_1 Evening FEV_1 PEF variability	Table 15.2.1.1.2: 1
Weekly treatment differences of PEF variability Morning PEF Evening PEF Morning FEV_1 Evening FEV_1 PEF variability	Table 15.2.1.1.2: 3
Weekly means of asthma symptom-free days	Table 15.2.1.2: 1 Table 15.2.1.2: 2 Table 15.2.1.2: 3
Level of asthma control (treatment differences)	Table 15.2.1.2: 4
Morning pre-dose FEV_1 at study visits (treatment means) Morning pre-dose FEV_1 response at study visits (treatment means) Morning pre-dose FEV_1 at study visits (treatment differences)	Table 15.2.1.3.1: 1 Table 15.2.1.3.2: 2 Table 15.2.1.3.2: 3
Morning pre-dose FVC at study visits (treatment means)	Table 15.2.1.4.1: 1

Morning pre-dose FVC response at study visits (treatment means)	Table 15.2.1.4.1: 2
Morning pre-dose FVC at study visits (treatment differences)	Table 15.2.1.4.1: 3
Weekly mean of MiniAQLQ and domains over time (treatment means)	Table 15.2.1.5: 1
Weekly mean of MiniAQLQ and domains response over time (treatment means)	Table 15.2.1.5: 2
Weekly mean of MiniAQLQ and domains over time (treatment differences)	Table 15.2.1.5: 3

Table 15.1.1: 1 Disposition of patients
Summary of conclusion of patient participation - blinded treatment phase

	Placebo N (%)	Tio R5 N (%)	Salmeterol N (%)	Total N (%)
Enrolled				530
Not entered/randomised				142
Entered/randomised	126	128	134	388
Not treated	0	0	0	0
Treated	126 (100.0)	128 (100.0)	134 (100.0)	388 (100.0)
Not prematurely discontinued from trial medication	119 (94.4)	120 (93.8)	128 (95.5)	367 (94.6)
Prematurely discontinued from trial medication	7 (5.6)	8 (6.3)	6 (4.5)	21 (5.4)
Adverse event	2 (1.6)	5 (3.9)	2 (1.5)	9 (2.3)
AE study dis. worse	1 (0.8)	2 (1.6)	1 (0.7)	4 (1.0)
AE other dis. worse	0 (0.0)	1 (0.8)	0 (0.0)	1 (0.3)
AE other	1 (0.8)	2 (1.6)	1 (0.7)	4 (1.0)
Lack of efficacy	2 (1.6)	1 (0.8)	0 (0.0)	3 (0.8)
Non compl. protocol	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Lost to follow-up	1 (0.8)	1 (0.8)	0 (0.0)	2 (0.5)
Refused cont. medica	1 (0.8)	0 (0.0)	1 (0.7)	2 (0.5)
Other	1 (0.8)	1 (0.8)	3 (2.2)	5 (1.3)

Table 15.2.1.1.2: 1 Adjusted weekly means (SE) of AM and PM PEF, PEF variability, and AM and PM FEV1 (treatment means) - FAS

Endpoint name	Number of week	Statistic	Placebo	Tio R5	Salmeterol
Mean FEV1 in the morning	Baseline	Mean (SE)	2.291 (0.000)	2.291 (0.000)	2.291 (0.000)
	Week 1	Mean (SE)	2.190 (0.022)	2.302 (0.022)	2.318 (0.021)
	Week 2	Mean (SE)	2.160 (0.026)	2.296 (0.026)	2.310 (0.025)
	Week 3	Mean (SE)	2.171 (0.027)	2.295 (0.027)	2.289 (0.026)
	Week 4	Mean (SE)	2.161 (0.025)	2.301 (0.026)	2.316 (0.024)
	Week 5	Mean (SE)	2.169 (0.026)	2.308 (0.026)	2.290 (0.025)
	Week 6	Mean (SE)	2.159 (0.028)	2.279 (0.028)	2.309 (0.027)
	Week 7	Mean (SE)	2.155 (0.028)	2.252 (0.029)	2.287 (0.027)
	Week 8	Mean (SE)	2.164 (0.028)	2.254 (0.028)	2.287 (0.027)
	Week 9	Mean (SE)	2.179 (0.028)	2.247 (0.029)	2.286 (0.027)
	Week 10	Mean (SE)	2.173 (0.031)	2.276 (0.031)	2.265 (0.030)
	Week 11	Mean (SE)	2.170 (0.031)	2.264 (0.031)	2.264 (0.030)
	Week 12	Mean (SE)	2.156 (0.030)	2.256 (0.030)	2.254 (0.029)
	Week 13	Mean (SE)	2.158 (0.029)	2.266 (0.030)	2.279 (0.028)
	Week 14	Mean (SE)	2.166 (0.030)	2.289 (0.030)	2.284 (0.028)
	Week 15	Mean (SE)	2.165 (0.030)	2.291 (0.031)	2.299 (0.029)
	Week 16	Mean (SE)	2.188 (0.029)	2.300 (0.030)	2.278 (0.028)

Means are adjusted for pooled centre, pre-treatment (treated or not treated with LABA) and baseline.

Source data: Appendix 16.1.9.2, Statdoc 6.1.1.2.1 efficacy\diary_am.sas 18NOV2008

Table 15.2.1.1.2: 1 Adjusted weekly means (SE) of AM and PM PEF, PEF variability, and AM and PM FEV1 (treatment means) - FAS

Endpoint name	Number of week	Statistic	Placebo	Tio R5	Salmeterol
Mean FEV1 in the evening	Baseline	Mean (SE)	2.332 (0.000)	2.332 (0.000)	2.332 (0.000)
	Week 1	Mean (SE)	2.260 (0.021)	2.349 (0.021)	2.332 (0.020)
	Week 2	Mean (SE)	2.254 (0.027)	2.361 (0.027)	2.340 (0.026)
	Week 3	Mean (SE)	2.252 (0.028)	2.369 (0.028)	2.325 (0.026)
	Week 4	Mean (SE)	2.250 (0.029)	2.369 (0.029)	2.318 (0.028)
	Week 5	Mean (SE)	2.227 (0.029)	2.345 (0.029)	2.318 (0.028)
	Week 6	Mean (SE)	2.258 (0.030)	2.361 (0.030)	2.317 (0.028)
	Week 7	Mean (SE)	2.238 (0.029)	2.327 (0.030)	2.309 (0.028)
	Week 8	Mean (SE)	2.239 (0.030)	2.320 (0.030)	2.301 (0.029)
	Week 9	Mean (SE)	2.237 (0.031)	2.321 (0.032)	2.313 (0.030)
	Week 10	Mean (SE)	2.229 (0.034)	2.312 (0.035)	2.295 (0.033)
	Week 11	Mean (SE)	2.241 (0.032)	2.322 (0.033)	2.288 (0.031)
	Week 12	Mean (SE)	2.231 (0.032)	2.310 (0.032)	2.299 (0.030)
	Week 13	Mean (SE)	2.235 (0.033)	2.315 (0.034)	2.296 (0.032)
	Week 14	Mean (SE)	2.215 (0.032)	2.318 (0.033)	2.283 (0.031)
	Week 15	Mean (SE)	2.229 (0.032)	2.309 (0.032)	2.284 (0.030)
	Week 16	Mean (SE)	2.215 (0.031)	2.343 (0.031)	2.291 (0.029)

Means are adjusted for pooled centre, pre-treatment (treated or not treated with LABA) and baseline.

Source data: Appendix 16.1.9.2, Statdoc 6.1.1.2.1 efficacy\diary_am.sas 18NOV2008

Table 15.2.1.1.2: 1 Adjusted weekly means (SE) of AM and PM PEF, PEF variability, and AM and PM FEV1 (treatment means) - FAS

Endpoint name	Number of week	Statistic	Placebo	Tio R5	Salmeterol
Mean morning PEFR	Baseline	Mean (SE)	357.919 (0.000)	357.919 (0.000)	357.919 (0.000)
	Week 1	Mean (SE)	337.536 (3.192)	367.940 (3.217)	361.529 (3.063)
	Week 2	Mean (SE)	335.407 (3.641)	364.805 (3.670)	357.706 (3.494)
	Week 3	Mean (SE)	335.915 (3.935)	362.477 (3.965)	355.935 (3.776)
	Week 4	Mean (SE)	335.515 (4.211)	360.695 (4.244)	359.762 (4.041)
	Week 5	Mean (SE)	335.428 (4.465)	359.693 (4.500)	356.208 (4.285)
	Week 6	Mean (SE)	331.819 (4.397)	356.162 (4.431)	355.564 (4.220)
	Week 7	Mean (SE)	332.488 (4.302)	356.142 (4.335)	354.836 (4.128)
	Week 8	Mean (SE)	330.193 (4.610)	355.420 (4.646)	350.530 (4.424)
	Week 9	Mean (SE)	334.651 (4.628)	357.903 (4.664)	349.877 (4.441)
	Week 10	Mean (SE)	335.149 (4.732)	356.356 (4.769)	348.728 (4.541)
	Week 11	Mean (SE)	333.516 (4.677)	356.965 (4.714)	350.824 (4.488)
	Week 12	Mean (SE)	332.808 (4.847)	359.050 (4.885)	351.300 (4.652)
	Week 13	Mean (SE)	334.539 (4.746)	358.370 (4.783)	352.422 (4.555)
	Week 14	Mean (SE)	335.056 (4.792)	357.722 (4.829)	354.806 (4.598)
	Week 15	Mean (SE)	333.475 (4.775)	358.647 (4.813)	356.561 (4.583)
	Week 16	Mean (SE)	334.525 (4.831)	355.619 (4.868)	355.799 (4.636)

Means are adjusted for pooled centre, pre-treatment (treated or not treated with LABA) and baseline.

Source data: Appendix 16.1.9.2, Statdoc 6.1.1.2.1 efficacy\diary_am.sas 18NOV2008

Table 15.2.1.1.2: 1 Adjusted weekly means (SE) of AM and PM PEF, PEF variability, and AM and PM FEV1 (treatment means) - FAS

Endpoint name	Number of week	Statistic	Placebo	Tio R5	Salmeterol
Mean evening PEFR	Baseline	Mean (SE)	369.746 (0.000)	369.746 (0.000)	369.746 (0.000)
	Week 1	Mean (SE)	352.738 (3.211)	376.028 (3.238)	368.641 (3.082)
	Week 2	Mean (SE)	347.593 (3.378)	377.033 (3.406)	366.334 (3.242)
	Week 3	Mean (SE)	349.336 (3.737)	375.295 (3.769)	364.308 (3.588)
	Week 4	Mean (SE)	348.344 (4.213)	374.496 (4.249)	366.219 (4.045)
	Week 5	Mean (SE)	347.245 (4.292)	370.771 (4.328)	364.922 (4.120)
	Week 6	Mean (SE)	342.174 (4.600)	366.165 (4.639)	363.494 (4.416)
	Week 7	Mean (SE)	344.737 (4.672)	368.494 (4.712)	361.150 (4.486)
	Week 8	Mean (SE)	345.299 (4.740)	368.758 (4.780)	359.586 (4.551)
	Week 9	Mean (SE)	344.241 (4.875)	365.646 (4.916)	359.677 (4.680)
	Week 10	Mean (SE)	343.403 (4.822)	365.746 (4.863)	359.924 (4.629)
	Week 11	Mean (SE)	345.713 (4.875)	364.567 (4.917)	357.378 (4.680)
	Week 12	Mean (SE)	344.291 (4.810)	366.282 (4.851)	362.010 (4.617)
	Week 13	Mean (SE)	343.516 (4.937)	366.804 (4.979)	359.912 (4.740)
	Week 14	Mean (SE)	341.613 (5.138)	365.975 (5.182)	361.035 (4.933)
	Week 15	Mean (SE)	341.283 (5.100)	365.740 (5.144)	360.706 (4.896)
	Week 16	Mean (SE)	340.099 (5.198)	363.657 (5.242)	360.304 (4.990)

Means are adjusted for pooled centre, pre-treatment (treated or not treated with LABA) and baseline.

Source data: Appendix 16.1.9.2, Statdoc 6.1.1.2.1 efficacy\diary_am.sas 18NOV2008

Table 15.2.1.1.2: 1 Adjusted weekly means (SE) of AM and PM PEF, PEF variability, and AM and PM FEV1 (treatment means) - FAS

Endpoint name	Number of week	Statistic	Placebo	Tio R5	Salmeterol
Mean PEF variability	Baseline	Mean (SE)	11.650 (0.000)	11.650 (0.000)	11.650 (0.000)
	Week 1	Mean (SE)	11.756 (0.546)	11.453 (0.551)	11.186 (0.526)
	Week 2	Mean (SE)	12.233 (0.584)	11.655 (0.589)	10.936 (0.563)
	Week 3	Mean (SE)	11.855 (0.608)	12.428 (0.613)	10.983 (0.586)
	Week 4	Mean (SE)	12.085 (0.606)	12.043 (0.611)	10.547 (0.584)
	Week 5	Mean (SE)	11.817 (0.667)	11.631 (0.673)	11.049 (0.643)
	Week 6	Mean (SE)	12.414 (0.687)	11.952 (0.693)	11.746 (0.662)
	Week 7	Mean (SE)	12.179 (0.643)	13.047 (0.649)	11.947 (0.621)
	Week 8	Mean (SE)	12.964 (0.689)	13.377 (0.695)	11.252 (0.664)
	Week 9	Mean (SE)	11.183 (0.632)	12.321 (0.638)	11.513 (0.610)
	Week 10	Mean (SE)	11.109 (0.605)	12.283 (0.611)	11.508 (0.584)
	Week 11	Mean (SE)	11.832 (0.632)	12.334 (0.638)	11.300 (0.610)
	Week 12	Mean (SE)	11.257 (0.648)	11.735 (0.654)	11.320 (0.625)
	Week 13	Mean (SE)	11.606 (0.649)	11.717 (0.654)	11.223 (0.626)
	Week 14	Mean (SE)	11.699 (0.664)	11.697 (0.670)	10.886 (0.641)
	Week 15	Mean (SE)	11.192 (0.622)	11.910 (0.627)	10.876 (0.599)
	Week 16	Mean (SE)	12.305 (0.650)	11.742 (0.656)	10.793 (0.627)

Means are adjusted for pooled centre, pre-treatment (treated or not treated with LABA) and baseline.

Source data: Appendix 16.1.9.2, Statdoc 6.1.1.2.1 efficacy\diary_am.sas 18NOV2008

Table 15.2.1.1.2: 3 Adjusted weekly means (SE) of AM and PM PEF, PEF variability, and AM and PM FEV1 (treatment differences) - FAS

Endpoint name	Number of week	Comparison	Difference	95% Confidence Interval	P-value (non-inferiority)	P-value (superiority)
Mean FEV1 in the morning°	Baseline	Placebo - Tio R5	0.000 (.)	(. , .)		.
		Placebo - Salmeterol	0.000 (.)	(. , .)		.
		Tio R5 - Salmeterol	0.000 (.)	(. , .)	.	.
	Week 1	Placebo - Tio R5	-0.112 (0.029)	(-0.168, -.056)		0.0001
		Placebo - Salmeterol	-0.128 (0.028)	(-0.184, -.073)		<.0001
		Tio R5 - Salmeterol	-0.016 (0.028)	(-0.072, 0.039)	0.2323	0.5616
	Week 2	Placebo - Tio R5	-0.136 (0.034)	(-0.202, -.069)		<.0001
		Placebo - Salmeterol	-0.150 (0.034)	(-0.216, -.084)		<.0001
		Tio R5 - Salmeterol	-0.015 (0.033)	(-0.080, 0.051)	0.2900	0.6637
	Week 3	Placebo - Tio R5	-0.123 (0.035)	(-0.193, -.054)		0.0005
		Placebo - Salmeterol	-0.118 (0.035)	(-0.187, -.049)		0.0008
		Tio R5 - Salmeterol	0.005 (0.035)	(-0.063, 0.073)	0.1127	0.8815
	Week 4	Placebo - Tio R5	-0.140 (0.034)	(-0.206, -.074)		<.0001
		Placebo - Salmeterol	-0.155 (0.033)	(-0.220, -.090)		<.0001
		Tio R5 - Salmeterol	-0.015 (0.033)	(-0.080, 0.050)	0.2849	0.6575
	Week 5	Placebo - Tio R5	-0.140 (0.034)	(-0.207, -.073)		<.0001
		Placebo - Salmeterol	-0.122 (0.034)	(-0.188, -.055)		0.0004
		Tio R5 - Salmeterol	0.018 (0.034)	(-0.048, 0.084)	0.0433	0.5919
	Week 6	Placebo - Tio R5	-0.120 (0.037)	(-0.192, -.048)		0.0012
		Placebo - Salmeterol	-0.151 (0.036)	(-0.222, -.079)		<.0001
		Tio R5 - Salmeterol	-0.030 (0.036)	(-0.101, 0.041)	0.5870	0.4021
	Week 7	Placebo - Tio R5	-0.097 (0.037)	(-0.170, -.023)		0.0099
		Placebo - Salmeterol	-0.132 (0.037)	(-0.204, -.059)		0.0004
		Tio R5 - Salmeterol	-0.035 (0.037)	(-0.107, 0.037)	0.6830	0.3403
	Week 8	Placebo - Tio R5	-0.090 (0.037)	(-0.162, -.018)		0.0143
		Placebo - Salmeterol	-0.123 (0.036)	(-0.194, -.051)		0.0008
		Tio R5 - Salmeterol	-0.033 (0.036)	(-0.103, 0.038)	0.6305	0.3643
	Week 9	Placebo - Tio R5	-0.068 (0.037)	(-0.141, 0.006)		0.0700

Means are adjusted for pooled centre, pre-treatment (treated or not treated with LABA) and baseline.
#: Non-inferiority: Difference is less than 20 litres
°: Non-inferiority: Difference is less than 0.05 litres
Source data: Appendix 16.1.9.2, Statdoc 6.1.1.2.1 efficacy\diary_am.sas 18NOV2008

Table 15.2.1.1.2: 3 Adjusted weekly means (SE) of AM and PM PEF, PEF variability, and AM and PM FEV1 (treatment differences) - FAS

Endpoint name	Number of week	Comparison	Difference	95% Confidence Interval	P-value (non-inferiority)	P-value (superiority)
Mean FEV1 in the morning°	Week 9	Placebo - Salmeterol	-0.107 (0.037)	(-0.180, -.034)		0.0041
		Tio R5 - Salmeterol	-0.039 (0.037)	(-0.112, 0.033)	0.7694	0.2868
	Week 10	Placebo - Tio R5	-0.104 (0.041)	(-0.184, -.024)		0.0113
		Placebo - Salmeterol	-0.092 (0.040)	(-0.172, -.013)		0.0231
		Tio R5 - Salmeterol	0.012 (0.040)	(-0.067, 0.090)	0.1252	0.7725
	Week 11	Placebo - Tio R5	-0.094 (0.041)	(-0.175, -.013)		0.0224
		Placebo - Salmeterol	-0.094 (0.041)	(-0.174, -.014)		0.0216
		Tio R5 - Salmeterol	0.000 (0.040)	(-0.079, 0.080)	0.2141	0.9961
	Week 12	Placebo - Tio R5	-0.100 (0.039)	(-0.177, -.022)		0.0117
		Placebo - Salmeterol	-0.098 (0.039)	(-0.175, -.021)		0.0128
		Tio R5 - Salmeterol	0.002 (0.039)	(-0.074, 0.078)	0.1812	0.9598
	Week 13	Placebo - Tio R5	-0.109 (0.039)	(-0.185, -.032)		0.0054
		Placebo - Salmeterol	-0.121 (0.039)	(-0.197, -.045)		0.0018
		Tio R5 - Salmeterol	-0.012 (0.038)	(-0.088, 0.063)	0.3266	0.7452
	Week 14	Placebo - Tio R5	-0.123 (0.039)	(-0.200, -.047)		0.0017
		Placebo - Salmeterol	-0.118 (0.039)	(-0.194, -.042)		0.0024
		Tio R5 - Salmeterol	0.005 (0.038)	(-0.071, 0.080)	0.1532	0.8978
	Week 15	Placebo - Tio R5	-0.126 (0.040)	(-0.204, -.047)		0.0018
		Placebo - Salmeterol	-0.134 (0.040)	(-0.212, -.056)		0.0008
		Tio R5 - Salmeterol	-0.008 (0.039)	(-0.086, 0.069)	0.2884	0.8351
	Week 16	Placebo - Tio R5	-0.113 (0.039)	(-0.189, -.036)		0.0040
		Placebo - Salmeterol	-0.091 (0.039)	(-0.166, -.015)		0.0193
		Tio R5 - Salmeterol	0.022 (0.038)	(-0.053, 0.097)	0.0609	0.5671

Means are adjusted for pooled centre, pre-treatment (treated or not treated with LABA) and baseline.
#: Non-inferiority: Difference is less than 20 litres
°: Non-inferiority: Difference is less than 0.05 litres
Source data: Appendix 16.1.9.2, Statdoc 6.1.1.2.1

Table 15.2.1.1.2: 3 Adjusted weekly means (SE) of AM and PM PEF, PEF variability, and AM and PM FEV1 (treatment differences) - FAS

Endpoint name	Number of week	Comparison	Difference	95% Confidence Interval	P-value (non-inferiority)	P-value (superiority)
Mean FEV1 in the evening°	Baseline	Placebo - Tio R5	0.000 (.)	(. , .)		.
		Placebo - Salmeterol	0.000 (.)	(. , .)		.
		Tio R5 - Salmeterol	0.000 (.)	(. , .)	.	.
	Week 1	Placebo - Tio R5	-0.088 (0.028)	(-0.142, -.034)		0.0015
		Placebo - Salmeterol	-0.072 (0.027)	(-0.125, -.018)		0.0092
		Tio R5 - Salmeterol	0.017 (0.027)	(-0.037, 0.070)	0.0144	0.5392
	Week 2	Placebo - Tio R5	-0.107 (0.035)	(-0.176, -.037)		0.0027
		Placebo - Salmeterol	-0.086 (0.035)	(-0.155, -.017)		0.0147
		Tio R5 - Salmeterol	0.021 (0.035)	(-0.048, 0.089)	0.0431	0.5519
	Week 3	Placebo - Tio R5	-0.117 (0.036)	(-0.188, -.046)		0.0014
		Placebo - Salmeterol	-0.073 (0.036)	(-0.144, -.002)		0.0442
		Tio R5 - Salmeterol	0.044 (0.036)	(-0.026, 0.115)	0.0087	0.2165
	Week 4	Placebo - Tio R5	-0.120 (0.038)	(-0.194, -.045)		0.0018
		Placebo - Salmeterol	-0.069 (0.038)	(-0.143, 0.005)		0.0693
		Tio R5 - Salmeterol	0.051 (0.037)	(-0.022, 0.125)	0.0072	0.1728
	Week 5	Placebo - Tio R5	-0.117 (0.038)	(-0.192, -.043)		0.0022
		Placebo - Salmeterol	-0.091 (0.038)	(-0.165, -.017)		0.0160
		Tio R5 - Salmeterol	0.026 (0.037)	(-0.047, 0.100)	0.0423	0.4842
	Week 6	Placebo - Tio R5	-0.103 (0.039)	(-0.180, -.026)		0.0085
		Placebo - Salmeterol	-0.059 (0.039)	(-0.135, 0.017)		0.1264
		Tio R5 - Salmeterol	0.044 (0.038)	(-0.032, 0.119)	0.0149	0.2539
	Week 7	Placebo - Tio R5	-0.089 (0.039)	(-0.165, -.013)		0.0219
		Placebo - Salmeterol	-0.071 (0.038)	(-0.147, 0.004)		0.0628
		Tio R5 - Salmeterol	0.017 (0.038)	(-0.057, 0.092)	0.0771	0.6478
	Week 8	Placebo - Tio R5	-0.081 (0.040)	(-0.159, -.003)		0.0414
		Placebo - Salmeterol	-0.062 (0.039)	(-0.139, 0.016)		0.1173
		Tio R5 - Salmeterol	0.019 (0.039)	(-0.057, 0.096)	0.0764	0.6192
	Week 9	Placebo - Tio R5	-0.084 (0.041)	(-0.165, -.002)		0.0439

Means are adjusted for pooled centre, pre-treatment (treated or not treated with LABA) and baseline.
#: Non-inferiority: Difference is less than 20 litres
°: Non-inferiority: Difference is less than 0.05 litres
Source data: Appendix 16.1.9.2, Statdoc 6.1.1.2.1 efficacy\diary_am.sas 18NOV2008

Table 15.2.1.1.2: 3 Adjusted weekly means (SE) of AM and PM PEF, PEF variability, and AM and PM FEV1 (treatment differences) - FAS

Endpoint name	Number of week	Comparison	Difference	95% Confidence Interval	P-value (non-inferiority)	P-value (superiority)
Mean FEV1 in the evening°	Week 9	Placebo - Salmeterol	-0.076 (0.041)	(-0.157, 0.005)		0.0655
		Tio R5 - Salmeterol	0.008 (0.041)	(-0.072, 0.088)	0.1573	0.8473
	Week 10	Placebo - Tio R5	-0.083 (0.045)	(-0.171, 0.006)		0.0672
		Placebo - Salmeterol	-0.066 (0.045)	(-0.154, 0.022)		0.1396
		Tio R5 - Salmeterol	0.017 (0.044)	(-0.071, 0.104)	0.1342	0.7093
	Week 11	Placebo - Tio R5	-0.082 (0.042)	(-0.165, 0.002)		0.0552
		Placebo - Salmeterol	-0.047 (0.042)	(-0.130, 0.036)		0.2649
		Tio R5 - Salmeterol	0.035 (0.042)	(-0.048, 0.117)	0.0437	0.4077
	Week 12	Placebo - Tio R5	-0.080 (0.042)	(-0.162, 0.002)		0.0561
		Placebo - Salmeterol	-0.068 (0.041)	(-0.149, 0.013)		0.1005
		Tio R5 - Salmeterol	0.012 (0.041)	(-0.069, 0.092)	0.1326	0.7738
	Week 13	Placebo - Tio R5	-0.080 (0.044)	(-0.166, 0.006)		0.0687
		Placebo - Salmeterol	-0.061 (0.044)	(-0.146, 0.025)		0.1632
		Tio R5 - Salmeterol	0.019 (0.043)	(-0.066, 0.104)	0.1096	0.6553
	Week 14	Placebo - Tio R5	-0.103 (0.043)	(-0.187, -.019)		0.0168
		Placebo - Salmeterol	-0.068 (0.042)	(-0.151, 0.016)		0.1115
		Tio R5 - Salmeterol	0.035 (0.042)	(-0.048, 0.118)	0.0440	0.4058
	Week 15	Placebo - Tio R5	-0.080 (0.042)	(-0.162, 0.001)		0.0537
		Placebo - Salmeterol	-0.055 (0.041)	(-0.136, 0.026)		0.1796
		Tio R5 - Salmeterol	0.025 (0.041)	(-0.055, 0.105)	0.0674	0.5411
	Week 16	Placebo - Tio R5	-0.128 (0.040)	(-0.207, -.048)		0.0017
		Placebo - Salmeterol	-0.076 (0.040)	(-0.155, 0.003)		0.0590
		Tio R5 - Salmeterol	0.052 (0.040)	(-0.027, 0.130)	0.0110	0.1948

Means are adjusted for pooled centre, pre-treatment (treated or not treated with LABA) and baseline.
#: Non-inferiority: Difference is less than 20 litres
°: Non-inferiority: Difference is less than 0.05 litres
Source data: Appendix 16.1.9.2, Statdoc 6.1.1.2.1

Table 15.2.1.1.2: 3 Adjusted weekly means (SE) of AM and PM PEF, PEF variability, and AM and PM FEV1 (treatment differences) - FAS

Endpoint name	Number of week	Comparison	Difference	95% Confidence Interval	P-value (non-inferiority)	P-value (superiority)
Mean morning PEFR#	Baseline	Placebo - Tio R5	0.000 (.)	(. , .)		.
		Placebo - Salmeterol	0.000 (.)	(. , .)		.
		Tio R5 - Salmeterol	0.000 (.)	(. , .)	.	.
	Week 1	Placebo - Tio R5	-30.404 (4.209)	(-38.681, -22.1)		<.0001
		Placebo - Salmeterol	-23.993 (4.172)	(-32.198, -15.8)		<.0001
		Tio R5 - Salmeterol	6.411 (4.133)	(-1.719, 14.54)	<.0001	0.1218
	Week 2	Placebo - Tio R5	-29.398 (4.801)	(-38.841, -20.0)		<.0001
		Placebo - Salmeterol	-22.299 (4.759)	(-31.659, -12.9)		<.0001
		Tio R5 - Salmeterol	7.098 (4.715)	(-2.176, 16.37)	<.0001	0.1331
	Week 3	Placebo - Tio R5	-26.562 (5.188)	(-36.766, -16.4)		<.0001
		Placebo - Salmeterol	-20.021 (5.142)	(-30.134, -9.91)		0.0001
		Tio R5 - Salmeterol	6.542 (5.095)	(-3.479, 16.56)	<.0001	0.2000
	Week 4	Placebo - Tio R5	-25.180 (5.552)	(-36.100, -14.3)		<.0001
		Placebo - Salmeterol	-24.248 (5.503)	(-35.071, -13.4)		<.0001
		Tio R5 - Salmeterol	0.933 (5.453)	(-9.792, 11.66)	0.0001	0.8643
	Week 5	Placebo - Tio R5	-24.265 (5.887)	(-35.844, -12.7)		<.0001
		Placebo - Salmeterol	-20.781 (5.835)	(-32.257, -9.30)		0.0004
		Tio R5 - Salmeterol	3.485 (5.782)	(-7.887, 14.86)	<.0001	0.5471
	Week 6	Placebo - Tio R5	-24.343 (5.798)	(-35.747, -12.9)		<.0001
		Placebo - Salmeterol	-23.745 (5.746)	(-35.047, -12.4)		<.0001
		Tio R5 - Salmeterol	0.598 (5.694)	(-10.601, 11.80)	0.0003	0.9164
	Week 7	Placebo - Tio R5	-23.654 (5.672)	(-34.810, -12.5)		<.0001
		Placebo - Salmeterol	-22.348 (5.622)	(-33.405, -11.3)		<.0001
		Tio R5 - Salmeterol	1.306 (5.570)	(-9.650, 12.26)	0.0002	0.8148
	Week 8	Placebo - Tio R5	-25.227 (6.079)	(-37.183, -13.3)		<.0001
		Placebo - Salmeterol	-20.338 (6.025)	(-32.188, -8.49)		0.0008
		Tio R5 - Salmeterol	4.889 (5.970)	(-6.853, 16.63)	<.0001	0.4134
	Week 9	Placebo - Tio R5	-23.252 (6.102)	(-35.254, -11.3)		0.0002

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Source data: Appendix 16.1.9.2, Statdoc 6.1.1.2.1 efficacy\diary_am.sas 18NOV2008

Table 15.2.1.1.2: 3 Adjusted weekly means (SE) of AM and PM PEF, PEF variability, and AM and PM FEV1 (treatment differences) - FAS

Endpoint name	Number of week	Comparison	Difference	95% Confidence Interval	P-value (non-inferiority)	P-value (superiority)
Mean morning PEFR#	Week 9	Placebo - Salmeterol	-15.226 (6.048)	(-27.122, -3.33)		0.0123
		Tio R5 - Salmeterol	8.026 (5.993)	(-3.761, 19.81)	<.0001	0.1813
	Week 10	Placebo - Tio R5	-21.207 (6.239)	(-33.478, -8.94)		0.0008
		Placebo - Salmeterol	-13.580 (6.184)	(-25.742, -1.42)		0.0288
		Tio R5 - Salmeterol	7.627 (6.127)	(-4.424, 19.68)	<.0001	0.2140
	Week 11	Placebo - Tio R5	-23.450 (6.167)	(-35.579, -11.3)		0.0002
		Placebo - Salmeterol	-17.309 (6.112)	(-29.330, -5.29)		0.0049
		Tio R5 - Salmeterol	6.141 (6.056)	(-5.771, 18.05)	<.0001	0.3113
	Week 12	Placebo - Tio R5	-26.243 (6.391)	(-38.814, -13.7)		<.0001
		Placebo - Salmeterol	-18.492 (6.335)	(-30.952, -6.03)		0.0037
		Tio R5 - Salmeterol	7.751 (6.277)	(-4.595, 20.10)	<.0001	0.2177
	Week 13	Placebo - Tio R5	-23.831 (6.258)	(-36.139, -11.5)		0.0002
		Placebo - Salmeterol	-17.883 (6.203)	(-30.082, -5.68)		0.0042
		Tio R5 - Salmeterol	5.948 (6.146)	(-6.140, 18.04)	<.0001	0.3338
	Week 14	Placebo - Tio R5	-22.666 (6.318)	(-35.092, -10.2)		0.0004
		Placebo - Salmeterol	-19.751 (6.262)	(-32.067, -7.43)		0.0018
		Tio R5 - Salmeterol	2.915 (6.205)	(-9.288, 15.12)	0.0003	0.6387
	Week 15	Placebo - Tio R5	-25.172 (6.297)	(-37.556, -12.8)		<.0001
		Placebo - Salmeterol	-23.086 (6.241)	(-35.361, -10.8)		0.0003
		Tio R5 - Salmeterol	2.086 (6.184)	(-10.077, 14.25)	0.0004	0.7361
	Week 16	Placebo - Tio R5	-21.093 (6.369)	(-33.620, -8.57)		0.0010
		Placebo - Salmeterol	-21.274 (6.313)	(-33.690, -8.86)		0.0008
		Tio R5 - Salmeterol	-0.180 (6.255)	(-12.483, 12.12)	0.0017	0.9770

Means are adjusted for pooled centre, pre-treatment (treated or not treated with LABA) and baseline.
#: Non-inferiority: Difference is less than 20 litres
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Source data: Appendix 16.1.9.2, Statdoc 6.1.1.2.1 efficacy\diary_am.sas 18NOV2008

Table 15.2.1.1.2: 3 Adjusted weekly means (SE) of AM and PM PEF, PEF variability, and AM and PM FEV1 (treatment differences) - FAS

Endpoint name	Number of week	Comparison	Difference	95% Confidence Interval	P-value (non-inferiority)	P-value (superiority)
Mean evening PEFR#	Baseline	Placebo - Tio R5	0.000 (.)	(. , .)		.
		Placebo - Salmeterol	0.000 (.)	(. , .)		.
		Tio R5 - Salmeterol	0.000 (.)	(. , .)	.	.
	Week 1	Placebo - Tio R5	-23.290 (4.235)	(-31.620, -15.0)		<.0001
		Placebo - Salmeterol	-15.903 (4.197)	(-24.157, -7.65)		0.0002
		Tio R5 - Salmeterol	7.387 (4.157)	(-0.789, 15.56)	<.0001	0.0764
	Week 2	Placebo - Tio R5	-29.440 (4.455)	(-38.203, -20.7)		<.0001
		Placebo - Salmeterol	-18.742 (4.415)	(-27.424, -10.1)		<.0001
		Tio R5 - Salmeterol	10.698 (4.373)	(2.098, 19.30)	<.0001	0.0149
	Week 3	Placebo - Tio R5	-25.959 (4.930)	(-35.655, -16.3)		<.0001
		Placebo - Salmeterol	-14.972 (4.885)	(-24.580, -5.36)		0.0023
		Tio R5 - Salmeterol	10.987 (4.839)	(1.470, 20.50)	<.0001	0.0238
	Week 4	Placebo - Tio R5	-26.152 (5.558)	(-37.084, -15.2)		<.0001
		Placebo - Salmeterol	-17.874 (5.507)	(-28.706, -7.04)		0.0013
		Tio R5 - Salmeterol	8.278 (5.455)	(-2.451, 19.01)	<.0001	0.1301
	Week 5	Placebo - Tio R5	-23.527 (5.662)	(-34.662, -12.4)		<.0001
		Placebo - Salmeterol	-17.677 (5.610)	(-28.710, -6.64)		0.0018
		Tio R5 - Salmeterol	5.850 (5.557)	(-5.080, 16.78)	<.0001	0.2932
	Week 6	Placebo - Tio R5	-23.991 (6.068)	(-35.925, -12.1)		<.0001
		Placebo - Salmeterol	-21.320 (6.012)	(-33.145, -9.50)		0.0004
		Tio R5 - Salmeterol	2.671 (5.955)	(-9.042, 14.38)	0.0002	0.6541
	Week 7	Placebo - Tio R5	-23.757 (6.163)	(-35.879, -11.6)		0.0001
		Placebo - Salmeterol	-16.413 (6.107)	(-28.425, -4.40)		0.0075
		Tio R5 - Salmeterol	7.344 (6.049)	(-4.554, 19.24)	<.0001	0.2256
	Week 8	Placebo - Tio R5	-23.459 (6.253)	(-35.757, -11.2)		0.0002
		Placebo - Salmeterol	-14.287 (6.195)	(-26.472, -2.10)		0.0217
		Tio R5 - Salmeterol	9.172 (6.137)	(-2.899, 21.24)	<.0001	0.1360
	Week 9	Placebo - Tio R5	-21.405 (6.431)	(-34.053, -8.76)		0.0010

Means are adjusted for pooled centre, pre-treatment (treated or not treated with LABA) and baseline.
#: Non-inferiority: Difference is less than 20 litres
°: Non-inferiority: Difference is less than 0.05 litres
Source data: Appendix 16.1.9.2, Statdoc 6.1.1.2.1 efficacy\diary_am.sas 18NOV2008

Table 15.2.1.1.2: 3 Adjusted weekly means (SE) of AM and PM PEF, PEF variability, and AM and PM FEV1 (treatment differences) - FAS

Endpoint name	Number of week	Comparison	Difference	95% Confidence Interval	P-value (non-inferiority)	P-value (superiority)
Mean evening PEFR#	Week 9	Placebo - Salmeterol	-15.436 (6.372)	(-27.968, -2.90)		0.0159
		Tio R5 - Salmeterol	5.969 (6.312)	(-6.445, 18.38)	<.0001	0.3450
	Week 10	Placebo - Tio R5	-22.343 (6.361)	(-34.854, -9.83)		0.0005
		Placebo - Salmeterol	-16.521 (6.303)	(-28.918, -4.13)		0.0091
		Tio R5 - Salmeterol	5.822 (6.243)	(-6.458, 18.10)	<.0001	0.3517
	Week 11	Placebo - Tio R5	-18.853 (6.431)	(-31.502, -6.20)		0.0036
		Placebo - Salmeterol	-11.664 (6.372)	(-24.197, 0.869)		0.0680
		Tio R5 - Salmeterol	7.189 (6.312)	(-5.226, 19.60)	<.0001	0.2555
	Week 12	Placebo - Tio R5	-21.991 (6.345)	(-34.469, -9.51)		0.0006
		Placebo - Salmeterol	-17.719 (6.286)	(-30.083, -5.35)		0.0051
		Tio R5 - Salmeterol	4.272 (6.227)	(-7.976, 16.52)	0.0001	0.4932
	Week 13	Placebo - Tio R5	-23.288 (6.513)	(-36.098, -10.5)		0.0004
		Placebo - Salmeterol	-16.396 (6.453)	(-29.088, -3.70)		0.0115
		Tio R5 - Salmeterol	6.892 (6.392)	(-5.681, 19.47)	<.0001	0.2817
	Week 14	Placebo - Tio R5	-24.362 (6.778)	(-37.693, -11.0)		0.0004
		Placebo - Salmeterol	-19.422 (6.716)	(-32.631, -6.21)		0.0041
		Tio R5 - Salmeterol	4.940 (6.652)	(-8.144, 18.02)	0.0002	0.4582
	Week 15	Placebo - Tio R5	-24.457 (6.728)	(-37.689, -11.2)		0.0003
		Placebo - Salmeterol	-19.423 (6.666)	(-32.535, -6.31)		0.0038
		Tio R5 - Salmeterol	5.033 (6.603)	(-7.954, 18.02)	0.0002	0.4464
	Week 16	Placebo - Tio R5	-23.559 (6.856)	(-37.043, -10.1)		0.0007
		Placebo - Salmeterol	-20.206 (6.793)	(-33.567, -6.84)		0.0031
		Tio R5 - Salmeterol	3.353 (6.729)	(-9.882, 16.59)	0.0006	0.6186

Means are adjusted for pooled centre, pre-treatment (treated or not treated with LABA) and baseline.
#: Non-inferiority: Difference is less than 20 litres
°: Non-inferiority: Difference is less than 0.05 litres
Source data: Appendix 16.1.9.2, Statdoc 6.1.1.2.1

Table 15.2.1.1.2: 3 Adjusted weekly means (SE) of AM and PM PEF, PEF variability, and AM and PM FEV1 (treatment differences) - FAS

Endpoint name	Number of week	Comparison	Difference	95% Confidence Interval	P-value (non-inferiority)	P-value (superiority)
Mean PEF variability	Baseline	Placebo - Tio R5	0.000 (.)	(. , .)		.
		Placebo - Salmeterol	0.000 (.)	(. , .)		.
		Tio R5 - Salmeterol	0.000 (.)	(. , .)		.
	Week 1	Placebo - Tio R5	0.304 (0.720)	(-1.113, 1.721)		0.6734
		Placebo - Salmeterol	0.571 (0.716)	(-0.837, 1.978)		0.4256
		Tio R5 - Salmeterol	0.267 (0.712)	(-1.134, 1.668)		0.7080
	Week 2	Placebo - Tio R5	0.578 (0.771)	(-0.938, 2.094)		0.4540
		Placebo - Salmeterol	1.297 (0.766)	(-0.209, 2.803)		0.0912
		Tio R5 - Salmeterol	0.719 (0.762)	(-0.779, 2.218)		0.3458
	Week 3	Placebo - Tio R5	-0.573 (0.802)	(-2.151, 1.004)		0.4751
		Placebo - Salmeterol	0.872 (0.797)	(-0.695, 2.439)		0.2747
		Tio R5 - Salmeterol	1.445 (0.793)	(-0.114, 3.005)		0.0692
	Week 4	Placebo - Tio R5	0.042 (0.799)	(-1.530, 1.614)		0.9582
		Placebo - Salmeterol	1.538 (0.794)	(-0.024, 3.099)		0.0536
		Tio R5 - Salmeterol	1.496 (0.790)	(-0.058, 3.050)		0.0592
	Week 5	Placebo - Tio R5	0.186 (0.880)	(-1.546, 1.917)		0.8329
		Placebo - Salmeterol	0.767 (0.875)	(-0.953, 2.488)		0.3808
		Tio R5 - Salmeterol	0.582 (0.870)	(-1.130, 2.293)		0.5044
	Week 6	Placebo - Tio R5	0.462 (0.906)	(-1.320, 2.244)		0.6102
		Placebo - Salmeterol	0.668 (0.900)	(-1.102, 2.438)		0.4584
		Tio R5 - Salmeterol	0.206 (0.896)	(-1.556, 1.968)		0.8184
	Week 7	Placebo - Tio R5	-0.869 (0.849)	(-2.539, 0.801)		0.3069
		Placebo - Salmeterol	0.232 (0.843)	(-1.427, 1.891)		0.7834
		Tio R5 - Salmeterol	1.101 (0.839)	(-0.550, 2.752)		0.1906
	Week 8	Placebo - Tio R5	-0.413 (0.909)	(-2.200, 1.375)		0.6501
		Placebo - Salmeterol	1.713 (0.903)	(-0.063, 3.488)		0.0586
		Tio R5 - Salmeterol	2.125 (0.898)	(0.358, 3.892)		0.0185
	Week 9	Placebo - Tio R5	-1.137 (0.834)	(-2.778, 0.503)		0.1736

Means are adjusted for pooled centre, pre-treatment (treated or not treated with LABA) and baseline.
#: Non-inferiority: Difference is less than 20 litres
°: Non-inferiority: Difference is less than 0.05 litres
Source data: Appendix 16.1.9.2, Statdoc 6.1.1.2.1

Table 15.2.1.1.2: 3 Adjusted weekly means (SE) of AM and PM PEF, PEF variability, and AM and PM FEV1 (treatment differences) - FAS

Endpoint name	Number of week	Comparison	Difference	95% Confidence Interval	P-value (non-inferiority)	P-value (superiority)
Mean PEF variability	Week 9	Placebo - Salmeterol	-0.330 (0.829)	(-1.960, 1.300)		0.6910
		Tio R5 - Salmeterol	0.808 (0.825)	(-0.814, 2.429)		0.3281
	Week 10	Placebo - Tio R5	-1.175 (0.799)	(-2.746, 0.396)		0.1423
		Placebo - Salmeterol	-0.400 (0.793)	(-1.960, 1.161)		0.6148
		Tio R5 - Salmeterol	0.775 (0.790)	(-0.778, 2.328)		0.3270
	Week 11	Placebo - Tio R5	-0.502 (0.834)	(-2.143, 1.139)		0.5479
		Placebo - Salmeterol	0.532 (0.829)	(-1.098, 2.163)		0.5211
		Tio R5 - Salmeterol	1.034 (0.825)	(-0.588, 2.657)		0.2108
	Week 12	Placebo - Tio R5	-0.477 (0.855)	(-2.160, 1.205)		0.5774
		Placebo - Salmeterol	-0.062 (0.850)	(-1.734, 1.609)		0.9415
		Tio R5 - Salmeterol	0.415 (0.846)	(-1.249, 2.078)		0.6242
	Week 13	Placebo - Tio R5	-0.111 (0.856)	(-1.794, 1.573)		0.8970
		Placebo - Salmeterol	0.383 (0.850)	(-1.289, 2.056)		0.6525
		Tio R5 - Salmeterol	0.494 (0.846)	(-1.170, 2.158)		0.5596
	Week 14	Placebo - Tio R5	0.002 (0.876)	(-1.722, 1.726)		0.9982
		Placebo - Salmeterol	0.813 (0.871)	(-0.900, 2.525)		0.3513
		Tio R5 - Salmeterol	0.811 (0.866)	(-0.893, 2.515)		0.3501
	Week 15	Placebo - Tio R5	-0.719 (0.820)	(-2.332, 0.895)		0.3815
		Placebo - Salmeterol	0.315 (0.815)	(-1.287, 1.918)		0.6989
		Tio R5 - Salmeterol	1.034 (0.811)	(-0.561, 2.629)		0.2031
	Week 16	Placebo - Tio R5	0.562 (0.858)	(-1.125, 2.250)		0.5126
		Placebo - Salmeterol	1.512 (0.853)	(-0.165, 3.189)		0.0770
		Tio R5 - Salmeterol	0.950 (0.848)	(-0.719, 2.618)		0.2639

Means are adjusted for pooled centre, pre-treatment (treated or not treated with LABA) and baseline.
#: Non-inferiority: Difference is less than 20 litres
°: Non-inferiority: Difference is less than 0.05 litres
Source data: Appendix 16.1.9.2, Statdoc 6.1.1.2.1

Table 15.2.1.2: 1 Adjusted weekly means (SE) of of asthma symptom free day (treatment means) - FAS

Endpoint name	Number of week	Statistic	Placebo	Tio R5	Salmeterol
Weekly average - Asthma symp free day	Baseline	Mean (SE)	1.403 (0.000)	1.403 (0.000)	1.403 (0.000)
	Week 1	Mean (SE)	1.690 (0.141)	1.708 (0.142)	1.864 (0.135)
	Week 2	Mean (SE)	1.398 (0.143)	1.806 (0.144)	1.761 (0.137)
	Week 3	Mean (SE)	1.411 (0.153)	1.790 (0.155)	2.091 (0.147)
	Week 4	Mean (SE)	1.474 (0.175)	1.641 (0.176)	2.118 (0.168)
	Week 5	Mean (SE)	1.512 (0.173)	1.644 (0.174)	2.187 (0.166)
	Week 6	Mean (SE)	1.473 (0.163)	1.519 (0.165)	1.726 (0.157)
	Week 7	Mean (SE)	1.330 (0.185)	1.772 (0.186)	1.927 (0.178)
	Week 8	Mean (SE)	1.490 (0.190)	2.152 (0.192)	2.258 (0.183)
	Week 9	Mean (SE)	1.652 (0.194)	1.959 (0.196)	2.215 (0.187)
	Week 10	Mean (SE)	1.528 (0.199)	1.963 (0.200)	2.267 (0.191)
	Week 11	Mean (SE)	1.564 (0.194)	1.913 (0.195)	2.435 (0.186)
	Week 12	Mean (SE)	1.410 (0.184)	1.901 (0.185)	2.226 (0.176)
	Week 13	Mean (SE)	1.298 (0.182)	1.712 (0.183)	2.002 (0.175)
	Week 14	Mean (SE)	1.592 (0.200)	1.924 (0.201)	2.343 (0.192)
	Week 15	Mean (SE)	1.611 (0.200)	1.871 (0.202)	2.370 (0.192)
	Week 16	Mean (SE)	1.228 (0.174)	1.336 (0.175)	1.848 (0.167)

Means are adjusted for pooled centre, pre-treatment (treated or not treated with LABA) and baseline.

Source data: Appendix 16.1.9.2, Statdoc 6.1.2.1

Table 15.2.1.2: 2 Adjusted weekly response means (SE) of asthma symptom free day (treatment means) - FAS

Endpoint name	Number of week	Statistic	Placebo	Tio R5	Salmeterol
Weekly average - Asthma symp free day	Baseline	Mean (SE)	0.000 (.)	0.000 (.)	0.000 (.)
	Week 1	Mean (SE)	0.287 (0.141)	0.305 (0.142)	0.461 (0.135)
	Week 2	Mean (SE)	-0.006 (0.143)	0.403 (0.144)	0.358 (0.137)
	Week 3	Mean (SE)	0.008 (0.153)	0.387 (0.155)	0.688 (0.147)
	Week 4	Mean (SE)	0.071 (0.175)	0.237 (0.176)	0.715 (0.168)
	Week 5	Mean (SE)	0.109 (0.173)	0.241 (0.174)	0.784 (0.166)
	Week 6	Mean (SE)	0.069 (0.163)	0.116 (0.165)	0.323 (0.157)
	Week 7	Mean (SE)	-0.073 (0.185)	0.369 (0.186)	0.524 (0.178)
	Week 8	Mean (SE)	0.087 (0.190)	0.749 (0.192)	0.855 (0.183)
	Week 9	Mean (SE)	0.249 (0.194)	0.556 (0.196)	0.812 (0.187)
	Week 10	Mean (SE)	0.125 (0.199)	0.560 (0.200)	0.864 (0.191)
	Week 11	Mean (SE)	0.161 (0.194)	0.510 (0.195)	1.032 (0.186)
	Week 12	Mean (SE)	0.007 (0.184)	0.498 (0.185)	0.823 (0.176)
	Week 13	Mean (SE)	-0.105 (0.182)	0.309 (0.183)	0.599 (0.175)
	Week 14	Mean (SE)	0.189 (0.200)	0.521 (0.201)	0.940 (0.192)
	Week 15	Mean (SE)	0.208 (0.200)	0.468 (0.202)	0.967 (0.192)
	Week 16	Mean (SE)	-0.175 (0.174)	-0.067 (0.175)	0.445 (0.167)

Means are adjusted for pooled centre, pre-treatment (treated or not treated with LABA) and baseline.

Source data: Appendix 16.1.9.2, Statdoc 6.1.2.2

Table 15.2.1.2: 3 Adjusted weekly means (SE) of asthma symptom free day (treatment differences) - FAS

Endpoint name	Number of week	Comparison	Difference	95% Confidence Interval	P-value (superiority)
Weekly average - Asthma symp free day	Baseline	Placebo - Tio R5	0.000 (.)	(. , .)	.
		Placebo - Salmeterol	0.000 (.)	(. , .)	.
		Tio R5 - Salmeterol	0.000 (.)	(. , .)	.
	Week 1	Placebo - Tio R5	-0.018 (0.186)	(-0.384, 0.348)	0.9235
		Placebo - Salmeterol	-0.174 (0.184)	(-0.537, 0.189)	0.3462
		Tio R5 - Salmeterol	-0.156 (0.183)	(-0.515, 0.203)	0.3933
	Week 2	Placebo - Tio R5	-0.409 (0.188)	(-0.779, -.039)	0.0305
		Placebo - Salmeterol	-0.363 (0.186)	(-0.730, 0.003)	0.0522
		Tio R5 - Salmeterol	0.045 (0.185)	(-0.318, 0.409)	0.8064
	Week 3	Placebo - Tio R5	-0.379 (0.202)	(-0.777, 0.018)	0.0615
		Placebo - Salmeterol	-0.680 (0.201)	(-1.075, -.286)	0.0008
		Tio R5 - Salmeterol	-0.301 (0.199)	(-0.692, 0.090)	0.1307
	Week 4	Placebo - Tio R5	-0.166 (0.230)	(-0.619, 0.286)	0.4706
		Placebo - Salmeterol	-0.644 (0.228)	(-1.092, -.195)	0.0051
		Tio R5 - Salmeterol	-0.477 (0.226)	(-0.922, -.033)	0.0354
	Week 5	Placebo - Tio R5	-0.132 (0.228)	(-0.581, 0.317)	0.5636
		Placebo - Salmeterol	-0.675 (0.226)	(-1.120, -.230)	0.0031
		Tio R5 - Salmeterol	-0.543 (0.224)	(-0.984, -.102)	0.0159
	Week 6	Placebo - Tio R5	-0.046 (0.215)	(-0.470, 0.378)	0.8306
		Placebo - Salmeterol	-0.253 (0.214)	(-0.673, 0.167)	0.2371
		Tio R5 - Salmeterol	-0.207 (0.212)	(-0.623, 0.209)	0.3288
	Week 7	Placebo - Tio R5	-0.442 (0.244)	(-0.921, 0.038)	0.0707
		Placebo - Salmeterol	-0.597 (0.242)	(-1.073, -.122)	0.0140
		Tio R5 - Salmeterol	-0.155 (0.239)	(-0.626, 0.315)	0.5168
	Week 8	Placebo - Tio R5	-0.662 (0.251)	(-1.156, -.169)	0.0087
		Placebo - Salmeterol	-0.769 (0.249)	(-1.258, -.279)	0.0022
		Tio R5 - Salmeterol	-0.106 (0.246)	(-0.591, 0.378)	0.6669

Means are adjusted for pooled centre, pre-treatment (treated or not treated with LABA) and baseline.

Table 15.2.1.2: 3 Adjusted weekly means (SE) of asthma symptom free day (treatment differences) - FAS

Endpoint name	Number of week	Comparison	Difference	95% Confidence Interval	P-value (superiority)
Weekly average - Asthma symp free day	Week 9	Placebo - Tio R5	-0.307 (0.256)	(-0.811, 0.197)	0.2313
		Placebo - Salmeterol	-0.563 (0.254)	(-1.063, -.063)	0.0274
		Tio R5 - Salmeterol	-0.256 (0.252)	(-0.750, 0.239)	0.3100
	Week 10	Placebo - Tio R5	-0.435 (0.262)	(-0.950, 0.080)	0.0975
		Placebo - Salmeterol	-0.739 (0.260)	(-1.250, -.229)	0.0047
		Tio R5 - Salmeterol	-0.304 (0.257)	(-0.810, 0.201)	0.2373
	Week 11	Placebo - Tio R5	-0.348 (0.256)	(-0.851, 0.154)	0.1738
		Placebo - Salmeterol	-0.870 (0.253)	(-1.369, -.372)	0.0007
		Tio R5 - Salmeterol	-0.522 (0.251)	(-1.016, -.028)	0.0383
	Week 12	Placebo - Tio R5	-0.491 (0.242)	(-0.967, -.014)	0.0436
		Placebo - Salmeterol	-0.816 (0.240)	(-1.289, -.344)	0.0008
		Tio R5 - Salmeterol	-0.326 (0.238)	(-0.793, 0.142)	0.1721
	Week 13	Placebo - Tio R5	-0.415 (0.240)	(-0.886, 0.057)	0.0846
		Placebo - Salmeterol	-0.705 (0.238)	(-1.172, -.237)	0.0033
		Tio R5 - Salmeterol	-0.290 (0.235)	(-0.753, 0.173)	0.2188
	Week 14	Placebo - Tio R5	-0.332 (0.264)	(-0.851, 0.187)	0.2089
		Placebo - Salmeterol	-0.751 (0.261)	(-1.265, -.237)	0.0043
		Tio R5 - Salmeterol	-0.419 (0.259)	(-0.928, 0.090)	0.1063
	Week 15	Placebo - Tio R5	-0.260 (0.264)	(-0.780, 0.259)	0.3245
		Placebo - Salmeterol	-0.759 (0.262)	(-1.274, -.244)	0.0040
		Tio R5 - Salmeterol	-0.499 (0.259)	(-1.009, 0.011)	0.0551
	Week 16	Placebo - Tio R5	-0.108 (0.230)	(-0.559, 0.344)	0.6389
		Placebo - Salmeterol	-0.620 (0.228)	(-1.068, -.172)	0.0068
		Tio R5 - Salmeterol	-0.512 (0.225)	(-0.955, -.069)	0.0237

Means are adjusted for pooled centre, pre-treatment (treated or not treated with LABA) and baseline.

Table 15.2.1.2: 4 Frequencies of level of athma control (weekly level rates) by treatment - FAS

	Uncontrolled		Partially controlled		Controlled		Total	
	N	(%)	N	(%)	N	(%)	N	(%)
Placebo								
Week 1	125	(100.0)	0	(0.0)	0	(0.0)	125	(100.0)
Week 2	125	(100.0)	0	(0.0)	0	(0.0)	125	(100.0)
Week 3	125	(100.0)	0	(0.0)	0	(0.0)	125	(100.0)
Week 4	125	(100.0)	0	(0.0)	0	(0.0)	125	(100.0)
Week 5	125	(100.0)	0	(0.0)	0	(0.0)	125	(100.0)
Week 6	125	(100.0)	0	(0.0)	0	(0.0)	125	(100.0)
Week 7	125	(100.0)	0	(0.0)	0	(0.0)	125	(100.0)
Week 8	125	(100.0)	0	(0.0)	0	(0.0)	125	(100.0)
Week 9	125	(100.0)	0	(0.0)	0	(0.0)	125	(100.0)
Week 10	125	(100.0)	0	(0.0)	0	(0.0)	125	(100.0)
Week 11	124	(99.2)	1	(0.8)	0	(0.0)	125	(100.0)
Week 12	125	(100.0)	0	(0.0)	0	(0.0)	125	(100.0)
Week 13	125	(100.0)	0	(0.0)	0	(0.0)	125	(100.0)
Week 14	124	(99.2)	1	(0.8)	0	(0.0)	125	(100.0)
Week 15	125	(100.0)	0	(0.0)	0	(0.0)	125	(100.0)
Week 16	125	(100.0)	0	(0.0)	0	(0.0)	125	(100.0)
Tio R5								
Week 1	127	(99.2)	0	(0.0)	1	(0.8)	128	(100.0)
Week 2	128	(100.0)	0	(0.0)	0	(0.0)	128	(100.0)
Week 3	128	(100.0)	0	(0.0)	0	(0.0)	128	(100.0)
Week 4	128	(100.0)	0	(0.0)	0	(0.0)	128	(100.0)
Week 5	127	(99.2)	1	(0.8)	0	(0.0)	128	(100.0)
Week 6	127	(99.2)	1	(0.8)	0	(0.0)	128	(100.0)
Week 7	128	(100.0)	0	(0.0)	0	(0.0)	128	(100.0)
Week 8	128	(100.0)	0	(0.0)	0	(0.0)	128	(100.0)
Week 9	128	(100.0)	0	(0.0)	0	(0.0)	128	(100.0)
Week 10	128	(100.0)	0	(0.0)	0	(0.0)	128	(100.0)
Week 11	128	(100.0)	0	(0.0)	0	(0.0)	128	(100.0)
Week 12	128	(100.0)	0	(0.0)	0	(0.0)	128	(100.0)
Week 13	128	(100.0)	0	(0.0)	0	(0.0)	128	(100.0)
Week 14	128	(100.0)	0	(0.0)	0	(0.0)	128	(100.0)
Week 15	127	(99.2)	1	(0.8)	0	(0.0)	128	(100.0)
Week 16	127	(99.2)	1	(0.8)	0	(0.0)	128	(100.0)

Table 15.2.1.2: 4 Frequencies of level of athma control (weekly level rates) by treatment - FAS

	Uncontrolled		Partially controlled		Controlled		Total	
	N	(%)	N	(%)	N	(%)	N	(%)
Salmeterol								
Week 1	134	(100.0)	0	(0.0)	0	(0.0)	134	(100.0)
Week 2	133	(99.3)	1	(0.7)	0	(0.0)	134	(100.0)
Week 3	134	(100.0)	0	(0.0)	0	(0.0)	134	(100.0)
Week 4	133	(99.3)	1	(0.7)	0	(0.0)	134	(100.0)
Week 5	134	(100.0)	0	(0.0)	0	(0.0)	134	(100.0)
Week 6	134	(100.0)	0	(0.0)	0	(0.0)	134	(100.0)
Week 7	133	(99.3)	1	(0.7)	0	(0.0)	134	(100.0)
Week 8	134	(100.0)	0	(0.0)	0	(0.0)	134	(100.0)
Week 9	134	(100.0)	0	(0.0)	0	(0.0)	134	(100.0)
Week 10	134	(100.0)	0	(0.0)	0	(0.0)	134	(100.0)
Week 11	134	(100.0)	0	(0.0)	0	(0.0)	134	(100.0)
Week 12	134	(100.0)	0	(0.0)	0	(0.0)	134	(100.0)
Week 13	134	(100.0)	0	(0.0)	0	(0.0)	134	(100.0)
Week 14	134	(100.0)	0	(0.0)	0	(0.0)	134	(100.0)
Week 15	134	(100.0)	0	(0.0)	0	(0.0)	134	(100.0)
Week 16	133	(99.3)	1	(0.7)	0	(0.0)	134	(100.0)

Table 15.2.1.3.1: 1 Adjusted mean (SE) FEV1 (Liters) over time (treatment means) - FAS

Visit number	Statistic	Placebo	Tio R5	Salmeterol
Baseline	Mean (SE)	2.395 (0.000)	2.395 (0.000)	2.395 (0.000)
Visit 3	Mean (SE)	2.299 (0.031)	2.471 (0.031)	2.401 (0.030)
Visit 4	Mean (SE)	2.266 (0.031)	2.467 (0.031)	2.442 (0.030)
Visit 5	Mean (SE)	2.290 (0.030)	2.439 (0.030)	2.457 (0.029)

Means are adjusted for pooled centre, pre-treatment (treated or not treated with LABA) and baseline.

Source data: Appendix 16.1.9.2, Statdoc 6.1.3.1

Table 15.2.1.3.2: 2 Adjusted mean (SE) of trough FEV1 response (treatment means) - FAS

Endpoint statistic	Visit number	Statistic	Placebo	Tio R5	Salmeterol
TROUGH	Baseline	Mean (SE)	0.000 (.)	0.000 (.)	0.000 (.)
	Visit 3	Mean (SE)	-0.096 (0.031)	0.076 (0.031)	0.006 (0.030)
	Visit 4	Mean (SE)	-0.129 (0.031)	0.073 (0.031)	0.047 (0.030)
	Visit 5	Mean (SE)	-0.105 (0.030)	0.044 (0.030)	0.062 (0.029)

Means are adjusted for pooled centre, pre-treatment (treated or not treated with LABA) and baseline.

Source data: Appendix 16.1.9.2, Statdoc 6.1.3.4

Table 15.2.1.3.2: 3 Adjusted mean (SE) of trough FEV1 (treatment differences) - FAS

Endpoint statistic	Visit number	Comparison	Difference	95% Confidence Interval	P-value (non-inferiority)	P-value (superiority)
TROUGH	Baseline	Placebo - Tio R5	0.000 (.)	(. , .)		.
		Placebo - Salmeterol	0.000 (.)	(. , .)		.
		Tio R5 - Salmeterol	0.000 (.)	(. , .)	.	.
	Visit 3	Placebo - Tio R5	-0.172 (0.041)	(-0.252, -.092)		<.0001
		Placebo - Salmeterol	-0.102 (0.040)	(-0.182, -.023)		0.0119
		Tio R5 - Salmeterol	0.070 (0.040)	(-0.009, 0.149)	0.0029	0.0808
	Visit 4	Placebo - Tio R5	-0.201 (0.041)	(-0.282, -.121)		<.0001
		Placebo - Salmeterol	-0.176 (0.041)	(-0.256, -.096)		<.0001
		Tio R5 - Salmeterol	0.026 (0.040)	(-0.053, 0.105)	0.0608	0.5252
	Visit 5	Placebo - Tio R5	-0.149 (0.040)	(-0.227, -.071)		0.0002
		Placebo - Salmeterol	-0.167 (0.039)	(-0.244, -.090)		<.0001
		Tio R5 - Salmeterol	-0.018 (0.039)	(-0.094, 0.059)	0.4089	0.6465

Means are adjusted for pooled centre, pre-treatment (treated or not treated with LABA) and baseline.
Non-inferiority: Difference is less than 0.05 litres

Source data: Appendix 16.1.9.2, Statdoc 6.1.3.3

Table 15.2.1.4.1: 1 Adjusted mean (SE) FVC (Liters) over time (treatment means) - FAS

Visit number	Statistic	Placebo	Tio R5	Salmeterol
Baseline	Mean (SE)	3.453 (0.000)	3.453 (0.000)	3.453 (0.000)
Visit 3	Mean (SE)	3.367 (0.034)	3.531 (0.034)	3.441 (0.033)
Visit 4	Mean (SE)	3.307 (0.034)	3.509 (0.035)	3.495 (0.033)
Visit 5	Mean (SE)	3.353 (0.034)	3.488 (0.034)	3.474 (0.033)

Means are adjusted for pooled centre, pre-treatment (treated or not treated with LABA) and baseline.

Source data: Appendix 16.1.9.2, Statdoc 6.1.4.1

Table 15.2.1.4.1: 2 Adjusted mean (SE) FVC response (Liters) over time (treatment means) - FAS

Visit number	Statistic	Placebo	Tio R5	Salmeterol
Baseline	Mean (SE)	0.000 (.)	0.000 (.)	0.000 (.)
Visit 3	Mean (SE)	-0.086 (0.034)	0.078 (0.034)	-0.012 (0.033)
Visit 4	Mean (SE)	-0.146 (0.034)	0.056 (0.035)	0.042 (0.033)
Visit 5	Mean (SE)	-0.100 (0.034)	0.035 (0.034)	0.021 (0.033)

Means are adjusted for pooled centre, pre-treatment (treated or not treated with LABA) and baseline.

Source data: Appendix 16.1.9.2, Statdoc 6.1.4.2

Table 15.2.1.4.1: 3 Adjusted mean (SE) FVC (Liters) over time (treatment differences) - FAS

Visit number	Comparison	Difference	95% Confidence Interval	P-value (non-inferiority)	P-value (superiority)
Baseline	Placebo - Tio R5	0.000 (.)	(. , .)		.
	Placebo - Salmeterol	0.000 (.)	(. , .)		.
	Tio R5 - Salmeterol	0.000 (.)	(. , .)	.	.
Visit 3	Placebo - Tio R5	-0.164 (0.045)	(-0.252, -.075)		0.0003
	Placebo - Salmeterol	-0.074 (0.045)	(-0.161, 0.014)		0.0992
	Tio R5 - Salmeterol	0.090 (0.044)	(0.003, 0.177)	0.0001	0.0423
Visit 4	Placebo - Tio R5	-0.203 (0.045)	(-0.292, -.113)		<.0001
	Placebo - Salmeterol	-0.188 (0.045)	(-0.277, -.100)		<.0001
	Tio R5 - Salmeterol	0.014 (0.045)	(-0.073, 0.102)	0.0349	0.7459
Visit 5	Placebo - Tio R5	-0.135 (0.045)	(-0.223, -.047)		0.0028
	Placebo - Salmeterol	-0.121 (0.044)	(-0.209, -.034)		0.0066
	Tio R5 - Salmeterol	0.013 (0.044)	(-0.073, 0.100)	0.0345	0.7611

Means are adjusted for pooled centre, pre-treatment (treated or not treated with LABA) and baseline.
Non-inferiority): Difference is less than 0.08 litres

Source data: Appendix 16.1.9.2, Statdoc 6.1.4.1

Table 15.2.1.5: 1 Adjusted mean (SE) of MiniAQLQ and domains over time (treatment means) - FAS

Endpoint name	Visit number	Statistic	Placebo	Tio R5	Salmeterol
MiniAQLQ Score	Baseline	Mean (SE)	5.175 (0.000)	5.175 (0.000)	5.175 (0.000)
	Visit 3	Mean (SE)	5.097 (0.067)	5.050 (0.067)	5.259 (0.064)
	Visit 4	Mean (SE)	5.078 (0.066)	5.233 (0.066)	5.399 (0.063)
	Visit 5	Mean (SE)	5.214 (0.067)	5.305 (0.068)	5.454 (0.064)
MiniAQLQ Activity Limitations Domain	Baseline	Mean (SE)	5.477 (0.000)	5.477 (0.000)	5.477 (0.000)
	Visit 3	Mean (SE)	5.425 (0.073)	5.391 (0.074)	5.515 (0.070)
	Visit 4	Mean (SE)	5.438 (0.073)	5.519 (0.073)	5.705 (0.070)
	Visit 5	Mean (SE)	5.550 (0.073)	5.609 (0.074)	5.744 (0.070)
MiniAQLQ Emotional Function Domain	Baseline	Mean (SE)	5.289 (0.000)	5.289 (0.000)	5.289 (0.000)
	Visit 3	Mean (SE)	5.228 (0.091)	5.166 (0.092)	5.438 (0.087)
	Visit 4	Mean (SE)	5.152 (0.093)	5.372 (0.094)	5.533 (0.089)
	Visit 5	Mean (SE)	5.275 (0.090)	5.452 (0.091)	5.602 (0.087)
MiniAQLQ Environmental Stimuli Domain	Baseline	Mean (SE)	4.804 (0.000)	4.804 (0.000)	4.804 (0.000)
	Visit 3	Mean (SE)	4.702 (0.084)	4.724 (0.085)	4.778 (0.081)
	Visit 4	Mean (SE)	4.684 (0.089)	4.924 (0.089)	4.991 (0.085)
	Visit 5	Mean (SE)	4.807 (0.089)	4.928 (0.089)	4.946 (0.085)
MiniAQLQ Symptoms Domain	Baseline	Mean (SE)	5.086 (0.000)	5.086 (0.000)	5.086 (0.000)
	Visit 3	Mean (SE)	5.008 (0.085)	4.928 (0.085)	5.247 (0.081)
	Visit 4	Mean (SE)	5.006 (0.080)	5.143 (0.081)	5.328 (0.077)
	Visit 5	Mean (SE)	5.169 (0.081)	5.228 (0.081)	5.447 (0.077)

Means are adjusted for pooled centre, pre-treatment (treated or not treated with LABA) and baseline.

Source data: Appendix 16.1.9.2, Statdoc 6.1.5.1

Table 15.2.1.5: 2 Adjusted mean (SE) of MiniAQLQ and domains response over time (treatment means) - FAS

Endpoint name	Visit number	Statistic	Placebo	Tio R5	Salmeterol
MiniAQLQ Score	Baseline	Mean (SE)	0.000 (.)	0.000 (.)	0.000 (.)
	Visit 3	Mean (SE)	-0.078 (0.067)	-0.124 (0.067)	0.085 (0.064)
	Visit 4	Mean (SE)	-0.097 (0.066)	0.059 (0.066)	0.224 (0.063)
	Visit 5	Mean (SE)	0.039 (0.067)	0.131 (0.068)	0.280 (0.064)
MiniAQLQ Activity Limitations Domain	Baseline	Mean (SE)	0.000 (.)	0.000 (.)	0.000 (.)
	Visit 3	Mean (SE)	-0.053 (0.073)	-0.087 (0.074)	0.038 (0.070)
	Visit 4	Mean (SE)	-0.039 (0.073)	0.042 (0.073)	0.227 (0.070)
	Visit 5	Mean (SE)	0.073 (0.073)	0.132 (0.074)	0.266 (0.070)
MiniAQLQ Emotional Function Domain	Baseline	Mean (SE)	0.000 (.)	0.000 (.)	0.000 (.)
	Visit 3	Mean (SE)	-0.062 (0.091)	-0.123 (0.092)	0.149 (0.087)
	Visit 4	Mean (SE)	-0.137 (0.093)	0.082 (0.094)	0.244 (0.089)
	Visit 5	Mean (SE)	-0.015 (0.090)	0.163 (0.091)	0.312 (0.087)
MiniAQLQ Environmental Stimuli Domain	Baseline	Mean (SE)	0.000 (.)	0.000 (.)	0.000 (.)
	Visit 3	Mean (SE)	-0.101 (0.084)	-0.080 (0.085)	-0.025 (0.081)
	Visit 4	Mean (SE)	-0.120 (0.089)	0.120 (0.089)	0.187 (0.085)
	Visit 5	Mean (SE)	0.003 (0.089)	0.125 (0.089)	0.142 (0.085)
MiniAQLQ Symptoms Domain	Baseline	Mean (SE)	0.000 (.)	0.000 (.)	0.000 (.)
	Visit 3	Mean (SE)	-0.078 (0.085)	-0.159 (0.085)	0.161 (0.081)
	Visit 4	Mean (SE)	-0.080 (0.080)	0.057 (0.081)	0.241 (0.077)
	Visit 5	Mean (SE)	0.083 (0.081)	0.141 (0.081)	0.361 (0.077)

Means are adjusted for pooled centre, pre-treatment (treated or not treated with LABA) and baseline.

Source data: Appendix 16.1.9.2, Statdoc 6.1.5.2 efficacy\minaq_am.sas 28MAY2009

Table 15.2.1.5: 3 Adjusted mean (SE) of MiniAQLQ and domains over time (treatment differences) - FAS

Endpoint name	Visit number	Comparison	Difference	95% Confidence Interval	P-value (superiority)
MiniAQLQ Score	Baseline	Placebo - Tio R5	0.000 (.)	(. , .)	.
		Placebo - Salmeterol	0.000 (.)	(. , .)	.
		Tio R5 - Salmeterol	0.000 (.)	(. , .)	.
	Visit 3	Placebo - Tio R5	0.047 (0.088)	(-0.126, 0.220)	0.5961
		Placebo - Salmeterol	-0.162 (0.087)	(-0.334, 0.009)	0.0638
		Tio R5 - Salmeterol	-0.209 (0.087)	(-0.379, -.039)	0.0163
	Visit 4	Placebo - Tio R5	-0.155 (0.086)	(-0.325, 0.014)	0.0728
		Placebo - Salmeterol	-0.321 (0.086)	(-0.489, -.152)	0.0002
		Tio R5 - Salmeterol	-0.165 (0.085)	(-0.332, 0.002)	0.0526
	Visit 5	Placebo - Tio R5	-0.091 (0.088)	(-0.265, 0.082)	0.3022
		Placebo - Salmeterol	-0.240 (0.088)	(-0.413, -.068)	0.0064
		Tio R5 - Salmeterol	-0.149 (0.087)	(-0.320, 0.022)	0.0871
MiniAQLQ Activity Limitations Domain	Baseline	Placebo - Tio R5	0.000 (.)	(. , .)	.
		Placebo - Salmeterol	0.000 (.)	(. , .)	.
		Tio R5 - Salmeterol	0.000 (.)	(. , .)	.
	Visit 3	Placebo - Tio R5	0.034 (0.096)	(-0.155, 0.224)	0.7239
		Placebo - Salmeterol	-0.090 (0.096)	(-0.278, 0.098)	0.3459
		Tio R5 - Salmeterol	-0.124 (0.095)	(-0.311, 0.062)	0.1909
	Visit 4	Placebo - Tio R5	-0.081 (0.096)	(-0.269, 0.108)	0.4005
		Placebo - Salmeterol	-0.266 (0.095)	(-0.454, -.079)	0.0054
		Tio R5 - Salmeterol	-0.186 (0.094)	(-0.371, 0.000)	0.0501
	Visit 5	Placebo - Tio R5	-0.059 (0.097)	(-0.249, 0.132)	0.5451
		Placebo - Salmeterol	-0.193 (0.096)	(-0.382, -.004)	0.0449
		Tio R5 - Salmeterol	-0.135 (0.095)	(-0.322, 0.053)	0.1583
MiniAQLQ Emotional Function Domain	Baseline	Placebo - Tio R5	0.000 (.)	(. , .)	.
		Placebo - Salmeterol	0.000 (.)	(. , .)	.

Means are adjusted for pooled centre, pre-treatment (treated or not treated with LABA) and baseline.

Table 15.2.1.5: 3 Adjusted mean (SE) of MiniAQLQ and domains over time (treatment differences) - FAS

Endpoint name	Visit number	Comparison	Difference	95% Confidence Interval	P-value (superiority)
MiniAQLQ Emotional Function Domain	Baseline	Tio R5 - Salmeterol	0.000 (.)	(. , .)	.
	Visit 3	Placebo - Tio R5	0.061 (0.120)	(-0.174, 0.297)	0.6081
		Placebo - Salmeterol	-0.211 (0.119)	(-0.445, 0.023)	0.0774
		Tio R5 - Salmeterol	-0.272 (0.118)	(-0.504, -.040)	0.0216
	Visit 4	Placebo - Tio R5	-0.219 (0.123)	(-0.461, 0.022)	0.0746
		Placebo - Salmeterol	-0.381 (0.122)	(-0.621, -.141)	0.0019
		Tio R5 - Salmeterol	-0.161 (0.121)	(-0.399, 0.076)	0.1820
	Visit 5	Placebo - Tio R5	-0.177 (0.119)	(-0.412, 0.057)	0.1374
		Placebo - Salmeterol	-0.327 (0.118)	(-0.560, -.094)	0.0060
		Tio R5 - Salmeterol	-0.150 (0.117)	(-0.380, 0.081)	0.2023
MiniAQLQ Environmental Stimuli Domain	Baseline	Placebo - Tio R5	0.000 (.)	(. , .)	.
		Placebo - Salmeterol	0.000 (.)	(. , .)	.
		Tio R5 - Salmeterol	0.000 (.)	(. , .)	.
	Visit 3	Placebo - Tio R5	-0.022 (0.111)	(-0.239, 0.196)	0.8456
		Placebo - Salmeterol	-0.076 (0.110)	(-0.293, 0.140)	0.4889
		Tio R5 - Salmeterol	-0.055 (0.109)	(-0.269, 0.159)	0.6158
	Visit 4	Placebo - Tio R5	-0.240 (0.116)	(-0.469, -.012)	0.0395
		Placebo - Salmeterol	-0.307 (0.116)	(-0.535, -.080)	0.0083
		Tio R5 - Salmeterol	-0.067 (0.114)	(-0.292, 0.158)	0.5582
	Visit 5	Placebo - Tio R5	-0.121 (0.116)	(-0.350, 0.108)	0.2993
		Placebo - Salmeterol	-0.139 (0.116)	(-0.367, 0.089)	0.2314
		Tio R5 - Salmeterol	-0.018 (0.115)	(-0.243, 0.208)	0.8763
MiniAQLQ Symptoms Domain	Baseline	Placebo - Tio R5	0.000 (.)	(. , .)	.
		Placebo - Salmeterol	0.000 (.)	(. , .)	.
		Tio R5 - Salmeterol	0.000 (.)	(. , .)	.
	Visit 3	Placebo - Tio R5	0.081 (0.111)	(-0.139, 0.300)	0.4700

Means are adjusted for pooled centre, pre-treatment (treated or not treated with LABA) and baseline.

Table 15.2.1.5: 3 Adjusted mean (SE) of MiniAQLQ and domains over time (treatment differences) - FAS

Endpoint name	Visit number	Comparison	Difference	95% Confidence Interval	P-value (superiority)
MiniAQLQ Symptoms Domain	Visit 3	Placebo - Salmeterol	-0.239 (0.111)	(-0.456, -.022)	0.0313
		Tio R5 - Salmeterol	-0.320 (0.109)	(-0.535, -.104)	0.0037
	Visit 4	Placebo - Tio R5	-0.137 (0.106)	(-0.345, 0.071)	0.1954
		Placebo - Salmeterol	-0.321 (0.105)	(-0.528, -.115)	0.0023
		Tio R5 - Salmeterol	-0.184 (0.104)	(-0.389, 0.020)	0.0769
	Visit 5	Placebo - Tio R5	-0.059 (0.106)	(-0.267, 0.150)	0.5810
		Placebo - Salmeterol	-0.278 (0.105)	(-0.485, -.072)	0.0085
		Tio R5 - Salmeterol	-0.220 (0.104)	(-0.425, -.015)	0.0356

Means are adjusted for pooled centre, pre-treatment (treated or not treated with LABA) and baseline.