

Supplementary Appendix

This appendix has been provided by the authors to give readers additional information about their work.

Supplement to: Price D, Musgrave SD, Shepstone L, et al. Leukotriene antagonists as first-line or add-on asthma-controller therapy. *N Engl J Med* 2011;364:1695-707.

Supplementary Appendix

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FULL STUDY METHODS

The primary funder and sponsor (National Coordinating Centre for Health Technology Assessment UK) had input to the study design through its commissioning and monitoring brief, but no role in data collection, analysis, or interpretation, writing of the article, or the decision to submit the article for publication. Pharmaceutical industry funders had no role in any aspect of the study. The study was designed by DP, LS, EFJ, JGA, SW, HMM, and IH. Data were gathered by DP, SDM, AB, and JM. LS had primary responsibility for analysis, supported by DP, SDM, and EJS. One of the authors (EVH) wrote the first draft of the paper, with review and revision by the other coauthors. All the authors made the decision to submit the manuscript for publication.

Patients

This study comprised two separate 2-year, pragmatic trials that were designed to collect quality of life (QoL) and asthma control data under real-world primary care practice conditions. One trial was a comparison of leukotriene receptor antagonist (LTRA) and inhaled corticosteroid (ICS) for patients initiating asthma controller therapy (first controller trial); the other trial was a comparison of LTRA and long-acting β_2 -agonist (LABA) add-on therapy for patients with uncontrolled asthma while receiving ICS (add-on therapy trial).

Patient eligibility criteria were similar for the two trials, varying only according to whether patients required initiation of controller therapy or a step-up in asthma controller therapy. Male and female patients, 12–80 years of age, with symptoms requiring regular control medication (first controller trial) or who had received an ICS for \geq 12 weeks and

who had symptoms of poorly controlled asthma (add-on therapy trial) were eligible for inclusion. Other eligibility criteria included screening peak expiratory flow (PEF) of >50% predicted after withholding inhaled β_2 agonist for ≥ 4 hours and, at the baseline visit, a score of ≤ 6 points (range, 1–7 with 7 being best) on the validated Mini Asthma Quality of Life Questionnaire (MiniAQLQ)¹ and/or ≥ 1 point (range, 0–6 with 6 being worst) on the validated Asthma Control Questionnaire (ACQ).^{2,3} An additional eligibility criterion was attending physician opinion that initiation of or increase in asthma controller therapy was required.

Patients were excluded if they were experiencing an acute asthma exacerbation, if they had treatment with systemic, intramuscular, or intra-articular corticosteroids within 2 weeks of screening, or if they had a substantial change in anti-asthma medication or other active, acute or chronic pulmonary disorder or unresolved respiratory infection within 12 weeks of screening. Patients were excluded from the first controller trial if they had treatment with an ICS or LTRA within the prior 12 weeks; patients were excluded from the add-on therapy trial if they had received an LTRA or LABA within 12 weeks of screening. Female patients of child-bearing potential agreed to use adequate contraception throughout the study.

Patients meeting initial eligibility criteria completed a validated asthma symptom diary⁴ (morning and evening) for 2 weeks before the baseline visit to capture PEF variability if it existed and for the physician to understand current symptoms. The diagnosis of asthma was made according to usual clinical practice, namely, by one or more of the following criteria: physician diagnosis of asthma, documented reversibility after inhaled short-acting β_2 -agonist, or PEF variability on asthma diary.

The study protocol was reviewed and approved by the Eastern Multi Centre Research Ethics Committee and by local (research consortia and Primary Care Trust) ethical and research governance committees. All patients (and parents or guardians for those under 16 years) gave written informed consent and were allocated a unique study number at screening. The study was supervised by an independent steering committee chaired by a non grant holder.

Study procedure

Practices were recruited through phone calls and mailings, and a total of 53 primary care practices in Norfolk, Suffolk, Essex, Sussex, Cambridgeshire, Bedfordshire, Hampshire, and Dorset, UK, enrolled patients into the study. Patients were recruited 1) through acute and routine respiratory care visits (screening) at which time potentially eligible patients were invited by practice staff to participate in the study and 2) by invitation letter sent by participating primary care practices to all patients aged 12–80 who had been prescribed a short acting bronchodilator (first controller trial) or an ICS (add-on therapy trial) during the prior year.

Patients were recruited from May 2002 to February 2005; the last clinical and QoL data were collected in January 2007. The final analysis was done when all patients had either been treated for 2 years or discontinued from all study procedures.

After screening (week -2) and baseline (week 0) visits, study assessments by telephone or in the clinic were scheduled at months 2, 6, 12, 18, and 24 (□21 days). The timing of the study assessments was designed to coincide with guideline recommended reviews following a change in asthma therapy.

At baseline, clinical history and prior medications were recorded, and patients completed a questionnaires pack that included the MiniAQLQ (primary outcome), the ACQ, the Mini Rhinoconjunctivitis Quality of Life Questionnaire (MiniRQLQ),⁵ and the personal objectives questions (see below). An automated computerized telephone center at the University of East Anglia assigned eligible patients at baseline to randomized treatment with an LTRA or ICS (first controller trial) or an LTRA or LABA (add-on therapy trial). Randomization was stratified by practice, with a block size of 6. Blinding of patients and health-care providers was not possible or desirable, as we were comparing oral and inhaled therapy and our goal was to assess treatment results under conditions of usual care. However, study research assistants, who collected diary cards, data on patient costs, and patient questionnaires, were blinded to treatment allocations.

In both trials, options for the LTRA were montelukast 10 mg once daily (Singulair, Merck Sharp & Dohme Ltd, Hoddesdon, UK) or zafirlukast 20 mg twice daily (Accolate, AstraZeneca UK Ltd, Luton, UK). In the first controller trial, options for ICS included beclomethasone dipropionate, budesonide, or fluticasone propionate. In the add-on therapy trial, randomized treatment assignment, on a background of ICS therapy, was either to add-on LTRA (montelukast or zafirlukast) or add-on LABA, prescribed per licenses, including salmeterol (as Serevent, Allen & Hanburys, Stockley Park, UK) or formoterol (as Foradil, Novartis Pharmaceuticals UK Ltd, Camberley, UK; or Oxis, AstraZeneca UK Ltd). The LABA could be prescribed also as the fixed-dose combination with ICS of fluticasone-salmeterol (Seretide, Allen & Hanburys) or budesonide-formoterol (Symbicort, AstraZeneca UK Ltd).

Approximately 3 to 4 weeks before each follow-up assessment, the questionnaire pack was posted to patients. Completed forms were sent to the main study center. At all follow-up assessments, the clinician administered the Royal College of Physicians 3-item questionnaire (RCP3)^{6,7} and recorded changes in asthma therapy and any adverse experiences; PEF was measured at clinic visits. Practices were asked to provide each patient with a personalized written asthma action plan for dealing with worsening asthma, according to asthma management guidelines, including information on self-treatment and when and how to seek help.

All individual drug and device choices within treatment allocations were made according to normal clinical practice and bearing in mind British asthma guidelines.⁸ Inhaled corticosteroids were permitted after randomization in both treatment arms of the first controller trial; however, patients in the LTRA arm were to be given every chance to manage without ICS, if clinically acceptable. In the add-on therapy trial, health-care providers were asked to prescribe LTRAs and LABAs only within the appropriate treatment arm. Patients were responsible for obtaining their own medications as would occur in real life. Other permitted asthma medications included as-needed inhaled short-acting β 2-agonist, theophylline, cromoglycate, nedocromil, or ipratropium if clinically indicated. In the event of a patient requiring, in the opinion of their primary care physician, a disallowed asthma medication, this fact was noted, the medication was given, and the patient remained in the study. For allergic rhinitis and conjunctivitis, the use of topical rather than systemic preparations was encouraged.

Patients who discontinued from the study continued to receive normal care at their primary care practice. Participating practices received a flat fee of £214.20 (~\$385)

in compensation for administrative time required by the study and an additional payment of £47.60 (~\$85) for each patient randomized, substantially less than standard rates for commercial research. Funding was predominantly from the NHS Health Technology Assessment Programme, which commissioned the research.

Outcome measures

The primary outcome measure was the MiniAQLQ,¹ a 15-item, validated, self-administered asthma-specific QoL questionnaire that measures the functional problems that are most troublesome to patients with asthma. Patients recall their experiences over the previous 2 weeks and respond to each question on a 7-point scale (1 = maximum impairment, 7 = no impairment). The overall score is the mean of the responses to the 15 items. There are four domains (symptoms, activity limitations, emotional function, environmental stimuli). A change in score of 0.5 has been shown to be clinically important (the minimal clinically important difference [MID]) and justifies a change in treatment.⁹

Secondary outcomes included three measures of asthma control: the ACQ, incidence of asthma exacerbations, and Royal College of Physicians 3-item questionnaire (RCP3).^{6,7} The ACQ² measures asthma control as defined by international guidelines (symptoms, activity limitations, bronchodilator use, and airway caliber), with each response scored from 0 (best) to 6, including patient-reported average number of puffs/day of short-acting bronchodilator for the prior week. In this study a shortened version of the ACQ, excluding airway caliber but including reliever treatment usage, was used.³ The ACQ score is the mean response to the 6 questions

(0 = total control, 6 = severe lack of control). The cut-point between adequate and inadequate control is approximately 1.0,¹⁰ and a change in score of 0.5 is the MID.³

The frequency of asthma exacerbations, defined as a course of oral corticosteroid or hospitalization for asthma, was captured by reviewing individual computerized case records. Courses of oral corticosteroids in UK practice are usually provided for a minimum of 5 days. Any two courses prescribed within a 14-day period or two or more consecutive courses issued within 3 days of one course completing and a second being issued were considered a single exacerbation. Physicians were not provided with any specific study-related guidelines on the determination of an asthma exacerbation; however, all physicians taking part in the study were reminded of the British Thoracic Society (BTS) asthma guidelines.⁸

The three questions of the RCP3 questionnaire were developed to evaluate patients' asthma symptoms over the 4 weeks before each asthma consultation.^{6,7} While the RCP3 questionnaire is not yet validated, a small pilot study reported strong correlations between changes in RCP3 and ACQ scores.¹¹

Each patient was also asked at study entry to choose three personal asthma treatment objectives to serve as a supplemental (not validated) outcome measure; then, at each visit, patients rated their ability to achieve these objectives on a visual analogue scale from 0 (not met at all) to 100 (fully met).

Patients also completed the validated 14-item Mini Rhinoconjunctivitis Quality of Life Questionnaire (MiniRQLQ),⁵ which measures the impact of rhinoconjunctivitis on patients' daily functioning. Like the MiniAQLQ, patients respond to each question on a

7-point scale; the overall score is the mean of all responses (0 = no impairment, 6 = maximum impairment), and the MID is 0.7.⁵

Other outcome measures included PEF measured at clinic visits and the frequencies of upper and lower respiratory tract infections and consultations for respiratory tract infection as determined through electronic case record review. Finally, as an exploratory measure in this pragmatic trial, patients were asked to complete the validated asthma diary card⁴ for the 2 weeks preceding each follow-up visit and were contacted by the study office 2 weeks before each visit to remind them to complete the diary. Study questionnaires were mailed to patients before each clinic visit; patients could return them at the clinic or by mail.

In addition, we tabulated any treatment changes from original randomized therapy class including the use of additional classes of asthma therapy. Prescribing data were extracted from patient case records. Adherence to therapy was assessed for patients who had clear treatment instructions and no change in therapy for at least 6 months after randomization.

Safety was assessed by monitoring and recording of adverse events throughout the study and for 14 days after the final visit.

Sample size calculations

Our sample size calculations for assessing treatment equivalence using the MiniAQLQ, made using nQuery Advisor v6.0 (Statistical Solutions, Ltd, Cork Ireland), were based on a published standard deviation of 0.78 for the AQLQ¹² and an equivalence boundary that we set conservatively at 0.3, well within the MID of 0.5 for the MiniAQLQ.⁹ Thus, a

sample size of 142 patients was required for each trial of this equivalence study, assuming no difference between treatments in QoL (two-tailed $\alpha = 0.05$, a power of 90% to declare equivalence, and upper limit of 0.3 for the 95% confidence limit for the difference between arms). Our goal, allowing for a 20% dropout rate, was to recruit 178 patients to each study arm, for a total of 356 patients in each trial.

Statistical methods

Study data collection and statistical analyses were performed by personnel blinded to treatment assignments: questionnaire-based data were collected blind, and routine practice data were extracted using dedicated software (Miquest [<http://www.connectingforhealth.nhs.uk/miquest>] and SQL Suite [Apollo Medical Systems, Sunderland, UK; <http://www.apollo-medical.com/products/sql.htm>]).

We used descriptive statistics to compare baseline patient characteristics and clinical measures. The baseline values of outcome measures were defined as the last values obtained before the start of randomized therapy, while baseline values of asthma diary card measures were defined as the average of all values obtained during the 14 days between screening and baseline visits.

The primary effectiveness analysis was an intention-to-treat (ITT) analysis of the MiniAQLQ score at 2 months (the primary time-point) and 2 years. Analysis of covariance was used, with treatment as a fixed effect, and baseline value as covariate. A 95% confidence interval (CI) for the adjusted difference between mean scores was derived. The study was powered for equivalence in MiniAQLQ score, with equivalence boundary set at a 95% CI of less than 0.3 for the MiniAQLQ score (i.e., equivalence

declared if the 95% CI was wholly included between -0.3 and +0.3). The difference was chosen using an a priori conservative approach based on 0.3 being substantially less than the 0.5 MID for the MiniAQLQ⁹ because of uncertainty of its variability in real-world patients.

Multiple imputation was used where data were missing for the 2-month or 2-year time point and was based on the assumption of a multivariate normal distribution of the MiniAQLQ scores at the follow-up time points.¹³ As monotonicity was not assumed a Monte Carlo Markov Chain approach was used to estimation. The data were assumed to be missing at random (MAR). Ten imputed data sets were constructed. The same analytic approach was used for the ACQ, although statistical analysis of ACQ score, as for other secondary endpoints, was for superiority rather than equivalence. Multiple imputation for missing data was carried out using the MI and MIANALYZE statistical procedures in SAS version 9.1.

We calculated the PEF values as percentage of predicted normal values using the Roberts equation¹⁴ and compared treatment groups at 2 months and 2 years using the Mann-Whitney test. Rates of asthma exacerbations, respiratory tract infections, and consultations for respiratory tract infections were determined using the Wald χ^2 test from the Poisson model. We analyzed other secondary outcome measures using the last observation carried forward (LOCF) for patients with missing follow-up data, including only those with data for at least one post-randomization time point and using an analysis of covariance, including treatment arm and baseline value as covariate.

We tabulated the numbers of patients who had a change in treatment by 2 months and 2 years. We determined adherence by calculating the total quantity of study

medication (LTRA, ICS, and LABA) issued to each patient during the study as a percentage of the amount that should have been consumed over 2 years according to the prescribing instructions (if the patient left the practice or changed randomized therapy, the analyzed time period was truncated accordingly). We compared median adherence between treatment groups using the Mann-Whitney test, capping adherence at 100% as several patients had adherence >100%.

We performed a per protocol analysis of MiniAQLQ and ACQ scores that included patients with data at the eligible time point who remained on randomized therapy but may have had a dose change or alternative drug within randomized treatment class. A second, more strict per protocol analysis included patients who had no possibility of change (thus excluding patients with flexible treatment regimens) or actual change, including any change of dose or formulation, in therapy post-randomization including the final study visit.

Subgroup analyses

We performed four predefined subgroup analyses of MiniAQLQ and ACQ scores at 2 months, comparing results for 1) patients who were current smokers versus non-smokers (ex-smokers excluded); 2) patients with baseline percent predicted PEF <80% versus \geq 80%; 3) patients with a rhinitis diagnosis and on current medication versus those without a rhinitis diagnosis (those with a diagnosis but not on current medication excluded); and 4) patients with baseline PEF reversibility of <15% versus \geq 15%.

A within-group analysis was performed to informally assess any evidence of a differential effect of treatment within subgroups. The unadjusted mean and standard

deviation for MiniAQLQ and ACQ score were examined by arm within subgroup. A general linear model was constructed within each subgroup with arm as a factor and baseline score as a covariate. The effect of treatment arm was compared informally between the subgroups via the difference in means (adjusted for baseline score) between treatment arms. The differences were presented with a 95% CI.

More formal evidence of a differential effect of treatment was assessed using a general linear model with treatment arm and subgroup as factors, baseline MiniAQLQ or ACQ score as a covariate and a treatment arm by subgroup interaction term. A statistically significant interaction term (set at the 5% level) was considered as evidence of a differential treatment effect. To aid interpretation, the general linear model (with interaction term) was used to estimate adjusted means for each treatment arm within subgroup (i.e., the expected means if each subgroup had the same baseline MiniAQLQ or ACQ score) along with a standard error for the estimate.

Natural logarithmic transformations of MiniAQLQ and ACQ scores were used infrequently but where necessary to improve model fit.

All statistical analyses were carried out using SAS version 9.1 and SPSS version 17.0.

RESULTS TEXT NOT INCLUDED IN MAIN PAPER

First controller trial

Of 449 patients who attended a screening visit, 123 were excluded, and 326 patients were randomized to treatment (Fig. E1). The mean (SD) age of those excluded (47 [17]) and those analyzed (45 [16]) were similar; however, the percentage of women among those excluded (65%) was higher than among those analyzed (50%).

Twenty patients were excluded post-randomization, and 13 of the remaining 306 patients (4%) were lost to follow-up. We had post-randomization data for 7 of the 13 lost to follow-up; thus, 300/306 patients (98%) had post-randomization data and were included in the primary effectiveness analyses (see Fig. E1). The per protocol population included 98/145 (68%) patients in the LTRA group and 120/155 (77%) patients in the ICS group; while the strict per protocol population included 65/145 (45%) patients in the LTRA group and 82/155 (53%) patients in the ICS group.

There were no clinically important differences between the two treatment groups at baseline. Although the mean age was slightly higher in the LTRA group (47.6 vs. 44.1 years), the numbers of patients over 75 years were similar, namely four in the LTRA group and three in the ICS group. Current smoking was more common among patients randomized to LTRA than to ICS (25% versus 19%, respectively), while never-smoking was less common (38% versus 46%, respectively).

The majority of patients randomized to treatment met both MiniAQLQ and ACQ score eligibility criteria (292/326, 90%), while 5 and 9 patients remained eligible on the basis of only MiniAQLQ or ACQ score, respectively. The mean percent predicted PEF was 85–86% in the two groups with ~9% reversibility in both groups. On the RCP3,

most patients reported daytime symptoms (125/135 [93%] and 142/151 [94%] in LTRA and ICS groups, respectively); more than half reported difficulty with sleep (79/137 [58%] and 86/153 [56%], respectively); and almost half reported that asthma interfered with their activities (65/134 [49%] and 74/150 [49%], respectively).

During the study, one serious reaction (increase in epileptic seizure frequency) was thought by the health-care provider to be related to montelukast treatment; the patient discontinued treatment and recovered. Disturbed sleep, headache, and an unidentified adverse reaction were each reported by one patient receiving montelukast; only the patient with headache discontinued treatment, and all patients recovered. Two patients receiving beclomethasone reported a total of three adverse reactions, including cough, breathlessness, and symptoms of esophagitis, each reported once; only the patient with esophagitis discontinued treatment, and both patients recovered.

Add-on therapy trial

The mean age of 121 patients excluded at screening and those randomized was the same (50 yrs). The excluded population had a somewhat higher percentage of male patients (44% vs. 38%).

Secondary to an error in how the block randomization calls were performed at one practice, 9 more patients were randomized to LABA (185) than to LTRA (176); however, there was no prior or biasing knowledge of the allocation on the part of the nurse performing the randomization.

Nine patients were excluded post-randomization (Fig. E2). Twelve of the remaining 352 patients were lost to follow-up; however, post-randomization data were

available for 10 of these 12 and thus a total of 350 patients were included in the primary ITT analysis, including 169 and 181 in LTRA and LABA groups, respectively. The per protocol population included 121/169 (72%) patients in the LTRA group and 176/181 (97%) patients in the LABA group; while the strict per protocol patients numbered 60/169 (36%) and 80/181 (44%), respectively, at study end.

At baseline, most patients (339/352, or 96%) met both ACQ and MiniAQLQ score eligibility criteria, with a minority meeting only ACQ (10/352, 3%) or MiniAQLQ (3/352, or 1%) score. There were no clinically relevant differences between the two treatment groups. No patients were under 16 years of age (Table 1), and only 18 were over 75 years (10 in LTRA group and 8 in LABA group). On the RCP3, with reference to the prior 4 weeks, 90% of patients overall reported daytime asthma symptoms, 50% reported difficulty sleeping because of asthma symptoms, and 46% reported that asthma had interfered with their usual activities.

Diary cards were completed by approximately 65% of patients at 2 months and 50% at 2 years (Tables E22–E24 for baseline and study diary card results). There were no significant differences between treatment groups in symptom scores at any time point. At 2 months, compared with those receiving LABA, patients in the LTRA group had significantly lower morning (399 vs. 419 L/min for LTRA vs. LABA, respectively) and evening (402 vs. 425 L/min) domiciliary PEF and required significantly more daytime (2.45 vs. 1.67) and night-time (0.91 vs. 0.60) puffs of short-acting β 2 agonist (online Table E23). By 2 years, the only significant difference between the two treatment groups was lower morning PEF for patients receiving LTRA (396 vs. 420 L/min in LTRA group; online Table E24).

Eleven patients reported a total of 13 adverse reactions to montelukast, none of them a serious adverse reaction. Disturbed sleep was reported by three patients, headache and lethargy were each reported by two patients, and bloating, swollen fingers, dry cough, mild altered mental status were each reported by one patient; the nature of two adverse reactions was not recorded. Two patients reported a total of four adverse reactions to salmeterol: one each palpitations and tingling in the arms, and the nature of two adverse reactions was not recorded. All other adverse reactions reported were consistent with the manufacturer's product information, and all patients recovered from the adverse reactions.

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Figure E1. Study Recruitment and Follow-up: First Controller Trial.

ACQ denotes Asthma Control Questionnaire, COPD chronic obstructive pulmonary disease, MiniAQLQ Mini Asthma Quality of Life Questionnaire

[figure pasted on next page]

Figure E1

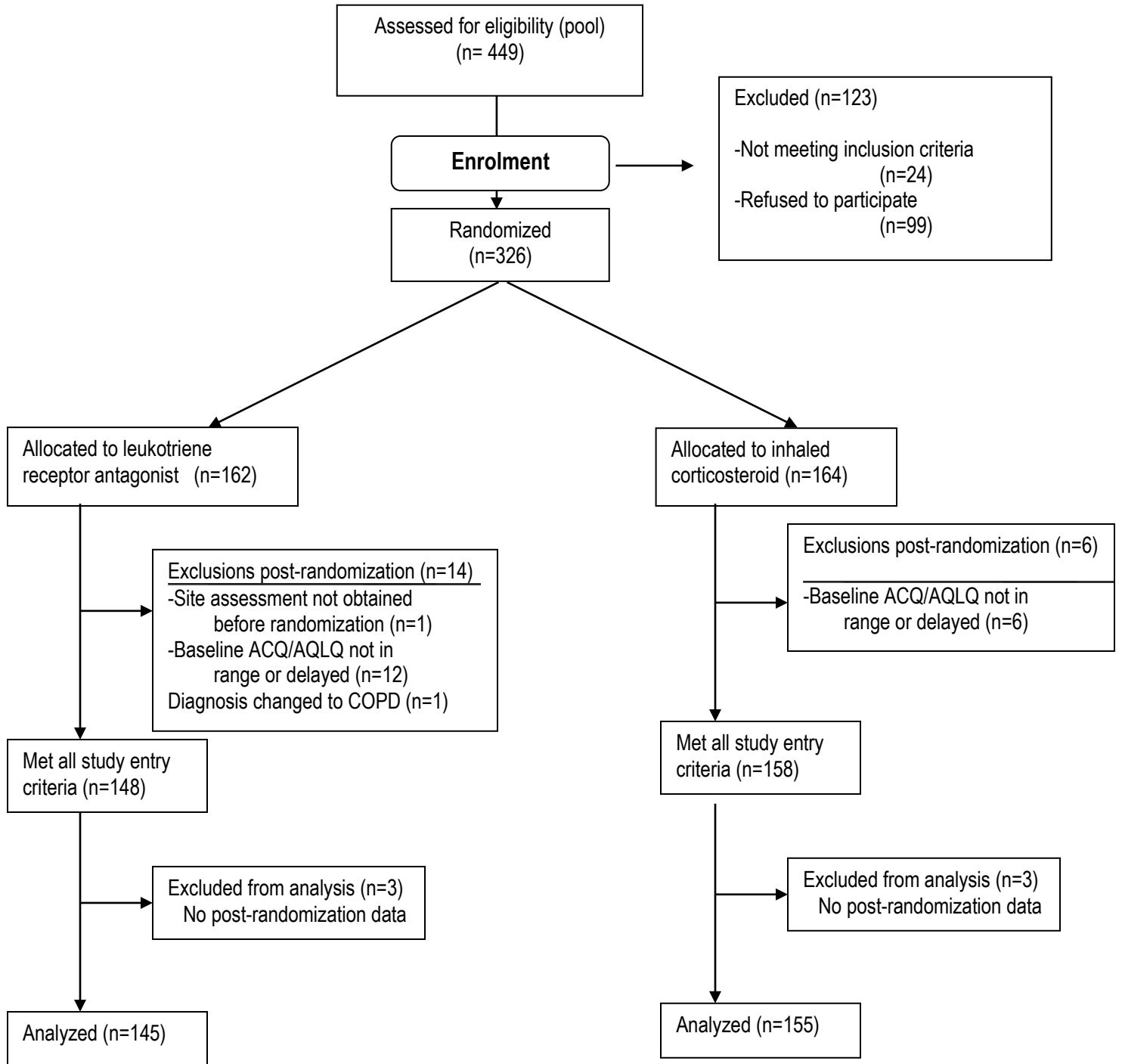
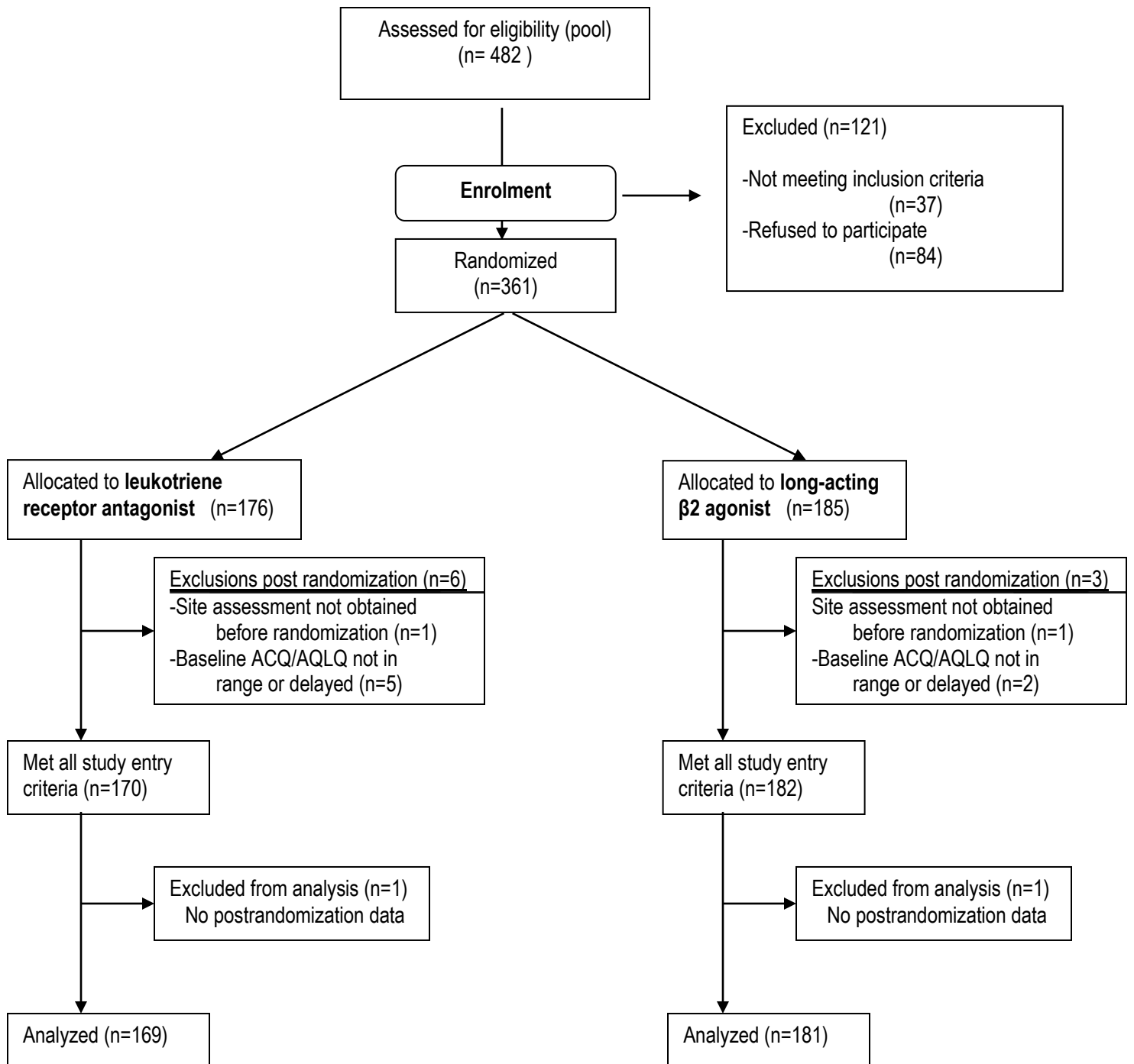


Figure E2. Study Recruitment and Follow-up: Add-On Therapy Trial.

ACQ denotes Asthma Control Questionnaire, MiniAQLQ Mini Asthma Quality of Life Questionnaire.

[figure pasted on next page]

Figure E2.



Supplementary tables

Appendix Table E1. First Controller Trial: Secondary Outcome Measures at 2 Months and 2 Years

	Leukotriene Antagonist		Inhaled Corticosteroid		Adjusted Difference*	
	<i>n</i>	Mean ±SD	<i>n</i>	Mean ±SD	(95%CI)	P Value
RCP3 score						
Baseline	133	2.07±0.81	146	2.06±0.79		
2 months	123	1.21±0.96	139	1.37±1.06	-0.13 (-0.38 to 0.12)	0.32
2 years†	147	1.23±0.99	155	1.14±0.98	0.11 (-0.12 to 0.34)	0.36
Personal objectives‡						
Baseline	99	43±18	118	39±18		
2 months	82	55±22	90	50±23	2 (-5 to 9)	0.50
2 years†	97	67±21	107	69±19	-5 (-11 to 2)	0.14
MiniRQLQ score:						
Baseline	113	1.58±1.29	131	1.78±1.35		
2 months	114	1.48±1.15	124	1.55±1.20	0.07 (-0.35 to 0.21)	0.64
2 years†	145	1.26±1.23	152	1.26±1.28	0.02 (-0.27 to 0.31)	0.90
PEF %pred -- median (IQR)						
Baseline	134	86.0 (77.4–94.2)	150	85.1 (73.9–95.4)		
2 months	98	88.2 (80.1–97.9)	106	86.6 (75.4–97.2)	--	0.23

2 yearst	100	88.8 (81.9–100.0)	112	87.6 (76.1–99.6)	--	0.20
					Rate Ratio§ (95%CI)	
Respiratory tract infections	148	1.01±1.68	158	1.06±1.57	0.95 (0.70 to 1.30)	0.76
Patients who had 1 – no. (%)		37 (25%)		37 (23%)		
Patients who had >1 – no. (%)		33 (22%)		42 (27%)		
Consultations for RTI	148	1.23±2.12	158	1.20±1.82	1.02 (0.74 to 1.41)	0.89
Patients who had 1 – no. (%)		33 (22%)		36 (23%)		
Patients who had >1 – no. (%)		37 (25%)		43 (27%)		

Plus-minus values are means ±SD. P value is for the comparison between treatment groups.

*Adjusted for baseline values.

†Last observation carried forward.

‡For personal objectives, the visual analogue scale ranged from 0 (not met at all) to 100 (fully met).

§Rate ratio from a Poisson model with treatment group as the sole explanatory variable.

IQR denotes interquartile range, MiniRQLQ Mini Rhinoconjunctivitis Quality of Life Questionnaire (scored from 0 best to 6 worst),

PEF %pred peak expiratory flow %predicted, RCP3 Royal College of Physicians 3-item questionnaire (scored from 0 best to 3

worst), RTI respiratory tract infection.

Appendix Table E2. First Controller Trial: Mini Asthma Quality of Life

Questionnaire Domain Scores at Baseline, 2 Months, and 2 Years

		Leukotriene Antagonist (N=82)	Inhaled Corticosteroid (N=96)
Symptoms domain			
	Baseline	4.66 (4.42 to 4.89)	4.53 (4.30 to 4.75)
	2 months	5.19 (4.93 to 5.45)	5.23 (4.98 to 5.48)
	2 years*	5.41 (5.14 to 5.69)	5.61 (5.35 to 5.87)
Activity domain			
	Baseline	5.36 (5.12 to 5.61)	5.18 (4.95 to 5.41)
	2 months	5.70 (5.43 to 5.97)	5.67 (5.42 to 5.91)
	2 years*	5.97 (5.71 to 6.23)	6.14 (5.91 to 6.37)
Environment domain			
	Baseline	5.00 (4.70 to 5.30)	4.60 (4.36 to 4.84)
	2 months	5.26 (4.98 to 5.55)	4.88 (4.57 to 5.18)
	2 years*	5.22 (4.86 to 5.57)	5.29 (4.97 to 5.61)
Emotions domain			
	Baseline	4.67 (4.35 to 5.00)	4.72 (4.45 to 4.99)
	2 months	5.33 (5.01 to 5.65)	5.23 (4.94 to 5.51)
	2 years*	5.49 (5.17 to 5.81)	5.72 (5.42 to 6.02)

Data are mean (95% CI).

*18-month data were carried forward when 2-year data were missing. There were no significant differences between treatment groups at any time point ($P>0.10$ for all).

Appendix Table E3. Change in Asthma Control Questionnaire (ACQ) Score for Question 6 from Baseline to Last Follow-Up Data (Last Value Minus Baseline)

	First Controller Trial		Add-On Therapy Trial	
	LTRA	ICS	LTRA	LABA
	(N=143)	(N=155)	(N=169)	(N=181)
Change in ACQ score, median	-1.0	-1.0	-1.0	-1.0
Semi-interquartile range	0.5	1.0	1.0	1.0
P value† (change from baseline to last data)	<0.0001	<0.0001	<0.0001	<0.0001

*P value =0.688 in first controller study and =0.620 in add-on therapy trial for between-group comparison by Wilcoxon 2-sample test. ICS denotes inhaled corticosteroid, LABA, long-acting β_2 -agonist, LTRA leukotriene receptor antagonist.

†within-group comparison by Wilcoxon one-sample test

Appendix Table E4. First Controller Trial: Asthma Control at 2 Months and 2 Years, Post Hoc Per Protocol

Population with No Change in Randomized Treatment Arm

Outcome Measure	Leukotriene Antagonist		Inhaled Corticosteroid		Mean Difference (95% CI)	Adjusted Mean
	<i>n</i>	Mean (SD)	<i>n</i>	Mean (SD)		Difference* (95% CI)
ACQ score:						
Baseline						
2 months	116	1.51 (0.93)	127	1.49 (0.98)	0.02 (-0.23 to 0.26)	0.02 (-0.21 to 0.24)
2 years	98	1.15 (0.96)	119	1.08 (0.90)	0.07 (-0.18 to 0.32)	0.09 (-0.12 to 0.29)

ACQ denotes Asthma Control Questionnaire, scored from 0 (best) to 6 (worst).

*Adjusted for baseline values.

Appendix Table E5. First Controller Trial: Baseline Characteristics of the Predefined Strict Per Protocol Population (Patients with No Change, However Minor, in Therapy)

	Leukotriene Antagonist (N=65)		Inhaled Corticosteroid (N=82)	
	<i>n</i>		<i>n</i>	
Age (years)	65	45.7 (17.1)	82	41.8 (16.0)
Sex (female)	65	28 (43%)	82	36 (44%)
Smoking habit	65		81	
Current smoker		17 (26%)		17 (21%)
Ex-smoker		20 (31%)		21 (26%)
Never smoked		28 (43%)		43 (53%)
Peak expiratory flow, %predicted	58	83.0 (75.0 to 90.5)	78	83.6 (73.1 to 92.1)
RCP3 score	59	1.83 (0.83)	76	2.11 (0.09)
Personal objectives (0–100 VAS)*	28	42 (19)	57	38 (2)
Mini RQLQ score	51	1.71 (1.14)	62	1.92 (0.17)

Data are *n* (%) or mean (SD), except PEF %predicted, which is median (interquartile range). MiniRQLQ denotes Mini Rhinoconjunctivitis Quality of Life Questionnaire, scored from 0 (best) to 6 (worst), RCP3 Royal College of Physicians 3-item questionnaire, scored from 0 (best) to 3 (worst), VAS visual analogue scale.

*For personal objectives, the visual analogue scale ranged from 0 (not met at all) to 100 (fully met).

Appendix Table E6. First Controller Trial: Asthma-Related Quality of Life and Asthma Control at 2 Months and 2 Years, Strict Per Protocol Population

Outcome Measure	Leukotriene Antagonist		Inhaled Corticosteroid		Mean Difference (95% CI)	Adjusted Mean Difference* (95% CI)
	<i>n</i>	Mean (SD)	<i>n</i>	Mean (SD)		
MiniAQLQ score:						
Baseline	65	4.78 (0.86)	82	4.65 (0.97)	--	--
2 months	57	5.47 (0.98)	66	5.35 (1.03)	0.12 (-0.24 to 0.48)	0.14 (-0.15 to 0.44)
2 years†	64	5.80 (1.04)	79	5.70 (1.18)	0.10 (-0.27 to 0.47)	0.05 (-0.28 to 0.37)
ACQ score:						
Baseline	65	1.92 (0.68)	82	2.07 (0.85)		
2 months	57	1.34 (0.85)	66	1.45 (0.99)	-0.12 (-0.45 to 0.21)	-0.10 (-0.38 to 0.19)
2 years†	64	0.97 (0.85)	79	1.12 (0.93)	-0.15 (-0.45 to 0.15)	-0.08 (-0.35 to 0.19)

*Adjusted for baseline values.

†Last observation carried forward.

ACQ denotes Asthma Control Questionnaire, scored from 0 (best) to 6 (worst), MiniAQLQ Mini Asthma Quality of Life Questionnaire, scored from 1 (worst) to 7 (best).

Appendix Table E7. First Controller Trial: Secondary Outcome Measures at 2 Months and 2 Years, Strict Per Protocol Population

	Leukotriene Antagonist		Inhaled Corticosteroid		Adjusted	P Value
	<i>n</i>	Mean (SD)	<i>n</i>	Mean (SD)	Difference* (95%CI)	
RCP3 score						
2 months	62	1.02 (0.95)	67	1.22 (0.92)	-0.18 (-0.56 to 0.20)	0.345
2 years	64	0.42 (0.69)	78	0.42 (0.71)	-0.14 (-0.46 to 0.18)	0.386
Personal objectives (VAS)						
2 months	45	61 (21)	30	54 (22)	6 (-5 to 18)	0.279
2 years	36	75 (16)	56	72 (18)	3 (-6 to 12)	0.395
MiniRQLQ score:						
2 months	50	1.31 (1.03)	60	1.53 (1.14)	-0.19 (-0.56 to 0.17)	0.297
2 years	64	1.09 (1.15)	76	1.22 (1.26)	0.00 (-0.45 to 0.44)	0.991
PEF %pred, median (IQR)						
2 months	46	88.3 (77.8 to 95.7)	51	87.6 (80.2 to 97.6)		0.942
2 years	42	91.3 (83.4 to 100.4)	55	85.8 (77.5 to 96.9)		0.058

Data are mean (SD) unless otherwise noted. P value is for the comparison between treatment groups.

*Adjusted for baseline values. IQR denotes interquartile range, MiniRQLQ Mini Rhinoconjunctivitis Quality of Life Questionnaire, PEF %pred peak expiratory flow %predicted, RCP3 Royal College of Physicians 3-item questionnaire, VAS visual analogue scale, 0–100.

Appendix Table E8. First Controller Trial: Secondary Outcome Measures at 2 Years, Strict Per Protocol

Population

	Leukotriene Antagonist		Inhaled Corticosteroid		Rate Ratio* (95%CI)	P value
	<i>n</i>		<i>n</i>			
Asthma exacerbations	65	0.20 (0.47)	82	0.15 (0.45)	1.37 (0.71 to 2.63)	0.352
Patients who had 1, n (%)		9 (14%)		6 (7%)		
Patients who had >1, n (%)		2 (3%)		3 (4%)		
Respiratory tract infections	65	0.91 (1.66)	82	0.91 (1.22)	0.99 (0.62 to 1.56)	0.975
Patients who had 1, n (%)		11 (17%)		20 (24%)		
Patients who had >1, n (%)		14 (21%)		20 (24%)		
Consultations for RTI	65	1.18 (2.28)	82	1.05 (1.53)	1.12 (0.69 to 1.82)	0.621
Patients who had 1, n (%)		10 (16%)		20 (24%)		
Patients who had >1, n (%)		15 (22%)		20 (24%)		

Data are mean (SD) unless otherwise noted. P value is for the comparison between treatment groups.

*From a Poisson model with treatment group as the sole explanatory variable. RTI denotes respiratory tract infection.

Appendix Table E9. First Controller Trial: Baseline Diary Card Symptom Scores, Peak Expiratory Flow, and Reliever Usage

	Leukotriene			
	Antagonist (N=148)		Inhaled Corticosteroid (N=158)	
	<i>n</i>		<i>n</i>	
Morning waking with symptoms	129	0.48 (0.36)	147	0.48 (0.34)
Puffs of reliever at night	125	0.78 (0.88)	141	0.99 (1.37)
Morning PEF, L/min	127	408.9 (99.1)	146	402.5 (100.2)
Daytime asthma symptom score*	129	1.88 (1.18)	145	1.81 (1.29)
Score for daytime 'bother from asthma symptoms'*	128	1.63 (1.18)	145	1.48 (1.23)
Daily activity score†	126	2.68 (1.12)	145	2.38 (1.27)
Score for interference on activities from asthma*	128	1.38 (1.24)	147	1.28 (1.33)
Puffs of reliever during the day	126	2.26 (1.67)	145	2.18 (1.99)
Evening PEF, L/min	127	420.6 (101.1)	147	413.9 (103.0)
Diurnal variation in PEF, %	127	7.1 (4.8)	147	7.7 (5.4)

Data are mean (SD). PEF denotes peak expiratory flow.

*scored from 0 = none to 6=all of the time or severely bothered.

†scored from 0=more exercise than normal to 6=less than usual.

Appendix Table E10. First Controller Trial: Diary Card Results at 2 Months

	Leukotriene		Inhaled		Difference (95% CI)	Adjusted Difference* (95% CI)
	Antagonist		Corticosteroid			
	(N=148)		(N=158)			
	<i>n</i>	Mean (SD)	<i>n</i>	Mean (SD)		
Morning waking with symptoms	76	0.29 (0.33)	81	0.29 (0.32)	-0.01 (-0.11 to 0.09)	0.01 (-0.08 to 0.10)
Puffs of reliever at night, original scale	69	0.67 (0.90)	73	0.77 (1.19)	-0.11	
Puffs of reliever at night, log scale	69	0.39 (0.47)	73	0.42 (0.51)	-0.03 (-0.19 to 0.14)	-0.01 (-0.16 to 0.13)
Morning PEF, L/min	74	417.0 (99.1)	81	419.4 (111.2)	-2.4 (-35.9 to 31.2)	-3.4 (-14.8 to 8.0)
Daytime asthma symptom score†	75	1.26 (1.12)	80	1.34 (1.14)	-0.08 (-0.44 to 0.28)	-0.08 (-0.40 to 0.25)
Score for daytime 'bother from asthma symptoms'†	75	1.10 (1.08)	80	1.14 (1.08)	-0.04 (-0.39 to 0.30)	-0.09 (-0.39 to 0.21)
Daily activity score‡	74	2.38 (1.21)	79	2.26 (1.32)	0.12 (-0.28 to 0.53)	0.02 (-0.35 to 0.38)
Score for interference on activities from asthma‡	75	0.96 (1.11)	80	1.08 (1.13)	-0.13 (-0.48 to 0.23)	-0.20 (-0.52 to 0.11)
Puffs of reliever during the day, original scale	70	1.57 (1.67)	78	1.42 (1.49)	0.15	
Puffs of reliever during the day, log scale	70	0.76 (0.60)	78	0.72 (0.56)	0.04 (-0.15 to 0.23)	0.03 (-0.14 to 0.20)
Evening PEF, L/min	74	426.9 (100.3)	81	423.7 (112.0)	3.3 (-30.6 to 37.1)	-2.4 (-13.0 to 8.2)

PEF diurnal variability, %	74	5.8 (4.3)	81	6.2 (4.4)	-0.4 (-1.8 to 0.9)	-0.3 (-1.7 to 1.0)
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*Adjusted for baseline values.

†scored from 0 = none to 6=all of the time or severely bothered.

‡scored from 0=more exercise than normal to 6=less than usual. PEF denotes peak expiratory flow. There were no significant differences between treatment groups.

Appendix Table E11. First Controller Trial: Diary Card Results at 2 Years

	Leukotriene		Inhaled		Difference (95% CI)	Adjusted Difference* (95% CI)
	Antagonist		Corticosteroid			
	(N=148)		(N=158)			
	<i>n</i>	Mean (SD)	<i>n</i>	Mean (SD)		
Morning waking with symptoms	47	0.31 (0.34)	57	0.21 (0.29)	0.10 (-0.02 to 0.23)	0.11 (-0.01 to 0.23)
Puffs of reliever at night, original scale	45	0.52 (0.79)	52	0.48 (0.96)	0.05	
Puffs of reliever at night, log scale	45	0.33 (0.41)	52	0.28 (0.42)	0.05 (-0.12 to 0.22)	0.03 (-0.14 to 0.21)
Morning PEF, L/min	47	412.4 (102.6)	54	419.2 (137.8)	-6.77 (-55.3 to 41.8)	-21.5 (-50.5 to 7.6)
Daytime asthma symptom score†	47	1.43 (1.15)	55	1.16 (1.21)	0.27 (-0.20 to 0.73)	0.12 (-0.31 to 0.55)
Score for daytime 'bother from asthma symptoms'†	47	1.24 (1.15)	56	1.14 (1.39)	0.11 (-0.37 to 0.61)	-0.01(-0.43 to 0.41)
Daily activity score‡	47	2.22 (1.37)	56	2.07 (1.44)	0.15 (-0.40 to 0.71)	0.02 (-0.57 to 0.62)
Score for interference on activities from asthma‡	47	1.08 (1.16)	55	0.88 (1.26)	0.19 (-0.29 to 0.67)	0.01 (-0.41 to 0.43)
Puffs of reliever during the day, original scale	45	1.67 (1.70)	56	1.24 (1.42)	0.43	
Puffs of reliever during the day, log scale	45	0.80 (0.60)	56	0.64 (0.57)	0.16 (-0.07 to 0.39)	0.16 (-0.07 to 0.38)
Evening PEF, L/min	46	419.6 (104.7)	57	408.8 (129.8)	10.8 (-36.1 to 57.7)	-12.5 (-37.6 to 12.5)

PEF diurnal variability, %	37	4.4 (3.4)	44	4.6 (3.0)	-0.1 (-1.6 to 1.3)	-0.2 (-1.7 to 1.2)
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*Adjusted for baseline values.

†scored from 0 = none to 6=all of the time or severely bothered.

‡scored from 0=more exercise than normal to 6=less than usual. PEF denotes peak expiratory flow. There were no significant differences between treatment groups.

Appendix Table E12. First Controller Trial: Subgroup Analyses: Unadjusted Asthma-Related Quality of Life and Asthma Control Scores at 2 Months

		Leukotriene Antagonist		Inhaled Corticosteroid	
		<i>n</i>	Mean (SD)	<i>n</i>	Mean (SD)
<i>Smoking*</i>					
MiniAQLQ	Smokers	24	5.55 (0.97)	22	5.12 (1.07)
	Nonsmokers	48	5.37 (0.91)	61	5.64 (1.02)
ACQ	Smokers	24	1.46 (0.94)	22	1.88 (0.94)
	Nonsmokers	48	1.48 (0.96)	61	1.24 (1.03)
<i>PEF %predicted</i>					
MiniAQLQ	PEF <80%	29	5.04 (1.07)	46	5.24 (1.06)
	PEF ≥80%	76	5.30 (1.02)	77	5.44 (1.04)
ACQ	PEF <80%	29	1.67 (0.78)	46	1.69 (1.03)
	PEF ≥80%	76	1.46 (0.98)	77	1.36 (0.95)
<i>Rhinitis</i>					
MiniAQLQ	Yes	14	5.30 (0.66)	24	5.28 (1.04)
	No	70	5.35 (1.08)	71	5.40 (0.97)
ACQ	Yes	14	1.52 (0.84)	24	1.44 (0.96)
	No	70	1.49 (0.99)	71	1.48 (0.95)
<i>PEF Reversibility</i>					
MiniAQLQ	<15%	86	5.25 (1.03)	92	5.30 (1.04)
	≥15%	15	5.40 (0.74)	24	5.64 (1.07)
ACQ	<15%	86	1.52 (0.94)	92	1.47 (0.96)
	≥15%	15	1.38 (0.64)	24	1.40 (1.19)

Subgroup analyses excluded any patients with change in medication or who were missing outcomes data at 2 months.

*Current smokers versus nonsmokers (ex-smokers excluded). ACQ denotes Asthma Control Questionnaire, MiniAQLQ Mini Asthma Quality of Life Questionnaire, PEF peak expiratory flow.

Appendix Table E13. First Controller Trial: Subgroup Analyses: Results for General Linear Models Within Groups and For Groups Combined at 2 Months

		MiniAQLQ		ACQ	
		Adjusted		Adjusted Difference	
Parameter		Difference in Means (95% CI)	P value	in Means (95% CI)	P value
Smoking					
<i>Within Group GLM</i>					
Smokers:	Arm (LTRA-ICS)	0.23 (-0.22, 0.69)	0.310	-0.27 (-0.73, 0.19)	0.237
Nonsmokers:	Arm (LTRA-ICS)	-0.15 (-0.48, 0.17)	0.359	0.24 (-0.12, 0.59)	0.180
<i>Combined Groups</i>					
	Smoking Status (Smokers-Nonsmokers)	-0.08 (-0.37, 0.21)	0.577	0.21 (-0.11, 0.54)	0.184
	Arm (LTRA-ICS)	0.05 (-0.24, 0.33)	0.742	-0.04 (-0.35, 0.28)	0.820
	Interaction (Smoking*Arm)	-	0.183	-	0.076
Lung Function					
<i>Within Group GLM</i>					
PEF <80%:	Arm (LTRA-ICS)	0.10 (-0.30, 0.49)	0.628	-0.11 (-0.52, 0.30)	0.599
PEF ≥80%:	Arm (LTRA-ICS)	-0.18 (-0.47, 0.12)	0.239	0.13 (-0.15, 0.41)	0.369
<i>Combined Groups</i>					
	PEF (<80% - ≥80%)	-0.09 (-0.34, 0.16)	0.482	0.15 (-0.11, 0.40)	0.263

	Arm (LTRA-ICS)	-0.06 (-0.31, 0.19)	0.630	0.01 (-0.25, 0.26)	0.961
	Interaction (PEF*Arm)	-	0.357	-	0.359
Rhinitis					
<i>Within Group GLM</i>					
	Rhinitis: Arm (LTRA-ICS)	0.01 (-0.57, 0.59)	0.965	0.16 (-0.36, 0.67)	0.539
	Non-Rhinitis: Arm (LTRA-ICS)	0.03 (-0.25, 0.30)	0.860	-0.05 (-0.36, 0.26)	0.746
<i>Combined Groups</i>					
	Rhinitis Status (Rhinitis- Non-Rhinitis)	0.12 (-0.20, 0.43)	0.648	-0.10 (-0.43, 0.24)	0.559
	Arm (LTRA-ICS)	0.01 (-0.31, 0.32)	0.974	0.04 (-0.29, 0.37)	0.805
	Interaction (Rhinitis*Arm)	-	0.942	-	0.568
PEF Reversibility					
<i>Within Group GLM</i>					
	< 15%: Arm (LTRA-ICS)	-0.10 (-0.35, 0.16)	0.469	0.06 (-0.19, 0.31)	0.629
	≥ 15%: Arm (LTRA-ICS)	-0.00 (-0.58, 0.57)	0.988	-0.17 (-0.87, 0.54)	0.638
<i>Combined Groups</i>					
	Reversibility (<15% - ≥15%)	-0.19 (-0.50, 0.12)	0.219	0.24 (-0.06, 0.55)	0.121
	Arm (LTRA-ICS)	-0.03 (-0.34, 0.27)	0.828	-0.00 (-0.31, 0.31)	0.984
	Interaction (Reversibility*Arm)	-	0.703	-	0.712

ACQ denotes Asthma Control Questionnaire, GLM general linear model, ICS inhaled corticosteroid, LTRA leukotriene receptor antagonist, MiniAQLQ Mini Asthma Quality of Life Questionnaire, PEF peak expiratory flow.

Appendix Table E14. First Controller Trial: Subgroup Analyses: Asthma-Related Quality of Life and Asthma Control Scores at 2 Months By Group and Treatment Arm: Least Squares Mean From General Linear Model With Interaction Term

		Leukotriene Antagonist	Inhaled Corticosteroid
		Estimated Mean (SE)	Estimated Mean (SE)
MiniAQLQ	Smokers	5.53 (0.17)	5.29 (0.18)
	Nonsmokers	5.41 (0.12)	5.56 (0.11)
ACQ	Smokers	1.40 (0.18)	1.73 (0.22)
	Nonsmokers	1.47 (0.13)	1.23 (0.11)
MiniAQLQ	PEF <80%	5.27 (0.17)	5.21 (0.13)
	PEF ≥80%	5.24 (0.10)	5.42 (0.10)
ACQ	PEF <80%	1.54 (0.17)	1.65 (0.13)
	PEF ≥80%	1.51 (0.10)	1.38 (0.10)
MiniAQLQ	Rhinitis	5.44 (0.23)	5.45 (0.17)
	Non-Rhinitis	5.33 (0.10)	5.32 (0.10)
ACQ	Rhinitis	1.48 (0.24)	1.34 (0.18)
	Non-Rhinitis	1.48 (0.11)	1.54 (0.11)
MiniAQLQ	Reversibility <15%	5.24 (0.09)	5.33 (0.09)
	Reversibility ≥15%	5.49 (0.22)	5.47 (0.17)
ACQ	Reversibility <15%	1.52 (0.10)	1.46 (0.09)
	Reversibility ≥15%	1.22 (0.21)	1.28 (0.17)

ACQ denotes Asthma Control Questionnaire, MiniAQLQ Mini Asthma Quality of Life Questionnaire, PEF peak expiratory flow, SE standard error.

Appendix Table E15. Add-On Therapy Trial: Mini Asthma Quality of Life

Questionnaire Domain Scores at Baseline, 2 Months, and 2 Years

	Leukotriene Antagonist (N=105)	Long-Acting β_2 -Agonist (N=112)
Symptoms domain		
Baseline	4.54 (4.33–4.76)	4.32 (4.11–4.53)
2 months	5.12 (4.87–5.36)	5.01 (4.78–5.24)
2 years*	5.42 (5.17–5.66)	5.30 (5.08–5.52)
Activity domain		
Baseline	4.91 (4.65–5.18)	4.74 (4.48–4.99)
2 months	5.37 (5.10–5.64)	5.44 (5.21–5.68)
2 years*	5.84 (5.58–6.10)	5.96 (5.74–6.17)
Environment domain		
Baseline	4.43 (4.14–4.71)	4.27 (4.00–4.53)
2 months	4.90 (4.63–5.18)	4.71 (4.43–4.98)
2 years*	5.12 (4.83–5.41)	4.95 (4.67–5.23)
Emotions domain		
Baseline	4.44 (4.14–4.74)	4.25 (3.99–4.51)
2 months	4.99 (4.67–5.31)	5.07 (4.77–5.36)
2 years*	5.45 (5.16–5.73)	5.58 (5.32–5.83)

Data are mean (95% CI).

*18-month data were carried forward when 2-year data were missing. There were no significant differences between treatment groups at any time point ($P>0.10$ for all).

Appendix Table E16. Add-On Therapy Trial: Secondary Outcome Measures at 2 Months and 2 Years

		Leukotriene Antagonist		Long-Acting β_2 -Agonist		Adjusted	
		<i>n</i>		<i>n</i>		Difference (95%CI)*	P Value
RCP3 score							
	Baseline	159	1.98±0.86	177	2.03±0.81		
	2 months	150	1.40±1.00	154	1.25±0.96	0.15 (-0.07 to 0.37)	0.18
	2 years†	167	1.01±0.94	181	1.14±0.93	-0.11 (-0.31 to 0.08)	0.26
Personal objectives‡							
	Baseline	130	38±19	142	36±19		
	2 months	106	52±24	115	55±25	-5 (-10 to 1)	0.11
	2 years†	120	66±23	146	67±20	-4 (-9 to 2)	0.17
MiniRQLQ score							
	Baseline	139	1.95±1.27	159	2.02±1.31		
	2 months	125	1.50±1.06	131	1.89±1.28	-0.26 (-0.50 to -0.03)	0.029
	2 years†	162	1.32±1.22	178	1.55±1.29	-0.13 (-0.38 to 0.11)	0.27
PEF %pred, median (IQR)							
	Baseline	152	90.5 (80.2–99.7)	167	88.6 (76.7–99.9)		
	2 months	131	93.2 (84.0–105.0)	142	92.8 (80.2–102.9)		0.45
	2 years†	120	91.4 (80.9–99.4)	136	89.7 (77.3–100.4)		0.56

					Rate Ratio§ (95% CI)	
Respiratory tract infections	170	1.23±2.01	182	1.33±1.72	0.93 (0.70 to 1.22)	0.58
Patients who had 1 – no. (%)		40 (24%)		52 (29%)		
Patients who had >1 – no. (%)		45 (26%)		55 (30%)		
Consultations for RTI	170	1.49±2.62	182	1.52±2.07	0.98 (0.74 to 1.30)	0.90
Patients who had 1 – no. (%)		35 (21%)		47 (26%)		
Patients who had >1 – no. (%)		50 (29%)		60 (33%)		

Plus-minus values are means ±SD. P value is for the comparison between treatment groups.

*Adjusted for baseline values.

†Last observation carried forward.

‡At baseline, patients chose three personal objectives for their asthma and rated their ability to achieve these objectives on a visual analogue scale from 0 (not met at all) to 100 (fully met).

§Rate ratio from a Poisson model with treatment group as the sole explanatory variable.

IQR denotes interquartile range, MiniRQLQ Mini Rhinoconjunctivitis Quality of Life Questionnaire (scored from 0 best to 6 worst),

PEF %pred peak expiratory flow %predicted, RCP3 Royal College of Physicians 3-item questionnaire (scored from 0 best to 3

worst), RTI respiratory tract infection

Appendix Table E17. Add-On Therapy Trial: Asthma Control at 2 Months and 2 Years, Post Hoc Per Protocol Population with No Change in Randomized Treatment Arm

Outcome Measure	Leukotriene Antagonist		Long-Acting β_2 -Agonist		Mean Difference (95% CI)	Adjusted Mean
	<i>n</i>	Mean (SD)	<i>n</i>	Mean (SD)		Difference* (95% CI)
ACQ score:						
2 months	147	1.61 (1.00)	156	1.60 (0.98)	0.00 (-0.22, 0.23)	0.11 (-0.09, 0.31)
2 years	121	1.20 (0.91)	175	1.33 (0.92)	-0.13 (-0.34, 0.08)	-0.06 (-0.24, 0.11)

*Adjusted for baseline values. ACQ denotes Asthma Control Questionnaire, scored from 0 (best) to 6 (worst).

Appendix Table E18. Add-On Therapy Trial: Baseline Characteristics of the Predefined, Strict Per Protocol Population (Patients with No Change, However Minor, in Therapy)

	Leukotriene Antagonist (N=60)		Long-Acting β_2 -Agonist (N=80)	
	<i>n</i>		<i>n</i>	
Age (years)	60	50.7 (15.5)	80	48.2 (16.9)
Sex (female)	60	35 (58%)	80	42 (53%)
Smoking habit	60		79	
Current smoker		7 (12%)		15 (19%)
Ex-smoker		27 (45%)		32 (41%)
Never smoked		26 (43%)		32 (41%)
Peak expiratory flow, %predicted	56	92.3 (82.1 to 101.9)	74	88.7 (76.7 to 99.9)
RCP3 score	59	1.81 (0.88)	80	2.13 (0.82)
Personal objectives (0–100 VAS)*	44	40 (19)	61	36 (16)
MiniRQLQ score	53	1.73 (1.24)	73	2.09 (1.23)

Data are n (%) or mean (SD), except PEF %predicted, which is median (interquartile range).

*For personal objectives, the visual analogue scale ranged from 0 (not met at all) to 100 (fully met).

MiniRQLQ denotes Mini Rhinoconjunctivitis Quality of Life Questionnaire, scored from 0 (best) to 6 (worst), RCP3 Royal College of Physicians 3-item questionnaire, scored from 0 (best) to 3 (worst), VAS visual analogue scale.

Appendix Table E19. Add-On Therapy Trial: Asthma-Related Quality of Life and Asthma Control at 2 Months and 2 Years, Strict Per Protocol Population

Outcome Measure	Leukotriene Antagonist		Long-Acting β_2 -Agonist		Mean Difference (95% CI)	Adjusted Mean Difference* (95% CI)
	<i>n</i>	Mean (SD)	<i>n</i>	Mean (SD)		
MiniAQLQ score						
Baseline	60	4.78 (1.01)	80	4.30 (1.06)	--	--
2 months	56	5.38 (1.10)	67	5.06 (1.22)	0.32 (-0.10 to 0.74)	-0.02 (-0.36 to 0.31)
2 years†	60	5.65 (0.92)	80	5.49 (1.08)	0.16 (-0.36 to 0.50)	-0.05 (-0.36 to 0.26)
ACQ score						
Baseline	60	1.91 (0.84)	80	2.25 (0.92)	--	--
2 months	56	1.37 (0.98)	67	1.47 (1.01)	-0.09 (-0.45 to 0.27)	0.11 (-0.22 to 0.44)
2 years†	60	1.07 (0.73)	80	1.20 (0.85)	-0.13 (-0.40 to 0.13)	-0.01 (-0.27 to 0.24)

*Adjusted for baseline values. †Last observation carried forward.

ACQ denotes Asthma Control Questionnaire, MiniAQLQ Mini Asthma Quality of Life Questionnaire.

Appendix Table E20. Add-On Therapy Trial: Secondary Outcome Measures at 2 Months and 2 Years, Strict Per Protocol Population

	Leukotriene Antagonist		Long-Acting β_2 -Agonist		Adjusted		P Value
	<i>n</i>		<i>n</i>		Difference (95%CI)*		
RCP3 score							
2 months	55	1.16 (0.92)	69	1.19 (0.96)	0.04 (-0.31 to 0.38)	0.839	
2 years	59	0.83 (0.77)	80	1.18 (0.92)	-0.28 (-0.57 to 0.02)	0.066	
Personal objectives (VAS)							
2 months	38	58 (21)	54	56 (23)	1 (-7 to 9)	0.823	
2 years	46	65 (25)	69	66 (19)	5 (-3 to 13)	0.220	
MiniRQLQ score							
2 months	47	1.26 (1.00)	55	1.79 (1.15)	-0.40(-0.77 to -0.04)	0.032	
2 years	59	1.10 (1.11)	78	1.24 (1.11)	0.08 (-0.28 to 0.43)	0.659	
PEF %pred, median (IQR)							
2 months	50	96.0 (86.6 to 106.1)	61	92.4 (80.0 to 101.6)	--	0.243	
2 years	44	90.2 (79.6 to 100.4)	55	89.8 (79.5 to 102.9)	--	0.949	

Data are mean (SD) unless otherwise noted. P value is for the comparison between treatment groups.

*Adjusted for baseline values. MiniRQLQ denotes Mini Rhinoconjunctivitis Quality of Life Questionnaire, PEF %pred peak expiratory flow %predicted, RCP3 Royal College of Physicians 3-item questionnaire, VAS visual analogue scale 0–100.

Appendix Table E21. Add-On Therapy Trial: Secondary Outcome Measures at 2 Years, Strict Per Protocol Population

	Leukotriene Antagonist		Long-Acting β_2 -Agonist		Rate Ratio* (95% CI)	P Value
	<i>n</i>		<i>n</i>			
Asthma exacerbations	60	0.33 (0.84)	80	0.43 (0.91)	0.79 (0.42 to 1.45)	0.441
Patients who had 1, n (%)		10 (17%)		14 (18%)		
Patients who had >1, n (%)		3 (5%)		7 (8%)		
Respiratory tract infections	60	1.07 (2.11)	80	1.25 (1.87)	0.85 (0.52 to 1.41)	0.534
Patients who had 1, n (%)		14 (23%)		17 (21%)		
Patients who had >1, n (%)		11 (19%)		23 (29%)		
Consultations for RTI	60	1.43 (3.00)	80	1.40 (2.14)	1.02 (0.62 to 1.69)	0.927
Patients who had 1, n (%)		10 (17%)		16 (20%)		
Patients who had >1, n (%)		15 (25%)		24 (30%)		

Data are mean (SD) unless otherwise noted. P value is for the comparison between treatment groups.

*From a Poisson model with treatment group as the sole explanatory variable. RTI denotes respiratory tract infection.

Appendix Table E22. Add-On Therapy Trial: Baseline Diary Card Symptom Scores, Peak Expiratory Flow, and Reliever Usage

	Leukotriene		Long-Acting β_2 -	
	Antagonist		Agonist	
	(N=170)		(N=182)	
	<i>n</i>		<i>n</i>	
Morning waking with symptoms	159	0.47 (0.35)	176	0.46 (0.36)
Puffs of reliever at night	153	0.95 (1.42)	168	0.91 (1.01)
Morning PEF, L/min	158	391.1 (101.5)	175	393.7 (104.7)
Daytime asthma symptom score*	159	1.91 (1.23)	176	1.91 (1.13)
Score for daytime 'bother from asthma symptoms'	159	1.65 (1.24)	174	1.68 (1.10)
Daily activity score†	156	2.58 (1.21)	173	2.45 (1.10)
Score for interference on activities from asthma*	157	1.38 (1.32)	174	1.52 (1.18)
Puffs of reliever during the day	154	2.73 (2.59)	175	2.74 (2.01)
Evening PEF, L/min	156	397.3 (100.0)	173	405.4 (101.5)
Diurnal variation in PEF, %	158	6.5 (4.4)	175	6.5 (4.4)

Data are mean (SD). PEF denotes peak expiratory flow.

*scored from 0=none to 6=all of the time or severely bothered.

†scored from 0=more exercise than normal to 6=less than usual.

Appendix Table E23. Add-On Therapy Trial: Diary Card Results at 2 Months

	Long-Acting β_2 -				Difference (95% CI)	Adjusted Difference* (95% CI)
	Leukotriene Antagonist		Agonist			
	(N=170)		(N=182)			
	<i>n</i>	Mean (SD)	<i>n</i>	Mean (SD)		
Morning waking with symptoms	113	0.31 (0.34)	123	0.25 (0.32)	0.06 (-0.02 to 0.15)	0.03 (-0.04 to 0.10)
Puffs of reliever at night, original scale	101	0.91 (1.38)	110	0.60 (0.99)	0.30	
Puffs of reliever at night, log scale	101	0.48 (0.53)	110	0.35 (0.47)	0.14 (0.00 to 0.27)†	0.12 (0.01 to 0.24)†
Morning PEF, L/min	112	399.0 (108.3)	121	419.1 (102.3)	-20.2 (-47.4 to 7.0)	-17.9 (-26.8 to -8.9)‡
Daytime asthma symptom score	113	1.63 (1.37)	122	1.53 (1.37)	0.10 (-0.25 to 0.46)	0.04 (-0.25 to 0.34)
Score for daytime 'bother from asthma symptoms'	112	1.46 (1.39)	122	1.39 (1.41)	0.07 (-0.29 to 0.43)	0.05 (-0.26 to 0.36)
Daily activity score	110	2.42 (1.28)	122	2.27 (1.37)	0.15 (-0.19 to 0.50)	0.08 (-0.23 to 0.39)
Score for interference on activities from asthma	111	1.41 (1.42)	121	1.32 (1.37)	0.09 (-0.27 to 0.46)	0.12 (-0.19 to 0.43)
Puffs of reliever during the day, original scale	108	2.45 (2.75)	118	1.67 (1.96)	0.78	
Puffs of reliever during the day, log scale	108	0.98 (0.70)	118	0.77 (0.63)	0.21 (0.04 to 0.39)†	0.19 (0.04 to 0.33)†
Evening PEF, L/min	112	402.0 (107.5)	122	425.2 (99.4)	-23.2 (-49.9 to 3.5)	-10.8 (-19.4 to -2.2)†
PEF diurnal variability, %	112	5.8 (4.4)	122	4.9 (3.6)	-0.9 (-0.1 to 1.9)	0.8 (-0.05 to 1.7)

PEF denotes peak expiratory flow. *Adjusted for baseline values. †P≤0.05. ‡P<0.001.

Appendix Table E24. Add-On Therapy Trial: Diary Card Results at 2 Years

	Leukotriene		Long-Acting β_2 -		Difference (95% CI)	Adjusted Difference* (95% CI)
	Antagonist		Agonist			
	(N=170)		(N=182)			
	<i>n</i>	Mean (SD)	<i>n</i>	Mean (SD)		
Morning waking with symptoms	85	0.29 (0.35)	98	0.24 (0.33)	0.05 (-0.05 to 0.15)	0.01(-0.07 to 0.10)
Puffs of reliever at night, original scale	75	0.69 (1.04)	87	0.63 (0.87)	0.07	
Puffs of reliever at night, log scale	75	0.38 (0.50)	87	0.37 (0.45)	0.01 (-0.14 to 0.15)	0.00 (-0.14 to 0.14)
Morning PEF, L/min	83	395.6 (105.9)	98	419.8 (97.0)	-24.2 (-54.0 to 5.6)	-13.7 (-25.6 to -1.8)†
Daytime asthma symptom score	85	1.40 (1.28)	97	1.44 (1.24)	-0.04 (-0.41 to 0.33)	-0.08(-0.40 to 0.23)
Score for daytime 'bother from asthma symptoms'	85	1.12 (1.19)	97	1.26 (1.27)	-0.14 (-0.50 to 0.23)	-0.06 (-0.37 to 0.26)
Daily activity score	83	2.23 (1.22)	97	2.32 (1.39)	-0.09 (-0.47 to 0.30)	-0.06 (-0.41 to 0.27)
Score for interference on activities from asthma	85	1.13 (1.25)	97	1.25 (1.39)	-0.12 (-0.51 to 0.27)	0.01 (-0.31 to 0.34)
Puffs of reliever during the day, original scale	84	1.89 (2.31)	95	1.49 (1.65)	0.40	
Puffs of reliever during the day, log scale	84	0.80 (0.70)	95	0.73 (0.60)	0.07 (-0.18 to 0.27)	0.08 (-0.09 to 0.25)
Evening PEF, L/min	83	401.7 (106.0)	98	425.8 (96.8)	-24.1 (-53.8 to 5.7)	-5.7 (-17.8 to 6.3)
PEF diurnal variability, %		5.7 (4.7)		5.2 (4.3)	0.6 (-0.9 to 2.0)	0.2 (-1.1 to 1.5)

PEF denotes peak expiratory flow. *Adjusted for baseline values. †P≤0.05.

Appendix Table E25. Add-On Therapy Trial: Subgroup Analyses: Unadjusted Asthma-Related Quality of Life and Asthma Control Scores at 2 Months

		Leukotriene Antagonist		Long-Acting β_2 - Agonist	
		<i>n</i>	Mean (SD)	<i>n</i>	Mean (SD)
<i>Smoking*</i>					
MiniAQLQ	Smokers	26	5.18 (1.29)	23	5.31 (1.08)
	Nonsmokers	65	5.14 (1.11)	66	5.05 (1.00)
ACQ	Smokers	26	1.79 (1.20)	23	1.59 (1.06)
	Nonsmokers	65	1.50 (0.91)	66	1.52 (0.96)
<i>PEF %predicted</i>					
MiniAQLQ	PEF <80%	34	4.83 (1.44)	43	5.15 (1.15)
	PEF \geq 80%	101	5.27 (0.99)	103	5.04 (1.09)
ACQ	PEF <80%	34	1.92 (1.32)	43	1.70 (1.23)
	PEF \geq 80%	101	1.48 (0.87)	103	1.55 (0.85)
<i>Rhinitis</i>					
MiniAQLQ	Yes	25	5.20 (1.01)	23	5.10 (0.98)
	No	79	5.15 (1.20)	84	4.94 (1.18)
ACQ	Yes	25	1.42 (0.72)	23	1.41 (0.91)
	No	79	1.60 (1.03)	84	1.77 (1.04)
<i>PEF Reversibility</i>					
MiniAQLQ	<15%	107	5.10 (1.10)	124	5.04 (1.08)
	\geq 15%	33	5.16 (1.29)	23	5.07 (1.16)
ACQ	<15%	107	1.57 (0.94)	124	1.61 (0.95)
	\geq 15%	33	1.70 (1.15)	23	1.51 (1.15)

Subgroup analyses excluded any patients with change in medication or who were missing outcomes data at 2 months.

*Current smokers versus nonsmokers (ex-smokers excluded). ACQ denotes Asthma Control Questionnaire, MiniAQLQ Mini Asthma Quality of Life Questionnaire, PEF peak expiratory flow.

Appendix Table E26. Add-On Therapy Trial: Subgroup Analyses: Results for General Linear Models Within Groups and For Groups Combined at 2 Months

		MiniAQLQ		ACQ	
		Adjusted		Adjusted Difference in Means (95% CI)	P value
Parameter		Difference in Means (95% CI)	P value		
Smoking					
<i>Within Group GLM</i>					
Smokers:	Arm (LTRA-LABA)	-0.28 (-0.80, 0.24)	0.287	0.23 (-0.32, 0.78)	0.405
Nonsmokers:	Arm (LTRA-LABA)	-0.05 (-0.34, 0.24)	0.720	0.15 (-0.13, 0.44)	0.294
<i>Combined Groups</i>					
	Smoking Status (Smokers-Nonsmokers)	0.11 (-0.18, 0.39)	0.455	0.07 (-0.21, 0.35)	0.644
	Arm (LTRA-LABA)	-0.17 (-0.45, 0.12)	0.252	0.21 (-0.07, 0.49)	0.135
	Interaction (Smoking*Arm)	-	0.442	-	0.767
Lung Function					
<i>Within Group GLM</i>					
PEF <80%:	Arm (LTRA-LABA)	-0.30 (-0.76, 0.15)	0.190	0.25 (-0.22, 0.71)	0.290

PEF \geq 80%:	Arm (LTRA-LABA)	-0.01 (-0.24, 0.23)	0.963	0.04 (-0.18, 0.25)	0.728
<i>Combined Groups</i>					
	PEF (<80% - \geq 80%)	0.03 (-0.20, 0.26)	0.798	0.10 (-0.13, 0.33)	0.385
	Arm (LTRA-LABA)	-0.16 (-0.39, 0.08)	0.187	0.15 (-0.07, 0.38)	0.187
	Interaction (PEF*Arm)	-	0.206	-	0.421
Rhinitis					
<i>Within Group GLM</i>					
Rhinitis:	Arm (LTRA-LABA)	0.06 (-0.52, 0.64)	0.835	0.03 (-0.41, 0.47)	0.897
Non-Rhinitis:	Arm (LTRA-LABA)	0.08 (-0.18, 0.34)	0.547	-0.05 (-0.32, 0.23)	0.747
<i>Combined Groups</i>					
	Rhinitis Status (Rhinitis- Non-Rhinitis)	0.17 (-0.12, 0.47)	0.240	-0.18 (-0.46, 0.10)	0.207
	Arm (LTRA-LABA)	0.03 (-0.26, 0.32)	0.838	-0.01 (-0.29, 0.27)	0.950
	Interaction (Rhinitis*Arm)	-	0.675	-	0.768
Reversibility					
<i>Within Group GLM</i>					
< 15%:	Arm (LTRA-LABA)	-0.05 (-0.28, 0.17)	0.647	0.06 (-0.16, 0.28)	0.585
\geq 15%:	Arm (LTRA-LABA)	-0.15 (-0.67, 0.37)	0.564	0.42 (-0.05, 0.89)	0.076
<i>Combined Groups</i>					

Reversibility (<15% - ≥15%)	0.01 (-0.25, 0.28)	0.930	0.01 (-0.24, 0.26)	0.950
Arm (LTRA-LABA)	-0.14 (-0.40, 0.13)	0.311	0.22 (-0.04, 0.47)	0.090
Interaction (Reversibility*Arm)	-	0.533	-	0.258

ACQ denotes Asthma Control Questionnaire, GLM general linear model, LABA, long-acting β 2-agonist, LTRA leukotriene receptor antagonist, MiniAQLQ Mini Asthma Quality of Life Questionnaire, PEF peak expiratory flow.

Appendix Table E27. Add-On Therapy Trial: Subgroup Analyses: Asthma-Related Quality of Life and Asthma Control Scores at 2 Months By Group and Treatment Arm: Least Squares Mean From General Linear Model With Interaction Term

		Leukotriene Antagonist Estimated Mean (SE)	Long-Acting β_2- Agonist Estimated Mean (SE)
MiniAQLQ	Smokers	5.07 (0.17)	5.35 (0.18)
	Non-smokers	5.08 (0.11)	5.13 (0.11)
ACQ	Smokers	1.74 (0.17)	1.48 (0.18)
	Non-smokers	1.63 (0.11)	1.46 (0.10)
MiniAQLQ	PEF <80%	4.97 (0.15)	5.28 (0.13)
	PEF \geq 80%	5.09 (0.09)	5.10 (0.09)
ACQ	PEF <80%	1.79 (0.15)	1.55 (0.13)
	PEF \geq 80%	1.60 (0.09)	1.54 (0.08)
MiniAQLQ	Rhinitis	5.18 (0.18)	5.22 (0.19)
	Non-Rhinitis	5.07 (0.10)	4.98 (0.10)
ACQ	Rhinitis	1.50 (0.17)	1.47 (0.18)
	Non-Rhinitis	1.64 (0.10)	1.69 (0.09)
MiniAQLQ	Reversibility <15%	5.05 (0.09)	5.11 (0.08)
	Reversibility \geq 15%	4.96 (0.16)	5.18 (0.19)
ACQ	Reversibility <15%	1.63 (0.08)	1.56 (0.08)
	Reversibility \geq 15%	1.77 (0.15)	1.41 (0.18)

ACQ denotes Asthma Control Questionnaire, MiniAQLQ Mini Asthma Quality of Life Questionnaire, PEF peak expiratory flow, SE standard error.

Appendix Table E28. Study Outcome Results as Compared with Results of GOAL,¹⁵ FACET,¹⁶ and OPTIMA¹⁷ Studies

Quality Of Life	Current Study	GOAL	Current Study	GOAL
	Step 2	Stratum 1	Step 3	Stratum 2
Baseline:	N=306	FP: N=275	N=352	SFC: N=339
MiniAQLQ or AQLQ score	4.7±0.9	4.5±1.0	4.5±1.0	4.7±1.1
Results:	LTRA / ICS	FP	LTRA / LABA	SFC
2 mo or GOAL Phase 1	5.3±1.0 / 5.3±1.1	5.8±1.0	5.1±1.2 / 5.0±1.1	5.9±1.0
2 yr or GOAL Phase 2	5.5±1.1 / 5.6±1.2	5.9±1.1	5.4±1.1 / 5.4±1.1	6.0±1.0
Change at 2yr (1yr in GOAL)	0.8 / 0.9	1.4	0.9 / 0.9	1.3
AQLQ in FACET				
	Bud200	Bud200/form	Bud800	Bud800/form
	N=118	N=116	N=115	N=117
Baseline	5.1	5.0	5.0	5.1
At 1 year (estimate from fig)	5.6	5.6	5.6	5.8
Exacerbation* Rate				
Our Study	Step 2 LTRA	Step 2 ICS	Step 3 LTRA	Step 3 LABA
Over 2 years	0.44	0.35	0.62	0.61
OPTIMA				
Group A	Placebo	Bud200	Bud200/form	
	N=239	N=228	N=231	
Over 1 year	0.77	0.29	0.34	
Group B	Bud200	Bud200/form	Bud400	Bud400/form
	N=322	N=323	N=312	N=315
Over 1 year	0.92	0.56	0.96	0.36

*Exacerbations were defined in our study as need for oral steroids or hospitalization and in OPTIMA “as need for treatment with oral corticosteroids, as judged by the investigator, or hospital admission or emergency treatment for worsening asthma, or a decrease in morning PEF >25% from baseline on two consecutive days.”

AQLQ denotes Asthma Quality of Life Questionnaire, Bud budesonide, form formoterol, FP fluticasone propionate, ICS inhaled corticosteroid, LABA long-acting β_2 -agonist. LTRA leukotriene receptor antagonist, SFC salmeterol/fluticasone combination, Step 2 First Controller Trial, Step 3 Add-On Therapy Trial.