

Abbreviations used

ACQ: Asthma Control Questionnaire
 AQLQ: Asthma Quality of Life Questionnaire
 ICS: Inhaled corticosteroid
 LABA: Long-acting β -agonist
 LTRA: Leukotriene receptor antagonist
 MID: Minimal important difference
 MTC: Mixed treatment comparison
 PRO: Patient-reported outcome
 RCT: Randomized controlled trial

Assessment of recent placebo-controlled studies of new controller treatments in patients with severe asthma (eg, omalizumab and tiotropium) reveals that improvements in AQLQ and ACQ responses are smaller than might be expected.^{8,9} For example, in trials of tiotropium in patients whose symptoms are uncontrolled with at least an ICS and a long-acting β -agonist (LABA), group mean differences in AQLQ and ACQ scores compared with placebo did not exceed the MID for either instrument. These observations call into question the performance of these instruments and the interpretation of results obtained with them, particularly when multiple treatments are being used.⁹ It is worth noting that both the AQLQ and the ACQ were developed and their reliability, validity, and responsiveness were assessed in a patient population that was largely steroid naive or receiving ICSs alone.^{4,5,10,11}

The MID for clinical outcomes is estimated by means of a process of triangulation that compares the outcome of interest with changes in other measures to arrive at the smallest difference that might represent benefit.¹² At both the group and individual levels, the MID might depend on the clinical context and patient management decision at hand, the baseline from which the patient starts, and whether the patient's symptoms are improving or deteriorating.¹³ The initial derivation of the MID for both the AQLQ and the ACQ was based largely on the physician's judgment of change in patients whose symptoms improved on monotherapy with an ICS, with placebo as a control. To the authors' knowledge, the MID has not been correlated with other important measures of interest in asthma, such as exacerbations or the frequency of hospitalization. Furthermore, to date, there has been no critical review of the extent to which the MID is achievable when treatments are added to highly effective medications, such as ICSs or ICS plus LABA combinations.

We report here a systematic review and meta-analysis of clinical trials in patients with asthma in which the AQLQ, ACQ, or both was used to examine the achievability of between-group mean differences of 0.5 or more with established asthma treatments.

METHODS**Search strategy**

A systematic literature search using PubMed, Embase, and the National Health Service Economic Evaluation Database was conducted on April 5, 2012, and updated on June 14, 2013 (details are provided in the [Methods](#) section and [Table E1](#) in this article's Online Repository at www.jacionline.org). In addition, the bibliographies of existing literature reviews and meta-analyses, the clinicaltrials.gov study register, and the 2011 and 2012 conference Web sites of the American Thoracic Society and European Respiratory Society were searched. No limits regarding publication date or language were applied.

Inclusion criteria and selection of studies

Using predefined inclusion and exclusion criteria, 2 reviewers (C.C. and M.F.) independently scanned titles and abstracts of the identified studies at level 1 screening to evaluate potential study relevance; full texts of studies selected at level 1 were reviewed at level 2 screening (see the [Methods](#) section in this article's Online Repository for full details). Discrepancies were reconciled between the 2 reviewers or by a third reviewer (D.E.), if necessary.

Double-blind randomized controlled trials (RCTs) of adolescent and adult patients with uncontrolled, symptomatic, or persistent asthma at baseline were included if the overall score changes from baseline values for the AQLQ, ACQ, or both were reported after patients received 1 or more of the following treatments: an ICS, a LABA, a leukotriene receptor antagonist (LTRA), a short-acting β -agonist, omalizumab, or theophylline. Data from all the instrument versions of the AQLQ, such as the Standardized AQLQ and the MiniAQLQ,^{10,11} and of the ACQ, such as the 5-item and 6-item versions (ACQ-5 and ACQ-6),⁶ were collected.

Data extraction and assessment of risk of bias

Data from the original studies were extracted by using a standardized abstraction form developed in Microsoft Excel (see the [Methods](#) section in this article's Online Repository for details), which included study design information. To consistently capture key study differences, run-in and background treatments were defined as stable comedications if they were taken by at least 50% of patients in addition to the study medication before randomization, after randomization, or both. Data were independently checked for accuracy by 2 reviewers (C.C. and M.F.); the risk of bias of individual studies was assessed at the study and outcome level by using the quality criteria presented in the National Institute for Health and Care Excellence single technology appraisal guidance¹⁴ and the Centre for Reviews and Dissemination's guidance (see the [Methods](#) section in this article's Online Repository for details).¹⁵

Outcome measures

The meta-analysis assessed AQLQ and ACQ score changes from baseline, where baseline was defined as the last visit before the start of the treatment phase. The extracted assessments were based on the time point of the study primary end point, as designated in the publication, or the latest available time point (if no time point was designated as primary).

Statistical methods

For each outcome, a mixed treatment comparison (MTC) combined with meta-regression was performed. Linear mixed models with the SE of mean change from baseline in the instrument used as a weighting variable and trials as random effects were constructed by using the PROC MIXED procedure in SAS (version 9.3; SAS Institute, Cary, NC). If the SE was not available, it was either derived or imputed (see the [Methods](#) section in this article's Online Repository for details). Adjusted least-squares means for each treatment and adjusted mean differences between any 2 treatments, along with 95% CIs, were estimated. Multiple covariates were assessed, both individually and in combination, for inclusion in the MTC model to address heterogeneity¹⁶ and reduce inconsistency between treatment comparisons (see the [Methods](#) section in this article's Online Repository for details).¹⁷ Covariates with *P* values of .05 or less were included in the model.

By comparing the estimated mean changes from baseline and their CIs with the MID,¹⁸ the size of the treatment responses were further classified as follows:

- *no effect* if the point estimate did not reach the MID and the 95% CI included zero;
- *no clinically significant effect* if the point estimate did not reach the MID and the 95% CI was between zero and the MID;
- *not significantly less than the MID* if the point estimate did not reach the MID and the 95% CI was greater than zero but contained the MID;
- *probable clinically significant effect* if the point estimate exceeded the MID but the 95% CI contained the MID; and
- *large clinically significant effect* if the point estimate exceeded the MID and the 95% CI exceeded the MID.

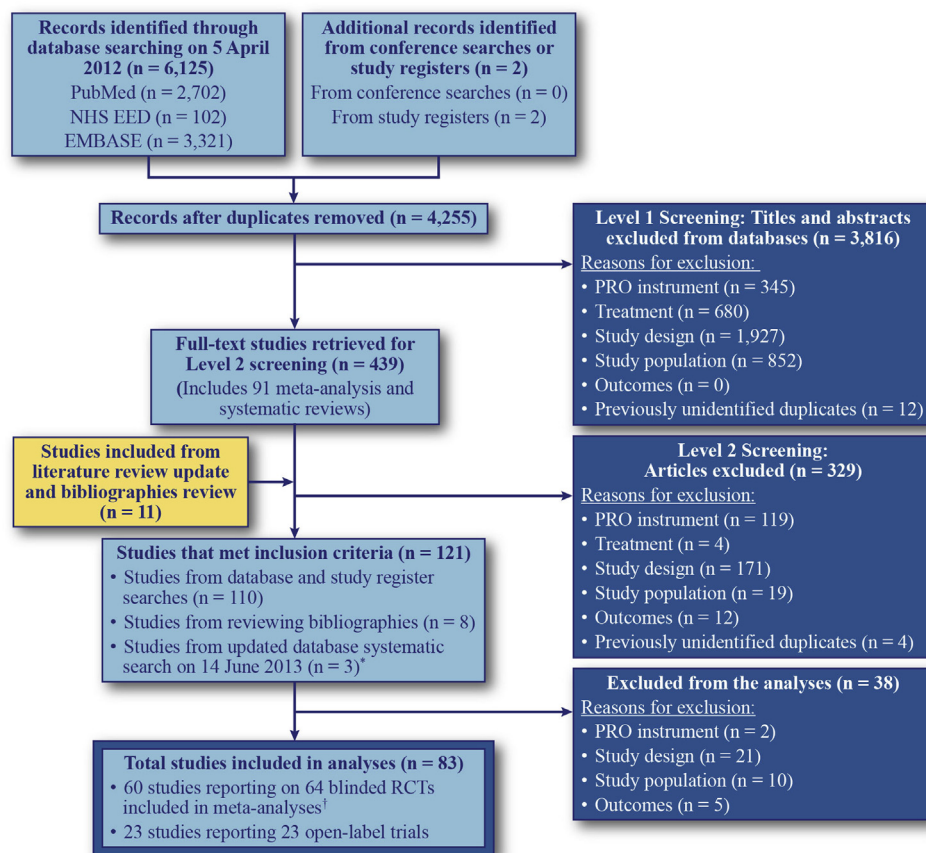


FIG 1. Flow diagram of study selection. *The update of the database systematic search was conducted from March 26, 2012, to June 14, 2013, with the objective of capturing additional blind RCTs. †Only blind RCTs identified in this search were included in the meta-analysis. NHS EED, National Health Service Economic Evaluation Database.

TABLE I. Summary of baseline characteristics

Treatment	No. of studies	No. of patients	Mean age (y)	Mean body mass index (kg/m ²)	Reversibility* (%)	Female (%)	White (%)	Never smoked (%)	Baseline mean FEV ₁ (L)
ICS	33	8,525	40.3	26.6	23.0	59.0	77.0	80.9	2.32
LABA	17	4,811	40.2	NA	22.0	57.8	81.6	NA	2.31
ICS + LABA	25	14,988	41.2	27.7	23.6	60.2	54.9	81.6	2.21
LTRA	19	5,336	37.5	NA	17.8	56.6	78.3	74.4	2.43
SABA	5	1,763	41.6	NA	23.3	59.1	NA	NA	2.18
Omalizumab	6	1,407	41.5	NA	24.6	58.5	80.4	76.2	2.58
Theophylline	1	161	41.0	NA	NA	75.0	60.0	NA	NA
Placebo	33	5,536	39.1	NA	25.0	57.0	78.8	79.5	2.40
All treatments	64	42,527	40.2	26.7	22.9	58.8	73.5	80.3	2.3

NA, Data not available; SABA, short-acting β -agonist.

*Reversibility as the mean percentage increase in FEV₁ after β_2 -agonist inhalation at baseline or screening.

Sensitivity analyses were performed to assess the effect of data imputation for the SE and the effect of including in the analysis studies that compared treatments within the same treatment classes. Inconsistency of the network was also evaluated.¹⁹⁻²¹ A test result was declared significant if the *P* value was .05 or less.

RESULTS

Systematic review and summary of included trials

Sixty articles reporting on 64 RCTs (42,527 patients) were identified (see Fig 1 and the Results section in this article's Online Repository at www.jacionline.org for details).

Table I presents a weighted average of the baseline characteristics by treatment. In general, baseline characteristics were similar across treatments.

Overall, the quality of the studies was good (see Table E2 in this article's Online Repository at www.jacionline.org). Most studies reported the differences in dropouts between the treatment groups and the reasons for patient withdrawal, although reporting of randomization methods, concealment allocation, and blinding of participants was not clear in many of the studies. The risk of bias in the analyses was not clear in several studies because the conduct of intention-to-treat analyses was poorly described and

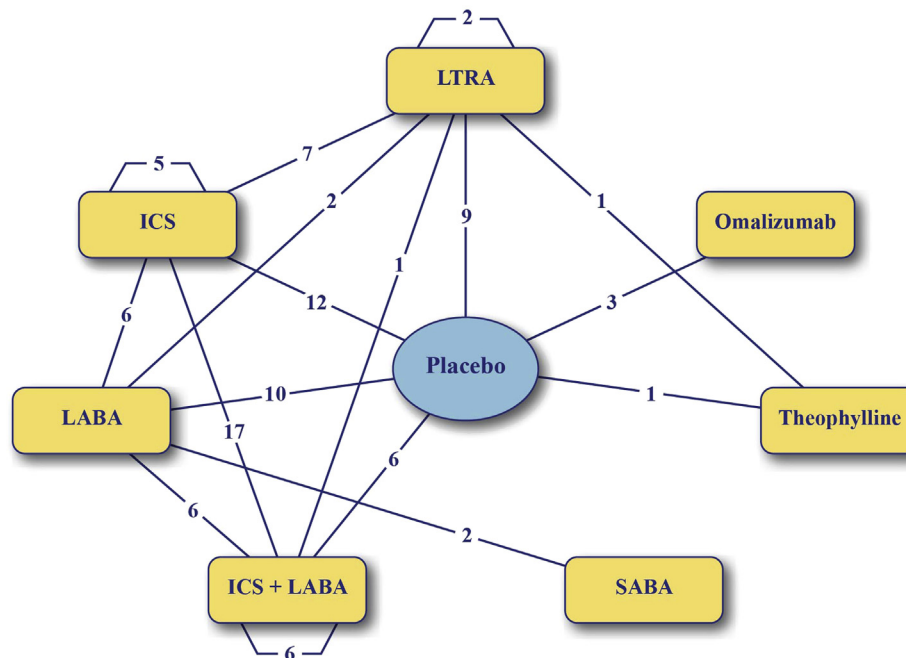


FIG 2. AQLQ network of evidence. Numbers indicate the number of studies with comparisons of AQLQ score changes between treatments (which could include different drugs in the same class) in RCTs of patients with asthma. See Table E3 in this article's Online Repository for the list of studies included in this network. SABA, Short-acting β -agonist.

applied. For example, the number of patients used in the calculations of health-related quality of life often was not clearly reported.

MTC of AQLQ results

The AQLQ was included as an end point in 54 of the 64 blinded RCTs. Fig 2 shows the AQLQ network diagram; numbered lines indicate the number of studies included in the comparison (see Table E3 in this article's Online Repository at www.jacionline.org for more detailed information on the individual studies). Higher AQLQ scores indicate better health-related quality of life, such that increases from baseline are considered favorable.

During the run-in period, subjects in 9 (17%) RCTs had no medication (or no run-in period), in 9 (17%) RCTs they received placebo, and in 36 (66%) RCTs they received an ICS. During the treatment phase, subjects in 38 (72%) RCTs had no background treatment, and in 15 (28%) RCTs they continued ICS use as background treatment. Overall, 41 (76%) RCTs used the original AQLQ instrument, whereas 13 (24%) RCTs used alternate versions (Standardized AQLQ [20%] or MiniAQLQ [4%]).

Study treatment, run-in treatment (none [or no run-in period], placebo, or ICS), background treatment (none or ICS), AQLQ type (original or other), and study treatment by background treatment were statistically significant covariates included in the final MTC multivariable model for the AQLQ.

Changes in AQLQ scores from baseline (within-treatment comparisons)

Adjusted AQLQ estimates of change from baseline for pooled treatment groups in trials with or without background medication or with different run-in treatments and type of AQLQ

are presented in detail in Table E4 in this article's Online Repository at www.jacionline.org. Fig 3 shows AQLQ score changes from baseline for situations considered representative of asthma clinical studies by using the AQLQ original version and various combinations of run-in period and background treatment (ie, no run-in treatment and no ICS background, placebo run-in period and no ICS background, ICS run-in period and ICS background).

In trials with no run-in period and no concurrent (background) controller treatment during the treatment period, the estimated AQLQ changes from baseline achieved in the ICS plus LABA, ICS, LTRA, and LABA treatment groups were all greater than 0.5 and categorized as large and clinically significant. However, placebo also achieved a mean improvement greater than 0.5 units (0.553; 95% CI, 0.367-0.739), which was categorized as probably clinically significant.

When a run-in period was present during which placebo was used and there was no concurrent therapy during the active phase of the trials, the estimated AQLQ change from baseline was large and clinically significant only for the ICS plus LABA (0.919; 95% CI, 0.734-1.104) and ICS (0.729; 95% CI, 0.549-0.909) treatment groups. For LTRA (0.504; 95% CI, 0.324-0.685), the increase exceeded 0.5 and was of probable clinical significance, but LABA treatment alone (0.419; 95% CI, 0.223-0.616) did not exceed the MID threshold and thus was not clinically significant.

When an ICS formed part of the treatment during the run-in period and was used as background treatment, the estimated AQLQ improvements from baseline for the LABA, LTRA, and omalizumab groups were large and clinically significant; however, those for theophylline, short-acting β -agonist, and placebo were also greater than 0.5 units but only fulfilled the criteria for probable clinical significance (Fig 3).

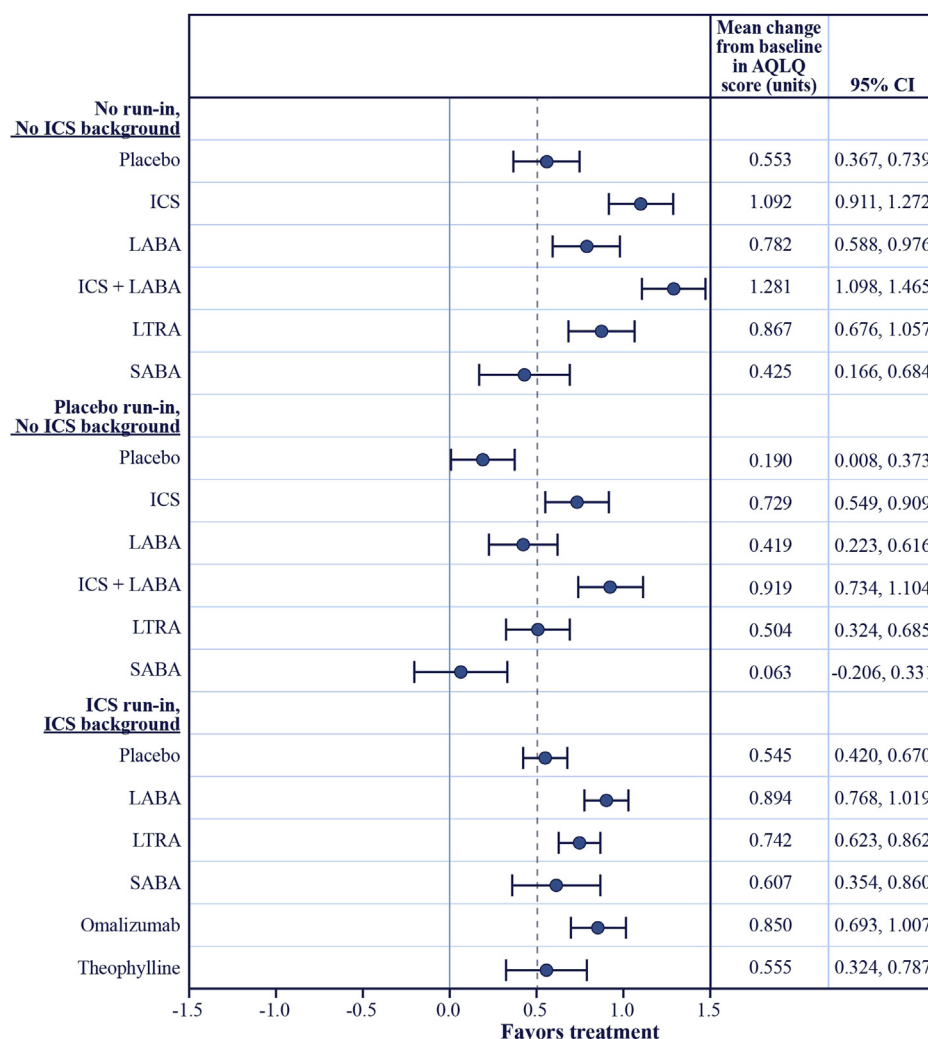


FIG 3. Adjusted mean change from baseline in overall AQLQ score using the AQLQ original version. SABA, Short-acting β -agonist.

Comparisons between treatments

Comparison of active versus placebo treatments in patients with and without background ICSs using the same treatment during the run-in period are presented in Fig 4. When background treatment did not include a controller ICS, only ICS plus LABA and ICS alone achieved a mean improvement of greater than 0.5 units. For ICS plus LABA treatment, the increase was large and clinically significant (0.729; 95% CI, 0.658-0.799), but for ICS treatment, the increase was of only probable clinical significance (0.539; 95% CI, 0.479-0.599). LABAs and LTRAs added to concurrent ICS treatment achieved increases of only 0.229 (95% CI, 0.135-0.323) and 0.314 (95% CI, 0.230-0.398), respectively, which were not clinically significant (Fig 4).

When the background concurrent treatment during the active treatment phase of trials was an ICS, improvements in AQLQ scores achieved with active treatments relative to placebo were considerably smaller. With the addition of a LABA (0.349; 95% CI, 0.271-0.427), LTRA (0.198; 95% CI, 0.127-0.269), or omalizumab (0.305; 95% CI, 0.202-0.408), the change was not clinically significant, and theophylline (0.011; 95% CI, -0.198 to 0.219) had no effect (Fig 4).

Adjusted AQLQ relative effect estimates are presented in Table E5 in this article's Online Repository at www.jacionline.org.

Results of sensitivity analyses were generally similar to the main analysis findings, although the statistical significance of some covariates included in the models changed. The consistency tests showed a disagreement between direct and indirect evidence for the ICS-placebo-LTRA and ICS-LABA-LTRA loops, indicating that covariate adjustment was justified. However, the exact level of significance at which to reject the null hypothesis was no longer .05 because the tested loops and therefore the consistency test were not independent.¹⁹

MTC of ACQ results

The ACQ was an end point in 11 of the 64 blinded RCTs. Fig 5 shows the ACQ network diagram; numbered lines indicate the number of studies included in the comparison (see Table E6 in this article's Online Repository at www.jacionline.org for more detailed information on the individual studies). Lower ACQ scores indicate better control of asthma symptoms, such that decreases from baseline are considered favorable.

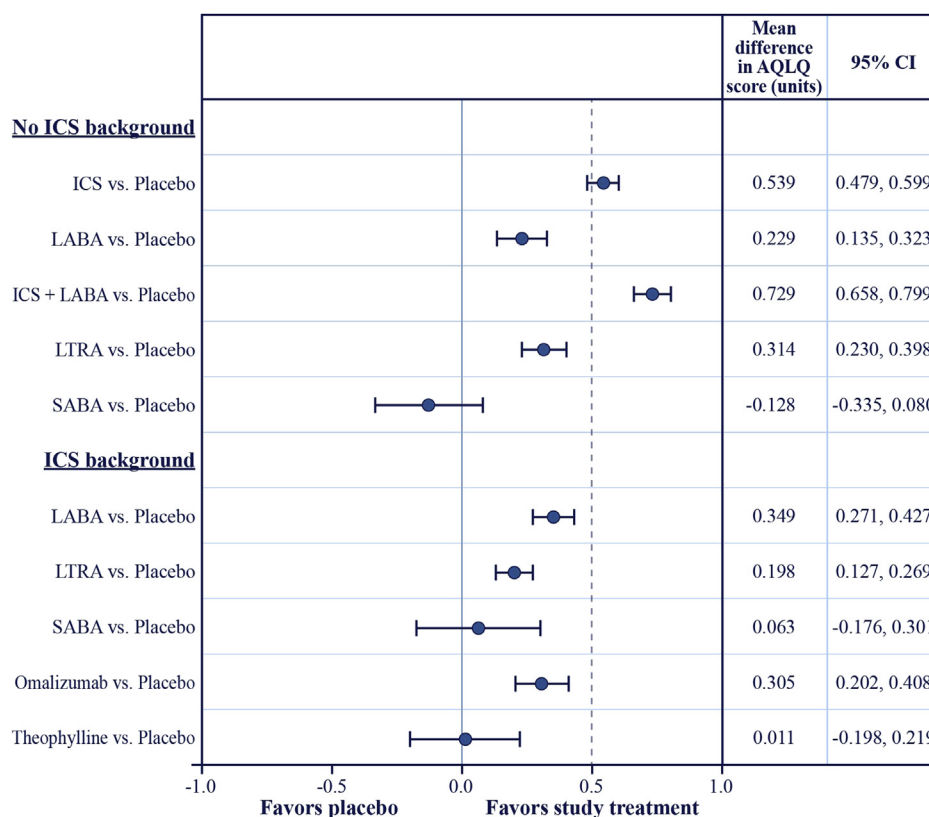


FIG 4. Differences in adjusted mean change from baseline in overall AQLQ score between treatments versus placebo. Values are presented for comparisons of active treatments with placebo in trials with the same design (ie, the same ICS background, the same run-in treatment, and the same AQLQ version). *SABA*, Short-acting β -agonist.

During the run-in period, all RCTs included ICS treatment; during the treatment phase, 7 (64%) RCTs had no background treatment, and 4 (36%) RCTs had ICS background treatment. Overall, 7 (64%) RCTs used the ACQ original version (ie, ACQ-7), and 4 (36%) RCTs used the ACQ, 5-item version. With the exception of study treatment, no statistically significant covariates were found for inclusion in the model.

Changes in ACQ scores from baseline (within-treatment comparisons)

Fig 6 presents the unadjusted least-squares means by treatment for the ACQ overall score change from baseline. No studies showed clinically significant changes in ACQ scores. The effects on ACQ least-squares mean changes from baseline were “probably clinically significant” (see the Results section in this article’s Online Repository for details)¹⁸ only for the ICS plus LABA pooled treatment group (-0.625 ; 95% CI, -0.767 to -0.482).

Comparisons between treatments

Fig 7 and Table E7 in this article’s Online Repository at www.jacionline.org present the unadjusted relative treatment effects of ACQ overall score change from baseline versus placebo. None of the pooled treatment groups had effects on ACQ score mean change that exceeded the MID in comparison with placebo change from baseline. Mean reductions in ACQ

scores ranged from -0.102 (95% CI, -0.306 to 0.101) for the addition of theophylline to -0.364 (95% CI, -0.471 to -0.257) for the comparison of LABA plus ICS with ICS alone (Fig 7). Thus all estimates revealed either no effect or no clinically significant effect. Results of the sensitivity analyses were similar to those of the main analysis. The results of these analyses should be interpreted with caution because of the small sample size and because no covariate adjustments could be made.

DISCUSSION

Our study provides several important insights into the performance of the AQLQ and ACQ in clinical trials in patients with asthma. First, it confirms that most established asthma therapies achieve a clinically significant improvement in the mean AQLQ score change when compared with baseline values. Second, it confirms that for all active asthma treatments, the placebo effect is greatest when there is no run-in period and when no controller is permitted as concurrent medication during the study period. Third, improvements in AQLQ score in placebo arms are also high in studies when ICSs are used during the run-in period. Thus not surprisingly, compared with placebo treatment arms, only groups receiving ICS plus LABA achieve a clinically significant change, and in our analysis the improvement with ICS achieved only a probably clinically significant level. Finally, when a second controller is added to ICS treatment (ie, in comparisons of placebo vs controller added to patients receiving

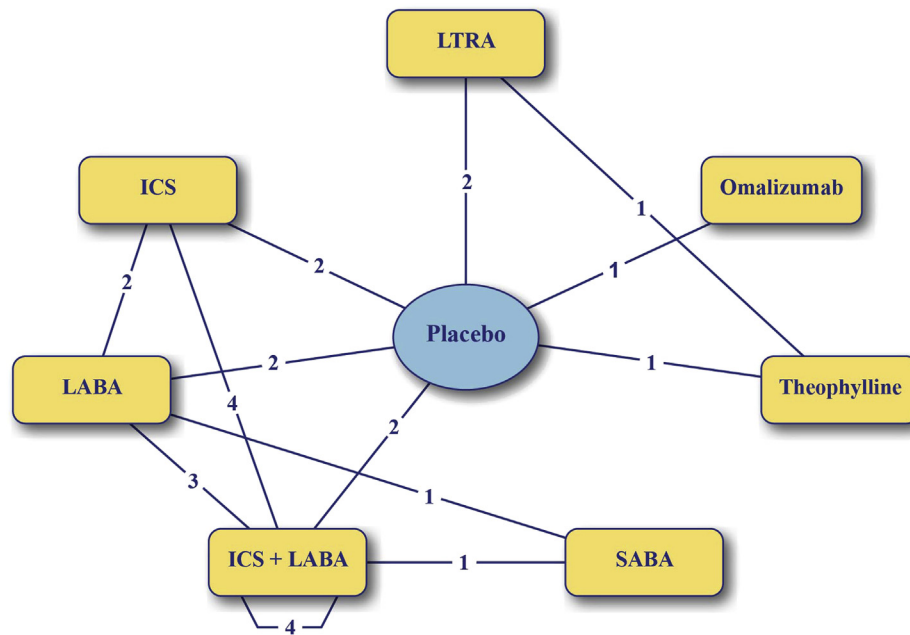


FIG 5. ACQ network of evidence. Numbers indicate the number of studies with comparisons of ACQ score changes between treatments (which could include different drugs in the same class) or different drugs in the same class in RCTs of patients with asthma. See Table E6 in this article's Online Repository for a list of studies included in this network. *SABA*, Short-acting β -agonist.

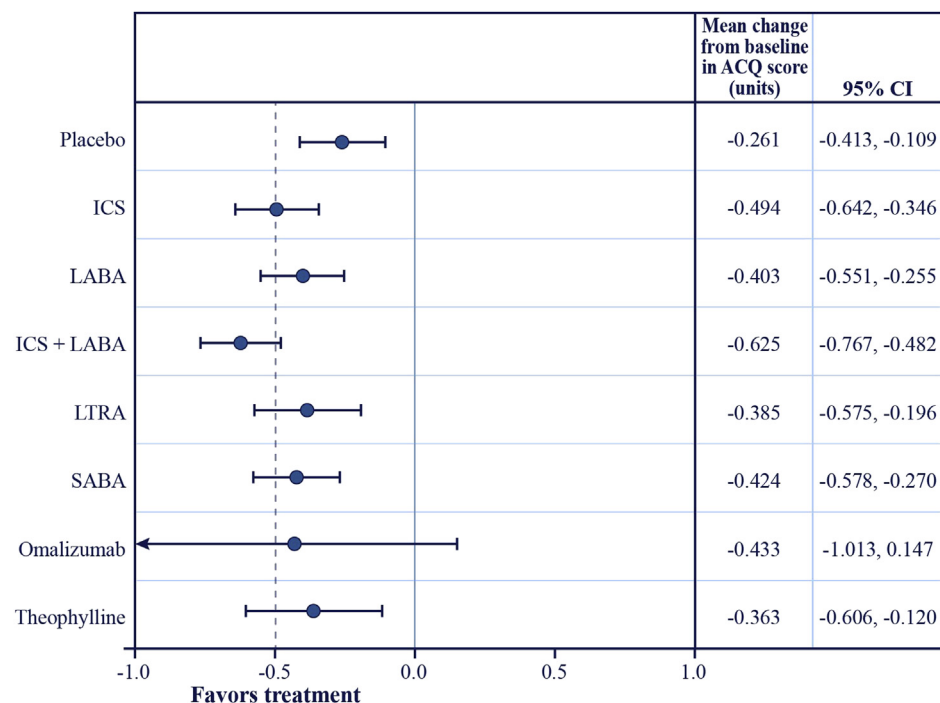


FIG 6. Adjusted mean change from baseline in overall ACQ score. *SABA*, Short-acting β -agonist.

ICSs during the active treatment phase), none of the comparators achieve a clinically significant or even a probably clinically significant result.

The results of our analysis of the ACQ are in line with those for the AQLQ, with none of the differences from placebo exceeding the MID and ICS-based treatments showing the

greatest effect. However, this conclusion should be interpreted with caution because of the smaller number of studies suitable for analysis.

This study has several limitations. Reports of trials do not present score values in a consistent manner, and baseline score values were available for only three quarters of the trials. SEs had

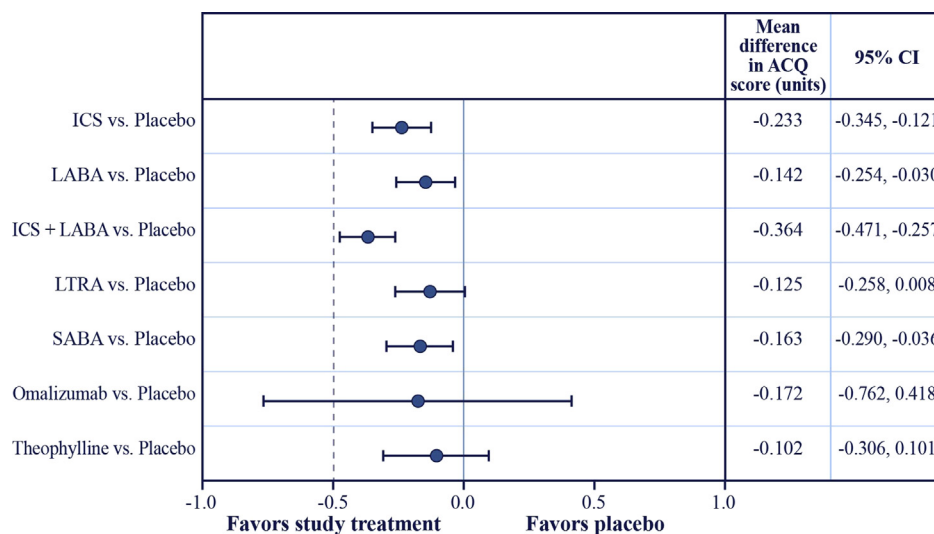


FIG 7. Differences in adjusted mean change from baseline in overall ACQ score between treatments versus placebo. *SABA*, Short-acting β -agonist.

to be derived for more than one half of the trials. Several variables (eg, FEV₁ and baseline AQLQ score) could not be used as covariates in the MTC model because of missing values.

Surprisingly, few studies with the ACQ instrument were found in the literature. In fact, only 1 double-blind RCT of omalizumab using the ACQ instrument met our inclusion criteria.²² This might be explained by a reporting bias (ie, underreporting of negative trial results).

A strength of our study was our attempt to include all reports containing usable data. Moreover, the inclusion of data for most accepted controller treatments for asthma provided the opportunity to compare the results of PROs with the accepted general efficacy of different classes of treatment. In general, the relative effects of treatments on AQLQ and ACQ responses were consistent with their place in treatment guidelines.

The results raise several questions regarding use of these widely accepted instruments in clinical studies of asthma. Both have been developed and validated by using standard methodologies and fulfill the characteristics of an evaluative instrument.^{2,5,6,10} The size (0.5 units) of the MID might be questioned. However, the finding that a 0.5-point change on a 7-point scale is the smallest change that patients can reliably report has been observed with other PROs, such as the Chronic Respiratory Disease Questionnaire.^{5,18,23} Thus it is rather a limitation and threshold of subjective perception of change than a weakness of the test and appears to be appropriate for within-subject changes. What is in question is the use of the MID for comparisons between patients or groups of patients. Although group mean improvements greater than 0.5 might be highly desirable, our analysis confirms that this is achieved only with a favorable trial design that minimizes the placebo effect and compares ICS or ICS plus LABA with placebo. The prospect of demonstrating a mean incremental benefit of greater than 0.5 through addition of a second or third controller in addition to an ICS, other controllers, or both appears remote. In these trials the Hawthorne effect²⁴ might be particularly pronounced because improved adherence with background treatment can result in improvements in all outcomes from baseline and a reduced opportunity to demonstrate benefit of the new treatment.

Faced with this limitation, how is the benefit of new treatments, particularly treatments that are added to a first- or second-line controller, to be quantified? Guyatt et al⁷ advised that even small mean differences between treatment and control might have an important effect on patients and that the method for establishing this proportion is a continuous variable suitable for analysis. The value of the change to the patients who benefit and to society or the payer is a different consideration.

The results of our study lend support to the view that these PROs should be presented in a different way, first as a comparison of responder rates or as a net treatment benefit analysis (number of responders less those who deteriorated on the treatment) from which numbers needed to treat can be calculated. Treatment comparisons can be further expressed as a “minimum worthwhile incremental advantage,” which was defined by Jones et al²³ as the percentage of patients in a treated population who experience improvement at or greater than the MID, which is considered a worthwhile benefit for the intervention.

Several factors need to be considered in arriving at a minimum worthwhile incremental advantage. A first consideration is patient need. The minimum worthwhile incremental advantage might be small in patients with severe disease (eg, asthma with frequent exacerbations, some of which might be life-threatening) in whom any benefit can be considered worthwhile. Consensus among doctors and discussion with patients can be used to test the value proposition. Considerations of adverse effects and cost to patients and society might also be relevant. For subjective outcomes, discrete-choice modeling techniques might assist in this decision.^{25,26}

Our study highlights the importance of clinical study design if the difference between treatments is under study. It is essential to use methods that reduce the placebo effect seen in patients receiving an ICS as background treatment during clinical trials. These include ensuring clinical stability of asthma control during baseline, longer run-in periods (≥ 4 weeks), avoidance of changes in medications for extended periods before and during the run-in period, and rigorous assessment of treatment adherence before and after randomization. The use of an electronic dose-monitoring device might be of value in assessing

patient behavior and adherence during run-in and treatment phases.²⁷ This is of increasing importance in assessing the utility of more expensive treatments in development for severe asthma.

Initiatives such as the Critical Path Institute, which aims to develop new PRO tools for use in asthma research, may lead to instruments that are more responsive to complex interventions,²⁸ but the threshold for the subjective perception of change might remain a limiting factor.

In conclusion, this network analysis of the magnitude of AQLQ and ACQ responses achieved with commonly used controllers for the treatment of persistent asthma confirms that for most treatments, particularly when controllers are combined, the mean difference between treatment groups exceeding the MID is probably not achievable. Future research should focus on responder analyses and consider an individualized approach based on the value of the intervention for those who respond and secondarily for society.

We thank Kate Lothman for careful and helpful edits.

Clinical implications: When compared with placebo, only an ICS, with or without a LABA, achieved the MID. A responder analysis might be more appropriate for expressing the clinical benefit of add-on treatments in patients with asthma.

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Online Repository

METHODS

Search strategy

Table E1 presents the search strategy developed for PubMed using a combination of Medical Subject Heading (MeSH) terms and key words for the studies and the treatments of interest. In some trials, values for Asthma Quality of Life Questionnaire (AQLQ) and Asthma Control Questionnaire (ACQ) scores were secondary endpoints and were not always included in the abstract of a trial publication; therefore, the search strategy was broadly developed to capture a large number studies that potentially could contain information on the questionnaires of interest. The PubMed search strategy then was translated for searching the Embase and the National Health Service Economic Evaluation Database. An updated systematic search of the three databases was conducted for the period of March 26, 2012 to June 14, 2013, with the objective of capturing new double-blind randomized controlled trials (RCTs) published during this period.

Inclusion criteria

Studies were included if they met the following PICOS criteria:

- Population: Adult and adolescent patients (i.e., aged ≥ 12 years) with uncontrolled, symptomatic, or persistent asthma at baseline
- Intervention and comparators:

- Inhaled corticosteroids (ICSs): beclomethasone, budesonide, ciclesonide, fluticasone, mometasone, triamcinolone
 - Long-acting beta-agonists (LABAs): formoterol, salmeterol
 - ICS + LABA combinations: fluticasone + salmeterol, budesonide + formoterol, mometasone + formoterol
 - Short-acting beta-agonists (SABAs): salbutamol (albuterol), terbutaline
 - Leukotriene receptor antagonists (LTRAs): montelukast (also including zafirlukast, pranlukast, and zileuton)
 - Omalizumab
 - Theophylline
 - Sodium cromoglycate
 - Placebo
- Outcomes: overall score values at baseline and at endpoint (changes from baseline to endpoint) of the AQLQ (original version or the Standardized AQLQ [AQLQ(S)], AQLQ for 12 Years and Older [AQLQ(+12)], or MiniAQLQ) and/or the ACQ (including the 5-item and 6-item versions [ACQ-5 and ACQ-6])
 - Study design: randomized controlled clinical trials (blinded or open-label trials) with 50 or more patients for trials reporting AQLQ endpoints and without size restrictions for trials reporting ACQ endpoints

The following studies were excluded: studies of patients with controlled asthma at baseline; studies of different interventions from those listed previously; validation studies of the AQLQ and ACQ; noncomparative or single-arm studies; studies with an intense treatment period with oral corticosteroids during run-in or during the study period; crossover studies; and step-down studies.

Data extraction and assessment of risk of bias

Seventy-two variables were extracted using a standardized data abstraction form developed in Microsoft Excel. To adjust for different study designs, variables such as treatment during run-in period and background medications (concomitant treatments with the intervention) also were captured. However, only the treatments placebo, ICS, LABA, or ICS + LABA were captured for the run-in period if at least 50% of patients took such medications during the run-in period; otherwise, the run-in variable was set to “none.” Similarly, for the background variable, only the treatments ICS, LABA, or ICS + LABA were captured if at least 50% of patients took such medications along with the intervention.

Two reviewers (CC and MF) independently assessed the methodological quality of the included RCTs using the National Institute for Health and Care Excellence single technology appraisal guidance^{E1} and the Centre for Reviews and Dissemination’s guidance^{E2} by answering seven questions (Table E2). For each study, each question was answered “Yes,” “No,” or “Not clear,” as appropriate, or “N/A” if the question did not apply. Information for the quality appraisal was first obtained from the original publication, but previous publications were examined for those studies for which study design or selected results had

been published previously. Disagreements between the two reviewers were resolved by consensus or by a third reviewer (DE).

Statistical methods

Based on clinical considerations and data availability, we explored the following covariates for inclusion in the mixed treatment comparison (MTC) model:

- Treatment during run-in period (i.e., none [or no run-in period], placebo, ICS, ICS + LABA)
- Duration of run-in period in weeks
- Treatments for background treatments that patients were taking during the treatment period aside from the investigational treatment (i.e., none, ICS, ICS + LABA)
- ICS dosage (i.e., none and low, medium and high)
- Asthma severity at baseline before randomization (i.e., Global Initiative for Asthma [GINA] step categories: steroid-naïve [1], mild to moderate [1, 2; or 2; or 1, 2, 3; or 2, 3], moderate to severe [3; or 3, 4; or 3, 4, 5; or 4, 5; or 5], or broad [1, 2, 3, 4; or 1, 2, 3, 4, 5; or 2, 3, 4] asthma)
- Time when measurement was captured
- ACQ instrument version (i.e., ACQ, ACQ-5) or AQLQ instrument version (AQLQ, AQLQ(S), MiniAQLQ) or AQLQ instrument type (original or other)

These covariates were considered for inclusion in the different MTC models if their *P* values were less than or equal to 0.05.

Standard error (SE) was derived from standard deviation (SD) or 95% confidence interval (CI) using the formulas (1) and (2), respectively:

$$SE = SD \cdot \sqrt{n} \quad (1)$$

$$SE = (UB - LB) / (2 \cdot 1.96) \quad (2)$$

where n is the treatment arm sample size and UB and LB are the upper and lower bounds, respectively, of the 95% CI. If neither SD nor 95% CI was provided, the SE of the AQLQ or ACQ mean change from baseline was imputed as follows: a weighted (using treatment arm size) average SD was computed using data from the studies in which SDs were extracted, and the SE then was determined according to formula (1).

In a few instances in which the treatment arm sample size used in the respective analysis could not be extracted, the randomized sample size was used instead.

Inconsistency (also called incoherence) between direct and indirect evidence, which is caused by an imbalance in the distribution of covariates between the evidence in the trials,^{E4} was tested by applying Bucher's original method^{E5} to all loops of treatments obtained from the network diagram.^{E6} Under the null hypothesis of consistency, the difference between the direct and indirect estimates divided by its variance follows a standard normal distribution. Hence, an absolute value greater than 1.965 will be an indication of inconsistency between direct and indirect evidence in the loop.

RESULTS

Systematic review and summary of included trials

The literature search identified 4,255 unique records once duplicates were removed. After level 1 and level 2 screening, 121 studies met the inclusion criteria, including 3 double-blind RCTs that were identified by the updated systematic search conducted for the period of March 26, 2012 to June 14, 2013. Of the 121 articles, 38 articles were further excluded from the meta-analysis for the following reasons: the study population was not comparable (e.g., stable asthma after the run-in period, chronic obstructive pulmonary disease and asthma mixed population, patients who left the emergency department after an asthma attack); the relevant outcomes were not reported or could not be extracted (e.g., AQLQ or ACQ scores were presented in figures and could not be read accurately, no overall scores were reported, or differences in scores were presented between treatment arms and not from baseline); the study design was not comparable (e.g., step-down study, crossover study, subanalysis of a previous trial, intense treatment period with oral corticosteroids).

Of the 83 studies remaining, 60 studies reported on 64 blinded RCTs and were included in this network meta-analysis. The 23 open-label studies were not included in this network meta-analysis.

Table E2 describes the quality assessments of the double-blinded randomized trials included in the meta-analysis.

Theophylline, omalizumab, and SABA treatment were included in fewer trials than the other treatments. For each treatment, the majority of patients were Caucasian (60%-81.6%); there

were slightly more females (56.6%-60.2%) than males, except in the theophylline trial (75% female); and the weighted mean patient age was between 37.5 and 41.6 years. Mean baseline forced expiratory volume in 1 second (FEV₁) (L) ranged from 2.18 for SABAs to 2.58 for omalizumab, and in all groups FEV₁ reversibility of > 12% was observed (see additional details in Table E3).

Table E3 presents the values of change from baseline and covariates assessed for inclusion in the MTC models for the studies with the AQLQ as an endpoint. If the SE was missing, then it was derived as described in the statistical methods summary. Tables E4 and E5 present the treatment effects and relative treatments effects on AQLQ change from baseline, respectively.

Table E6 presents the values of change from baseline and covariates assessed for inclusion in the MTC models for the studies with the ACQ as endpoint. If the SE was missing, then it was derived as described in statistical methods. Table E7 presents the relative treatments effects on ACQ change from baseline.

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Table E1. PubMed literature search strategy

Search Number	
Health condition of interest	
#1	"Asthma"[Mesh] OR asthma*[Text Word]
Questionnaires and additional terms	
#2	"Asthma Control Questionnaire"[Text Word] OR "ACQ"[Text Word] OR "Asthma Quality of Life Questionnaire"[Text Word] OR "AQLQ"[Text Word] OR "asthma control"[Text Word] OR "quality"[Text Word]
Trials	
#3	#1 AND #2 AND ("Clinical Trial, Phase III"[Publication Type] OR "Clinical Trial, Phase IV"[Publication Type] OR "Controlled Clinical Trial"[Publication Type] OR "Clinical Trials, Phase II as Topic"[Mesh] OR "Clinical Trial, Phase II"[Publication Type] OR "Multicenter Study"[Publication Type] OR "Randomized Controlled Trial"[Publication Type] OR "Clinical Trials, Phase III as Topic"[Mesh] OR "Clinical Trials, Phase IV as Topic"[Mesh] OR "Controlled Clinical Trials as Topic"[Mesh] OR "Multicenter Studies as Topic"[Mesh] OR clinical trial*[Title/Abstract] OR clinical trial*[Text Word] OR "randomized"[Title/Abstract] OR "randomised"[Title/Abstract] OR "randomized"[Text Word] OR "randomised"[Text Word] OR "randomization"[Title/Abstract] OR "randomisation"[Title/Abstract] OR "randomization"[Text Word] OR "randomisation"[Text Word] OR "open label"[Text Word])
Treatments	
#4	#1 AND #2 AND ("Seretide"[Text Word] OR "Advair"[Text Word] OR "Viani"[Text Word] OR "Adoair"[Text Word] OR "ForAir"[Text Word] OR "Foxair"[Text Word] OR "Symbicort"[Text Word] OR "Symbicord"[Text Word] OR "Rilast"[Text Word] OR "Vannair"[Text Word] OR "Dulera"[Text Word] OR "Zenhale"[Text Word] OR "Fostair"[Text Word] OR "Qvar"[Text Word] OR "beclomethasone"[Text Word] OR "Rhinocort"[Text Word] OR "Rhinosol"[Text Word] OR "Pulmicort"[Text Word] OR "Budicort"[Text Word] OR "Entocort"[Text Word] OR "budesonide"[Text Word] OR "Flovent"[Text Word] OR "Flixotide"[Text Word] OR "fluticasone"[Text Word] OR "mometasone"[Text Word] OR "Foradil"[Text Word] OR "Oxeze"[Text Word] OR "Oxis"[Text Word] OR "Atock"[Text Word] OR "Atimos"[Text Word] OR "formoterol"[Text Word] OR "eformoterol"[Text Word] OR "Serevent"[Text Word] OR "salmeterol"[Text Word] OR "vilanterol"[Text Word] OR "indacaterol"[Text Word] OR "montelukast"[Text Word] OR "Singulair"[Text Word] OR "pranlukast"[Text Word] OR "zafirlukast"[Text Word] OR "omalizumab"[Text Word] OR "Xolair"[Text Word] OR "salbutamol"[Text Word] OR "levalbuterol"[Text Word] OR "pirbuterol"[Text Word] OR "terbutaline"[Text Word] OR "fenoterol"[Text Word] OR "reproterol"[Text Word] OR "prednisolone"[Text Word] OR "prednisone"[Text Word] OR "methylprednisolone"[Text Word] OR "theophylline"[Text Word] OR "sodium cromoglycate"[Text Word])
Exclusion terms	
#5	"Animals"[Mesh] NOT "Humans"[Mesh]
#6	"Comment"[Publication Type] OR "Letter"[Publication Type] OR "Editorial"[Publication Type]
#7	"Clinical Trial, Phase I"[Publication Type] OR "Clinical Trials, Phase I as Topic"[Mesh] OR "Case Reports"[Publication Type] OR "Guideline"[Publication Type] OR "Guidelines as Topic"[Mesh] OR case report*[Title/Abstract] OR "case series"[Title/Abstract] OR "case study"[Title/Abstract] OR "case studies"[Title/Abstract] OR retrospective stud*[Title/Abstract] OR "Retrospective Studies"[Mesh] OR "prognostic"[Title/Abstract] OR animal model*[Title/Abstract]
Total with limits	
#8	(#3 OR #4) NOT (#5 OR #6 OR #7)

Note: No limits regarding date of publication or language of publication were applied for this literature search.

Table E2. Summary of quality assessments of blinded RCTs

	Was randomisation carried out appropriately?	Was the concealment of treatment allocation adequate?	Were the groups similar at the outset of the study in terms of prognostic factors, for example, severity of disease?	Were the care providers, participants and outcome assessors blind to treatment allocation? If any of these people were not blinded, what might be the likely impact on the risk of bias (for each outcome)?	Were there any unexpected imbalances in dropouts between groups? If so, were they explained or adjusted for?	Is there any evidence to suggest that the authors measured more outcomes than they reported?	Did the analysis include an intention-to-treat analysis? If so, was this appropriate and were appropriate methods used to account for missing data?
Studies evaluating ICS or ICS + LABA							
R_2: Banov et al., 2003 ^{E7}	Not clear	Not clear	Yes	Not clear	No	No	Not clear
234: Bateman et al., 2008 ^{E8}	Not clear	Not clear	Yes	Not clear	No	No	Not clear
R_6: Pearlman et al., 2005 ^{E9}	Not clear	Not clear	Yes	Not clear	No	No	Yes
102: Dahl et al., 2010 ^{E10}	Yes	Not clear	Yes	Not clear	No	No	Not clear
1396: Gross, 1998 ^{E11}	Not clear	Not clear	Yes	Yes	No	No	Yes
474: Bergmann et al., 2004 ^{E12}	Yes	Yes	Yes	Not clear	No	No	Not clear
155: Edin et al., 2009 ^{E13}	Not clear	Not clear	Yes	Not clear	No	No	Yes
R_12: NCT00461500 ^{E14}	Not clear	Not clear	Yes	Not clear	No	No	No
478: Juniper et al., 2002 ^{E15}	Not clear	Not clear	Yes	Not clear	No	No	No
267: Price et al., 2007 ^{E16}	Yes	Yes	Yes	Yes	No	No	Not clear
T_64: Bodzenta-Lukaszyk et al., 2012 ^{E17}	Yes	Not clear	Yes	Yes	No	No	Not clear
R_3: Bateman et al., 2004 ^{E18}	Yes	Not clear	Yes	Not clear	No	No	Not clear
36: Meltzer et al., 2012 ^{E19}	Not clear	Not clear	Yes	Not clear	No	No	Yes

	Was randomisation carried out appropriately?	Was the concealment of treatment allocation adequate?	Were the groups similar at the outset of the study in terms of prognostic factors, for example, severity of disease?	Were the care providers, participants and outcome assessors blind to treatment allocation? If any of these people were not blinded, what might be the likely impact on the risk of bias (for each outcome)?	Were there any unexpected imbalances in dropouts between groups? If so, were they explained or adjusted for?	Is there any evidence to suggest that the authors measured more outcomes than they reported?	Did the analysis include an intention-to-treat analysis? If so, was this appropriate and were appropriate methods used to account for missing data?
R_10: Nathan et al., 2010 ^{E20}	Not clear	Not clear	Yes	Not clear	No	No	No
R_11: NCT00941798 ^{E21}	Not clear	Not clear	Not clear	Yes	No	No	No
87: Weinstein et al., 2010 ^{E22}	Yes	Not clear	Yes	Not clear	No	No	No
718: Juniper et al., 1999 ^{E23}	Not clear	Not clear	Yes	Yes	No	No	No
176: Chervinsky et al., 2008 ^{E24}	Yes	Yes	Yes	Yes	No	No	No
449: Hampel et al., 2004 ^{E25}	Not clear	Not clear	Yes	Not clear	No	No	Not clear
563: Price et al., 2002 ^{E26}	Not clear	Not clear	Yes	Not clear	No	No	Yes
20: Spector et al., 2012 ^{E27}	Yes	Not clear	Yes	Not clear	No	No	No
T_63: Atienza et al., 2013 ^{E28}	Yes	Not clear	Yes	Yes	No	No	Yes
R_4: Bousquet et al., 2007 ^{E29}	Yes	Not clear	Yes	Not clear	No	No	Yes
13: Hoshino et al., 2012 ^{E30}	Not clear	Not clear	Yes	Yes	No	No	Not clear
283: Kuna et al., 2007 ^{E31}	Yes	Yes	Yes	Not clear	No	No	Not clear
251: Morice et al., 2007 ^{E32}	Yes	Yes	Yes	Not clear	No	No	Not clear
228: Murphy et al., 2008 ^{E33}	Yes	Not clear	Yes	Not clear	No	No	Not clear
319: Rabe et al., 2006 ^{E34}	Yes	Not clear	Yes	Not clear	No	No	Yes

	Was randomisation carried out appropriately?	Was the concealment of treatment allocation adequate?	Were the groups similar at the outset of the study in terms of prognostic factors, for example, severity of disease?	Were the care providers, participants and outcome assessors blind to treatment allocation? If any of these people were not blinded, what might be the likely impact on the risk of bias (for each outcome)?	Were there any unexpected imbalances in dropouts between groups? If so, were they explained or adjusted for?	Is there any evidence to suggest that the authors measured more outcomes than they reported?	Did the analysis include an intention-to-treat analysis? If so, was this appropriate and were appropriate methods used to account for missing data?
Studies evaluating LABAs							
505: Stahl et al., 2003 ^{E35}	Yes	Yes	Yes	Yes	No	No	Not clear
763: van der Molen et al., 1998 ^{E36}	Not clear	Not clear	Yes	Not clear	No	No	Not clear
396: LaForce et al., 2005 ^{E37}	Yes	Not clear	Yes	Yes	No	No	Yes
422: Busse et al., 2004 ^{E38}	Yes	Not clear	Yes	Yes	No	No	Not clear
734: Busse et al., 1998 ^{E39}	Not clear	Not clear	Yes	Not clear	No	No	No
780: Kemp et al., 1998 ^{E40}	Not clear	Not clear	Yes	Not clear	No	No	Not clear
742: Lockey et al., 1999 ^{E41}	Not clear	Not clear	Yes	Not clear	No	No	Not clear
Studies evaluating LTRA modifiers							
579: Meltzer et al., 2002 ^{E42}	Yes	Not clear	Yes	Not clear	No	No	Not clear
593: Pearlman et al., 2002 ^{E43}	Yes	Not clear	Yes	Not clear	No	No	Yes
312: American Lung Association Asthma Clinical Research Centers, 2007 ^{E44}	Not clear	Not clear	Yes	Not clear	No	No	Not clear
600: Dahlen et al., 2002 ^{E45}	Yes	Not clear	Yes	Not clear	No	No	Yes
770: Noonan et al., 1998 ^{E46}	Yes	Yes	Yes	Not clear	No	No	Yes
744: Malmstrom et al., 1999 ^{E47}	Yes	Yes	Yes	Yes	No	No	No

	Was randomisation carried out appropriately?	Was the concealment of treatment allocation adequate?	Were the groups similar at the outset of the study in terms of prognostic factors, for example, severity of disease?	Were the care providers, participants and outcome assessors blind to treatment allocation? If any of these people were not blinded, what might be the likely impact on the risk of bias (for each outcome)?	Were there any unexpected imbalances in dropouts between groups? If so, were they explained or adjusted for?	Is there any evidence to suggest that the authors measured more outcomes than they reported?	Did the analysis include an intention-to-treat analysis? If so, was this appropriate and were appropriate methods used to account for missing data?
392: Zeiger et al., 2005 ^{E48}	Yes	Not clear	Yes	Not clear	No	No	Not clear
140: Wise et al., 2009 ^{E49}	Yes	Yes	Yes	Yes	No	No	Yes
444: Ilowite et al., 2004 ^{E50}	Yes	Not clear	Yes	Not clear	No	No	Yes
539: Vaquerizo et al., 2003 ^{E51}	Yes	Not clear	Yes	Yes	No	No	Yes
538: Price et al., 2003 ^{E52}	Not clear	Not clear	Yes	Not clear	Not clear	No	Not clear
500: Bjermer et al., 2003 ^{E53}	Yes	Yes	Yes	Not clear	No	No	Yes
296: Lazarus et al., 2007 ^{E54}	Yes	Yes	Yes	Yes	No	No	Not clear
756: Nathan et al., 1998 ^{E55}	Yes	Not clear	Yes	Not clear	No	No	No
631: Busse et al., 2001 ^{E56}	Yes	Not clear	Yes	Yes	No	No	Not clear
664: Kim et al., 2000 ^{E57}	Yes	Not clear	Yes	Not clear	No	No	Not clear
1422_B: Israel et al., 1996 ^{E58}	Yes	Yes	Yes	Yes	Not clear	Not clear	Not clear
590_B: Wenzel et al., 2007 ^{E59}	Not clear	Not clear	Yes	Not clear	No	No	No

	Was randomisation carried out appropriately?	Was the concealment of treatment allocation adequate?	Were the groups similar at the outset of the study in terms of prognostic factors, for example, severity of disease?	Were the care providers, participants and outcome assessors blind to treatment allocation? If any of these people were not blinded, what might be the likely impact on the risk of bias (for each outcome)?	Were there any unexpected imbalances in dropouts between groups? If so, were they explained or adjusted for?	Is there any evidence to suggest that the authors measured more outcomes than they reported?	Did the analysis include an intention-to-treat analysis? If so, was this appropriate and were appropriate methods used to account for missing data?
Studies evaluating omalizumab							
543: Finn et al., 2003 ^{E60}	Not clear	Not clear	Yes	Not clear	No	No	Yes
T_12: Garcia et al., 2013 ^{E61}	Not clear	Not clear	Yes	Not clear	No	No	Yes
49: Hanania et al., 2011 ^{E62}	Yes	Yes	Yes	Yes	No	No	Not clear
411: Humbert et al., 2005 ^{E63}	Not clear	Not clear	Not clear	Yes	Not clear	Yes	Yes
454: Vignola et al., 2004 ^{E64}	Not clear	Not clear	Yes	Not clear	No	No	Yes
557: Buhl et al., 2002 ^{E65}	Not clear	Not clear	Yes	Not clear	No	No	Yes
Studies evaluating other treatments (SABAs)							
772: Wenzel et al., 1998 ^{E66}	Not clear	Not clear	Yes	Yes	No	No	Not clear

ICS, inhaled corticosteroid; LABA, long-acting beta-agonist; LTRA, leukotriene receptor antagonist; RCT, randomized controlled trial; SABA, short-acting beta-agonist

Table E3. AQLQ studies: change from baseline and covariates

Study ID	Primary author (year)	AQLQ instrument	Time point (weeks)	Treatment class	AQLQ mean (SE)	Baseline AQLQ	Asthma severity at randomization	ICS dosage	Run-in treatment	Run-in duration (weeks)	Background treatment class
312	American Lung Association (2007) ^{E44}	AQLQ	24	LTRA	0.8 (0.10)	4.2	Broad	None	ICS	2	ICS
				THEOPH	0.7 (0.08)	4.2	Broad	None	ICS	2	ICS
				PLCBO	0.8 (0.10)	4.2	Broad	None	ICS	2	ICS
R_2	Banov (2003) ^{E7}	AQLQ	12	ICS	1.1 (0.08)	4.1	Steroid-naïve	Low	None	2	None
				PLCBO	0.6 (0.11)	4.0	Steroid-naïve	None	None	2	None
R_3_a	Bateman (2004) ^{E18}	AQLQ	36	ICS	1.4 (0.10)	4.5	Steroid-naïve	High	None	4	None
				ICS + LABA	1.6 (0.10)	4.4	Steroid-naïve	High	None	4	None
R_3_b	Bateman (2004) ^{E18}	AQLQ	36	ICS	1.2 (0.10)	4.5	Mild to moderate	High	ICS	4	None
				ICS + LABA	1.3 (0.10)	4.7	Mild to moderate	High	ICS	4	None
R_3_c	Bateman (2004) ^{E18}	AQLQ	24	ICS	1.0 (0.10)	4.5	Moderate to severe	High	ICS	4	None
				ICS + LABA	1.2 (0.10)	4.5	Moderate to severe	High	ICS	4	None
234	Bateman (2008) ^{E8}	AQLQ(S)	12	ICS	0.3 (0.06)	.	Moderate to severe	Low	ICS	4	None
				ICS	0.5 (0.06)	.	Moderate to severe	High	ICS	4	None
474	Bergmann (2004) ^{E12}	AQLQ	12	ICS	0.8 (0.08)	.	Moderate to severe	High	ICS	2	None
				ICS + LABA	1.1 (0.09)	.	Moderate to severe	Medium	ICS	2	None
500	Bjermer (2003) ^{E53}	AQLQ	48	LABA	0.8 (0.04)	4.7	Mild to moderate	None	ICS	4	ICS
				LTRA	0.7 (0.04)	4.7	Mild to moderate	None	ICS	4	ICS

Study ID	Primary author (year)	AQLQ instrument	Time point (weeks)	Treatment class	AQLQ mean (SE)	Baseline AQLQ	Asthma severity at randomization	ICS dosage	Run-in treatment	Run-in duration (weeks)	Background treatment class
T_64	Bodzenta-Lukaszyk (2012) ^{E17}	AQLQ	12	ICS + LABA	0.8 (0.09)	.	Mild to moderate	Medium	ICS	4	None
				ICS + LABA	0.8 (0.09)	.	Mild to moderate	Medium	ICS	4	None
734	Busse (1998) ^{E39}	AQLQ	12	LABA	1.2 (0.08)	3.9	Mild to moderate	None	ICS	2	ICS
				PLCBO	0.7 (0.07)	4.0	Mild to moderate	None	ICS	2	ICS
176	Chervinsky (2008) ^{E24}	AQLQ(S)	12	ICS	0.2 (0.11)	5.1	Mild to moderate	Medium	ICS	2	None
				LABA	-0.1 (0.11)	5.2	Mild to moderate	None	ICS	2	None
				ICS + LABA	0.6 (0.11)	5.2	Mild to moderate	Medium	ICS	2	None
				ICS + LABA	0.4 (0.11)	5.3	Mild to moderate	Medium	ICS	2	None
				PLCBO	-0.2 (0.11)	5.2	Mild to moderate	None	ICS	2	None
102	Dahl (2010) ^{E10}	AQLQ(S)	24	ICS	0.4 (0.05)	5.5	Steroid-naive	Low	None	4	None
				ICS	0.5 (0.05)	5.5	Steroid-naive	Low	None	4	None
600	Dahlen (2002) ^{E45}	AQLQ	4	LTRA	0.5 (0.15)	.	Broad	None	ICS	2	ICS
				PLCBO	0.1 (0.17)	.	Broad	None	ICS	2	ICS
155a	Edin (2009) ^{E13}	AQLQ	12	ICS	0.8 (0.12)	4.8	Mild to moderate	Low	ICS	2	None
				LABA	0.5 (0.12)	4.9	Mild to moderate	None	ICS	2	None
				ICS + LABA	1.3 (0.12)	4.6	Mild to moderate	Low	ICS	2	None
				PLCBO	0.2 (0.12)	4.9	Mild to moderate	None	ICS	2	None

Study ID	Primary author (year)	AQLQ instrument	Time point (weeks)	Treatment class	AQLQ mean (SE)	Baseline AQLQ	Asthma severity at randomization	ICS dosage	Run-in treatment	Run-in duration (weeks)	Background treatment class
155b	Edin (2009) ^{E13}	AQLQ	12	ICS	0.4 (0.12)	5.1	Moderate to severe	Low	ICS	2	None
				LABA	0.3 (0.12)	4.8	Moderate to severe	None	ICS	2	None
				ICS + LABA	0.9 (0.11)	4.9	Moderate to severe	Low	ICS	2	None
				PLCBO	-0.2 (0.12)	4.9	Moderate to severe	None	ICS	2	None
543	Finn (2003) ^{E60}	AQLQ	16	OMALZ	0.9 (0.07)	4.0	Mild to moderate	None	ICS	6	ICS
				PLCBO	0.7 (0.07)	4.2	Mild to moderate	None	ICS	6	ICS
1396	Gross (1998) ^{E11}	AQLQ	24	ICS	0.4 (0.11)	.	Mild to moderate	Medium	ICS	3	None
				ICS	0.0 (0.11)	.	Mild to moderate	Low	ICS	3	None
				PLCBO	-0.5 (0.11)	.	Mild to moderate	None	ICS	3	None
449	Hampel (2004) ^{E25}	AQLQ	12	ICS	0.4 (0.12)	4.9	Broad	Low	ICS	2	None
				PLCBO	-0.4 (0.12)	4.7	Broad	None	ICS	2	None
49	Hanania (2011) ^{E62}	AQLQ(S)	48	OMALZ	1.2 (0.05)	4.0	Moderate to severe	None	ICS + LABA	4	ICS + LABA
				PLCBO	0.9 (0.05)	3.9	Moderate to severe	None	ICS + LABA	4	ICS + LABA
13	Hoshino (2012) ^{E30}	AQLQ	24	ICS	0.7 (0.23)	.	Steroid-naïve	Medium	None	0	None
				ICS + LABA	1.1 (0.21)	.	Steroid-naïve	Medium	None	0	None
411	Humbert (2005) ^{E63}	AQLQ	28	OMALZ	0.9 (0.08)	3.9	Moderate to severe	None	ICS + LABA	8	ICS + LABA
				PLCBO	0.5 (0.08)	3.9	Moderate to severe	None	ICS + LABA	8	ICS + LABA
444	Ilowite (2004) ^{E50}	AQLQ	48	LABA	0.9 (0.03)	4.8	Mild to moderate	None	ICS	4	ICS
				LTRA	0.8 (0.03)	4.7	Mild to moderate	None	ICS	4	ICS

Study ID	Primary author (year)	AQLQ instrument	Time point (weeks)	Treatment class	AQLQ mean (SE)	Baseline AQLQ	Asthma severity at randomization	ICS dosage	Run-in treatment	Run-in duration (weeks)	Background treatment class
1422	Israel (1996) ^{E58}	AQLQ	13	LTRA	0.6 (0.11)	4.2	Steroid-naïve	None	Placebo	1.5	None
				LTRA	0.8 (0.11)	4.2	Steroid-naïve	None	Placebo	1.5	None
				PLCBO	0.4 (0.11)	4.1	Steroid-naïve	None	Placebo	1.5	None
718	Juniper (1999) ^{E23}	AQLQ	12	ICS	1.1 (0.09)	4.5	Mild to moderate	Medium	None	2	None
				ICS	1.2 (0.09)	4.5	Mild to moderate	Low	None	2	None
				PLCBO	0.2 (0.09)	4.5	Mild to moderate	None	None	2	None
478	Juniper (2002) ^{E15}	AQLQ	12	ICS	0.4 (0.10)	.	Moderate to severe	High	ICS	2	None
				ICS + LABA	0.9 (0.11)	.	Moderate to severe	Medium	ICS	2	None
780	Kemp (1998) ^{E40}	AQLQ	12	LABA	1.1 (0.08)	4.3	Mild to moderate	None	ICS	2	ICS
				PLCBO	0.6 (0.07)	4.3	Mild to moderate	None	ICS	2	ICS
664	Kim (2000) ^{E57}	AQLQ	6	ICS	0.6 (0.07)	.	Mild to moderate	Low	ICS	1	None
				LTRA	0.1 (0.08)	.	Mild to moderate	None	ICS	1	None
283	Kuna (2007) ^{E31}	AQLQ(S)	24	ICS + LABA	0.8 (0.03)	.	Moderate to severe	Medium	ICS	2	None
				ICS + LABA	0.8 (0.03)	.	Moderate to severe	Medium	ICS	2	None
				ICS + LABA	0.8 (0.03)	.	Moderate to severe	Medium	ICS	2	None
296_a	Lazarus (2007) ^{E54}	AQLQ	8	ICS	0.1 (0.10)	6.0	Steroid-naïve	Low	Placebo	8	None
				LTRA	0.2 (0.10)	6.0	Steroid-naïve	None	Placebo	8	None
296_b	Lazarus (2007) ^{E54}	AQLQ	8	ICS	0.1 (0.13)	5.6	Steroid-naïve	Low	Placebo	8	None
				LTRA	0.1 (0.13)	5.6	Steroid-naïve	None	Placebo	8	None
742	Lockey (1999) ^{E41}	AQLQ	12	LABA	1.4 (0.07)	3.9	Mild to moderate	None	ICS	2	ICS
				PLCBO	0.7 (0.07)	4.0	Mild to moderate	None	ICS	2	ICS

Study ID	Primary author (year)	AQLQ instrument	Time point (weeks)	Treatment class	AQLQ mean (SE)	Baseline AQLQ	Asthma severity at randomization	ICS dosage	Run-in treatment	Run-in duration (weeks)	Background treatment class
744	Malmstrom (1999) ^{E47}	AQLQ	12	ICS	0.8 (0.08)	.	Steroid-naïve	Low	Placebo	2	None
				LTRA	0.6 (0.07)	.	Steroid-naïve	None	Placebo	2	None
				PLCBO	0.3 (0.08)	.	Steroid-naïve	None	Placebo	2	None
579	Meltzer (2002) ^{E42}	AQLQ	24	ICS	1.3 (0.10)	.	Steroid-naïve	Low	None	2	None
				LTRA	1.0 (0.10)	.	Steroid-naïve	None	None	2	None
36	Meltzer (2012) ^{E19}	AQLQ(S)	26	ICS	0.4 (0.08)	5.7	Mild to moderate	Low	ICS	3	None
				LABA	0.2 (0.08)	5.7	Mild to moderate	None	ICS	3	None
				ICS + LABA	0.4 (0.08)	5.7	Mild to moderate	Low	ICS	3	None
				PLCBO	0.1 (0.08)	5.8	Mild to moderate	None	ICS	3	None
251	Morice (2007) ^{E32}	AQLQ(S)	12	ICS	0.4 (0.08)	4.8	Mild to moderate	Medium	ICS	2	None
				ICS + LABA	0.8 (0.07)	4.6	Mild to moderate	Medium	ICS	2	None
				ICS + LABA	0.7 (0.07)	4.7	Mild to moderate	Medium	ICS	2	None
228	Murphy (2008) ^{E33}	AQLQ(S)	12	ICS	0.7 (0.11)	5.1	Steroid-naïve	Low	Placebo	2	None
				LABA	0.4 (0.12)	5.1	Steroid-naïve	None	Placebo	2	None
				ICS + LABA	0.8 (0.11)	5.2	Steroid-naïve	Low	Placebo	2	None
				PLCBO	0.1 (0.11)	5.1	Steroid-naïve	None	Placebo	2	None
R_12	NCT00461500 (2012) ^{E14}	AQLQ	12	ICS	1.1 (0.16)	.	Steroid-naïve	Low	None	0	None
				ICS + LABA	1.0 (0.16)	.	Steroid-naïve	Low	None	0	None
756	Nathan (1998) ^{E55}	AQLQ	13	LTRA	0.8 (0.08)	4.3	Steroid-naïve	None	Placebo	3	None
				PLCBO	0.5 (0.08)	4.3	Steroid-naïve	None	Placebo	3	None

Study ID	Primary author (year)	AQLQ instrument	Time point (weeks)	Treatment class	AQLQ mean (SE)	Baseline AQLQ	Asthma severity at randomization	ICS dosage	Run-in treatment	Run-in duration (weeks)	Background treatment class
R_10	Nathan (2010) ^{E20}	AQLQ(S)	26	ICS	0.4 (0.06)	5.4	Moderate to severe	Medium	ICS	3	None
				LABA	0.1 (0.06)	5.5	Moderate to severe	None	ICS	3	None
				ICS + LABA	0.5 (0.06)	5.4	Moderate to severe	Medium	ICS	3	None
				PLCBO	−0.0 (0.06)	5.6	Moderate to severe	None	ICS	3	None
770	Noonan (1998) ^{E46}	AQLQ	3	LTRA	0.7 (0.10)	.	Mild to moderate	None	Placebo	2	None
				LTRA	0.5 (0.10)	.	Mild to moderate	None	Placebo	2	None
				LTRA	0.8 (0.10)	.	Mild to moderate	None	Placebo	2	None
				PLCBO	0.4 (0.13)	.	Mild to moderate	None	Placebo	2	None
593	Pearlman (2002) ^{E43}	AQLQ	12	ICS + LABA	1.7 (0.08)	4.2	Steroid-naïve	Low	None	2	None
				LTRA	1.2 (0.07)	4.2	Steroid-naïve	None	None	2	None
R_6	Pearlman (2005) ^{E9}	AQLQ	12	ICS	0.6 (0.06)	4.7	Steroid-naïve	Low	Placebo	4	None
				ICS	0.7 (0.06)	4.7	Steroid-naïve	Medium	Placebo	4	None
				ICS	0.5 (0.06)	4.6	Steroid-naïve	Low	Placebo	4	None
				PLCBO	0.1 (0.06)	4.8	Steroid-naïve	None	Placebo	4	None
563	Price (2002) ^{E26}	MiniAQLQ	4	ICS	0.5 (0.06)	.	Mild to moderate	Medium	ICS	2	None
				ICS + LABA	0.7 (0.06)	.	Mild to moderate	Medium	ICS	2	None
538	Price (2003) ^{E52}	AQLQ	12	ICS	0.6 (0.05)	4.7	Moderate to severe	High	ICS	4	None
				LTRA	0.7 (0.05)	4.7	Moderate to severe	None	ICS	4	ICS
267	Price (2007) ^{E16}	AQLQ	52	ICS + LABA	0.9 (0.07)	4.8	Moderate to severe	Medium	ICS	2	None
				ICS + LABA	1.1 (0.07)	4.8	Moderate to severe	Medium	ICS	2	None

Study ID	Primary author (year)	AQLQ instrument	Time point (weeks)	Treatment class	AQLQ mean (SE)	Baseline AQLQ	Asthma severity at randomization	ICS dosage	Run-in treatment	Run-in duration (weeks)	Background treatment class
20	Spector (2012) ^{E27}	AQLQ(S)	12	ICS	0.3 (0.10)	.	Mild to moderate	Medium	ICS	2	None
				ICS + LABA	0.6 (0.09)	.	Mild to moderate	Medium	ICS	2	None
505	Stahl (2003) ^{E35}	AQLQ	12	LABA	0.4 (0.08)	4.9	Mild to moderate	None	ICS	2	ICS
				SABA	0.2 (0.08)	4.8	Mild to moderate	None	ICS	2	ICS
763	van der Molen (1998) ^{E36}	AQLQ	28	LABA	0.2 (0.15)	5.7	Mild to moderate	None	ICS	4	ICS
				PLCBO	0.1 (0.15)	5.7	Mild to moderate	None	ICS	4	ICS
539	Vaquerizo (2003) ^{E51}	AQLQ	16	LTRA	0.6 (0.05)	.	Mild to moderate	None	ICS	2	ICS
				PLCBO	0.5 (0.05)	.	Mild to moderate	None	ICS	2	ICS
87	Weinstein (2010) ^{E22}	AQLQ(S)	12	ICS	0.5 (0.05)	4.9	Moderate to severe	High	ICS	3	None
				ICS + LABA	0.6 (0.05)	5.0	Moderate to severe	High	ICS	3	None
				ICS + LABA	0.5 (0.05)	4.9	Moderate to severe	High	ICS	3	None
772	Wenzel (1998) ^{E66}	AQLQ	12	LABA	0.8 (0.07)	4.7	Mild to moderate	None	None	2	None
				SABA	0.5 (0.07)	4.7	Mild to moderate	None	None	2	None
590_B	Wenzel (2007) ^{E59}	AQLQ	26	LTRA	0.7 (0.04)	4.7	Mild to moderate	None	ICS	2	ICS
				PLCBO	0.6 (0.06)	4.6	Mild to moderate	None	ICS	2	ICS
140	Wise (2009) ^{E49}	MiniAQLQ	4	LTRA	0.5 (0.08)	5.0	Broad	None	ICS	2	ICS
				PLCBO	0.4 (0.08)	5.1	Broad	None	ICS	2	ICS
392	Zeiger (2005) ^{E48}	AQLQ	12	ICS	0.8 (0.08)	5.1	Steroid-naïve	Low	Placebo	3	None
				LTRA	0.7 (0.08)	5.0	Steroid-naïve	None	Placebo	3	None

AQLQ, Asthma Quality of Life Questionnaire; AQLQ(S), Standardized Asthma Quality of Life Questionnaire; *GINA*, Global Initiative for Asthma; *ICS*, inhaled corticosteroid; *LABA*, long-acting beta-agonist; *LTRA*, leukotriene receptor antagonist; *OMALZ*, omalizumab; *PLCBO*, placebo; *SABA*, short-acting beta-agonist; *SE*, standard error; *THEOPH*, theophylline.

Table E4. Estimated AQLQ change from baseline by treatment, run-in treatment, background treatment, and AQLQ instrument type

Treatment	Adjusted estimates (95% CI)					
	No run-in		Placebo run-in		ICS run-in	
	No ICS background	ICS background	No ICS background	ICS background	No ICS background	ICS background
Original AQLQ						
ICS	1.092 (0.911 to 1.272)	N/A	0.729 (0.549 to 0.909)	N/A	0.632 (0.512 to 0.753)	N/A
LABA	0.782 (0.588 to 0.976)	1.353 (1.135 to 1.570)	0.419 (0.223 to 0.616)	0.990 (0.773 to 1.207)	0.323 (0.178 to 0.467)	0.894 (0.768 to 1.019)
ICS + LABA	1.281 (1.098 to 1.465)	N/A	0.919 (0.734 to 1.104)	N/A	0.822 (0.698 to 0.946)	N/A
LTRA	0.867 (0.676 to 1.057)	1.202 (0.990 to 1.414)	0.504 (0.324 to 0.685)	0.839 (0.628 to 1.051)	0.407 (0.269 to 0.546)	0.742 (0.623 to 0.862)
SABA	0.425 (0.166 to 0.684)	1.067 (0.756 to 1.377)	0.063 (−0.206 to 0.331)	0.704 (0.394 to 1.015)	−0.034 (−0.268 to 0.200)	0.607 (0.354 to 0.860)
Omalizumab	N/A	1.309 (1.071 to 1.548)	N/A	0.947 (0.709 to 1.185)	N/A	0.850 (0.693 to 1.007)
Theophylline	N/A	1.015 (0.722 to 1.307)	N/A	0.652 (0.360 to 0.944)	N/A	0.555 (0.324 to 0.787)
Placebo	0.553 (0.367 to 0.739)	1.004 (0.785 to 1.223)	0.190 (0.008 to 0.373)	0.642 (0.423 to 0.860)	0.093 (−0.036 to 0.223)	0.545 (0.420 to 0.670)

Treatment	Adjusted estimates (95% CI)					
	No run-in		Placebo run-in		ICS run-in	
	No ICS background	ICS background	No ICS background	ICS background	No ICS background	ICS background
AQLQ(S) or MiniAQLQ						
ICS	0.902 (0.666 to 1.138)	N/A	0.539 (0.304 to 0.775)	N/A	0.442 (0.292 to 0.593)	N/A
LABA	0.592 (0.347 to 0.837)	1.163 (0.883 to 1.443)	0.230 (−0.017 to 0.476)	0.800 (0.520 to 1.081)	0.133 (−0.035 to 0.300)	0.704 (0.525 to 0.883)
ICS + LABA	1.092 (0.855 to 1.329)	N/A	0.729 (0.491 to 0.967)	N/A	0.632 (0.481 to 0.784)	N/A
LTRA	0.677 (0.432 to 0.922)	1.012 (0.737 to 1.287)	0.314 (0.077 to 0.552)	0.649 (0.375 to 0.924)	0.217 (0.050 to 0.385)	0.552 (0.380 to 0.725)
SABA	0.235 (−0.064 to 0.534)	0.877 (0.518 to 1.235)	−0.127 (−0.434 to 0.180)	0.514 (0.156 to 0.873)	−0.224 (−0.474 to 0.025)	0.417 (0.132 to 0.703)
Omalizumab	N/A	1.119 (0.824 to 1.415)	N/A	0.757 (0.461 to 1.052)	N/A	0.660 (0.460 to 0.860)
Theophylline	N/A	0.825 (0.483 to 1.166)	N/A	0.462 (0.121 to 0.804)	N/A	0.365 (0.100 to 0.630)
Placebo	0.363 (0.123 to 0.603)	0.814 (0.533 to 1.095)	0.000 (−0.237 to 0.238)	0.452 (0.171 to 0.732)	−0.096 (−0.254 to 0.061)	0.355 (0.177 to 0.533)

AQLQ, Asthma Quality of life Questionnaire; *CI*, confidence interval; *ICS*, inhaled corticosteroid; *LABA*, long-acting beta-agonist; *LTRA*, leukotriene receptor antagonist; *N/A*, no trials were available; *SABA*, short-acting beta-agonist.

Table E5. Relative treatment effects for AQLQ change from baseline

Treatment A (background)	Mean difference A-B (95% CI) [P value]											
	Treatment B (background)											
	ICS (none)	LABA (none)	LABA (ICS)	ICS + LABA (none)	LTRA (none)	LTRA (ICS)	SABA (none)	SABA (ICS)	OMALZ (ICS)	THEOPH (ICS)	PLCBO (none)	PLCBO (ICS)
ICS (none)	N/A	0.310 (0.221 to 0.399) [< 0.001]	−0.261 (−0.389 to −0.133) [< 0.001]	−0.190 (−0.242 to −0.138) [< 0.001]	0.225 (0.147 to 0.303) [< 0.001]	−0.110 (−0.228 to 0.008) [0.068]	0.667 (0.461 to 0.872) [< 0.001]	0.025 (−0.232 to 0.282) [0.848]	−0.218 (−0.380 to −0.055) [0.009]	0.077 (−0.158 to 0.312) [0.517]	0.539 (0.479 to 0.599) [< 0.001]	0.088 (−0.042 to 0.218) [0.184]
LABA (none)	−0.310 (−0.399 to −0.221) [< 0.001]	N/A	−0.571 (−0.725 to −0.417) [< 0.001]	−0.500 (−0.591 to −0.408) [< 0.001]	−0.085 (−0.198 to 0.028) [0.140]	−0.420 (−0.565 to −0.274) [< 0.001]	0.357 (0.170 to 0.544) [< 0.001]	−0.285 (−0.556 to −0.014) [0.039]	−0.527 (−0.710 to −0.345) [< 0.001]	−0.233 (−0.482 to 0.017) [0.067]	0.229 (0.135 to 0.323) [< 0.001]	−0.222 (−0.377 to −0.067) [0.005]
LABA (ICS)	0.261 (0.133 to 0.389) [< 0.001]	0.571 (0.417 to 0.725) [< 0.001]	N/A	0.071 (−0.063 to 0.206) [0.297]	0.486 (0.338 to 0.634) [< 0.001]	0.151 (0.091 to 0.211) [< 0.001]	0.928 (0.687 to 1.168) [< 0.001]	0.286 (0.059 to 0.513) [0.014]	0.044 (−0.085 to 0.172) [0.502]	0.338 (0.125 to 0.552) [0.002]	0.800 (0.661 to 0.939) [< 0.001]	0.349 (0.271 to 0.427) [< 0.001]
ICS + LABA (none)	0.190 (0.138 to 0.242) [< 0.001]	0.500 (0.408 to 0.591) [< 0.001]	−0.071 (−0.206 to 0.063) [0.297]	N/A	0.415 (0.328 to 0.502) [< 0.001]	0.080 (−0.046 to 0.205) [0.210]	0.856 (0.650 to 1.063) [< 0.001]	0.215 (−0.046 to 0.475) [0.105]	−0.028 (−0.195 to 0.139) [0.743]	0.267 (0.028 to 0.505) [0.029]	0.729 (0.658 to 0.799) [< 0.001]	0.278 (0.142 to 0.414) [< 0.001]
LTRA (none)	−0.225 (−0.303 to −0.147) [< 0.001]	0.085 (−0.028 to 0.198) [0.140]	−0.486 (−0.634 to −0.338) [< 0.001]	−0.415 (−0.502 to −0.328) [< 0.001]	N/A	−0.335 (−0.475 to −0.195) [< 0.001]	0.442 (0.225 to 0.658) [< 0.001]	−0.200 (−0.468 to 0.068) [0.142]	−0.443 (−0.621 to −0.264) [< 0.001]	−0.148 (−0.394 to 0.098) [0.237]	0.314 (0.230 to 0.398) [< 0.001]	−0.137 (−0.287 to 0.012) [0.071]
LTRA (ICS)	0.110 (−0.008 to 0.228) [0.068]	0.420 (0.274 to 0.565) [< 0.001]	−0.151 (−0.211 to −0.091) [< 0.001]	−0.080 (−0.205 to 0.046) [0.210]	0.335 (0.195 to 0.475) [< 0.001]	N/A	0.777 (0.541 to 1.012) [< 0.001]	0.135 (−0.099 to 0.369) [0.255]	−0.108 (−0.231 to 0.016) [0.088]	0.187 (−0.021 to 0.395) [0.077]	0.649 (0.519 to 0.779) [< 0.001]	0.198 (0.127 to 0.269) [< 0.001]
SABA (none)	−0.667 (−0.872 to −0.461) [< 0.001]	−0.357 (−0.544 to −0.170) [< 0.001]	−0.928 (−1.168 to −0.687) [< 0.001]	−0.856 (−1.063 to −0.650) [< 0.001]	−0.442 (−0.658 to −0.225) [< 0.001]	−0.777 (−1.012 to −0.541) [< 0.001]	N/A	−0.642 (−0.969 to −0.314) [< 0.001]	−0.884 (−1.144 to −0.624) [< 0.001]	−0.589 (−0.900 to −0.279) [< 0.001]	−0.128 (−0.335 to 0.080) [0.226]	−0.579 (−0.820 to −0.338) [< 0.001]

Mean difference A-B (95% CI) [P value]												
Treatment A (background)	Treatment B (background)											
	ICS (none)	LABA (none)	LABA (ICS)	ICS + LABA (none)	LTRA (none)	LTRA (ICS)	SABA (none)	SABA (ICS)	OMALZ (ICS)	THEOPH (ICS)	PLCBO (none)	PLCBO (ICS)
SABA (ICS)	−0.025 (−0.282 to 0.232) [0.848]	0.285 (0.014 to 0.556) [0.039]	−0.286 (−0.513 to −0.059) [0.014]	−0.215 (−0.475 to 0.046) [0.105]	0.200 (−0.068 to 0.468) [0.142]	−0.135 (−0.369 to 0.099) [0.255]	0.642 (0.314 to 0.969) [< 0.001]	N/A	−0.243 (−0.502 to 0.017) [0.066]	0.052 (−0.258 to 0.362) [0.740]	0.514 (0.251 to 0.777) [< 0.001]	0.063 (−0.176 to 0.301) [0.604]
OMALZ (ICS)	0.218 (0.055 to 0.380) [0.009]	0.527 (0.345 to 0.710) [< 0.001]	−0.044 (−0.172 to 0.085) [0.502]	0.028 (−0.139 to 0.195) [0.743]	0.443 (0.264 to 0.621) [< 0.001]	0.108 (−0.016 to 0.231) [0.088]	0.884 (0.624 to 1.144) [< 0.001]	0.243 (−0.017 to 0.502) [0.066]	N/A	0.295 (0.063 to 0.526) [0.013]	0.756 (0.586 to 0.927) [< 0.001]	0.305 (0.202 to 0.408) [< 0.001]
THEOPH (ICS)	−0.077 (−0.312 to 0.158) [0.517]	0.233 (−0.017 to 0.482) [0.067]	−0.338 (−0.552 to −0.125) [0.002]	−0.267 (−0.505 to −0.028) [0.029]	0.148 (−0.098 to 0.394) [0.237]	−0.187 (−0.395 to 0.021) [0.077]	0.589 (0.279 to 0.900) [< 0.001]	−0.052 (−0.362 to 0.258) [0.740]	−0.295 (−0.526 to −0.063) [0.013]	N/A	0.462 (0.221 to 0.703) [< 0.001]	0.011 (−0.198 to 0.219) [0.920]
PLCBO (none)	−0.539 (−0.599 to −0.479) [< 0.001]	−0.229 (−0.323 to −0.135) [< 0.001]	−0.800 (−0.939 to −0.661) [< 0.001]	−0.729 (−0.799 to −0.658) [< 0.001]	−0.314 (−0.398 to −0.230) [< 0.001]	−0.649 (−0.779 to −0.519) [< 0.001]	0.128 (−0.080 to 0.335) [0.226]	−0.514 (−0.777 to −0.251) [< 0.001]	−0.756 (−0.927 to −0.586) [< 0.001]	−0.462 (−0.703 to −0.221) [< 0.001]	N/A	−0.451 (−0.592 to −0.310) [< 0.001]
PLCBO (ICS)	−0.088 (−0.218 to 0.042) [0.184]	0.222 (0.067 to 0.377) [0.005]	−0.349 (−0.427 to −0.271) [< 0.001]	−0.278 (−0.414 to −0.142) [< 0.001]	0.137 (−0.012 to 0.287) [0.071]	−0.198 (−0.269 to −0.127) [< 0.001]	0.579 (0.338 to 0.820) [< 0.001]	−0.063 (−0.301 to 0.176) [0.604]	−0.305 (−0.408 to −0.202) [< 0.001]	−0.011 (−0.219 to 0.198) [0.920]	0.451 (0.310 to 0.592) [< 0.001]	N/A

The MTC model includes treatment, run-in treatment, background treatment, AQLQ instrument type, and treatment by background treatment interaction as fixed effects and study as a random effect. Treatment As are presented in the first column; treatment Bs are presented in the first row; each cell presents the mean difference between the corresponding A and B in change of AQLQ from baseline.

AQLQ, Asthma Quality of Life Questionnaire; CI, confidence interval; ICS, inhaled corticosteroid; LABA, long-acting beta-agonist; LTRA, leukotriene receptor antagonist; MTC, mixed treatment comparison; N/A, data not available; OMALZ, omalizumab; PLCBO, placebo; SABA, short-acting beta-agonist; THEOPH, theophylline.

Table E6. ACQ studies: change from baseline and covariates

Study ID	Primary author (year)	ACQ instrument	Time point (weeks)	Treatment class	ACQ mean (SE)	Baseline ACQ	Asthma severity at randomization	ICS dosage	Run-in treatment	Run-in duration (weeks)	Background treatment class
312	American Lung Association (2007) ^{E44}	ACQ	24	LTRA	−0.7 (0.05)	2.3	Broad	None	ICS	2	ICS
				THEOPH	−0.7 (0.08)	2.4	Broad	None	ICS	2	ICS
				PLCBO	−0.7 (0.08)	2.3	Broad	None	ICS	2	ICS
T_63	Atienza (2013) ^{E28}	ACQ	52	ICS + LABA	−0.6 (0.03)	1.9	Moderate to severe	Medium	ICS + LABA	2	None
				ICS + LABA	−0.7 (0.03)	1.9	Moderate to severe	Medium	ICS + LABA	2	None
R_4	Bousquet (2007) ^{E29}	ACQ-5	24	ICS + LABA	−0.8 (0.03)	1.9	Moderate to severe	High	ICS + LABA	2	None
				ICS + LABA	−0.8 (0.03)	1.8	Moderate to severe	Medium	ICS + LABA	2	None
T_12	Garcia (2013) ^{E61}	ACQ-5	16	OMALZ	−0.5 (0.22)	2.2	Moderate to severe	None	ICS + LABA	2	ICS + LABA
				PLCBO	−0.5 (0.31)	2.2	Moderate to severe	None	ICS + LABA	2	ICS + LABA
283	Kuna (2007) ^{E31}	ACQ-5	24	ICS + LABA	−0.8 (0.03)	.	Moderate to severe	Medium	ICS	2	None
				ICS + LABA	−0.7 (0.03)	.	Moderate to severe	Medium	ICS	2	None
				ICS + LABA	−0.8 (0.03)	.	Moderate to severe	Medium	ICS	2	None
36	Meltzer (2012) ^{E19}	ACQ	26	ICS	−0.3 (0.07)	1.3	Mild to moderate	Low	ICS	3	None
				LABA	−0.1 (0.07)	1.4	Mild to moderate	None	ICS	3	None
				ICS + LABA	−0.4 (0.07)	1.3	Mild to moderate	Low	ICS	3	None
				PLCBO	−0.1 (0.07)	1.2	Mild to moderate	None	ICS	3	None

Study ID	Primary author (year)	ACQ instrument	Time point (weeks)	Treatment class	ACQ mean (SE)	Baseline ACQ	Asthma severity at randomization	ICS dosage	Run-in treatment	Run-in duration (weeks)	Background treatment class
R_11	NCT00941798 (2012) ^{E21}	ACQ	84	ICS	−0.3 (0.05)	.	Moderate to severe	Medium	ICS + LABA	2	None
				ICS + LABA	−0.6 (0.05)	.	Moderate to severe	Medium	ICS + LABA	2	None
R_10	Nathan (2010) ^{E20}	ACQ	26	ICS	−0.2 (0.05)	1.5	Moderate to severe	Medium	ICS	3	None
				LABA	0.1 (0.05)	1.4	Moderate to severe	None	ICS	3	None
				ICS + LABA	−0.4 (0.06)	1.5	Moderate to severe	Medium	ICS	3	None
				PLCBO	0.1 (0.05)	1.4	Moderate to severe	None	ICS	3	None
319	Rabe (2006) ^{E34}	ACQ-5	52	LABA	−0.5 (0.03)	1.9	Moderate to severe	None	ICS	2	ICS
				ICS + LABA	−0.6 (0.03)	1.9	Moderate to severe	Low	ICS	2	ICS
				SABA	−0.5 (0.03)	1.9	Moderate to severe	None	ICS	2	ICS
87	Weinstein (2010) ^{E22}	ACQ	12	ICS	−0.4 (0.04)	1.9	Moderate to severe	High	ICS	3	None
				ICS + LABA	−0.6 (0.04)	1.9	Moderate to severe	High	ICS	3	None
				ICS + LABA	−0.6 (0.04)	2.0	Moderate to severe	High	ICS	3	None
140	Wise (2009) ^{E49}	ACQ	4	LTRA	−0.4 (0.08)	1.6	Broad	None	ICS	2	ICS
				PLCBO	−0.2 (0.05)	1.5	Broad	None	ICS	2	ICS

ACQ, Asthma Control Questionnaire; ACQ-5, Asthma Control Questionnaire, 5-item version; GINA, Global Initiative for Asthma; ICS, inhaled corticosteroid; LABA, long-acting beta-agonist; LTRA, leukotriene receptor antagonist; OMALZ, omalizumab; PLCBO, placebo; SABA, short-acting beta-agonist; SE, standard error; THEOPH, theophylline

Table E7. Relative Treatment Effects for ACQ change from baseline

Treatment A	Mean difference A-B (95% CI) [P value]							
	Treatment B							
	ICS	LABA	ICS + LABA	LTRA	SABA	OMALZ	THEOPH	PLCBO
ICS	N/A	−0.091 (−0.180 to −0.002) [0.045]	0.131 (0.060 to 0.201) [0.001]	−0.109 (−0.280 to 0.062) [0.201]	−0.070 (−0.174 to 0.033) [0.173]	−0.061 (−0.653 to 0.531) [0.832]	−0.131 (−0.361 to 0.099) [0.249]	−0.233 (−0.345 to −0.121) [< 0.001]
LABA	0.091 (0.002 to 0.180) [0.045]	N/A	0.222 (0.153 to 0.291) [< 0.001]	−0.017 (−0.188 to 0.153) [0.834]	0.021 (−0.061 to 0.102) [0.601]	0.030 (−0.562 to 0.622) [0.918]	−0.040 (−0.270 to 0.190) [0.722]	−0.142 (−0.254 to −0.030) [0.015]
ICS + LABA	−0.131 (−0.201 to −0.060) [0.001]	−0.222 (−0.291 to −0.153) [< 0.001]	N/A	−0.239 (−0.407 to −0.072) [0.007]	−0.201 (−0.283 to −0.119) [< 0.001]	−0.192 (−0.782 to 0.398) [0.507]	−0.262 (−0.489 to −0.035) [0.026]	−0.364 (−0.471 to −0.257) [< 0.001]
LTRA	0.109 (−0.062 to 0.280) [0.201]	0.017 (−0.153 to 0.188) [0.834]	0.239 (0.072 to 0.407) [0.007]	N/A	0.038 (−0.143 to 0.220) [0.665]	0.047 (−0.555 to 0.650) [0.872]	−0.022 (−0.210 to 0.165) [0.806]	−0.125 (−0.258 to 0.008) [0.065]
SABA	0.070 (−0.033 to 0.174) [0.173]	−0.021 (−0.102 to 0.061) [0.601]	0.201 (0.119 to 0.283) [< 0.001]	−0.038 (−0.220 to 0.143) [0.665]	N/A	0.009 (−0.586 to 0.604) [0.975]	−0.061 (−0.298 to 0.177) [0.601]	−0.163 (−0.290 to −0.036) [0.014]
OMALZ	0.061 (−0.531 to 0.653) [0.832]	−0.030 (−0.622 to 0.562) [0.918]	0.192 (−0.398 to 0.782) [0.507]	−0.047 (−0.650 to 0.555) [0.872]	−0.009 (−0.604 to 0.586) [0.975]	N/A	−0.070 (−0.691 to 0.552) [0.818]	−0.172 (−0.762 to 0.418) [0.552]
THEOPH	0.131 (−0.099 to 0.361) [0.249]	0.040 (−0.190 to 0.270) [0.722]	0.262 (0.035 to 0.489) [0.026]	0.022 (−0.165 to 0.210) [0.806]	0.061 (−0.177 to 0.298) [0.601]	0.070 (−0.552 to 0.691) [0.818]	N/A	−0.102 (−0.306 to 0.101) [0.308]

Mean difference A-B (95% CI) [P value]								
Treatment A	Treatment B							
	ICS	LABA	ICS + LABA	LTRA	SABA	OMALZ	THEOPH	PLCBO
PLCBO	0.233 (0.121 to 0.345) [< 0.001]	0.142 (0.030 to 0.254) [0.015]	0.364 (0.257 to 0.471) [< 0.001]	0.125 (−0.008 to 0.258) [0.065]	0.163 (0.036 to 0.290) [0.014]	0.172 (−0.418 to 0.762) [0.552]	0.102 (−0.101 to 0.306) [0.308]	N/A

The MTC model includes treatment as a fixed effect and study as a random effect. Treatment As are presented in the first column; treatment Bs are presented in the first row; each cell presents the mean difference between the corresponding A and B in change of ACQ from baseline.

ACQ, Asthma Control Questionnaire; CI, confidence interval; ICS, inhaled corticosteroid; LABA, long-acting beta-agonist; LTRA, leukotriene receptor antagonist; MTC, mixed treatment comparison; N/A, data not available; OMALZ, omalizumab; PLCBO, placebo; SABA, short-acting beta-agonist; THEOPH, theophylline.