

The Safety and Efficacy of Anti-IL-13 Treatment with Tralokinumab (CAT-354) in Moderate to Severe Asthma: A Systematic Review and Meta-Analysis



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What is already known about this topic? Several clinical studies have evaluated the use of tralokinumab (CAT-354) administration in patients with moderate to severe asthma; no consensus on tralokinumab's efficacy and safety was reached. Thus, further analysis is required on the efficacy and safety of tralokinumab as an asthma biologic.

What does this article add to our knowledge? In this pooled analysis of 6 randomized clinical trials, treatment with tralokinumab was well tolerated and it modestly improved FEV₁ and forced vital capacity in patients with moderate to severe asthma. It did not render clinically important improvements in asthma control and asthma-related quality of life, and nor did it reduce asthma exacerbations.

How does this study impact current management guidelines? Use of the drug confers modest improvements in lung function and quality of life that are of limited clinical relevance to individual patients. Further analysis of efficacy within specific subgroups is warranted.

BACKGROUND: Several clinical studies have evaluated the use of tralokinumab (CAT-354) administration in patients with moderate to severe asthma; no consensus on tralokinumab efficacy and safety was reached. Thus, further analysis is required on the efficacy and safety of tralokinumab as an asthma biologic. **OBJECTIVE:** To assess the efficacy and safety of subcutaneous injection of tralokinumab in patients with moderate to severe asthma.

METHODS: Clinical trials were identified from MEDLINE, EMBASE, Cochrane Central Register of Controlled Trials, and [ClinicalTrials.gov](https://www.clinicaltrials.gov) from their inception to November 4, 2018. Only randomized clinical trials (RCTs) with tralokinumab versus placebo treatment in patients with moderate to severe asthma were evaluated. Efficacy and safety outcomes were extracted, and a meta-analysis was performed using a random-effects model. The Cochrane Collaboration's risk-of-bias assessment tool was used to assess the risk of bias.

RESULTS: Five studies describing 6 RCTs (including 2928 adults with moderate to severe asthma) were pooled and analyzed in this study. Absolute FEV₁ was statistically improved in patients receiving tralokinumab at 300 mg every 2 weeks (mean difference [MD], 0.14 L; 95% CI, 0.08-0.21) and 600 mg every 2 weeks (MD, 0.20 L; 95% CI, 0.01-0.39), as well as FEV₁% changes (MD, 5.82%, 95% CI, 3.58-8.06, and MD, 11.8%, 95% CI, 0.79-22.81, respectively). Also, absolute forced vital capacity volume changes (MD, 0.11 L; 95% CI, 0.01-0.21) and percentage changes (MD, 4.44%; 95% CI, 0.84-8.04) improved in tralokinumab at 300 mg every 2 weeks. Asthma Quality of Life Questionnaire scores were not significantly different, and absolute Asthma Control Questionnaire 6 scores were statistically improved but did not reach the clinically meaningful difference. Tralokinumab treatment did not decrease annualized asthma exacerbation rate in unselected patients with moderate to severe asthma, but it was associated with improved annualized asthma exacerbation rate in patients with severe asthma with high fractional exhaled nitric oxide levels (rate ratio, 0.72; 95% CI, 0.53-0.97). Tralokinumab was not associated with an increased incidence of serious adverse events, but it did show an increase in mild injection-site reactions (odds ratio, 5.92; 95% CI, 1.61-21.76).

CONCLUSION: This pooled analysis of 6 RCTs suggested that tralokinumab was well tolerated and it modestly improved FEV₁ and forced vital capacity in patients with moderate to severe asthma. It did not render clinically important improvements in asthma-related quality of life, and nor did it reduce asthma exacerbations. © 2019 American Academy of Allergy, Asthma & Immunology (J Allergy Clin Immunol Pract 2019;7:2661-71)

Key words: Moderate to severe asthma; IL-13; Tralokinumab; Efficacy; Safety

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Abbreviations used

AAER- Annualized asthma exacerbation rate
 ACQ-6- Asthma control questionnaire 6
 AE- adverse effect
 AQLQ- Asthma quality of life questionnaire
 FENO- Fractional exhaled nitric oxide
 FVC- Forced vital capacity
 MD- Mean difference
 MID- Minimally important difference
 RCT- Randomized clinical trial
 RR- Relative risk

INTRODUCTION

Asthma is a chronic inflammatory disease of the airways affecting approximately 300 million people worldwide.^{1,2} Despite sufficient medical therapy, approximately 20% of patients are unable to control their symptoms and asthma exacerbations, leading to frequent hospitalization.³ Severe uncontrolled asthma is characterized by excessive symptoms such as persistent dyspnea despite administration of high doses of inhaled corticosteroids in addition to a second controller.⁴

Asthma is associated with T_H2 inflammatory response modulated by the release of cytokines IL-4, IL-5, and IL-13.⁵ Increased expression of IL-13 mRNA has been reported in bronchial biopsies of patients with asthma,^{6,7} whereas upregulated concentrations of IL-13 in the sputum have been detected in corticosteroid-naïve patients with asthma compared with those who were treated with corticosteroids.⁸ Multiple animal studies have demonstrated that IL-13 mediates mucus production, goblet cell hyperplasia, IgE synthesis, airway remodeling, and fibrosis.⁹⁻¹³ Thus, targeting IL-13 may have clinical benefits for the treatment of asthma.

Talokinumab (CAT-354) is a fully humanized IgG₄ mAb, which specifically and effectively neutralizes IL-13 interaction with IL-13 receptor α 1/2.^{14,15} Recently, several clinical studies have evaluated the efficacy and safety of talokinumab (CAT-354) for the treatment of moderate to severe asthma. However, the reported efficacy of talokinumab therapy on lung function, frequency of asthma exacerbation, and quality of life has been inconsistent. In this meta-analysis, we systematically analyzed and evaluated the safety and efficacy of talokinumab in moderate to severe asthma to determine its clinical potential.

METHODS

The present study was conducted in accordance with the Preferred Reporting Items for Systematic Reviews and Meta-Analyses guidelines¹⁶ and registered in PROSPERO (http://www.crd.york.ac.uk/PROSPERO/display_record.php?ID=CRD42018116113).

Search strategy

We searched and retrieved data from EMBASE, MEDLINE, Cochrane Central Register of Controlled Trials (CENTRAL), and the Latin American and Caribbean Health Science Information databases to include studies from their inception to November 4, 2018. Search terms included “asthma” AND “talokinumab” OR “CAT-354.” The following Chinese medical databases were also searched: Wanfang, China National Knowledge Infrastructure, Chinese Scientific Journals Database/VIP Information, and Chinese

Biomedical Literature Database. In addition, we searched the ClinicalTrials.gov, the metaRegister of Controlled Trials, the Australian New Zealand Clinical Trials Registry (ANZCTR), the World Health Organization International Clinical Trials Registry Platform (WHO ICTRP), and the European Union Clinical Trials Register.

We also searched the unpublished trials from the US Food and Drug Administration. Publications in English, French, Spanish, German, and Chinese were considered.

Study selection

Two independent reviewers (Y.Z. and J.C.) screened the titles and abstracts using the aforementioned search strategies to identify and assess potentially eligible studies. A third reviewer (Y.L.) resolved disagreements between the first 2 reviewers. All the trials met the inclusion and exclusion criteria described herein.

Inclusion criteria. Eligible studies met the following PICOS (participants, interventions, comparators, outcomes, and study design) criteria. The included study types were randomized clinical trials (RCTs). Participants had physician-diagnosed moderate to severe asthma, with no restrictions on age, sex, race, or ethnicity. The intervention was talokinumab (CAT-354), irrespective of dosage, frequency, and course duration. The comparator was placebo, and efficacy and safety outcomes were evaluated.

Exclusion criteria. Duplicate publications, nonhuman studies, conference abstracts, and studies that did not report on prespecified outcomes were excluded.

Data extraction

The following information was extracted and included in the analysis: study features including first author and year of publication, ClinicalTrials.gov identifier, source of funding, asthma clinical phenotypes, number of participants, sex, age, intervention details (dosage and frequency of drugs, duration of treatment), and pre-specified outcomes.

Outcomes

The efficacy outcomes included in the study were (1) lung function: FEV₁ volume (L) and percentage changes from baseline and forced vital capacity (FVC) volume (L) and percentage changes from baseline; (2) asthma control: Asthma Control Questionnaire 6 (ACQ-6) score and Asthma Quality of Life Questionnaire (AQLQ) score; and (3) asthma exacerbation: annualized asthma exacerbation rate (AAER).

The safety outcomes included in the study were at least 1 adverse effect (AE), at least 1 serious AE, treatment discontinuation due to AEs, upper respiratory tract infection, headache, gastrointestinal disorders, and injection-site reaction.

All the efficacy outcomes were reported consistently as end-of-study measurements across the included studies. The ACQ-6 is a patient-reported questionnaire that assesses the asthma control with 6 items.¹⁷ The AQLQ is a questionnaire with 32 items to evaluate the quality of life of patients with asthma.¹⁸ The ACQ-6 and AQLQ are widely used patient-reported outcomes in asthma clinical trials. For both instruments, the accepted minimally important difference (MID) is 0.5 unit, which represents the smallest difference in a score that can be perceived as having a clinically significant effect in patients' management.^{19,20} The MID for improvement and worsening in FEV₁ is about 10%^{21,22}; however, this was based on patient perception and is not well established. An asthma exacerbation was defined as an increase

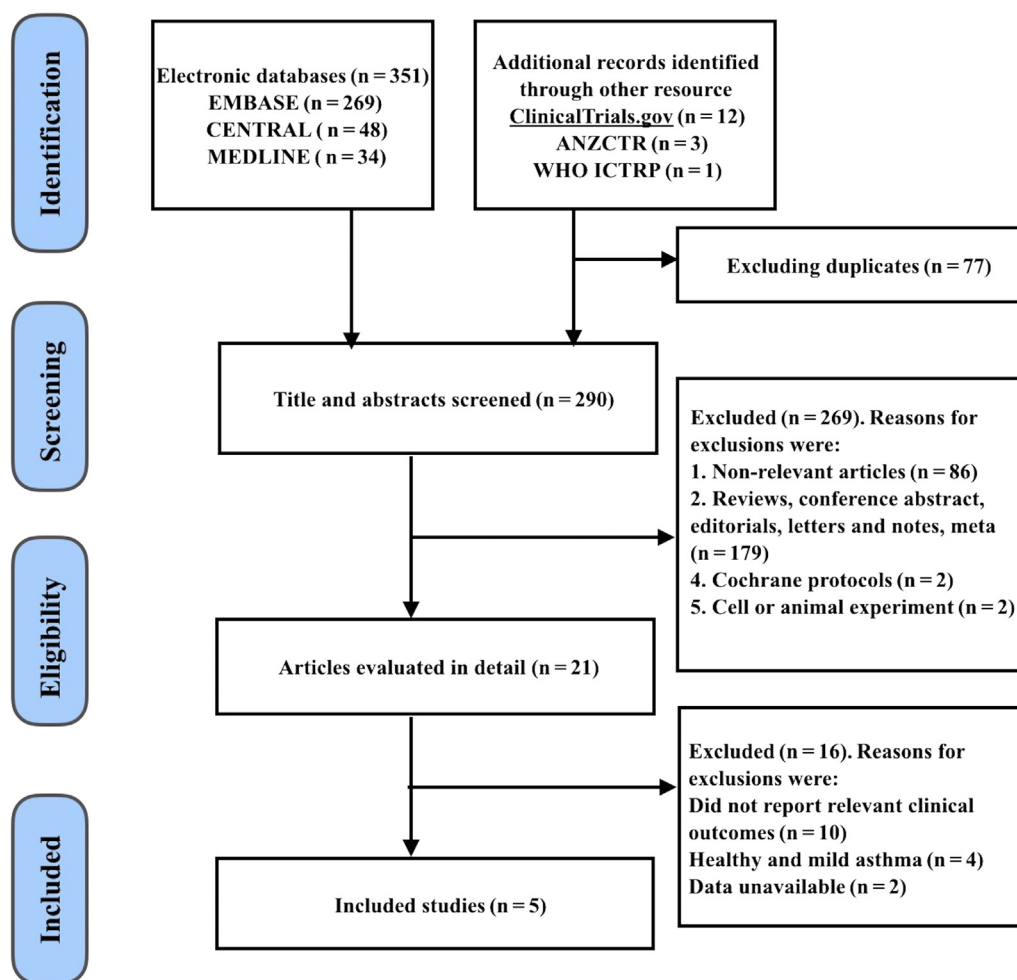


FIGURE 1. Flow diagram of literature search and study selection.

in asthma symptoms that led to a temporary increase in systemic corticosteroids for more than 3 consecutive days or that resulted in an emergency department visit or urgent care because of asthma that led to a temporary increase in systemic corticosteroids or an in-patient hospitalization because of asthma. AAER was calculated using the following equation: $AAER = \text{Number of exacerbations} \times 365.25 / (\text{Follow-up date} - \text{Date of randomization} + 1)$.

Assessment of risk of bias

Two reviewers (Y.Z. and J.C.) independently performed a quality assessment of the included RCTs according to the *Cochrane Handbook for Systematic Reviews of Interventions*.²³ The included RCTs were assessed for random sequence generation, allocation concealment, blinding of participants and health care personnel, blinding of outcome assessment, incomplete outcome data, selective reporting, and other biases. Disagreements were resolved by a third reviewer (Y.L.).

Assessment of reporting bias

We could not examine a funnel plot to explore possible publication bias for fewer than 10 trials.

Statistical analysis

The statistical analysis was performed using Review Manager 5.3 software (The Nordic Cochrane Centre, Copenhagen,

Denmark). Dichotomous data were summarized by relative risk (RR) and 95% CIs. Continuous data using similar scales were calculated by using mean differences (MDs) and SDs. When appropriate, SDs were calculated from the reported standard error. Statistical significance was assumed at a *P* value of less than .05. Random-effects model was used to pool the data in this meta-analysis, which enables the generalizability of results by assuming that the analyzed studies are a random sample of effect sizes and take into account both within-study and between-study variability. Heterogeneity was assessed using the Cochran Q test and quantified with the I^2 statistic. An I^2 value of greater than 50% or a *P* value of less than .10 was defined as substantial heterogeneity.

Specific subgroups based on the dosage and frequency of tralokinumab treatment were planned. In addition, fractional exhaled nitric oxide (FENO) level has been used as a biomarker of type 2 or eosinophilic-dominated inflammation by allergen exposure because IL-4- and IL-13-mediated epithelial stress leads to the production of nitric oxide. Baseline FENO level of 37 ppb or higher was first identified as the optimal biomarker to predict an enhanced response to tralokinumab in the study of STRATOS 1,²⁴ and this cutoff value of FENO was subsequently applied to the studies of STRATOS 2²⁴ and TROPOS.²⁵ Therefore, a post hoc meta-analysis with respect to AAER was conducted on the basis of FENO levels (cutoff value = 37 ppb).

TABLE I. Characteristics of the included studies (RCTs)

Participant characteristics																
Study	Clinical trial identified	Study design	Source of funding	Asthma severity	Participant characteristics								Tralokinumab dosage/ frequency	Duration of treatment	Assessed outcomes	
					Tralokinumab group				Placebo group							
					No. of participants/ no. of males Age (y)	Race (%)	Lung function	Life quality	No. of participants/ no. of males Age (y)	Race (%)	Lung function	Life quality				
Piper et al ²⁷	NCT00873860	A phase IIa, randomized, double-blind, placebo-controlled, parallel-group, multicenter study	MedImmune	Moderate to severe asthma	FEV ₁ reversibility $\geq 12\%$ and ≥ 200 mL either documented within the previous year or at screening), prebronchodilator FEV ₁ $\geq 40\%$ predicted value, ACQ-6 ≥ 1.5 at screening and randomization, and 1 or more asthma exacerbation that required medical intervention in the past year	146/63 47.4 $\pm$ 11.1	White (93.2)	FEV ₁ 2.01 $\pm$ 0.65 FVC 3.26 $\pm$ 1.02 AQLQ 4.07 $\pm$ 0.87	ACQ-6 2.68 $\pm$ 0.63 AQLQ 4.07 $\pm$ 0.87	48/15 47.2 $\pm$ 9.8	White (87.5)	FEV ₁ 1.94 $\pm$ 0.48 FVC 3.25 $\pm$ 0.80 AQLQ 4.15 $\pm$ 0.83	ACQ-6 2.60 $\pm$ 0.54 AQLQ 4.15 $\pm$ 0.83	Tralokinumab (150, 300, or 600 mg) or placebo (Q2W)	12 wk	ACQ-6, FEV1, FVC, and AEs
Brightling et al ²⁸	NCT01402986	A randomized, double-blind, multicenter, placebo-controlled phase IIb trial	MedImmune	Severe uncontrolled asthma	A documented history of asthma ≥ 1 y, and either a documented increase in postbronchodilator FEV ₁ $\geq 12\%$ or 200 mL or a positive methacholine challenge ($PC_{20} \leq 8$ mg/mL) in the previous 3 y, or an increase in postbronchodilator FEV ₁ $\geq 12\%$ or 200 mL	301/101 50.1 $\pm$ 12.0	Asian (35) White (56) Others (9)	FEV ₁ 1.93 $\pm$ 0.69 FVC 2.55 $\pm$ 1.02 AQLQ 3.99 $\pm$ 1.02	ACQ-6 2.55 $\pm$ 1.02 AQLQ 3.99 $\pm$ 1.02	151/54 50.3 $\pm$ 12.9	Asian (34) White (56) Others (10)	FEV ₁ 1.92 $\pm$ 0.60 FVC 2.54 $\pm$ 0.88 AQLQ 4.01 $\pm$ 1.03	ACQ-6 2.54 $\pm$ 0.88 AQLQ 4.01 $\pm$ 1.03	Tralokinumab 300 mg (Q2W, Q4W) or placebo	52 wk	AAER, FEV1, ACQ-6, AQLQ, and AEs
Russell et al ²⁶	NCT02449473 (MESOS)	A multicenter, double-blind, randomized, placebo-controlled phase II trial	AstraZeneca	Moderate to severe asthma inadequately controlled with ICS	A documented history of physician-diagnosed asthma for ≥ 12 mo, requiring treatment with ICS (≥ 250 μ g/d of fluticasone or equivalent) at a stable dose with or without other asthma controller medications; postbronchodilator FEV ₁ reversibility $\geq 12\%$ or ≥ 200 mL, and ACQ-6 ≥ 1.5 during the run-in period	39/16 47.1 $\pm$ 14.3	White (87) Black (5) Asian (8)	FEV ₁ 2.46 $\pm$ 0.79 FVC 2.24 $\pm$ 0.83 3.74 $\pm$ 1.08	ACQ-6 2.24 $\pm$ 0.83	40/20 50.1 $\pm$ 14.2	White (98) Black (3) Asian (0)	FEV ₁ 2.37 $\pm$ 0.62 FVC 2.12 $\pm$ 0.86 3.73 $\pm$ 0.91	ACQ-6 2.12 $\pm$ 0.86	Tralokinumab 300 mg (Q2W) or placebo	12 wk	ACQ-6, FEV1, FVC, and AEs

Panettieri et al ²⁴	NCT02161757 (STRATOS1)	A global randomized, double-blind, parallel-group, placebo-controlled phase III clinical trial	AstraZeneca	Severe asthma inadequately controlled with ICS/LABA	A history of physician-diagnosed asthma for >1 y, requiring medium- to high-dose ICS (total daily dose ≥ 500 μ g fluticasone or equivalent) and a LABA for at least 3 mo before visit 1; postbronchodilator FEV ₁ reversibility of $\geq 12\%$ and ≥ 200 mL	802/269 50.3 $\pm$ 14.1	White (71.6) Black (5.3) Asian (13.3)	FEV ₁ 1.8 $\pm$ 0.6 FVC 2.8 $\pm$ 0.9	ACQ-6 2.6 $\pm$ 0.8 AQLQ 4.2 $\pm$ 0.9	400/135 51.4 $\pm$ 14.3	White (72) Black (3.5) Asian (13.8)	FEV ₁ 1.8 $\pm$ 0.6 FVC 2.8 $\pm$ 0.9	ACQ-6 2.60 $\pm$ 0.90 AQLQ 4.20 $\pm$ 1.0	Tralokinumab 300 mg or placebo (Q2W, Q4W)	52 wk	AAER, FEV1, ACQ-6, AQLQ, and AEs
	NCT02194699 (STRATOS2)	A global randomized, double-blind, parallel-group, placebo-controlled phase III clinical trial	AstraZeneca	Severe asthma inadequately controlled with ICS/LABA	A history of physician-diagnosed asthma for >1 y, requiring medium- to high-dose ICS (total daily dose ≥ 500 μ g fluticasone or equivalent) and a LABA for at least 3 mo before visit 1; postbronchodilator FEV ₁ reversibility of $\geq 12\%$ and ≥ 200 mL	420/144 47.3 $\pm$ 15.6	White (67.4) Black (6.4) Asian (19.8)	FEV ₁ 1.8 $\pm$ 0.6 FVC 2.8 $\pm$ 0.9	ACQ-6 2.4 $\pm$ 0.9 AQLQ 4.3 $\pm$ 1.0	417/127 48.0 $\pm$ 15.5	White (67.4) Black (5.8) Asian (21.1)	FEV ₁ 1.8 $\pm$ 0.6 FVC 2.7 $\pm$ 0.8	ACQ-6 2.60 $\pm$ 0.90 AQLQ 4.10 $\pm$ 1.0	Tralokinumab 300 mg or placebo (Q2W)	52 wk	AAER, FEV1, ACQ-6, AQLQ, and AEs
Busse et al ²⁵	NCT02281357 (TROPOS)	A multicenter, randomized, double-blind, parallel-group, placebo-controlled phase III study	AstraZeneca	Severe asthma that requires maintenance OCS in addition to ICS/LABA	Asthma history ≥ 12 mo, with a daily requirement of medium- or high-dose ICS (total daily dose ≥ 500 μ g fluticasone propionate dry powder or an equivalent delivered dose) for ≥ 6 mo of the 12 mo before enrollment; physician-prescribed ICS (total daily dose ≥ 500 μ g fluticasone propionate dry powder formulation equivalent) and a LABA for ≥ 3 mo before enrollment; OCS treatment for 6 mo before visit 1; and a stable OCS daily dose between ≥ 7.5 mg and ≤ 30 mg (prednisone or prednisolone equivalent) daily or daily equivalent for ≥ 1 mo before enrollment	70/22 54 $\pm$ 11.05	White (94.3) Others (5.7)	FEV ₁ 1.69 $\pm$ 0.59 FVC 2.87 $\pm$ 0.84	ACQ-6 2.4 $\pm$ 1.12 AQLQ 4.4 $\pm$ 1.15	70/31 55.4 $\pm$ 10.26	White (90) Others (10)	FEV ₁ 1.65 $\pm$ 0.68 FVC 2.81 $\pm$ 0.98	ACQ-6 2.5 $\pm$ 1.26 AQLQ 4.4 $\pm$ 1.29	Tralokinumab 300 mg or placebo (Q2W)	40 wk	FEV1, ACQ-6, AQLQ, AAER, and AEs

Note. Participant characteristics are presented as mean $\pm$ SD.

ICS, Inhaled corticosteroid; LABA, long-acting β -agonist; OCS, oral corticosteroid; Q2W, every 2 wk; Q4W, every 4 wk.

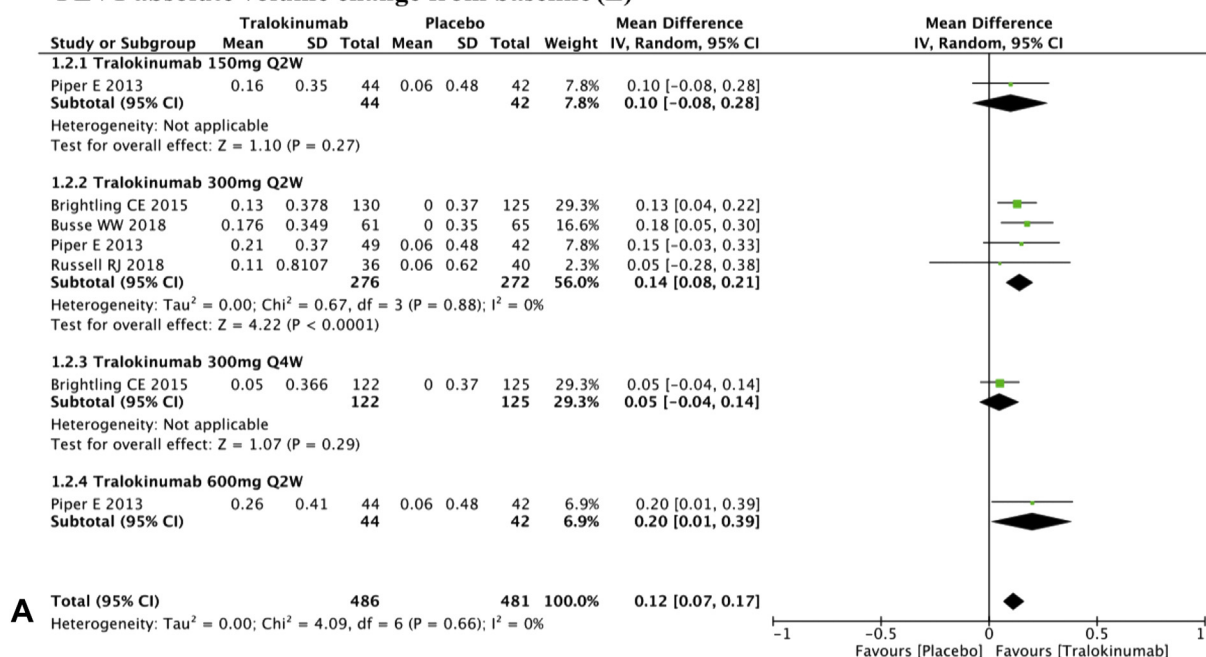
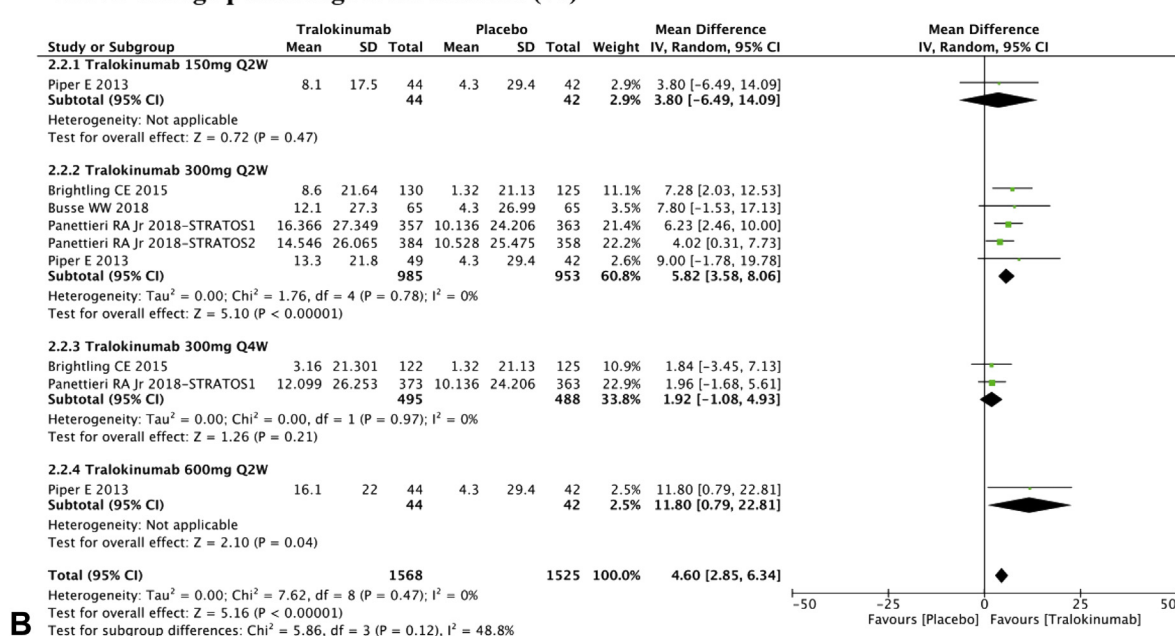
FEV₁ absolute volume change from baseline (L)**FEV₁ change percentage from baseline (%)**

FIGURE 2. Effect of tralokinumab vs placebo on change in FEV₁ from baseline. **A**, Forest plot for absolute FEV₁ volume changes (L) from baseline between the tralokinumab group and the placebo group. **B**, Forest plot for absolute FEV₁ volume percentage changes from baseline between the tralokinumab group and the placebo group.

RESULTS**Search results and characteristics of included studies**

We identified 351 citations in the CENTRAL, MEDLINE, and EMBASE databases, and 16 records from other resources of ClinicalTrials.gov, ANZCTR, and WHO ICTRP. We excluded 346 articles on the basis of duplications, screening titles, and

published abstracts. An additional 16 articles were excluded after reviewing the full texts. Finally, a total of 5 studies that included 6 RCTs met our selection criteria.²⁴⁻²⁸ The flowchart for screening studies is shown in [Figure 1](#). Data from 2928 patients with moderate to severe asthma were included in this meta-analysis. All the included RCTs were randomized, double-blind, placebo-controlled, parallel-group, and multicenter

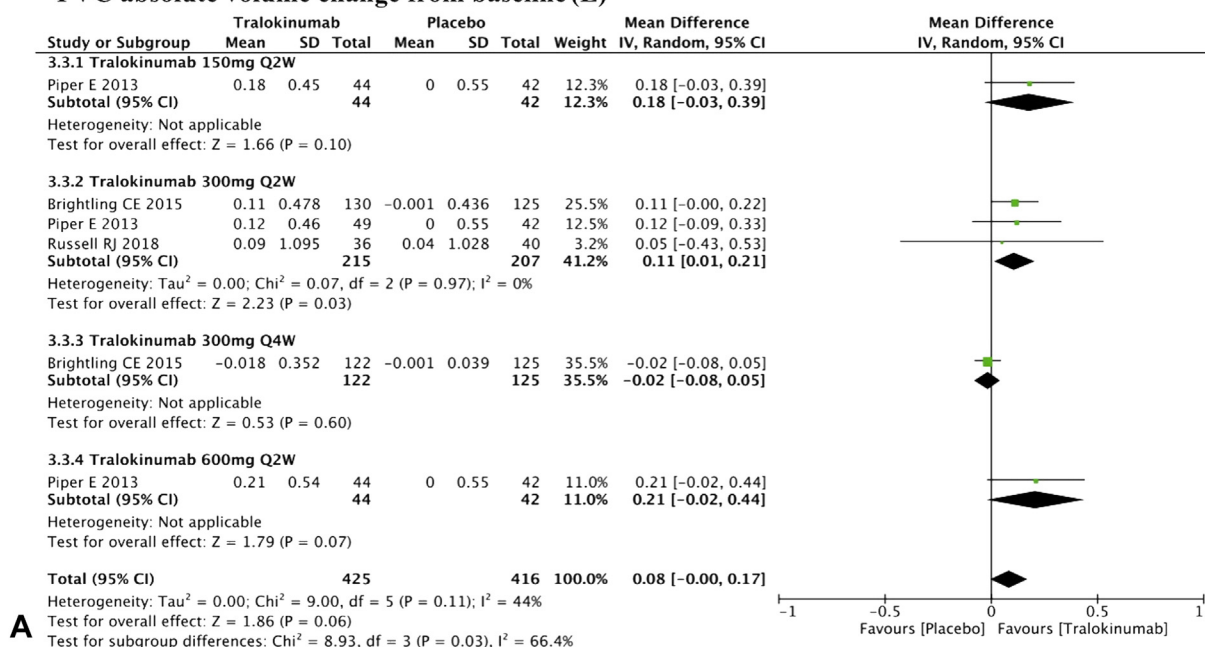
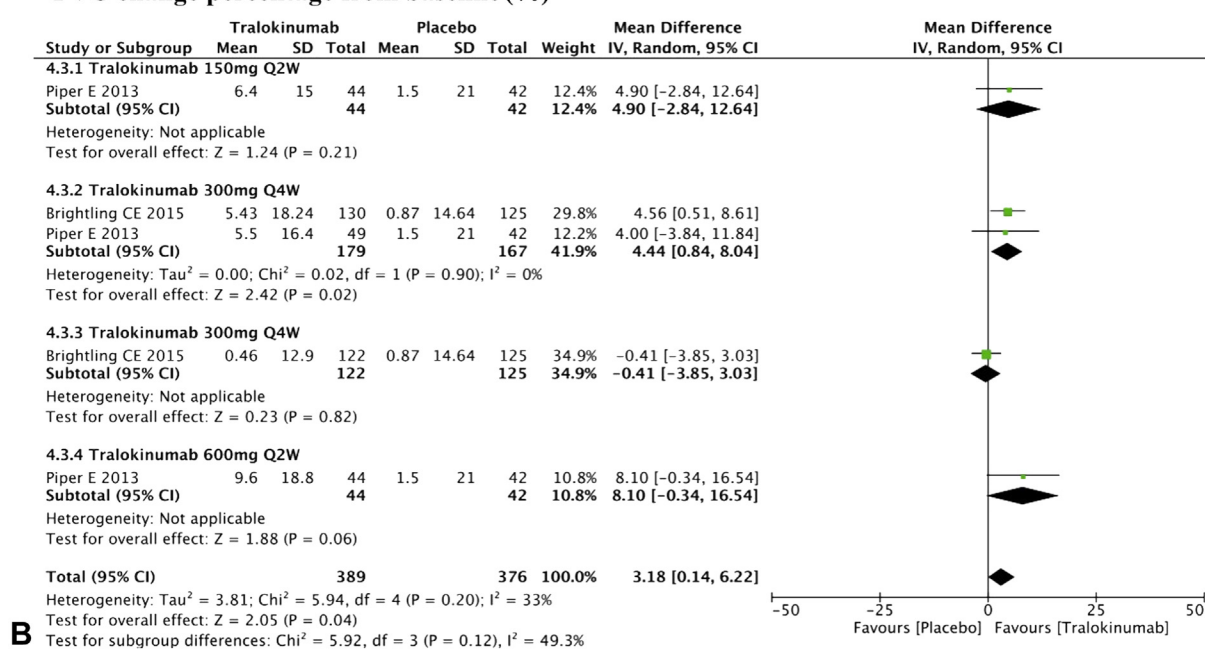
FVC absolute volume change from baseline (L)**FVC change percentage from baseline (%)**

FIGURE 3. Effect of tralokinumab vs placebo on change in FVC from baseline. **A**, Forest plot for absolute FVC volume changes (L) from baseline between the tralokinumab group and the placebo group. **B**, Forest plot for absolute FVC volume percentage changes from baseline between the tralokinumab group and the placebo group.

studies. Sample sizes ranged from 79²⁶ to 1202 patients.²⁴ All the included studies used subcutaneous placebo as the comparator, and all the patients continued with their previous medication treatment during the clinical trials. Treatment duration varied from 12 weeks^{26,27} to 52 weeks.^{24,28} Four different dosages and frequencies (150 mg every 2 weeks [Q2W], 300 mg Q2W, 300 mg every 4 weeks [Q4W], and 600 mg Q2W) of the drug

were administered. The characteristics of the included studies are presented in Table I.

Outcomes

Lung function. FEV₁ and FVC were the most commonly used parameters to evaluate lung function in patients with asthma. Pooled data from our meta-analysis that included 5

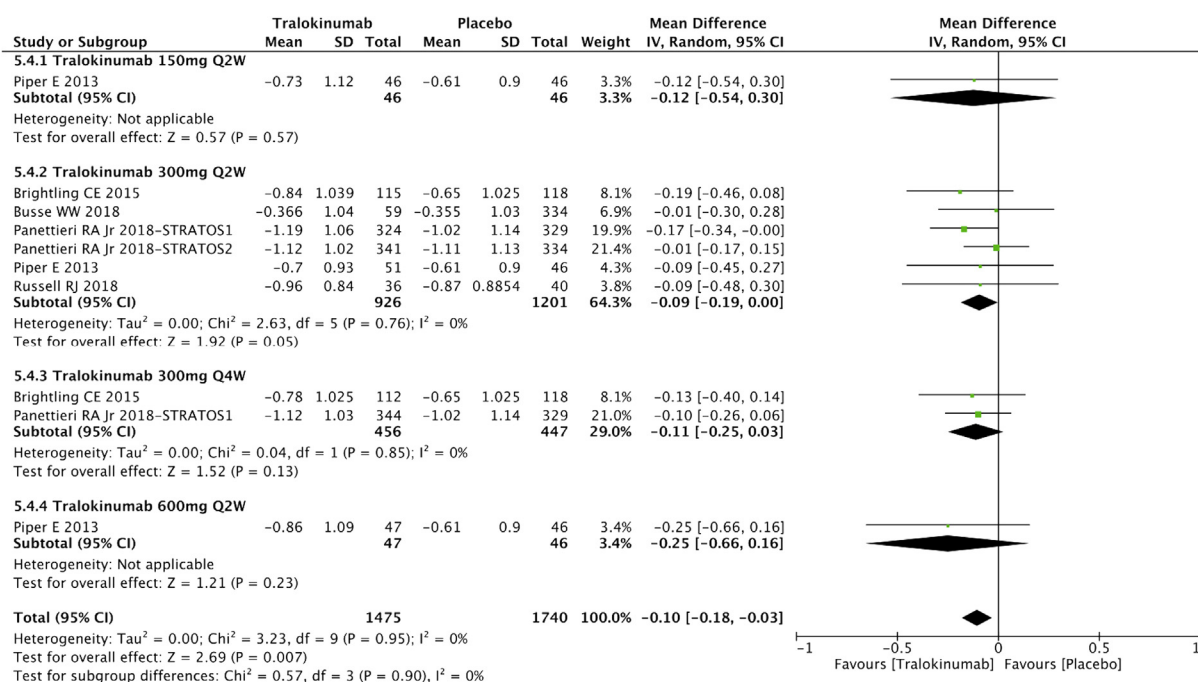


FIGURE 4. Effect of tralokinumab vs placebo on change in the ACQ-6 score from baseline.

RCTs showed a significant improvement in the absolute FEV₁ in the prebronchodilator phase with tralokinumab in the 300-mg Q2W group (MD, 0.14 L; 95% CI, 0.08-0.21; Figure 2, A) and the 600-mg Q2W group (MD, 0.20 L; 95% CI, 0.01-0.39; Figure 2, A) compared with placebo controls. Similarly, the absolute FEV₁% changes were also significantly increased in the tralokinumab 300-mg Q2W group (MD, 5.82%; 95% CI, 3.58-8.06; Figure 2, B) and the 600-mg Q2W group (MD, 11.8%; 95% CI, 0.79-22.81; Figure 2, B) compared with placebo controls. The FVC absolute volume changes from pooled baseline showed a significant increase in the tralokinumab 300-mg Q2W group compared with placebo controls (MD, 0.11 L; 95% CI, 0.01-0.21; Figure 3, A). Indeed, FVC% changes were also observed (MD, 4.44%; 95% CI, 0.84-8.04; Figure 3, B).

Asthma control. Pooled data from 6 RCTs showed that tralokinumab at 300 mg Q2W had statistical improvement in the ACQ-6 score when compared with the statistical improvement achieved with placebo (MD, -0.09; 95% CI, -0.19 to -0.00; Figure 4). However, the small improvement in the ACQ-6 score did not reach the MID threshold of 0.5 unit. AQLQ scores from 4 RCTs suggested no statistical improvement for patients with moderate to severe asthma (see Figure E1 in this article's Online Repository at www.jaci-inpractice.org).

Asthma exacerbation. AAER outcome from 4 RCTs showed that there was no significant improvement after tralokinumab treatment compared with placebo controls (RR, 0.92; 95% CI, 0.81-1.05; Figure 5, A). However, a post hoc subgroup analysis was performed on the basis of the FENO level from 3 RCTs and showed that tralokinumab could significantly decrease the AAER in patients with severe asthma with high FENO levels (≥ 37 ppb) (RR, 0.72; 95% CI, 0.53-0.97; Figure 5, B), but not in patients with low FENO levels (< 37 ppb) (RR, 1.06; 95% CI, 0.88-1.28; Figure 5, B).

Safety

According to our analysis, tralokinumab was well tolerated with no significant differences with regard to the risk of the following adverse outcomes: at least 1 serious AE, treatment discontinuation due to AEs, upper respiratory tract infection, headaches, and gastrointestinal disorders. However, the tralokinumab group showed an increased risk for injection-site reactions compared with placebo controls (odds ratio, 5.92; 95% CI, 1.61-21.76), which may explain the increased risk for at least 1 AE (odds ratio, 1.31; 95% CI, 1.10-1.57) (Table II).

Risk of bias of included studies

Risk of bias of each included study was evaluated and is summarized in Figure E2 in this article's Online Repository at www.jaci-inpractice.org. All the included RCT studies are multicentered, randomized, double-blind, parallel-group, and placebo-controlled clinical trials. Only 1 study²⁷ did not report the detailed description of allocation concealment, blinding of participants and health care personnel, and blinding of outcome assessment. The evidence profile on assessment of the risk of bias about the included RCTs is presented in Table E1 in this article's Online Repository at www.jaci-inpractice.org.

DISCUSSION

Our meta-analysis study suggested that tralokinumab is well tolerated in all patients. Increased injection-site reactions such as pain, erythema, rash, and pruritus with tralokinumab treatment were observed in patients with moderate to severe asthma compared with placebo controls. However, most of the injection-site reactions were mild and transient. We showed that the absolute FEV₁ and FVC volume were modestly improved in the tralokinumab group compared with placebo controls in patients with moderate to severe asthma. Tralokinumab also marginally improved the ACQ-6 score without reaching the MID threshold compared with placebo controls. No differences in the AQLQ

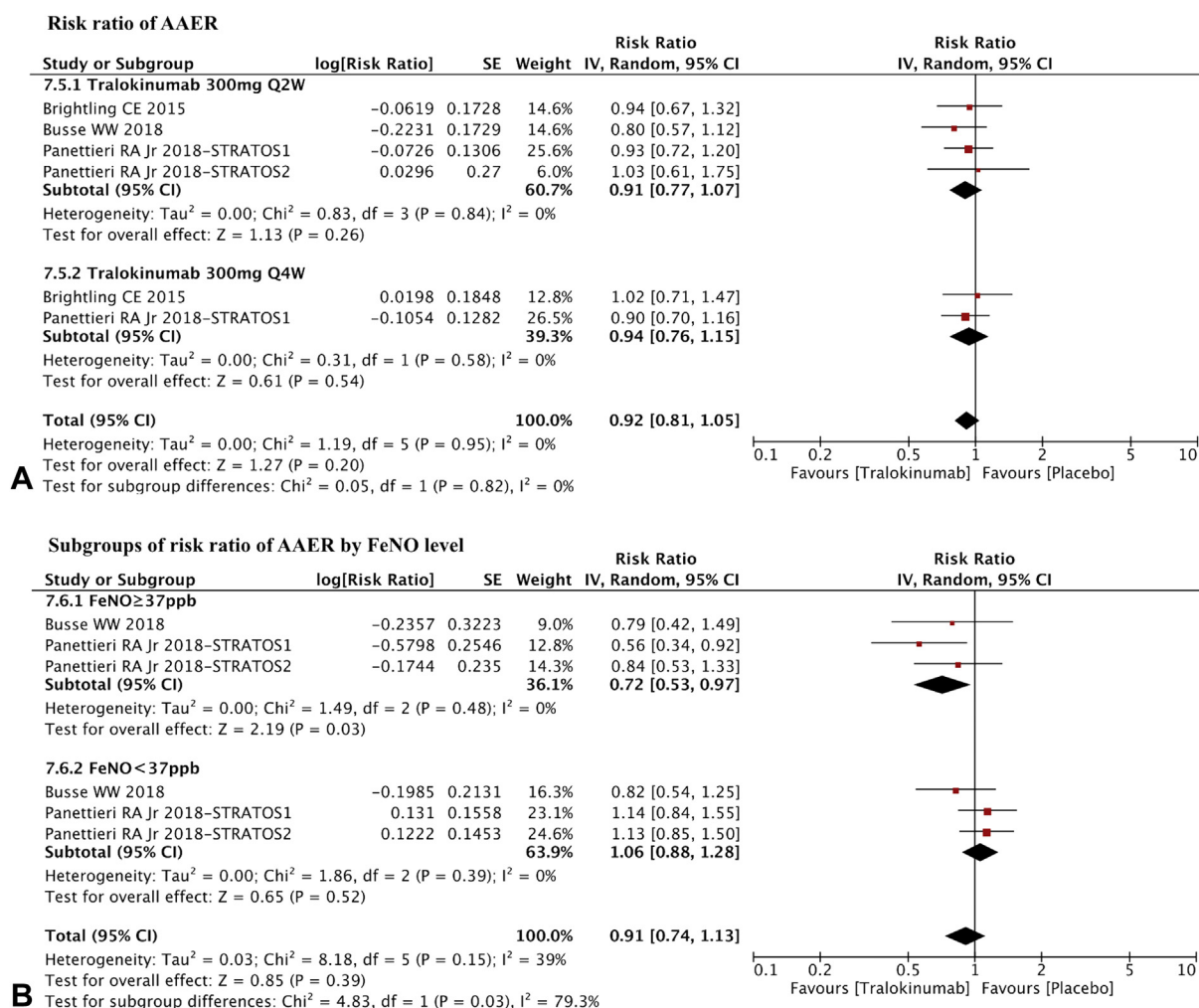


FIGURE 5. Effect of tralokinumab vs placebo on risk ratio of AAER. **A**, Forest plot for risk ratio of AAER between tralokinumab and placebo groups. **B**, Forest plot for risk ratio of AAER between patients with severe asthma with FeNO high levels and those with low FeNO levels.

TABLE II. AEs associated with tralokinumab

AEs	Events/total		Odds ratio, Mantel-Haenszel, random (95% CI)	P value
	Tralokinumab group	Placebo group		
At least 1 AE ²⁴⁻²⁸	1243/1641	870/1241	1.31 (1.10-1.57)	.002
At least 1 serious AE ^{24,25,27,28}	130/1340	127/1090	0.82 (0.63-1.07)	.150
Treatment discontinuation due to AE ^{24,25,28}	68/1194	26/1043	2.21 (0.71-6.88)	.170
Upper respiratory tract infection ^{24,28}	95/1124	83/973	0.91 (0.66-1.25)	.560
Headache ^{24,25,27,28}	124/1340	78/1090	1.27 (0.94-1.72)	.120
Gastrointestinal disorders ²⁶⁻²⁸	53/486	46/238	0.88 (0.25-3.05)	.840
Injection-site reaction ²⁴⁻²⁸	160/1379	26/1130	5.92 (1.61-21.76)	.007

score were observed. The pooled data did not show a significant improvement in AAER in the tralokinumab group compared with placebo controls, but the post hoc subgroup analysis demonstrated that tralokinumab may significantly decrease the risk ratio of AAER in patients with severe asthma with high FeNO levels (≥ 37 ppb). Collectively, tralokinumab was well tolerated and showed modest improvement in lung function but did not

render clinical improvements in asthma control, quality of life, or asthma exacerbation.

Subgroup analysis in this study, on the basis of dosage and frequency of tralokinumab treatment, showed that tralokinumab improved lung function (FEV₁ and FVC) in a dose-dependent way. This difference, which accounted for approximately 100 mL/4% improvement in FEV₁, reaches the lower boundary of

patients' detectable benefit. However, it was suggested that an FEV₁ improvement of 200 mL/10% may be needed to ensure clinical benefits and confidence.^{21,22} The pooled data showed that the mean improvement in FEV₁ in the tralokinumab 300-mg Q2W subgroup and the 600-mg Q2W subgroup exceeded 100 mL/4%, but only the 600-mg Q2W subgroup exceeded 200 mL/10%, which indicated a modest benefit for improving lung function in moderate to severe asthma. Dose-exposure-response relationship of tralokinumab in patients with severe uncontrolled asthma showed a near-maximal FEV₁ increase at a dose of 300 mg Q2W.²⁹ Combined with our finding, the administration of tralokinumab at 300 mg Q2W might be chosen for the phase III clinical development program for treatment in moderate to severe asthma.

For the outcomes of control and quality of life, tralokinumab treatment marginally statistically improved the ACQ-6 score without reaching the MID threshold of 0.5 unit,^{19,20} but not the AQLQ score. These results suggest that tralokinumab treatment did not improve quality of life in patients with moderate to severe asthma.

Asthma exacerbation is the primary cause of morbidity in uncontrolled asthma and drives health care use and costs.³⁰ The pooled data in this study did not show that tralokinumab was effective for decreasing asthma exacerbation in patients with moderate to severe asthma. In addition, the reported effects of tralokinumab on rescue use of medications in patients with severe asthma have been conflicting. Piper et al²⁷ reported that tralokinumab treatment produced a significantly greater reduction in the rescue use of β_2 agonists compared with placebo.²⁷ However, there was no significant beneficial effect of tralokinumab on the rescue use of oral corticosteroids in patients with severe asthma who required continuous oral corticosteroid in addition to inhaled corticosteroid/long-acting β -agonist in the TROPOS study.²⁵

The post hoc analysis showed that tralokinumab significantly decreased the rate of asthma exacerbation in patients with severe asthma with high FENO levels (≥ 37 ppb), but not in patients with low FENO levels (< 37 ppb). Tralokinumab treatment has been shown to decrease FENO levels, which indicated that tralokinumab might be effective in blocking the effects of IL-13-induced nitric oxide production in airway epithelial cells.^{24,26} This observation was also confirmed in a clinical study of treatment with lebrikizumab.³¹ Moreover, tralokinumab appeared to perform better in patients with positive sputum IL-13 levels (≥ 10 pg/mL).²⁷ A subset of patients with severe asthma with elevated periostin concentration or elevated dipeptidyl peptidase 4 concentration also achieved significant improvements in lung function, asthma exacerbation, and ACQ-6 score compared with those with low concentrations of periostin or dipeptidyl peptidase 4 in the MESOS study.²⁸ A previous meta-analysis evaluated another IL-13 antibody (lebrikizumab) and demonstrated that patients with uncontrolled asthma with high periostin levels had greater exacerbation rate reductions and FEV₁ improvements than did those with low periostin levels.³² All these observations indicate the importance of appropriate patient selection by the fact that tralokinumab has only modest efficacy on lung function improvement in patients who were not selected by using specific biomarkers and clinical features relevant to the target population. Further analysis of efficacy within specific populations would be required and warranted.

Overall, the 6 included RCTs displayed low heterogeneity in each comparison. This strengthens the evidence that tralokinumab has modestly clinical potential for improvement of lung

function in patients with moderate to severe asthma, but not for asthma-related quality of life and asthma exacerbation, and the results are reproducible.

Study limitations

Limitations of the present meta-analysis included the fact that there was a variable duration of tralokinumab treatment in the included clinical trials (12-52 weeks) and these studies were underpowered to detect the effect of tralokinumab on the basis of different time points. Moreover, publication bias could not be well assessed because of the limited included studies.

CONCLUSIONS

In this pooled analysis of 6 RCTs, treatment with tralokinumab was well tolerated and it modestly improved FEV₁ and FVC in patients with moderate to severe asthma. It did not render clinically important improvements in asthma control and asthma-related quality of life, and nor did it reduce asthma exacerbations. Further powered clinical trials would be required to detect whether certain populations of individuals with asthma experience a better clinical response from tralokinumab, thus enabling more efficient management of IL-13-mediated asthma compared with currently available therapies. In addition, studies should be required to evaluate the safety, efficacy, and cost of tralokinumab in comparison with other available anti-T_H2 cytokine mAbs.

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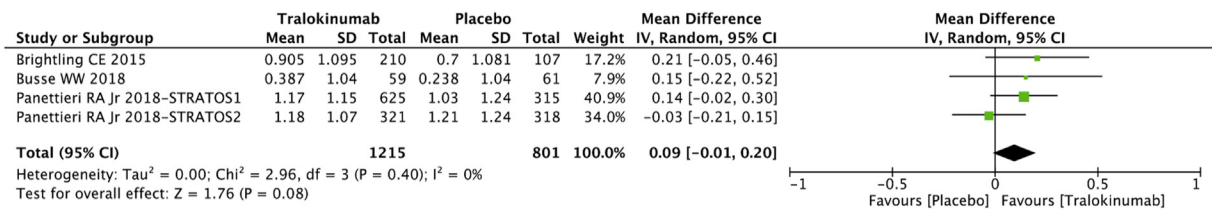


FIGURE E1. Effect of tralokinumab vs placebo on change in the AQLQ score from baseline.

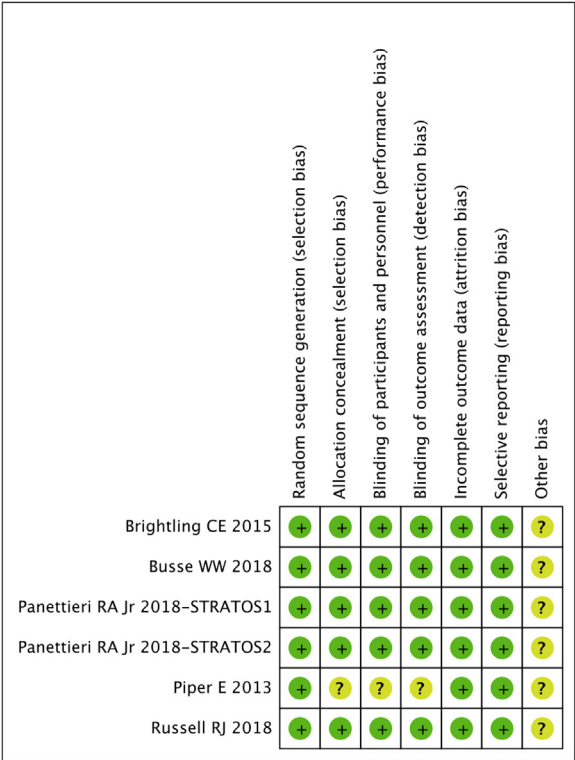


FIGURE E2. Risk of bias for included studies.

TABLE E1. Detailed assessment of bias risk

Bias	Authors' judgment	Support for judgment
Piper et al ²⁷		
Random sequence generation (selection bias)	Low	Randomized according to a computer-generated randomization list
Allocation concealment (selection bias)	Unclear	Randomized, no description
Blinding of participants and personnel (performance bias)	Unclear	Double-blinded, no description
Blinding of outcome assessment (detection bias)	Unclear	Double-blinded, no description
Incomplete outcome data (attrition bias)	Low	4/48 (8.3%) losses in the placebo group, 3/51 (5.8%) losses in tralokinumab 300-mg group, no losses in tralokinumab 150-mg and 600-mg groups, with ITT analysis
Selective reporting (reporting bias)	Low	All relevant outcomes were described.
Other bias	Unclear	Unclear
Brightling et al ²⁸		
Random sequence generation (selection bias)	Low	Randomized via an interactive (voice or web) system
Allocation concealment (selection bias)	Low	Randomized and provided the assignment of blinded investigational product kit numbers to the subject. Because tralokinumab and placebo are visually distinct, the investigational product was handled by an unblinded investigational manager and administered by an unblinded study team member who was not involved in the management of study subjects.
Blinding of participants and personnel (performance bias)	Low	Neither the subject nor any of the investigator or sponsor staff involved in the treatment or clinical evaluation of the subjects was aware of the treatment received.
Blinding of outcome assessment (detection bias)	Low	Neither the subject nor any of the investigator or sponsor staff involved in the treatment or clinical evaluation of the subjects was aware of the treatment received.
Incomplete outcome data (attrition bias)	Low	17/150 (11.3%) losses in the placebo group, 15/150 (10%) losses in tralokinumab Q2W group, 22/151 (14.6%) losses in tralokinumab Q4W group, with ITT analysis
Selective reporting (reporting bias)	Low	All relevant outcomes were described.
Other bias	Unclear	Unclear
Russell et al ²⁶		
Random sequence generation (selection bias)	Low	Randomized by an interactive web-based system or voice response system
Allocation concealment (selection bias)	Low	Randomized; randomization codes, prepared by an internal AstraZeneca computerized system, were assigned sequentially as participants became eligible for randomization. Randomization numbers were grouped in blocks and participants who discontinued from the trial were not replaced. Participants, site staff and investigators, and sponsor personnel were masked to treatment allocation until trial completion and the database had been locked.
Blinding of participants and personnel (performance bias)	Low	Double-blinded; participants, site staff and investigators, and sponsor personnel were masked to treatment allocation until trial completion and the database had been locked.
Blinding of outcome assessment (detection bias)	Low	Double-blinded; participants, site staff and investigators, and sponsor personnel were masked to treatment allocation until trial completion and the database had been locked.
Incomplete outcome data (attrition bias)	Low	0/40 (0%) losses in the placebo group, 3/39 (7.7%) losses in the tralokinumab group, with ITT analysis
Selective reporting (reporting bias)	Low	All relevant outcomes were described.
Other bias	Unclear	Unclear
Panettieri et al ²⁴ (STRATOS 1)		
Random sequence generation (selection bias)	Low	Randomized by an interactive web or voice response system

(continued)

TABLE E1. (Continued)

Bias	Authors' judgment	Support for judgment
Allocation concealment (selection bias)	Low	Randomized; tralokinumab and placebo are visually distinct and so were administered by an unmasked team member not involved in the management of participants to maintain masking. Participants and trial-site personnel assessing outcomes were unaware of the treatment allocation.
Blinding of participants and personnel (performance bias)	Low	Double-blinded; participants and trial-site personnel assessing outcomes were unaware of the treatment allocation.
Blinding of outcome assessment (detection bias)	Low	Double-blinded; participants and trial-site personnel assessing outcomes were unaware of the treatment allocation.
Incomplete outcome data (attrition bias)	Low	40/400 (10%) losses in the placebo group, 69/401 (17.2%) losses in tralokinumab Q2W group and 51/406 (12.6%) losses in tralokinumab Q4W group; FAS analysis was done without ITT analysis.
Selective reporting (reporting bias)	Low	All relevant outcomes were described.
Other bias	Unclear	Unclear
Panettieri et al ²⁴ (STRATOS 2)		
Random sequence generation (selection bias)	Low	Randomized by an interactive web or voice response system
Allocation concealment (selection bias)	Low	Randomized; tralokinumab and placebo are visually distinct and so were administered by an unmasked team member not involved in the management of participants to maintain masking. Participants and trial-site personnel assessing outcomes were unaware of the treatment allocation.
Blinding of participants and personnel (performance bias)	Low	Double-blinded; participants and trial-site personnel assessing outcomes were unaware of the treatment allocation.
Blinding of outcome assessment (detection bias)	Low	Double-blinded; participants and trial-site personnel assessing outcomes were unaware of the treatment allocation.
Incomplete outcome data (attrition bias)	Low	60/428 (14.0%) losses in the placebo group, 55/428 (12.9%) losses in tralokinumab Q2W group; FAS analysis was done without ITT analysis.
Selective reporting (reporting bias)	Low	All relevant outcomes were described.
Other bias	Unclear	Unclear
Busse et al ²⁵		
Random sequence generation (selection bias)	Low	Randomized. A fixed block randomization list was created using an internal AstraZeneca computerized system (GRand). Randomization codes were assigned strictly sequentially in each stratum as subjects became eligible for randomization, using an interactive voice/web recognition system.
Allocation concealment (selection bias)	Low	Randomized. Because tralokinumab and placebo were visually distinct, they were handled by an unblinded investigational product manager at the site and were administered by an unblinded investigational site trial team member, who were not involved in the management of the trial patients (could be the same person).
Blinding of participants and personnel (performance bias)	Low	Double-blinded; all the patients, investigators, and sponsor staff who were involved in the treatment, clinical evaluation, and monitoring of the patients were blinded to the trial.
Blinding of outcome assessment (detection bias)	Low	Double-blinded; all the patients, investigators, and sponsor staff who were involved in the treatment, clinical evaluation, and monitoring of the patients were blinded to the trial.
Incomplete outcome data (attrition bias)	Low	4/70 (5.7%) losses in the placebo group and 7/70 (10%) losses in the tralokinumab group; FAS analysis was done without ITT analysis.
Selective reporting (reporting bias)	Low	All relevant outcomes were described.
Other bias	Unclear	Unclear

FAS, Full analysis set; ITT, intention to treat; Q2W, every 2 wk; Q4W, every 4 wk.