Tralokinumab did not demonstrate oral corticosteroid-sparing effects in severe asthma

William W. Busse[1], Guy G. Brusselle[2], Stephanie Korn[3], Piotr Kuna[4], Antoine Magnan[5], David Cohen[6], Karin Bowen[6], Teresa Piechowiak[7], Millie M. Wang[8] and Gene Colice[6]

Affiliations: [1]Dept of Medicine, University of Wisconsin School of Medicine and Public Health, Madison, WI, USA. [2]Dept of Respiratory Medicine, Ghent University Hospital, Ghent, Belgium. [3]Pulmonary Dept, Mainz University Hospital, Mainz, Germany. [4]Dept of Internal Medicine, Asthma and Allergy, Medical University of Lodz, Lodz, Poland. [5]Institut du Thorax, INSERM CNRS, Université de Nantes, CHU de Nantes, Nantes, France. [6]AstraZeneca, Gaithersburg, MD, USA. [7]AstraZeneca, Mississauga, ON, Canada. [8]AstraZeneca, Cambridge, UK.

Correspondence: William W. Busse, University of Wisconsin School of Medicine and Public Health, 600 Highland Avenue, Madison, WI 53792-0001, USA. E-mail: wwb@medicine.wisc.edu

@ERSpublications
Tralokinumab did not demonstrate significant OCS-sparing benefits *versus* placebo in severe asthma
http://ow.ly/kzCt30mC43j

Cite this article as: Busse WW, Brusselle GG, Korn S, *et al*. Tralokinumab did not demonstrate oral corticosteroid-sparing effects in severe asthma. *Eur Respir J* 2019; 53: 1800948 [https://doi.org/10.1183/13993003.00948-2018].

ABSTRACT Long-term oral corticosteroid (OCS) use in patients with severe asthma is associated with significant adverse effects.

This 40-week, randomised, double-blind trial evaluated the OCS-sparing potential of tralokinumab in patients with severe, uncontrolled asthma requiring maintenance OCS treatment plus inhaled corticosteroids/long-acting β_2-agonists. Overall, 140 patients were randomised to tralokinumab 300 mg or placebo (n=70 in each group) administered subcutaneously every 2 weeks. The primary end-point was percentage change from baseline in average OCS dose at week 40, while maintaining asthma control. Secondary end-points included proportion of patients with a prescribed maintenance OCS dose of $\leqslant$5 mg, those with a $\geqslant$50% reduction in prescribed maintenance OCS dose and asthma exacerbation rate. Safety was also assessed.

At week 40, the percentage reduction from baseline in the final daily average OCS dose was not significantly different between tralokinumab and placebo (37.62% *versus* 29.85%; p=0.271). There were no significant between-treatment differences for any secondary end-point. Overall, reporting of adverse events and serious adverse events were similar for the tralokinumab and placebo groups. Although a greater proportion of tralokinumab-treated patients reported upper respiratory tract infections (35.7% *versus* 14.3%), there were no reported cases of pneumonia.

Overall, tralokinumab did not demonstrate an OCS-sparing effect in patients with severe asthma.

This article has supplementary material available from erj.ersjournals.com

Received: May 21 2018 | Accepted after revision: Oct 30 2018

This study is registered at clinicaltrials.gov with identifier NCT02281357. Data underlying the findings described in this manuscript may be obtained in accordance with AstraZeneca's data sharing policy described at https://astrazenecagrouptrials.pharmacm.com/ST/Submission/Disclosure

Introduction

Asthma is a heterogeneous disease characterised by chronic airway inflammation and hyperresponsiveness that affects ~334 million people worldwide [1]. Of these, an estimated 5–10% of patients have severe asthma that remains inadequately controlled despite treatment with high-dose inhaled corticosteroids (ICS)/long-acting β_2-agonists (LABA) [2]. These patients may be prescribed maintenance oral corticosteroids (OCS) to manage their symptoms and/or to prevent exacerbations [2]. However, cumulative use (including frequent and intermittent use) of OCS is associated with significant adverse effects [3, 4], which in turn diminish the patient's health-related quality of life [4]. Therefore, new therapies that reduce the need for frequent OCS exposure are required in the setting of severe asthma.

Interleukin (IL)-13, a pleiotropic cytokine that can induce inflammation [5, 6], has been identified as a potential therapeutic target in patients with severe, uncontrolled asthma [7, 8]. Tralokinumab, an immunoglobulin G_4 human monoclonal antibody, potently and specifically neutralises IL-13, thereby inhibiting signalling through the IL-13 receptor [9, 10]. In phase 2 trials in patients with severe, uncontrolled asthma, tralokinumab improved lung function, but did not reduce the annual asthma exacerbation rate (AAER) or improve measures of asthma control [11, 12]. However, in a *post hoc* subgroup analysis of a subpopulation of patients with evidence of an activated IL-13 axis, such as elevated levels of serum periostin or dipeptidyl peptidase-4, tralokinumab improved the AAER [11]. This observation suggested that certain subpopulations of patients with severe asthma might respond to tralokinumab treatment. Two large phase 3 trials, STRATOS 1 and 2, reported ahead of TROPOS, confirmed that tralokinumab did not improve the AAER in the all-comers population with severe asthma [13]. In addition, in contrast to the phase 2 trial, periostin and dipeptidyl peptidase-4 were not shown to predict response to tralokinumab treatment in either STRATOS 1 and 2. However, these trials did suggest that in a subpopulation of patients with severe asthma with fractional exhaled nitric oxide (F_{ENO}) concentrations ⩾37 ppb, there might be an enhanced benefit with tralokinumab [13].

Given the need to reduce the requirement of OCS in patients with severe asthma, treatments that may allow tapering of OCS without loss of disease control are needed. However, at the beginning of this trial, no clinical trial had been conducted in patients with severe asthma on maintenance OCS with agents that attenuate IL-13 signalling. Consequently, the purpose of this phase 3 TROPOS trial (NCT02281357) was to evaluate the ability of tralokinumab to reduce OCS use in patients with severe asthma requiring maintenance OCS treatment in combination with ICS/LABA. The primary objective was to determine whether add-on treatment with tralokinumab provided OCS-sparing benefits compared with placebo. Secondary objectives were to assess the effect of tralokinumab on the proportion of these patients with a prescribed OCS maintenance dosage ⩽5 mg at the end of the treatment period, and the proportion of patients with ⩾50% reduction in prescribed OCS maintenance dosage, both compared with placebo. In addition, the effect of tralokinumab on the AAER was assessed.

Methods

Trial design and patients

Full details of the trial design have been published previously [14]. In brief, this was a randomised, double-blind, placebo-controlled, parallel-group, multicentre, phase 3 trial in patients with severe, uncontrolled asthma requiring maintenance ICS/LABA and OCS. Male and female patients aged 12–75 years were eligible and were required to have the following criteria for inclusion: asthma for ⩾12 months, with a daily requirement of medium- or high-dose ICS (total daily dose ⩾500 µg fluticasone propionate dry powder or an equivalent delivered dose) for ⩾6 months of the 12 months prior to enrolment; physician-prescribed ICS (total daily dose ⩾500 µg fluticasone propionate dry powder formulation equivalent) and a LABA for ⩾3 months prior to enrolment; OCS treatment for 6 months prior to 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 month prior to enrolment. Full inclusion and exclusion criteria are provided in section 1 of the online supplementary appendix.

After initial enrolment (visit 1), patients entered either a 2-week run-in period (if there had been a documented failure of OCS dose reduction ⩽6 months prior to visit 1) or a 2-week run-in period plus an up to 8-week optimisation period (the optimisation period was shorter in some patients (*i.e.* those in whom the optimal dose was reached earlier)) to establish a minimum effective OCS dose (established by dose titration every 2 weeks (Q2W); figure 1).

Eligible patients were randomised in a 1:1 ratio at week 0 (baseline) to receive either tralokinumab 300 mg or placebo *s.c.* Q2W and entered a 40-week treatment period comprising three phases: a 12-week induction phase, a 20-week OCS dose-reduction phase and an 8-week maintenance phase. Randomised patients were stratified by age group (adults *versus* adolescents) and baseline OCS dose (adults only; ⩽10 mg *versus* >10 mg prednisone or prednisolone). The follow-up period consisted of two visits at weeks

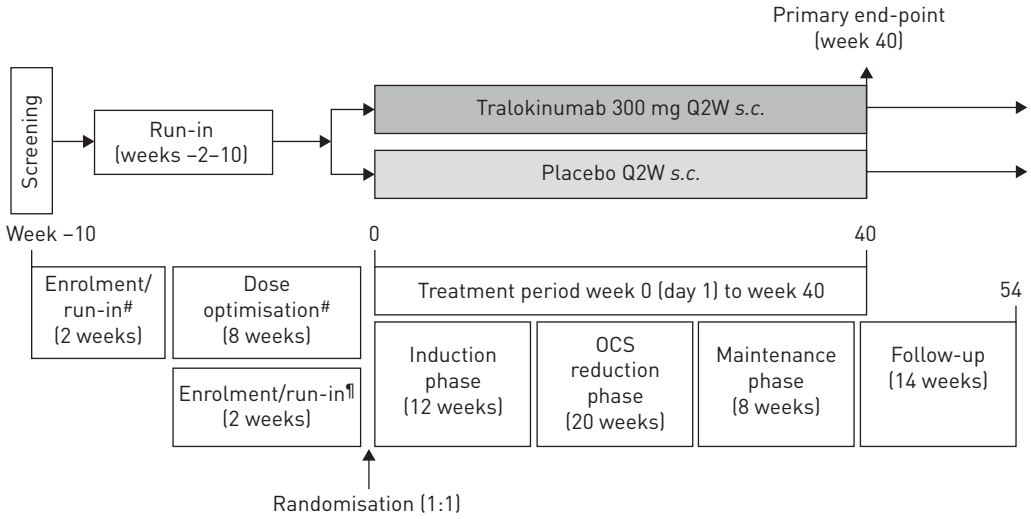

FIGURE 1 TROPOS trial design. After initial enrolment (visit 1), patients entered either a 2-week run-in period or a 2-week run-in period plus an up to 8-week optimisation period to establish the minimum effective dose of the prescribed oral corticosteroid (OCS). Patients were maintained on their currently prescribed inhaled corticosteroid/long-acting β_2-agonist and any additional controller medication, without change, from enrolment, throughout the run-in/optimisation and treatment periods. All patients underwent randomisation (1:1) and entered the 40-week treatment period consisting of an induction, OCS dose reduction and maintenance phase. For safety assessments, there was a 14-week follow-up period (post-treatment at weeks 44 and 54). #: patients without a documented failure in OCS dose reduction ⩽6 months prior to visit 1 were required to complete the 8-week OCS dose optimisation period (established by dose titration every 2 weeks (Q2W)), after completing the 2-week run-in period; ¶: patients with a documented failure in OCS dose reduction ⩽6 months prior to visit 1 were deemed to be on the optimal OCS dose and directly entered a 2-week run-in period.

44 and 54 for safety assessments. Details on randomisation and blinding (including processes used to administer the trial drug) and full trial procedures are provided in section 2 of the online supplementary appendix.

This trial was conducted in accordance with the Declaration of Helsinki and Good Clinical Practice (International Conference on Harmonisation) and the AstraZeneca policy on Bioethics. The trial was approved by the independent ethics committees at all participating centres and all patients provided written informed consent.

End-points

The primary efficacy end-point was the percentage change from baseline in the final daily average OCS dose at week 40, while maintaining asthma control. Secondary end-points included the proportion of patients with a prescribed maintenance OCS dose of ⩽5 mg, the proportion of patients with a ⩾50% reduction in prescribed maintenance OCS dose and the AAER up to week 40. An asthma exacerbation was defined as worsening of asthma that required a temporary increase in systemic corticosteroids for ⩾3 days or that resulted in an emergency-room or urgent-care visit resulting from asthma that led to a temporary increase in systemic corticosteroids for ⩾3 days to treat symptoms or an inpatient hospitalisation due to asthma.

Exploratory end-points included the proportion of patients with a decrease from baseline in their final daily average OCS dose, percentage and least squares (LS) mean absolute change from baseline in prebronchodilator forced expiratory volume in 1 s (FEV_1), change from baseline in the Asthma Control Questionnaire (ACQ)-6 and Asthma Quality of Life Questionnaire (AQLQ; standardised for patients aged ⩾12 years) scores and an assessment of the relationship between baseline biomarker (F_{ENO}) and the effect of tralokinumab on OCS dose reduction and clinical efficacy. Safety end-points included the incidence and frequencies of adverse events and serious adverse events (SAEs) and collection of blood samples for determination of clinical chemistry, haematology and urinalysis. Safety aspects of the trial were monitored by an independent Data and Safety Monitoring Board. All hospitalisations, emergency-room and urgent-case visits, malignancy events and cardiovascular/cerebrovascular events were adjudicated by an independent committee of experts. Potential anaphylaxis events were evaluated by a blinded external evaluator. Additional details on the assessment of trial end-points are provided in section 3 of the supplementary appendix.

Statistical analysis

It was estimated that ⩾55 patients per group would be required for the trial to detect a difference of 50% in the primary end-point between tralokinumab and placebo, with 90% power, using a two-sided test at a 5% significance level. Based on the findings from an analysis of the STRATOS 1 trial, which identified *F*eNO high (⩾37 ppb) as a biomarker-positive population [14], the trial protocol was amended to include patients with *F*eNO ⩾37 ppb as the primary analysis population, provided that >50% of the trial population had high *F*eNO levels (⩾37 ppb). If <50% of the trial population had *F*eNO ⩾37 ppb, the primary analysis population would instead include patients with *F*eNO ⩾30 ppb. If <50% of the population had *F*eNO ⩾30 ppb, the all-comers population (*i.e.* all patients with any level of *F*eNO) would become the primary population for analysis. To account for multiplicity, a hierarchical testing strategy was used for the primary and secondary outcomes. The statistical analyses were performed by Biometrics and Information Sciences, AstraZeneca, using SAS (version 9.4; SAS Institute, Cary, NC, USA) and additional validated software (where appropriate). Further details of the statistical analysis methodology, analysis of the primary, secondary and exploratory end-points can be found in section 4 of the supplementary appendix. The impact of missing data on primary, secondary and exploratory end-points were explored using sensitivity analyses (section 5 of the supplementary appendix).

Results

Patient demographics and baseline disease characteristics

The trial was conducted from February 2015 through September 2017. A total of 218 patients were enrolled from 56 participating sites in Europe and USA. Of these, 140 patients from 44 sites were randomised to treatment with either tralokinumab (n=70) or placebo (n=70), of whom 129 (92%) completed the trial and 124 (89%) completed treatment (figure 2). Reasons for trial withdrawal are summarised in supplementary table S1. Patient baseline demographics and clinical characteristics were well balanced across treatment groups (table 1 and supplementary table S2). At baseline, patients had a mean age of 54.7 years, with the median time since asthma diagnosis being 24.0 years. The majority of patients were female (62.1%). The mean±SD baseline *F*eNO level was 35.22±29.50 ppb; ∼51% of patients in each treatment group had *F*eNO levels <30 ppb. Thus, the primary population for efficacy analysis was the all-comers population.

Overall, 48 (69%) patients in each treatment group entered the 8-week OCS dose-optimisation phase prior to randomisation, with an average dose reduction of 1.36 mg in the tralokinumab group and 0.99 mg in the placebo group (supplementary table S3).

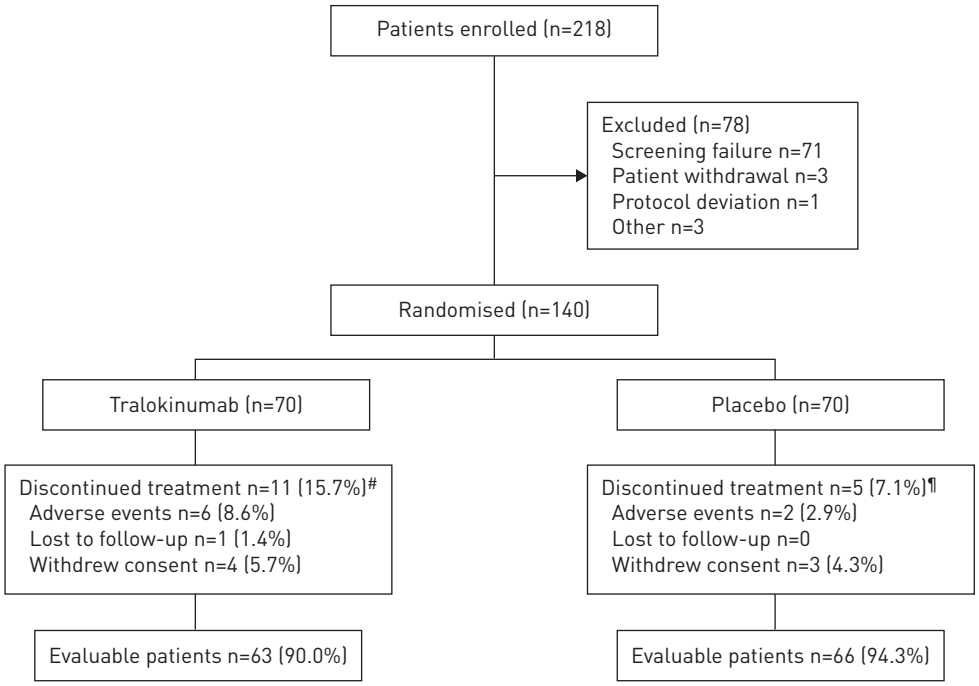

FIGURE 2 Patient enrolment and disposition. #: in the tralokinumab group, 11 patients discontinued treatment, of whom four completed the trial; ¶: out of the five patients who discontinued treatment in the placebo group, one patient completed the trial.

TABLE 1 Patient baseline demographics and clinical characteristics (full analysis set)[#]

	Tralokinumab	Placebo	Total
Patients	70	70	140
Age years	54.0±11.05	55.4±10.26	54.7±10.65
Female	48 (68.6)	39 (55.7)	87 (62.1)
BMI kg·m^{-2}	28.1±5.07	30.8±6.84	29.4±6.15
Race			
Caucasian	66 (94.3)	63 (90.0)	129 (92.1)
Other	4 (5.7)	7 (10.0)	11 (7.8)
Smoking history			
Never-smokers	57 (81.4)	50 (71.4)	107 (76.4)
Ex-smokers[¶]	13 (18.6)	20 (28.6)	33 (23.6)
Pack-years[+]	4.5±2.37	4.7±3.10	4.6±2.79
Time since asthma diagnosis[§] years	21.5 (3–52)	25.5 (1.6–55.0)	24.0 (1.6–55.0)
Exacerbations in the past 1 year			
0	9 (12.9)	11 (15.7)	20 (14.3)
1	19 (27.1)	24 (34.3)	43 (30.7)
2	21 (30.0)	17 (24.3)	38 (27.1)
⩾3	21 (30.0)	18 (25.7)	39 (27.8)
Asthma medications at baseline			
ICS[f]	69 (98.6)	70 (100)	139 (99.3)
LABA	70 (100)	70 (100)	140 (100)
OCS dose at trial entry mg	14.14±6.03	13.50±5.18	13.82±5.61
Optimised total daily OCS dose[##] mg	13.21±6.17	12.82±4.96	13.02±5.58
Prebronchodilator FEV_1			
Volume L	1.69±0.59	1.65±0.68	1.67±0.63
% predicted	56.67±15.58	54.74±17.67	55.71±16.63
Prebronchodilator FVC L	2.87±0.84	2.81±0.98	2.84±0.91
Percentage reversibility of FEV_1[¶¶]	17.22±14.04	18.19±19.24	17.71±16.79
Total asthma symptom score	2.3±1.14	2.3±1.25	Not done
ACQ-6 score	2.4±1.12	2.5±1.26	Not done
AQLQ score	4.4±1.15	4.4±1.29	Not done
F_{ENO} ppb	28.3 (6.4–175.2)	23.9 (4.2–134.9)	27.55 (4.1–175.2)
F_{ENO} distribution			
High ⩾37 ppb	23 (32.9)	21 (30.0)	44 (31.4)
Mid ⩾30 and <37 ppb	11 (15.7)	11 (15.7)	22 (15.7)
Low <30 ppb	36 (51.4)	36 (51.4)	72 (51.4)
No baseline assessment	0	2 (2.9)	2 (1.4)

Data are presented as n, mean±SD, n (%) or median (range). BMI: body mass index; ICS: inhaled corticosteroids; LABA: long-acting β_2-agonists; OCS: oral corticosteroids; FEV_1: forced expiratory volume in 1 s; FVC: forced vital capacity; ACQ-6: Asthma Control Questionnaire-6; AQLQ: Asthma Quality of Life Questionnaire (standardised for patients aged ⩾12 years); F_{ENO}: fractional exhaled nitric oxide. [#]: the full analysis set consisted of all patients who were randomised and received any dose of either tralokinumab or placebo, irrespective of their protocol adherence and continued participation in the trial. [¶]: stopped smoking ⩾3 months before enrolment. [+]: for patients who had stopped smoking (former smokers). [§]: calculated as (date of asthma diagnosis/date when asthma symptoms started – date of randomisation) + 1. [f]: one patient in the tralokinumab group was not receiving ICS at trial entry, and one patient in the tralokinumab group was receiving a lower ICS daily dose than the required limit. These infractions were considered as important protocol deviations. More patients in the placebo group were using asthma medications other than ICS/LABA. [##]: for patients entering the optional OCS dose optimisation on visit 2. [¶¶]: this was the first post-bronchodilation measurement taken after four, six or eight inhalations of a short-acting β_2-agonist. The percentage reversibility of the FEV_1 was calculated with FEV_1 values obtained before and after bronchodilation at baseline: reversibility (%) = ([post-bronchodilation FEV_1 – prebronchodilation FEV_1]/prebronchodilation FEV_1) × 100.

Efficacy

Primary end-point

At week 40, the percentage reduction from baseline in the final daily average OCS dose (LS means) was not significantly different between the tralokinumab and placebo groups (37.62% *versus* 29.85%; p=0.271 (table 2 and figure 3). The change in OCS dose over time suggested that there was no treatment effect with tralokinumab at earlier time points (figure 3).

TABLE 2 Primary and secondary outcomes (all-comers population)[#]

	Tralokinumab	Placebo
Patients	70	70
Primary end-point		
Percentage change in final daily average OCS dose from baseline		
Percentage reduction in LS mean	−37.62±4.98	−29.85±4.98
Difference in LS mean (95% CI)	−7.78 (−21.70–6.15)	
p-value	0.271	
Secondary end-points		
Proportion of patients with final daily average OCS dose ⩽5 mg		
Patients with OCS dose ⩽5 mg	32 (45.7)	28 (40.0)
OR (95% CI)	1.33 (0.65–2.73)	
p-value	0.442	
Proportion of patients with ⩾50% reduction from baseline in final daily average OCS dose		
Patients with ⩾50% reduction in OCS dose	31 (44.3)	26 (37.1)
OR (95% CI)	1.38 (0.70–2.74)	
p-value	0.356	
Asthma exacerbations		
AAER (95% CI)	1.84 (1.43–2.36)	2.31 (1.83–2.92)
Rate ratio (95% CI)	0.80 (0.57–1.12)	
p-value	0.186	

Data are presented as n, least squared (LS) mean±SE or n (%), unless otherwise stated. OCS: oral corticosteroids; AAER: annual asthma exacerbation rate; [#]: the all-comers population consisted of all patients with any level of fractional exhaled nitric oxide.

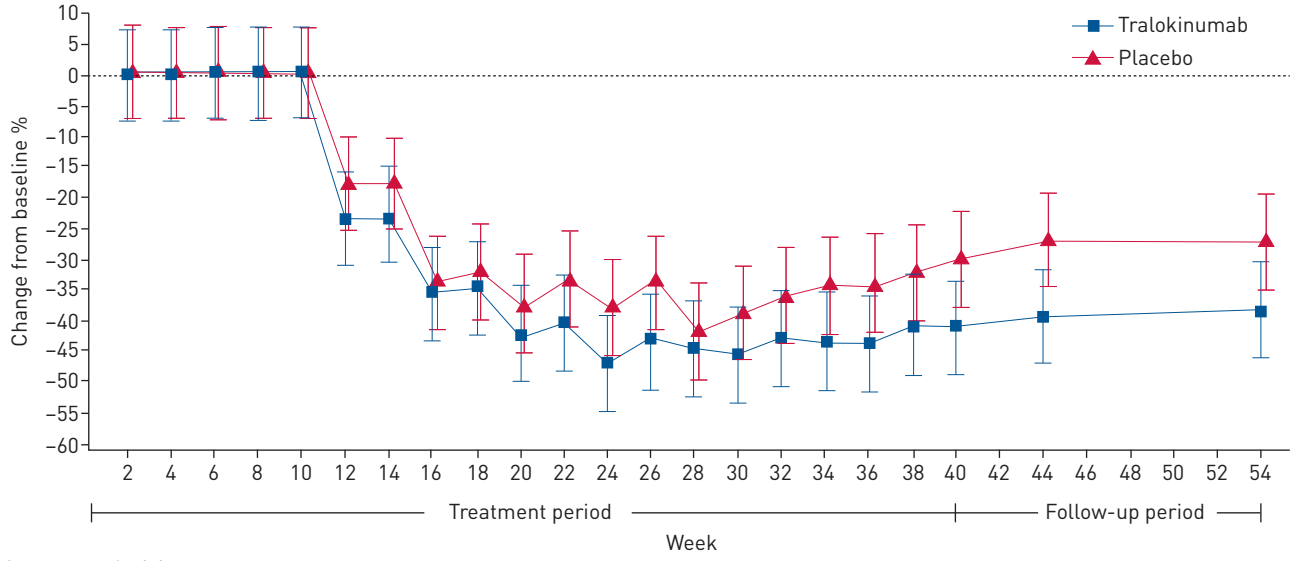

FIGURE 3 Percentage change from baseline in the final daily average oral corticosteroid (OCS) dose over time (full analysis set). Data are presented as least-squares means (95% CI); the number of patients in both groups at each visit are shown below the graph. Baseline was defined as the daily average OCS dose prior to randomisation. The full analysis set consisted of all patients who were randomised and received any dose of either tralokinumab or placebo, irrespective of their protocol adherence and continued participation in the trial.

Secondary end-points

There were no statistically significant differences observed between the tralokinumab and placebo groups for any secondary end-point (table 2). The proportion of patients with a final daily average OCS dose of ⩽5 mg at week 40 was 45.7% in the tralokinumab group *versus* 40.0% in the placebo group (OR 1.33, 95% CI 0.65–2.73; p=0.442). Overall, 44.3% of patients had a ⩾50% reduction from baseline in the final daily average OCS dose at week 40 in the tralokinumab group compared with 37.1% of patients in the placebo group (OR 1.38, 95% CI 0.70–2.74; p=0.356).

Some 67.1% of patients treated with tralokinumab experienced at least one asthma exacerbation during the 40-week treatment period, with 925 total exacerbation days, compared with 75.7% of patients treated with placebo, with 1201 total exacerbation days (supplementary table S4). The AAER was 20% lower in the tralokinumab group through week 40 (1.84 *versus* 2.31; rate ratio 0.80, 95% CI 0.57–1.12; p=0.186).

Exploratory end-points

The proportion of patients with an OCS dose reduction of ⩾75% to <90% was 21.4% in the tralokinumab group compared with 8.6% in the placebo group (supplementary table S5). Although no statistically significant difference was noted between the tralokinumab and placebo groups in the LS mean percentage change from baseline in prebronchodilator FEV_1 at week 40 (12.1% *versus* 4.3%; figure 4a), a nominally statistically significant and clinically meaningful improvement in LS mean absolute change from baseline in prebronchodilator FEV_1 (litres) was noted at week 40 for tralokinumab compared with placebo (LS mean difference 0.17, 95% CI 0.05–0.29; p=0.0053; figure 4b). No statistically significant improvements were observed in mean changes from baseline in the ACQ-6 and AQLQ scores at week 40 for tralokinumab compared with placebo (supplementary figures S1 and S2).

In the population of patients with either F_{ENO} high (⩾37 ppb) or F_{ENO} low (<37 ppb), no significant differences were observed between the tralokinumab and placebo groups in the LS mean percentage reduction in the final daily average OCS dose at week 40 (F_{ENO} high 37.73% *versus* 32.27%, 95% CI –31.03–20.12; F_{ENO} low 37.56% *versus* 28.62%, 95% CI –26.15–8.28; supplementary table S5). Likewise, there were no significant differences between tralokinumab and placebo groups for any of the secondary end-points in the F_{ENO} high or F_{ENO} low populations (supplementary table S6).

Safety

127 (90.7%) patients experienced at least one adverse event during the 40-week treatment period (65 (92.9%) patients in the tralokinumab group and 62 (88.6%) patients in the placebo group; table 3). The most frequently reported adverse events (>5%), which differed between the tralokinumab and placebo treatment groups, were viral upper respiratory tract infection (URTI; 35.7% *versus* 14.3%), bronchitis (15.7% *versus* 24.3%), asthma (11.4% *versus* 22.9%) and back pain (10.0% *versus* 2.9%). During treatment, 14 (10.0%) patients experienced injection site reactions (11 (15.7%) patients in the tralokinumab group and three (4.3%) patients in the placebo group). The most common injection site reactions were erythema (six (8.6%) patients in the tralokinumab group) and pain (six (8.6%) patients in the tralokinumab group and two (2.9%) patients in the placebo group).

Overall, 25 (17.9%) patients had at least one SAE (nine (12.9%) patients in the tralokinumab group and 16 (22.9%) patients in the placebo group; supplementary table S7). Asthma was the most common SAE, being reported in five (7.1%) patients in the tralokinumab group and eight (11.4%) patients in the placebo group. A total of eight (5.7%) patients discontinued treatment due to adverse events (six (8.6%) patients in the tralokinumab group and two (2.9%) patients in the placebo group). All adverse events were single events. One patient in each treatment group discontinued due to worsening asthma and one female patient in the tralokinumab group discontinued due to breast cancer. Adverse events leading to treatment discontinuation were judged to be related to treatment in three patients receiving tralokinumab (two injection site events and one event of angio-oedema). 11 (7.9%) patients experienced severe infections during the treatment period (six (8.6%) patients in the tralokinumab group and five (7.1%) patients in the placebo group). There were no reported cases of pneumonia during the trial. Information on severe infections is provided in supplementary table S8.

At week 40, the mean eosinophil count increased from 243 cells·μL^{-1} at baseline to 382 cells·μL^{-1} in the tralokinumab group; in the placebo group, the mean eosinophil count changed from 210 cells·μL^{-1} at baseline to 246 cells·μL^{-1} at week 40. A total of eight patients (seven patients in the tralokinumab group and one in the placebo group) experienced blood eosinophilia (>1500 cells·μL^{-1}). The patient in the placebo group with this increase had an adverse event of chronic eosinophilic pneumonia of moderate intensity 225 days post-first dose of the investigational product. The event was nonserious and considered not related to the investigational product by the investigator. The patient eventually recovered from the event. No major cardiovascular or cerebrovascular events or cases of anaphylaxis were reported in this trial. No patients died during the treatment period. There were no detectable anti-drug antibodies observed in either the tralokinumab 300 mg or placebo group.

Discussion

Results from this phase 3 TROPOS trial did not demonstrate a significant OCS-sparing effect of tralokinumab compared with placebo in patients with severe asthma. Tralokinumab did not result in a statistically significant reduction in the final daily average OCS dose at week 40 compared with placebo

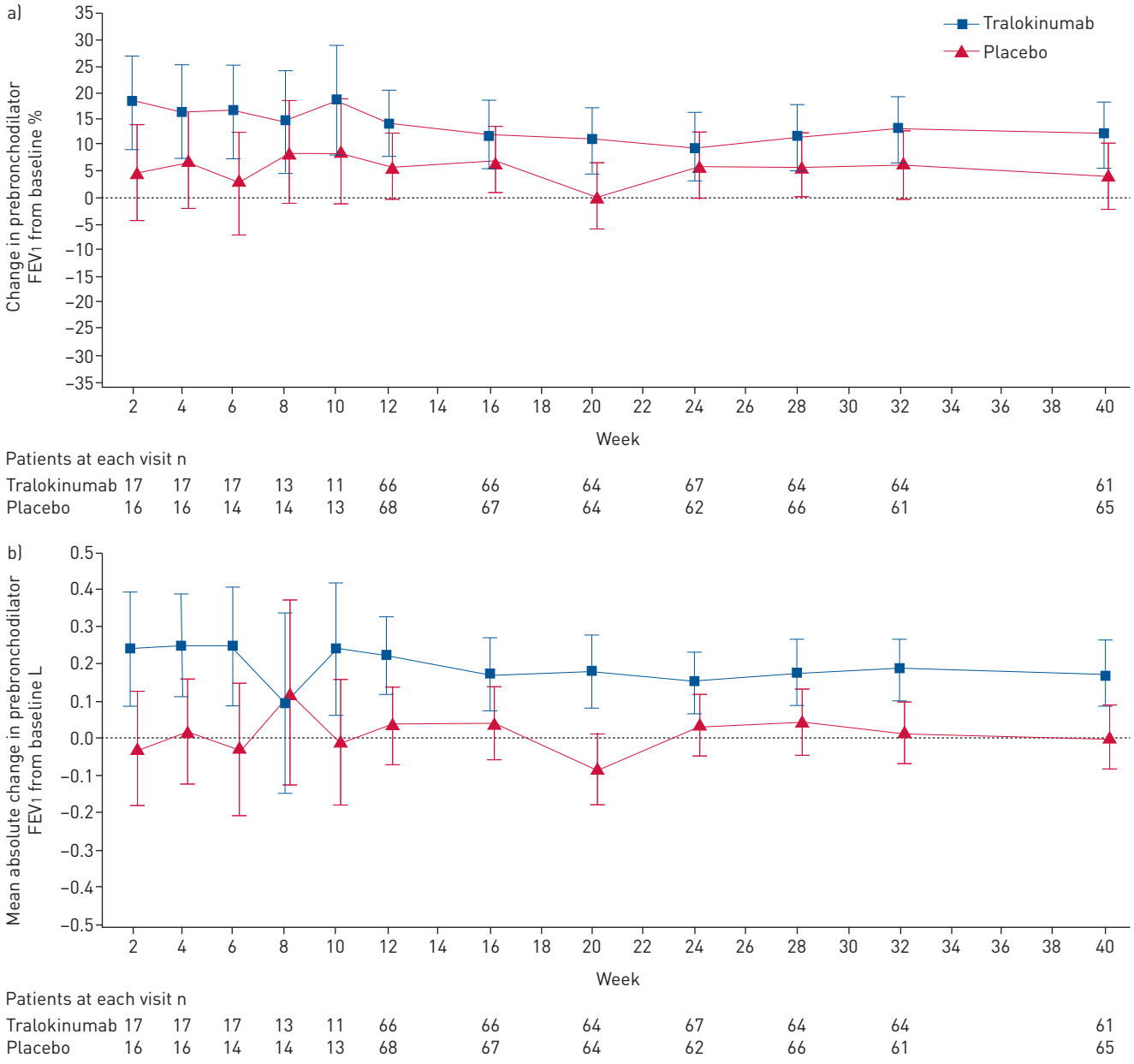

FIGURE 4 Changes in prebronchodilator forced expiratory volume in 1 s (FEV_1) over time (full analysis set). a) Percentage change from baseline in prebronchodilator FEV_1; b) mean absolute change from baseline in prebronchodilator FEV_1. Data are presented as least squares means (95% CI); the number of patients in both groups at each visit are shown below the graphs. Baseline was the last non-missing measurement recorded prior to randomisation (typically visit 6). The full analysis set consisted of all patients who were randomised and received any dose of either tralokinumab or placebo, irrespective of their protocol adherence and continued participation in the trial.

(primary end-point). In addition, no significant effects were observed between tralokinumab and placebo in the proportion of patients with a final daily average OCS dose of ⩽5 mg, the proportion of patients with a ⩾50% reduction in their final daily average OCS dose from baseline and the AAER (secondary end-points). There was a 20% reduction in the AAER with tralokinumab treatment compared with placebo, but this was not statistically significant.

In contrast to TROPOS, several other trials that examined the OCS-sparing effect of monoclonal antibodies (benralizumab, mepolizumab and dupilumab) in patients with severe asthma have reported positive findings [15–17]. The ZONDA trial reported that two benralizumab dosing regimens (30 mg administered *s.c.* every 4 or 8 weeks) significantly reduced the median final OCS dose from baseline by 75% ($p<0.001$ for both comparisons) in patients with severe asthma [15]. Likewise, results from the VENTURE trial reported that dupilumab treatment reduced OCS use while decreasing the rate of severe

TABLE 3 Most common adverse events (>5%) reported during the treatment period (safety analysis set)[#]

	Tralokinumab	Placebo
Patients	70	70
Any adverse event	65 (92.9)	62 (88.6)
Viral upper respiratory tract infection	25 (35.7)	10 (14.3)
Headache	14 (20.0)	11 (15.7)
Bronchitis	11 (15.7)	17 (24.3)
Asthma	8 (11.4)	16 (22.9)
Back pain	7 (10.0)	2 (2.9)
Injection site erythema	6 (8.6)	0
Injection site pain	6 (8.6)	2 (2.9)
Injection site pruritus	5 (7.1)	0
Sinusitis	5 (7.1)	4 (5.7)
Cough	4 (5.7)	1 (1.4)
Dyspnoea	4 (5.7)	2 (2.9)
Hypertension	4 (5.7)	2 (2.9)
Fatigue	3 (4.3)	5 (7.1)
Arthralgia	2 (2.9)	6 (8.6)
Oral candidiasis	2 (2.9)	4 (5.7)
Urinary tract infection	2 (2.9)	5 (7.1)

Data are presented as n or n (%). [#]: the safety set consisted of all patients who received any treatment.

exacerbations and increasing FEV_1 (percentage change in OCS dose was −70.1% in the dupilumab group *versus* −41.9% in the placebo group; p<0.001) [17]. The failure of tralokinumab to provide OCS-sparing benefits or reduce asthma exacerbations in TROPOS is probably explained by a lack of anti-inflammatory effect and the functional redundancy of IL-13 and IL-4 cytokines in asthma [18]. Indeed, results from a recent tralokinumab phase 2 MESOS trial, in which patients with moderate to severe asthma underwent bronchial biopsies before and after 12 weeks of treatment with tralokinumab reported no effect on airway eosinophil inflammation [19]. This lack of anti-inflammatory effect probably explains why previous trials of therapies targeting IL-13, such as lebrikizumab, did not demonstrate consistent reductions in asthma exacerbations [20, 21].

Notably, and in line with results from the phase 2 trials [11, 12], treatment with tralokinumab improved lung function (exploratory end-point), with a significant and clinically meaningful improvement in prebronchodilator FEV_1 at week 40. Interestingly, results from the MESOS phase 2 trial [19] and a *post hoc* analysis of data from a subset of patients in the tralokinumab phase 2b trial suggest that tralokinumab may improve lung function by affecting airway smooth muscle tone [22]. However, tralokinumab treatment did not lead to significant improvements in other exploratory end-points relating to asthma control or quality of life in TROPOS.

F_{ENO} is a well-established biomarker for airway inflammation, which is induced through IL-13 axis-mediated pathways [23, 24]. In the pivotal STRATOS 1 trial a subpopulation of patients with severe asthma with F_{ENO} ⩾37 ppb was identified as most likely to have an enhanced response to tralokinumab [13]. For this reason, prior to unblinding of trial results and following consultation with the United States Food and Drug Administration, the statistical analysis plan for TROPOS was revised to perform the primary analysis in a F_{ENO} high subpopulation (F_{ENO} ⩾37 ppb) if there were a sufficient proportion of patients. Given the small sample size for this subpopulation, contingency plans were devised to ensure that the primary analysis would only be performed in a F_{ENO} high subpopulation if ⩾70 patients were included (thresholds of ⩾37 ppb then ⩾30 ppb). In TROPOS, more than half of the patients had F_{ENO} levels below the lower 30 ppb threshold, and therefore, the primary and secondary analyses were performed in the all-comers population. However, exploratory analyses of the primary and secondary end-points based on F_{ENO} levels did not reveal that higher F_{ENO} levels (⩾37 ppb) were predictive of a greater treatment effect with tralokinumab. The pivotal phase 3 trial STRATOS 2 also failed to show meaningful reductions in the AAER in F_{ENO} high patients [13].

Tralokinumab demonstrated an acceptable safety profile, which was consistent with previous reports [11, 12]. Overall, the incidence of adverse events was comparable between the tralokinumab and placebo groups, although patients treated with tralokinumab reported a higher incidence of URTIs and injection site reactions. The explanation for the disparity in rates of URTIs remains unclear, since there were no

reported cases of pneumonia in this trial and the proportion of patients with severe infections were similar across treatment groups. Interestingly, similar observations were observed in the VENTURE trial, where the most frequent adverse event was URTI (9% of patients in the dupilumab group and 18% of patients in the placebo group) [17]. Likewise, results from the LIBERTY ASTHMA trial, in which patients received add-on dupilumab at a dose of 200 or 300 mg or placebo for 52 weeks, also reported that URTI was the most commonly reported adverse event [25].

A small increase in mean blood eosinophil counts was observed for the tralokinumab group *versus* the placebo group, with more tralokinumab-treated patients having an increase in eosinophil counts above 1500 cells·μL^{-1} than placebo-treated patients (seven *versus* one). However, despite this finding, no associated adverse events were reported in those tralokinumab-treated patients with increased blood eosinophil counts. This finding is in line with that reported in the VENTURE trial, where transient blood eosinophilia was observed in more patients in the dupilumab group than the placebo group (14% *versus* 1%), without any clinical consequences or associated adverse events [17]. In the LIBERTY ASTHMA trial, eosinophilia was reported as an adverse event in 4.1% of patients who received dupilumab and 0.6% of patients who received placebo; however, in this instance, in 0.2% of the overall population, these adverse events were accompanied by clinical symptoms, with two events reported as SAEs (worsening of hypereosinophilia and chronic eosinophilic pneumonia) [25].

A strength of the current trial was the trial design, which to a large extent, replicated methods previously used in other OCS-sparing trials [15, 16, 26, 27], but with two notable exceptions. Firstly, based on findings from the tralokinumab development programme [11, 12], a 12-week induction phase was incorporated into the TROPOS trial design to ensure maximal effect on FEV_1. Secondly, the maintenance phase was extended to 8 weeks to assess longer term efficacy compared with previously reported OCS-sparing trials [16, 26–28]. Notably, the reduction in OCS use observed in the placebo group in TROPOS was similar to that reported in the ZONDA trial [15], indicating that the trial design was adequate to demonstrate an OCS-sparing effect. However, this trial had limitations, including the usual restrictions of selectivity and a relatively small sample size, which meant that several analyses, such as the impact of increased eosinophil levels, could not be performed.

In summary, tralokinumab did not demonstrate clinically significant OCS-sparing effects or improvements in asthma control compared with placebo in patients with severe, uncontrolled asthma. Higher levels of F_{ENO} ($\geqslant$37 ppb) were not predictive of a greater treatment effect with tralokinumab. Hence, the findings in this trial, along with the previously reported results of the STRATOS 1 and 2 trials, suggest that targeting IL-13 alone is not an effective strategy to manage severe asthma.

Acknowledgements: We thank the healthcare providers, research staff, patients and caregivers who participated in the trial. Medical writing support was provided by Khund Sayeed, Mohammed Najeeb and Frances Gambling of Cactus Communications (Mumbai, India), funded by AstraZeneca (Cambridge, UK), in accordance with Good Publication Practice (GPP3) guidelines (www.ismpp.org/gpp3). Presented as an abstract at the 28th International Congress of the European Respiratory Society, Paris, France; September 15–19, 2018.

Conflict of interest: W.W. Busse reports personal fees for consultancy from AstraZeneca, during the conduct of the study; personal fees for consultancy from 3M, Boehringer Ingelheim, GlaxoSmithKline, Novartis, Sanofi-Regeneron and Teva, personal fees for data and safety monitoring board work from Boston Scientific and Genentech, personal fees (royalties) from Elsevier, personal fees for educational videos from Medscape, personal fees for joint oversight committee work from ICON Clinical Research Limited, and personal fees from Pfizer, Roche, AstraZeneca and Circassia, and grants from NIH-NIAID and NIH-NHLBI, outside the submitted work. G.G. Brusselle reports honoraria for advisory boards and/or lectures from AstraZeneca, Boehringer-Ingelheim, Chiesi, GlaxoSmithKline, Novartis, Pfizer, Sanofi/Regeneron, Teva, UCB and Zambon, during the conduct of the study. S. Korn reports consulting and lecture fees from Almirall, AstraZeneca, Boehringer Ingelheim, Chiesi, Teva and Roche, and grants and personal fees from GlaxoSmithKline and Novartis, during the conduct of the study. P. Kuna reports personal fees from Adamed, Allergopharma, ALK, AstraZeneca, Bayer Celon Pharma, Chiesi, FAES, HAL Allergy, Lekam, Polpharma, Pfizer, Sandoz and Teva, during the conduct of the study; and personal fees from Berlin Chemie, Boehringer Ingelheim and Novartis, outside the submitted work. A. Magnan reports personal fees and non-financial support from GlaxoSmithKline, Novartis, Boehringer Ingelheim, AstraZeneca, Stallerg nes, ALK, MundiPharma, Teva, Menarini and Meda Pharma, during the the past 5 years. D. Cohen is an employee of AstraZeneca. K. Bowen is an employee of and own shares in AstraZeneca. T. Piechowiak is an employee of and owns stock options in AstraZeneca. M.M. Wang is an employee of and owns shares in AstraZeneca. G. Colice is an employee of and owns shares and stock options in AstraZeneca.

Support statement: This study was sponsored by AstraZeneca. Funding information for this article has been deposited with the Crossref Funder Registry.

References

1 Global Asthma Network. Global Asthma Report 2014. www.globalasthmareport.org/2014/resources/Global_Asthma_Report_2014.pdf Date last accessed: August 2018.
2 McCracken JL, Veeranki SP, Ameredes BT, *et al.* Diagnosis and management of asthma in adults: a review. *JAMA* 2017; 318: 279–290.

3 Voorham J, Xu X, Price D, *et al.* Health care resource utilization and costs associated with incremental systemic corticosteroid exposure in asthma. *Allergy* 2018; in press [https://doi.org/10.1111/all.13556].
4 Sweeney J, Patterson CC, Menzies-Gow A, *et al.* Comorbidity in severe asthma requiring systemic corticosteroid therapy: cross-sectional data from the Optimum Patient Care Research Database and the British Thoracic Difficult Asthma Registry. *Thorax* 2016; 71: 339–346.
5 Wills-Karp M, Luyimbazi J, Xu X, *et al.* Interleukin-13: central mediator of allergic asthma. *Science* 1998; 282: 2258–2261.
6 Elias JA, Zhu Z, Chupp G, *et al.* Airway remodeling in asthma. *J Clin Invest* 1999; 104: 1001–1006.
7 Barnes PJ. New drugs for asthma. *Nat Rev Drug Discov* 2004; 3: 831–844.
8 Fajt ML, Wenzel SE. Development of new therapies for severe asthma. *Allergy Asthma Immunol Res* 2017; 9: 3–14.
9 Lightwood D, O'Dowd V, Carrington B, *et al.* The discovery, engineering and characterisation of a highly potent anti-human IL-13 fab fragment designed for administration by inhalation. *J Mol Biol* 2013; 425: 577–593.
10 May RD, Monk PD, Cohen ES, *et al.* Preclinical development of CAT-354, an IL-13 neutralizing antibody, for the treatment of severe uncontrolled asthma. *Br J Pharmacol* 2012; 166: 177–193.
11 Brightling CE, Chanez P, Leigh R, *et al.* Efficacy and safety of tralokinumab in patients with severe uncontrolled asthma: a randomised, double-blind, placebo-controlled, phase 2b trial. *Lancet Respir Med* 2015; 3: 692–701.
12 Piper E, Brightling C, Niven R, *et al.* A phase II placebo-controlled study of tralokinumab in moderate-to-severe asthma. *Eur Respir J* 2013; 41: 330–338.
13 Panettieri R, Sjöbring U, Péterffy AM, *et al.* Tralokinumab for severe, uncontrolled asthma (STRATOS 1 and STRATOS 2): two randomised, placebo-controlled, phase 3 clinical trials. *Lancet Respir Med* 2018; 6: 511–525.
14 Busse WW, Wang M, Gibson J, *et al.* TROPOS: designing a clinical trial to evaluate the oral corticosteroid-sparing effect of a biologic in severe asthma. *Clin Invest* 2015; 5: 723–730.
15 Nair P, Wenzel S, Rabe KF, *et al.* Oral glucocorticoid-sparing effect of benralizumab in severe asthma. *N Engl J Med* 2017; 376: 2448–2458.
16 Bel EH, Wenzel SE, Thompson PJ, *et al.* Oral glucocorticoid-sparing effect of mepolizumab in eosinophilic asthma. *N Engl J Med* 2014; 371: 1189–1197.
17 Rabe KF, Nair P, Brusselle G, *et al.* Efficacy and safety of dupilumab in glucocorticoid-dependent severe asthma. *N Engl J Med* 2018; 378: 2475–2485.
18 Maes T, Joos GF, Brusselle GG. Targeting interleukin-4 in asthma: lost in translation? *Am J Respir Cell Mol Biol* 2012; 47: 261–270.
19 Russell RJ, Chachi L, FitzGerald JM, *et al.* Effect of tralokinumab, an interleukin-13 neutralising monoclonal antibody, on eosinophilic airway inflammation in uncontrolled moderate-to-severe asthma (MESOS): a multicentre, double-blind, randomised, placebo-controlled phase 2 trial. *Lancet Respir Med* 2018; 6: 499–510.
20 Hanania NA, Korenblat P, Chapman KR, *et al.* Efficacy and safety of lebrikizumab in patients with uncontrolled asthma (LAVOLTA I and LAVOLTA II): replicate, phase 3, randomised, double-blind, placebo-controlled trials. *Lancet Respir Med* 2016; 4: 781–796.
21 De Boever EH, Ashman C, Cahn AP, *et al.* Efficacy and safety of an anti-IL-13 mAb in patients with severe asthma: a randomized trial. *J Allergy Clin Immunol* 2014; 133: 989–996.
22 Brightling CE, Nordenmark LH, Jain M, *et al.* Effect of anti-IL-13 treatment on airway dimensions in severe asthma. *Am J Respir Crit Care Med* 2016; 194: 118–120.
23 Corren J. Role of interleukin-13 in asthma. *Curr Allergy Asthma Rep* 2013; 13: 415–420.
24 Dweik RA, Boggs PB, Erzurum SC, *et al.* An official ATS clinical practice guideline: interpretation of exhaled nitric oxide levels (F_{ENO}) for clinical applications. *Am J Respir Crit Care Med* 2011; 184: 602–615.
25 Castro M, Corren J, Pavord ID, *et al.* Dupilumab efficacy and safety in moderate-to-severe uncontrolled asthma. *N Engl J Med* 2018; 378: 2486–2496.
26 Bateman E, Karpel J, Casale T, *et al.* Ciclesonide reduces the need for oral steroid use in adult patients with severe, persistent asthma. *Chest* 2006; 129: 1176–1187.
27 Hummel S, Lehtonen L. Comparison of oral-steroid sparing by high-dose and low-dose inhaled steroid in maintenance treatment of severe asthma. *Lancet* 1992; 340: 1483–1487.
28 Lacronique J, Renon D, Georges D, *et al.* High-dose beclomethasone: oral steroid-sparing effect in severe asthmatic patients. *Eur Respir J* 1991; 4: 807–812.