

Tralokinumab for severe, uncontrolled asthma (STRATOS 1 and STRATOS 2): two randomised, double-blind, placebo-controlled, phase 3 clinical trials



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Summary

Background Tralokinumab is an anti-interleukin-13 human monoclonal antibody developed for the treatment of severe, uncontrolled asthma. These clinical trials aimed to assess the efficacy and safety of tralokinumab in this population.

Methods STRATOS 1 and STRATOS 2 were randomised, double-blind, parallel-group, placebo-controlled, phase 3 clinical trials that enrolled participants aged 12–75 years with severe asthma that was inadequately controlled despite use of inhaled corticosteroids (≥ 500 µg per day fluticasone or equivalent) and a long-acting β_2 agonist (but not oral corticosteroids). STRATOS 1 was done at 246 sites in 14 countries, and STRATOS 2 was done at 242 sites in 13 countries. In STRATOS 1, participants were randomly assigned (2:1) to receive tralokinumab 300 mg or matching placebo subcutaneously every 2 weeks or every 4 weeks for 52 weeks. In STRATOS 2, participants were randomly assigned (1:1) to receive tralokinumab 300 mg or matching placebo subcutaneously every 2 weeks for 52 weeks. STRATOS 1 attempted to identify a biomarker-positive population with enhanced tralokinumab benefit, which was then tested in STRATOS 2. The primary endpoint was the annualised asthma exacerbation rate (AAER) reduction at week 52 in the all-comers population for STRATOS 1 and in the biomarker-positive population for STRATOS 2. All efficacy analyses for both trials were done on the full analysis set by an intention-to-treat approach. The safety analysis set comprised any participant who received the investigational drug and was categorised by treatment received. These trials are registered with ClinicalTrials.gov, numbers NCT02161757 (STRATOS 1) and NCT02194699 (STRATOS 2), and with the EU Clinical Trials Register, EudraCT 2013-005614-35 (STRATOS 1) and EudraCT 2013-005615-27 (STRATOS 2).

Findings STRATOS 1 was done between June 13, 2014, and Feb 28, 2017. 1207 participants were randomly assigned and 1202 treated as follows: tralokinumab every 2 weeks (n=398), tralokinumab every 4 weeks (n=404), or placebo (n=400). STRATOS 2 was done between Oct 30, 2014, and Sept 21, 2017. 856 participants were randomly assigned and 849 treated as follows: tralokinumab every 2 weeks (n=427) and placebo every 2 weeks (n=422). In the STRATOS 1 all-comers population, tralokinumab every 2 weeks did not significantly reduce AAER compared with placebo (7·0% reduction [95% CI –20·8 to 28·4]; rate ratio 0·93 [95% CI 0·72 to 1·21]; p=0·59). Baseline fractional exhaled nitric oxide (FENO) 37 ppb or greater was identified as the preferred biomarker in STRATOS 1; in FENO-high participants, tralokinumab every 2 weeks (n=97) reduced AAER by 44·0% (95% CI 6·0 to 66·0; rate ratio 0·56 [95% CI 0·34 to 0·94]; p=0·028) compared with placebo (n=102). In the STRATOS 2 FENO-high population, tralokinumab every 2 weeks (n=108) did not significantly improve AAER (15·8% reduction [95% CI –33·7 to 47·0]; rate ratio 0·84 [95% CI 0·53 to 1·34]; p=0·47) compared with placebo (n=121). The safety profile was consistent with that of previous tralokinumab trials.

Interpretation Tralokinumab reduced AAER in participants with severe asthma with baseline FENO 37 ppb or higher in STRATOS 1, but not in STRATOS 2. These inconsistent effects on AAER do not support a key role for interleukin 13 in severe asthma exacerbations.

Funding AstraZeneca.

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Introduction

Asthma is a complex, heterogeneous, chronic inflammatory airway disorder, affecting approximately 315 million people worldwide.¹ Clinical presentation of asthma can vary widely, from exercise-induced bronchospasms to severe disease, which is present in up to 10% of people with asthma.² Severe asthma can remain

uncontrolled despite treatment with high-dose inhaled corticosteroids (ICS) plus long-acting β_2 agonists (LABA) and other controller medications.³ Indeed, people with severe asthma have an increased likelihood of having asthma exacerbations and poor health-related quality of life, are at increased risk of becoming dependent on oral corticosteroids (OCS) for disease control,² and—if their

Lancet Respir Med 2018

Published Online

May 20, 2018

[http://dx.doi.org/10.1016/S2213-2600\(18\)30184-X](http://dx.doi.org/10.1016/S2213-2600(18)30184-X)

See Online/Comment

[http://dx.doi.org/10.1016/S2213-2600\(18\)30194-2](http://dx.doi.org/10.1016/S2213-2600(18)30194-2)

See Online/Article

[http://dx.doi.org/10.1016/S2213-2600\(18\)30201-7](http://dx.doi.org/10.1016/S2213-2600(18)30201-7)

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Research in context

Evidence before this trial

We searched PubMed for reports of clinical trials investigating anti-interleukin-13 monoclonal antibodies for the treatment of asthma in humans published between Jan 1, 2008, and Jan 1, 2018. We used the search terms “asthma” AND “interleukin13” AND “antibody” and filtered for clinical trial reports, which yielded 17 results. 12 trials reported results for five biologics that inhibit interleukin-13 signalling. Lebrikizumab, the only anti-interleukin-13 biologic with published phase 3 trial results to date, did not show a consistent, significant reduction in asthma exacerbations in a biomarker-positive population with uncontrolled asthma.

Added value of this trial

The two studies reported here are, to our knowledge, the first to assess the efficacy and safety of tralokinumab in phase 3 clinical trials. In STRATOS 1, compared with placebo, tralokinumab 300 mg every 2 weeks or every 4 weeks did not significantly reduce asthma exacerbation rates in an all-comers population of participants with severe, uncontrolled asthma.

A biomarker predictive of enhanced tralokinumab efficacy (baseline fractional exhaled nitric oxide [FENO] ≥ 37 ppb) was identified on the basis of data from STRATOS 1 and assessed in STRATOS 2. Tralokinumab every 2 weeks did not significantly reduce exacerbation rates in the all-comers population (similar to STRATOS 1) or in the FENO-high population in STRATOS 2. In the all-comers and FENO-high populations in STRATOS 1, however, tralokinumab treatment resulted in clinically meaningful improvements in FEV₁ compared with placebo. Other biomarkers of type-2 inflammation, including periostin and dipeptidyl peptidase-4, were also unable to predict response to treatment.

Implications of all the available evidence

Our findings add to available evidence that interleukin-13 blockade alone is insufficient to reduce asthma exacerbations in people with severe, uncontrolled asthma, but it might improve lung function. By contrast, benefits have been observed in the management of severe asthma by targeting interleukin 13 and interleukin 4 concurrently.

disease is uncontrolled—account for the majority of asthma-related health-care resources.^{3–5}

In animal models, multiple studies have shown that interleukin 13, a type-2 pleiotropic cytokine, can induce airway hyper-responsiveness, goblet cell metaplasia, and lung eosinophilia, which contribute to the pathophysiology of asthma.^{6,7} Interleukin 13 has also been shown to contribute to airway remodelling via collagen deposition mediated by transforming growth factor- β (TGF- β).^{8,9} Additionally, blockade of interleukin 13 in ovalbumin-sensitised mice (unlike blockade of the closely related cytokine interleukin 4) prevents development of airway hyper-responsiveness.^{6,10} Subsequent clinical trials have supported a role for interleukin 13 in asthma, with bronchial biopsy samples showing an increased concentration of interleukin 13 in participants with both atopic and non-atopic disease, compared with healthy individuals.^{11–13} Therefore, anti-interleukin-13 agents might have clinical utility for treatment of severe asthma.

Tralokinumab, an IgG₄ monoclonal human antibody that potently and specifically neutralises interleukin 13 by preventing its interaction with the interleukin-13 receptor $\alpha 1$ and $\alpha 2$ subunits,¹⁴ was developed for the treatment of severe asthma. Significant improvements in lung function were observed in phase 2 trials in participants with asthma (NCT00873860¹⁵ and NCT01402986¹⁶), although tralokinumab did not improve asthma control or reduce exacerbations in the overall study populations. In a post-hoc analysis of the phase 2b trial, tralokinumab treatment was associated with a non-significant improvement in the annualised asthma exacerbation rate (AAER) compared with placebo, as well as an enhanced FEV₁ response, in a subgroup of participants with post-

bronchodilator FEV₁ reversibility of 12% or greater who were not taking regular OCS.¹⁶ The observations in this subgroup were carried forward to define the study population for the phase 3 trials. Further post-hoc analyses of phase 2b data suggested that participants from this subgroup who also had evidence of interleukin-13 axis activation (increased serum concentrations of periostin or dipeptidyl peptidase-4 [DPP-4]) had further benefits with tralokinumab.¹⁶ These observations were consistent with our understanding of severe asthma as a heterogeneous disease comprising various phenotypes, each based on different underlying patterns of inflammation that drive the disease.¹⁷ However, the phase 2 trials were not able to identify the most appropriate biomarker, or its threshold, for identifying a suitable subgroup with enhanced tralokinumab efficacy for enrolment in phase 3 trials.

Tralokinumab was investigated in late-stage clinical development in the ATMOSPHERE programme. This clinical programme consisted of five trials: the pivotal phase 3 clinical trials STRATOS 1 (NCT02161757) and STRATOS 2 (NCT02194699); a phase 3 OCS-sparing clinical trial, TROPOS (NCT02281357); a phase 2 mechanistic clinical trial, MESOS (NCT02449473); and an open-label, long-term trial in Japanese participants (NCT02902809).¹⁸ The ATMOSPHERE clinical programme took a novel approach towards assessing the efficacy and safety of tralokinumab treatment for severe asthma. Here, we report the findings of the STRATOS 1 and STRATOS 2 trials. STRATOS 1 aimed to assess the effect of tralokinumab on reducing the AAER in the overall trial (all-comers) population and identified a biomarker subgroup with an enhanced benefit from

tralokinumab. The second trial, STRATOS 2, which maintained blinding during STRATOS 1 readout, was intended to test the efficacy of tralokinumab in both the all-comers population and the biomarker-positive population, as identified in the STRATOS 1 analyses.

Methods

Study design and participants

STRATOS 1 and STRATOS 2 were two randomised, double-blind, parallel-group, placebo-controlled, global phase 3 clinical trials designed to assess the efficacy and safety of tralokinumab in participants with severe, uncontrolled asthma. STRATOS 1 was done at 246 sites in 14 countries (Argentina, Belgium, Bulgaria, Columbia, Germany, Hungary, Peru, Poland, Slovakia, South Korea, Spain, Ukraine, the USA, and Vietnam). STRATOS 2 was done at 242 sites in 13 countries (Canada, Chile, Czech Republic, Italy, Japan, Mexico, Philippines, Russia, South Africa, Taiwan, Ukraine, the UK, and the USA). STRATOS 1 and STRATOS 2 enrolled participants aged 12–75 years with physician-diagnosed asthma for at least a year before enrolment, who required medium to high dose ICS (total daily dose ≥ 500 μ g fluticasone or equivalent) and a LABA for at least 3 months before visit 1; use of systemic steroids was prohibited, but participants were allowed additional maintenance controller medications if required. Participants then entered a 4–6-week run-in period (during which a post-bronchodilator FEV₁ reversibility of $\geq 12\%$ and ≥ 200 mL was required), followed by a 52-week treatment period, and a 20-week safety follow-up (figure 1). The trial designs have been previously reported.^{18,19}

The STRATOS 1 and STRATOS 2 trials were done in accordance with the Declaration of Helsinki and the International Conference on Harmonisation Guidance for Good Clinical Practice. Independent ethics committee approval was obtained at all participating centres and all participants provided written informed consent. The full protocol and statistical analysis plan are available online.

Randomisation and masking

Participants in both trials were stratified at randomisation by median baseline serum periostin concentration (<16.44 ng/mL or ≥ 16.44 ng/mL), geographical region, and age group (adults [≥ 18 years] versus adolescents [≥ 12 years to <18 years]; appendix). The periostin cutoff for stratification was chosen on the basis of phase 2b results, in which participants with periostin concentrations higher than the baseline median showed enhanced responses to tralokinumab.¹⁶ As tralokinumab was being tested as an add-on therapy, all participants in both trials received a stable dose of ICS (≥ 500 μ g fluticasone propionate dry powder or equivalent) and a LABA throughout the treatment period.

In STRATOS 1, participants were randomly assigned (2:1) to receive tralokinumab 300 mg or placebo administered subcutaneously every 2 weeks or every 4 weeks for 52 weeks. In STRATOS 2, participants were

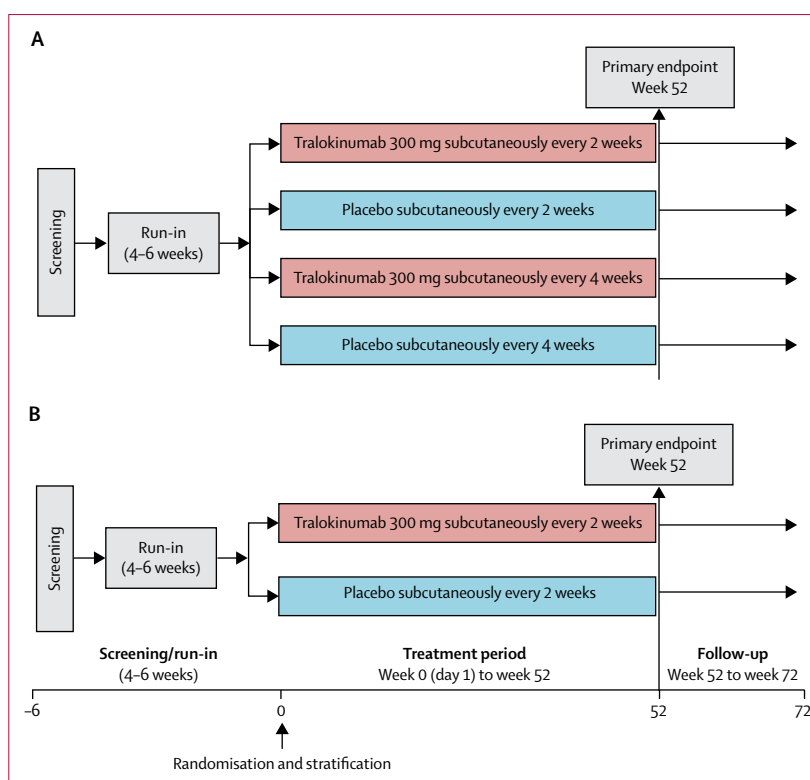


Figure 1: STRATOS 1 (A) and STRATOS 2 (B) trial designs
Reproduced with permission from Panettieri et al (2015).¹⁹

randomly assigned (1:1) to receive tralokinumab 300 mg or placebo administered subcutaneously every 2 weeks for 52 weeks. Previous pharmacokinetic and pharmacodynamic modelling analyses indicated near-maximal improvements in pre-bronchodilator FEV₁ with tralokinumab 300 mg administered subcutaneously every 2 weeks, justifying selection of this dose for phase 3 trials.²⁰ Pre-bronchodilator FEV₁ was chosen as the endpoint in this modelling analysis as tralokinumab did not significantly reduce AAER in the phase 2b trial.¹⁶ The regimen of tralokinumab 300 mg every 4 weeks was included in STRATOS 1 to characterise the dose-response and to test whether less frequent dosing could produce an acceptable efficacy profile.

In both trials, randomisation was done in blocks by use of an interactive web or voice response system, which sequentially assigned randomisation codes in each stratum as participants became eligible. Tralokinumab and placebo are visually distinct and so were administered by an unmasked team member not involved in the management of participants in order to maintain masking. Participants and trial site personnel assessing outcomes were unaware of the treatment allocation.

Outcomes

The primary endpoint in STRATOS 1 was to assess the effect of tralokinumab every 2 weeks versus placebo on

For the **study protocol and statistical analysis plan of STRATOS 1** see <https://astrazenecagrouptrials.pharmacm.com/ST/Submission/View?id=2324>

For the **study protocol and statistical analysis plan of STRATOS 2** see <https://astrazenecagrouptrials.pharmacm.com/ST/Submission/View?id=12407>

See Online for appendix

the AAER at week 52 in the all-comers population. If this endpoint was met, the effect of tralokinumab every 4 weeks versus placebo on the AAER at week 52 for the all-comers population would be tested. A predefined exploratory endpoint in STRATOS 1 was identification of a biomarker predictive of enhanced response to tralokinumab to inform the analysis of STRATOS 2. The predefined biomarkers assessed were blood eosinophils, fractional exhaled nitric oxide (FENO), serum DPP-4, serum periostin, and total serum IgE.

After the STRATOS 1 results became available, the primary endpoint for STRATOS 2 was amended to assess the effect of tralokinumab every 2 weeks versus placebo on the AAER at week 52 in the biomarker-positive population identified in STRATOS 1 (the primary population), and the all-comers population became a secondary population. In both trials, asthma exacerbations were defined as worsening of asthma that led to use of systemic corticosteroids for 3 or more days, an emergency department visit due to asthma that required systemic corticosteroid use, or admission to hospital because of asthma.

Key secondary endpoints assessed in STRATOS 1 and STRATOS 2 were the percentage change in pre-bronchodilator FEV₁ from baseline at week 52, and change from baseline in bi-weekly daily asthma symptom score, Standardised Asthma Quality of Life Questionnaire for 12 years and older (AQLQ) total score, and Asthma Control Questionnaire-6 (ACQ-6) score at week 52. Other secondary endpoints for both STRATOS 1 and STRATOS 2 were time to first exacerbation; proportion of participants with one or more exacerbations; AAER associated with emergency department visits, urgent care visits or admission to hospital; post-bronchodilator FEV₁; European Quality of Life-5 Dimension-5 Level Daily Living Questionnaire score; Work Productivity and Activity Impairment Questionnaire and Classroom Impairment Questionnaire scores; asthma-specific resource utilisation; rescue medication use; home morning and evening peak expiratory flow; night-time awakening due to asthma; pharmacokinetics; and immunogenicity. This report focuses on tralokinumab treatment every 2 weeks in STRATOS 1 and STRATOS 2; results of tralokinumab every 4 weeks from STRATOS 1 are included in the appendix.

In both trials, adverse events, including serious adverse events and adverse events leading to discontinuation, were recorded from the receipt of informed consent to the end of the follow-up period. Safety topics of special attention included injection-site reactions, anaphylaxis, severe infections, and eosinophil counts. Analyses of haematology, clinical chemistry, and urinalysis were also done. An independent data and safety monitoring board regularly reviewed unblinded safety data during both trials and monitored the safety of adolescent and adult participants throughout the double-blind treatment period. An endpoint adjudication committee that was

masked to treatment allocation assessed all deaths, hospital admissions, emergency department visits, and urgent care visits to ascertain whether they were asthma-related. This committee also reviewed all malignancies, cardiovascular events, and cerebrovascular events. All adverse events identified as occurring within 72 h of investigational drug administration and possibly representing anaphylactic events were reviewed by an independent allergist (who was masked to treatment allocation) by use of Sampson's criteria.²¹

Statistical analysis

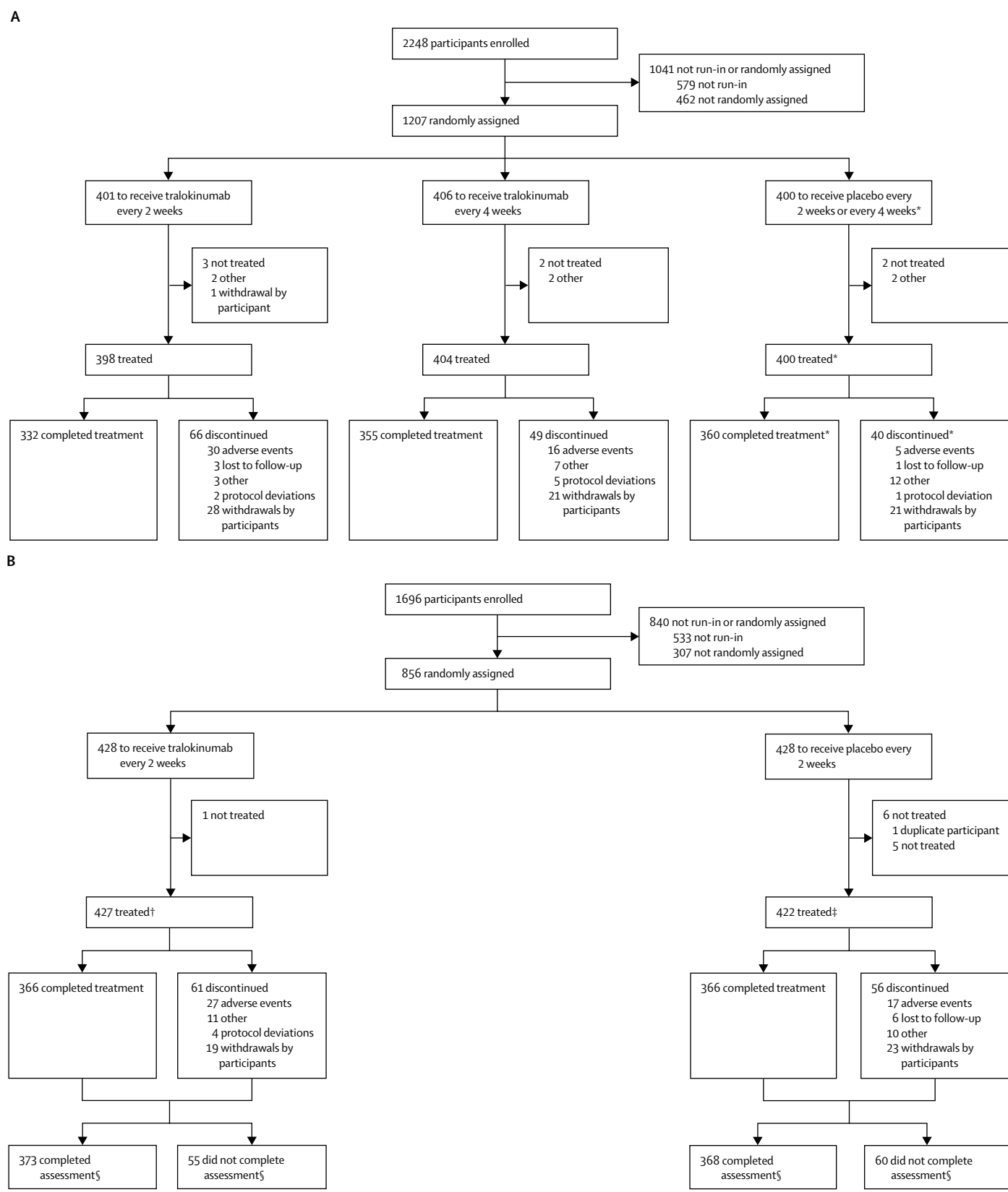
In STRATOS 1, a sample size of 1140 was considered to be sufficient to show a reduction in AAER for the two dosing regimens of tralokinumab versus the combined placebo group (380 participants in each active dosing regimen and 190 in each of the placebo [every 2 weeks and every 4 weeks] groups). In STRATOS 2, a sample size of 770 participants was considered sufficient. The sample size calculations for both trials assumed an AAER in the placebo group of 0·8. Assuming a uniform loss of 15% in both trials, these estimates were expected to produce 90% or higher power for observing reductions in AAER of 32% in STRATOS 1 and 37% in STRATOS 2. On June 12, 2017, the STRATOS 2 protocol was amended to define the FENO-high subgroup as the primary population; at this point it was estimated that, if 25% of the study population fulfilled the biomarker-positive criteria, a true AAER reduction of 50% would have 80% power to show superiority with a 5% significance level for the biomarker-positive subgroup.

In both trials, the AAER was assessed with a negative binomial model that included covariates of treatment group, geographical region, age group, periostin group at baseline (categorical), and number of exacerbations in the year before the study. The model for STRATOS 2 also included a variable for the biomarker subgroup (positive, negative) and a treatment-by-biomarker subgroup interaction term. Both trials used hierarchical testing strategies to provide strong global control of type I error; these strategies are described elsewhere.¹⁸ The statistical methods used to assess the key secondary endpoints are provided in the appendix.

All efficacy analyses for both trials were done by an intention-to-treat approach based on the full analysis set. The full analysis set in both STRATOS 1 and STRATOS 2 comprised all participants randomly assigned and receiving

Figure 2: Trial profiles

(A) STRATOS 1. (B) STRATOS 2. *The STRATOS 1 placebo treatment group is a combined treatment group (placebo every 2 weeks plus placebo every 4 weeks), where the two placebo cohorts were given weights proportional to the number of participants in each cohort. For STRATOS 2, eight participants on tralokinumab every 2 weeks and 11 on placebo were excluded from the full analysis set. †Two participants were duplicates and were not included in the safety set; these two participants and five who did not have the potential to receive 52 weeks of treatment were not included in the full analysis set. ‡Five participants did not have the potential to receive 52 weeks of treatment, so were not included in the full analysis set. §Of participants randomly assigned.



	All-comers population (n=798)		FENO-high (≥ 37 ppb) population (n=199)	
	Combined placebo* (n=400)	Talokinumab every 2 weeks (n=398)	Combined placebo* (n=102)	Talokinumab every 2 weeks (n=97)
Demographics				
Age, years	51.4 (14.3)	49.4 (14.3)	46.5 (15.1)	46.3 (13.9)
Women	265 (66.3%)	252 (63.3%)	70 (68.6%)	55 (56.7%)
Men	135 (33.8%)	146 (36.7%)	32 (31.4%)	42 (43.3%)
Race				
White	288 (72.0%)	285 (71.6%)	55 (53.9%)	56 (57.7%)
Black or African American	14 (3.5%)	21 (5.3%)	5 (4.9%)	7 (7.2%)
Asian	55 (13.8%)	53 (13.3%)	17 (16.7%)	16 (16.5%)
Other	43 (10.8%)	39 (9.8%)	25 (24.5%)	18 (18.6%)
BMI, kg/m ²	28.8 (6.4)	28.4 (6.3)	28.0 (6.2)	27.5 (6.5)
Clinical characteristics				
Pre-bronchodilator FEV ₁ , L	1.8 (0.6)	1.8 (0.6)	1.9 (0.6)	1.8 (0.6)
Pre-bronchodilator FEV ₁ , predicted	61.5% (13.3)	59.8% (12.8)	63.5% (13.8)	59.4% (12.4)
Pre-bronchodilator FVC, L	2.8 (0.9)	2.8 (0.9)	3.0 (0.9)	3.0 (0.9)
FEV ₁ reversibility†	23.1% (24.4)‡	22.6% (17.8)§	24.8% (20.7)	24.0% (17.0)
Time since asthma diagnosis, years	16.0 (6–31)	15.0 (7–29)	16.0 (7–25)	13.2 (6–23)
Number of exacerbations in the past 12 months	2.0 (2–2)	2.0 (2–2)	2.0 (2–3)	2.0 (2–2)
Total asthma symptom score	2.5 (1.0)¶	2.5 (1.0)	2.5 (1.0)	2.5 (0.9)
ACQ-6 score	2.6 (0.9)**	2.6 (0.8)	2.6 (0.9)	2.7 (0.8)
AQLQ score	4.2 (1.0)††	4.2 (0.9)‡‡	4.1 (1.1)§§	4.0 (0.8)¶¶
Baseline eosinophil count, cells per μ L	254 (203.8)	308 (468.4)	359 (286.6)***	474 (763.9)
Baseline FENO concentration, ppb	29.6 (28.2)**	30.5 (30.6)†††	64.9 (1.9)	69.5 (1.9)
Baseline asthma medication				
ICS dosage				
Low	3 (0.8%)	1 (0.3%)	40 (39.2%)‡‡‡	45 (46.4%)‡‡‡
Medium	194 (48.5%)	204 (51.3%)	40 (39.2%)‡‡‡	45 (46.4%)‡‡‡
High	203 (50.8%)	193 (48.5%)	62 (60.8%)	52 (53.6%)
LABA	400 (100.0%)	397 (99.7%)	102 (100.0%)	97 (100.0%)
Data are n (%), mean (SD), or median (IQR). FENO=fractional exhaled nitric oxide. BMI=body-mass index. FVC=forced vital capacity. ACQ-6=Asthma Control Questionnaire-6. AQLQ=Standardised Asthma Quality of Life Questionnaire. ICS=inhaled corticosteroids. LABA=long-acting β_2 adrenoreceptor agonist. *The STRATOS 1 placebo treatment group is a combined treatment group (placebo every 2 weeks plus placebo every 4 weeks) where the two placebo cohorts were given weights proportional to the number of participants in each cohort. †The FEV ₁ , post-bronchodilator measurement in the reversibility derivation could be the post-bronchodilator measurement after four, six, or eight short-acting β_2 adrenoreceptor agonist inhalations, depending on when the reversibility assessment was considered complete. ‡n=399. §n=397. ¶n=399. n=397. **n=398. ††n=378. ‡‡n=368. §§n=97. ¶¶n=89. n=393. ***n=100. †††n=395. ‡‡‡Combined low and medium dosage ICS.				

Table 1: Demographics and baseline characteristics in the STRATOS 1 full analysis set

any investigational drug, and was restricted to those who had the potential to receive the investigational drug for 52 weeks in STRATOS 2. Biomarker-positive participants met the criteria for inclusion in the full analysis set and also had biomarker concentrations greater than or equal to the cutoff identified in STRATOS 1. In both trials, any participant who received the investigational drug was included in the safety analysis set and was categorised by treatment received. The pharmacokinetic analysis set comprised all participants in the full analysis set who received talokinumab, and included pharmacokinetic blood samples that were assumed not to be affected by factors such as protocol deviations (eg, disallowed medication or incorrect study medication received).

A biomarker analysis plan was developed to statistically assess STRATOS 1 to identify baseline

biomarkers likely to predict talokinumab efficacy and to define a biomarker population in which the treatment effect of talokinumab might be enhanced; this biomarker population was then tested in STRATOS 2. The predictive properties of the continuous biomarkers (blood eosinophil counts, FENO, serum DPP-4, serum periostin, and total serum IgE) were assessed on the basis of AAER by use of negative binomial and generalised additive models, and the subgroup identification based on differential effect search (SIDES) algorithm.^{22,23} The SIDES analysis was supported by robustness and sensitivity checks (including assessment of consistency with regard to secondary variables) that used bootstrapping and permutation approaches to mitigate risks associated with subgroup identification, such as false discovery,

	All-comers population (n=837)		FENO-high (≥37 ppb) population (n=229)	
	Placebo (n=417)	Tralokinumab every 2 weeks (n=420)	Placebo (n=121)	Tralokinumab every 2 weeks (n=108)
Demographics				
Age, years	48·0 (15·5)	47·3 (15·6)	45·1 (16·7)	45·1 (15·1)
Women	290 (69·5%)	276 (65·7%)	76 (62·8%)	68 (63·0%)
Men	127 (30·5%)	144 (34·3%)	45 (37·2%)	40 (37·0%)
Race				
White	281 (67·4%)	283 (67·4%)	71 (58·7%)	63 (58·3%)
Black or African American	24 (5·8%)	27 (6·4%)	11 (9·1%)	13 (12·0%)
Asian	88 (21·1%)	83 (19·8%)	31 (25·6%)	26 (24·1%)
Other	24 (5·8%)	27 (6·4%)	8 (6·6%)	6 (5·6%)
BMI, kg/m ²	27·9 (6·6)*	28·6 (7·1)†	27·2 (7·6)	27·9 (5·9)
Clinical characteristics				
Pre-bronchodilator FEV ₁ , L	1·8 (0·6)	1·8 (0·6)†	1·8 (0·6)	1·8 (0·6)
Pre-bronchodilator FEV ₁ , predicted	61·0 (14·7)	60·8 (13·5)†	62·1 (14·9)	61·1 (12·7)
Pre-bronchodilator FVC, L	2·7 (0·8)	2·8 (0·9)†	2·9 (0·8)	2·9 (0·9)
FEV ₁ reversibility‡	25·7% (24·5)	23·4% (17·5)†	27·5% (22·9)	23·1% (17·5)
Time since asthma diagnosis years	15·0 (7–28)	15·0 (8–30)	15·9 (9–27)	14·8 (6–26)
Number of exacerbations in the past 12 months	2·0 (2–3)	2·0 (2–2)	2·0 (2–3)	2·0 (2–2)
Total asthma symptom score	2·4 (1·0)§	2·3 (0·9)†	2·5 (1·0)¶	2·4 (0·9)
ACQ-6 score	2·6 (0·9)	2·4 (0·9)	2·7 (1·0)	2·6 (0·9)
AQLQ score	4·1 (1·0)	4·3 (1·0)	4·0 (0·9)	4·1 (1·0)
Baseline eosinophil count, cells per µL	269 (228·2)§	286 (232·9)**	333 (214·7)	353 (252·0)††
Baseline FENO concentration, ppb	31·7 (27·7)‡‡	29·0 (25·2)*	64·0 (30·8)	61·4 (28·6)
Baseline asthma medication				
ICS dosage				
Low	14 (3·4%)	8 (1·9%)	5 (4·1%)	2 (1·9%)
Medium	196 (47·0%)	186 (44·3%)	62 (51·2%)	52 (48·1%)
High	207 (49·6%)	226 (53·8%)	54 (44·6%)	54 (50·0%)
LABA	417 (100·0%)	420 (100·0%)	121 (100·0%)	108 (100·0%)

Data are n (%), mean (SD), or median (IQR). FENO=fractional exhaled nitric oxide. BMI=body-mass index. FVC=forced vital capacity. ACQ-6=Asthma Control Questionnaire-6. AQLQ=Standardised Asthma Quality of Life Questionnaire. ICS=inhaled corticosteroids. LABA=long-acting β₂ adrenoreceptor agonists. *n=416. †n=419. ‡The FEV₁ post-bronchodilator measurement in the reversibility derivation could be the post-bronchodilator measurement after four, six, or eight short-acting β₂ adrenoreceptor agonist inhalations, depending on when the reversibility assessment was considered complete. §n=415. ¶n=120. ||n=394. **n=412. ††n=106. ‡‡n=411.

Table 2: Demographics and baseline characteristics in the STRATOS 2 full analysis set

overfitting, and overoptimistic belief in the subgroup. The potential predictive properties of the biomarkers were also assessed on the basis of key secondary endpoints of percentage change from baseline in pre-bronchodilator FEV₁ and change from baseline in ACQ-6, AQLQ, and asthma symptom scores. The methodology for the sample size estimates¹⁸ has been previously reported.

Both trials are registered with ClinicalTrials.gov, numbers NCT02161757 (STRATOS 1) and NCT02194699 (STRATOS 2), and with the EU Clinical Trials Register, EudraCT 2013-005614-35 (STRATOS 1) and EudraCT 2013-005615-27 (STRATOS 2).

Role of the funding source

The funder of the trial contributed to study design, data collection, data analysis, data interpretation, and writing of the report. All authors had full access to all the data in

the study and the corresponding author had final responsibility for the decision to submit for publication.

Results

STRATOS 1 was done between June 13, 2014, and Feb 28, 2017. 2248 participants were enrolled; 1669 entered the run-in period. Of the 579 participants who did not enter the run-in period, 534 did not meet the eligibility criteria. An additional 462 enrolled participants failed screening, primarily because they did not meet the eligibility criteria. 1207 participants were therefore randomly assigned and 1202 were treated as follows: tralokinumab every 2 weeks (n=398), tralokinumab every 4 weeks (n=404), or placebo every 2 weeks or every 4 weeks (n=400). 1047 (86·7%) of 1207 participants completed treatment (figure 2A). STRATOS 2 was done between Oct 30, 2014, and Sept 21, 2017. 1696 participants were enrolled, of whom 1163 entered the run-in period.

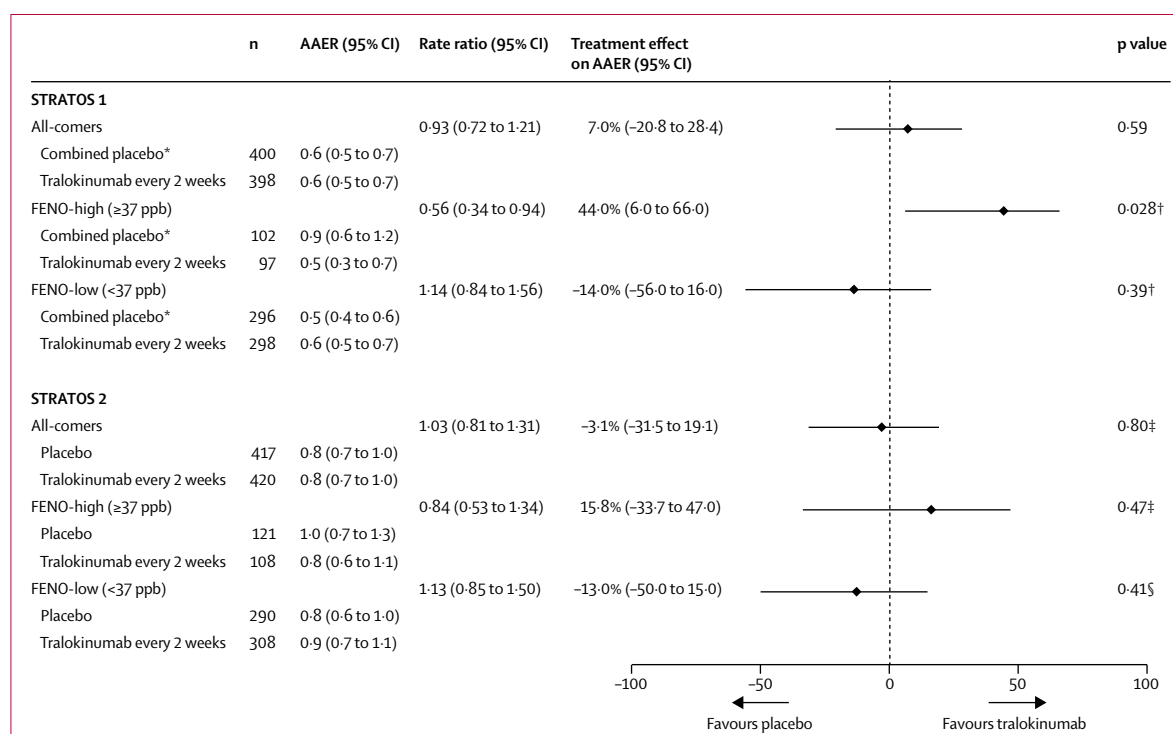


Figure 3: AAER at week 52 in STRATOS 1 and STRATOS 2 (full analysis set)

AAER=annualised asthma exacerbation rate. FENO=fractional exhaled nitric oxide. *The STRATOS 1 placebo treatment group is a combined treatment group (placebo every 2 weeks plus placebo every 4 weeks) where the two placebo cohorts were given weights proportional to the number of participants in each cohort. †p values for STRATOS 1 biomarker analyses are nominal and were not adjusted for multiplicity. ‡Not significant as per STRATOS 2 multiple testing procedure. §Not controlled for multiplicity as a FENO-low group was not included in the STRATOS 2 multiple testing procedure.

856 participants were randomly assigned and 849 were treated as follows: tralokinumab every 2 weeks (n=427) or placebo every 2 weeks (n=422). 732 (85.5%) of 856 participants completed treatment (figure 2B). Participant demographics were similar across the groups in both STRATOS trials (tables 1, 2; appendix).

In STRATOS 1, the primary endpoint was not met in the all-comers population; the AAER reduction at week 52 with tralokinumab 300 mg every 2 weeks compared with placebo was 7.0% (95% CI -20.8 to 28.4; rate ratio 0.93 [95% CI 0.72 to 1.21]; $p=0.59$; figure 3). As per the study protocol, the hierarchical testing was stopped and all subsequent results were declared non-significant. Similar findings were observed for the group receiving tralokinumab every 4 weeks (appendix).

At week 52, the percentage change from baseline in pre-bronchodilator FEV_1 was nominally significant for the group receiving tralokinumab every 2 weeks compared with placebo (difference in least squares mean 6.03% [95% CI 2.34 to 9.73]; $p=0.0014$; table 3). This difference translated into clinically meaningful changes (>100 mL)²⁴ in FEV_1 between the group receiving tralokinumab every 2 weeks (265 mL) and the placebo group (153 mL; figure 4A). The change from baseline in ACQ-6 score at week 52 was also nominally significant for the group receiving tralokinumab every 2 weeks compared with the placebo group (difference in least

squares mean -0.16 [95% CI -0.29 to -0.02]; $p=0.022$; table 3); however, this difference was not clinically meaningful. No relevant findings were observed for the other secondary endpoints (table 3; appendix).

The distribution of each of the five biomarker concentrations was similar at baseline across the treatment groups in the full analysis set (tables 1, 2; appendix). Initial interaction testing (nominally significant interaction; $p<0.10$) indicated no predictive relationship for tralokinumab efficacy with baseline blood eosinophils (appendix), serum DPP-4, or total serum IgE. Serum periostin (as a continuous variable) showed a nominally significant interaction in the group receiving tralokinumab every 4 weeks ($p=0.090$) but not in the group receiving tralokinumab every 2 weeks ($p=0.48$). A nominally significant interaction effect ($p<0.10$) was seen in both tralokinumab treatment groups for FENO as a continuous variable ($p=0.038$ for the 2-week group and $p=0.086$ for the 4-week group). Further analyses identified a subgroup of participants in the group receiving treatment every 2 weeks with baseline FENO 37 ppb or greater (FENO-high) as having a nominally significant AAER reduction of 44.0% (95% CI 6.0 to 66.0; rate ratio 0.56 [95% CI 0.34 to 0.94]; $p=0.028$; figure 3). No significant AAER reduction was observed with tralokinumab in participants with baseline FENO less than 37 ppb (FENO-low; figure 3).

	Pre-bronchodilator FEV ₁	AQLQ score	ACQ-6 score	Total asthma symptom score
STRATOS 1				
All-comers population				
Tralokinumab every 2 weeks (n)	357	304	324	313
Placebo* (n)	363	315	329	312
Difference in LS means (95% CI)	6.03% (2.34 to 9.73)	0.15 (−0.01 to 0.31)	−0.16 (−0.29 to −0.02)	−0.09 (−0.23 to 0.04)
p value	0.0014	0.061	0.022	0.18
FENO-high population				
Tralokinumab every 2 weeks (n)	87	74	75	71
Placebo* (n)	92	83	83	68
Difference in LS means (95% CI)	12.80% (5.34 to 20.26)	0.53 (0.22 to 0.84)	−0.43 (−0.71 to −0.16)	−0.05 (−0.34 to 0.24)
p value†	0.00079	0.00077	0.0022	0.72
STRATOS 2				
All-comers population				
Tralokinumab every 2 weeks	384	321	341	297
Placebo (n)	358	318	334	309
Difference in LS means (95% CI)	2.95% (−0.73 to 6.62)	0.06 (−0.10 to 0.22)	−0.08 (−0.21 to 0.05)	−0.04 (−0.18 to 0.10)
p value	0.12‡	0.45‡	0.24‡	0.58‡
FENO-high population				
Tralokinumab every 2 weeks (n)	99	77	85	79
Placebo (n)	103	84	86	81
Difference in LS means (95% CI)	1.86% (−5.16 to 8.88)	0.27 (−0.04 to 0.57)	−0.27 (−0.53 to −0.01)	−0.20 (−0.47 to 0.07)
p value	0.60‡	0.087‡	0.040‡	0.15‡

ACQ-6=Asthma Control Questionnaire-6. AQLQ=Standardized Asthma Quality of Life Questionnaire. LS=least squares. FENO=fractional exhaled nitric oxide. *The STRATOS 1 placebo treatment group is a combined treatment group (placebo every 2 weeks plus placebo every 4 weeks) where the two placebo cohorts were given weights proportional to the number of participants in each cohort. †p values for STRATOS 1 biomarker analyses are nominal and were not adjusted for multiplicity. ‡Not significant as per STRATOS 2 multiple testing procedure.

Table 3: Change from baseline at week 52 in key secondary efficacy endpoints in the STRATOS 1 and STRATOS 2 full analysis sets

In the FENO-high subgroup, a nominally significant increase from baseline in pre-bronchodilator FEV₁ was seen with tralokinumab treatment every 2 weeks compared with placebo (12.80% [95% CI 5.34 to 20.26]; $p=0.00079$; table 3). This difference translated into a clinically meaningful improvement in absolute FEV₁ of approximately 340 mL by week 8 of tralokinumab initiation, representing an approximately 200 mL greater increase from baseline than placebo that was maintained up to week 52 (figure 4B). No clinically meaningful effect on pre-bronchodilator FEV₁ was observed in the FENO-low population (figure 4C). Nominally significant improvements from baseline were also observed in both AQLQ score (apparent within 12–16 weeks) and ACQ-6 score (apparent by 26 weeks) with tralokinumab treatment every 2 weeks in the FENO-high subgroup versus placebo; no nominally significant differences in total asthma symptom score were observed at week 52 (table 3). Non-significant differences were observed between the treatment groups compared with placebo for pre-bronchodilator FEV₁, AQLQ, ACQ-6, and total asthma symptom scores for the FENO-low subgroup (appendix).

The FENO-high subgroup showed a clinically meaningful decrease in FENO concentrations within 4–8 weeks of tralokinumab initiation (appendix). At

week 8, the estimated difference in FENO change from baseline between tralokinumab and placebo was -20.2 ppb (95% CI -24.5 to -15.9 ; nominal $p<0.0001$). Non-significant changes in FENO concentrations were seen in the FENO-low subgroup at week 52. Aside from the nominally significant interaction with tralokinumab treatment every 4 weeks, periostin was not able to predict tralokinumab efficacy (appendix). On the basis of these analyses, baseline FENO was the biomarker selected for investigation in STRATOS 2 at a cutoff of 37 ppb (FENO-high).

In STRATOS 2, a significant interaction between FENO (as a continuous variable) and tralokinumab treatment was identified ($p=0.042$). In the STRATOS 2 FENO-high population, the AAER reduction did not significantly differ for participants receiving tralokinumab versus those receiving placebo (15.8% [95% CI -33.7 to 47.0]; rate ratio 0.84 [95% CI 0.53 to 1.34]; $p=0.47$; figure 3). Additionally, no significant difference in AAER was observed between groups in the all-comers population (-3.1% [95% CI -31.5 to 19.1]; rate ratio 1.03 [95% CI 0.81 to 1.31]; $p=0.80$) or the FENO-low population (-13.0% [-50.0 to 15.0]; rate ratio 1.13 [0.85 to 1.50]; $p=0.41$; figure 3).

A clinically meaningful numerical improvement in pre-bronchodilator FEV₁ from baseline at week 52 was

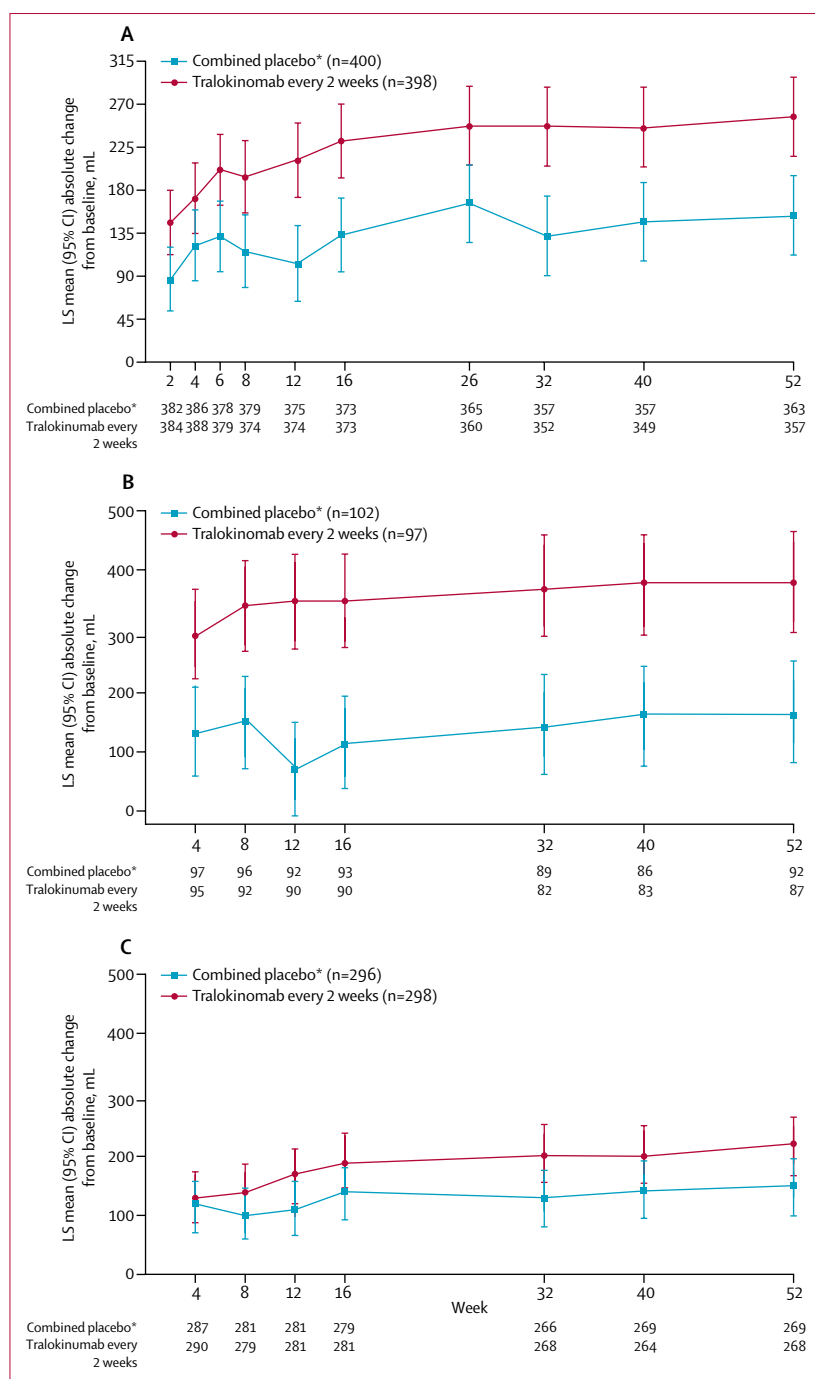


Figure 4: LS mean absolute change from baseline in pre-bronchodilator FEV₁ over time in STRATOS 1 in the full analysis set

(A) All-comers population. (B) High fractional exhaled nitric oxide (FENO) population (≥ 37 ppb at baseline). (C) Low FENO (< 37 ppb at baseline) population. LS=least squares. *The STRATOS 1 placebo treatment group is a combined treatment group (placebo every 2 weeks plus placebo every 4 weeks), where the two placebo cohorts were given weights proportional to the number of participants in each cohort.

observed in the FENO-high subgroup in response to tralokinumab in STRATOS 2, but this difference was not significant when compared with placebo because of a

large placebo effect (least squares mean difference 1.86% [-5.16 to 8.88]; $p=0.60$; table 3). This difference translated to an absolute change in pre-bronchodilator FEV₁ from baseline of 320 mL with tralokinumab and 253 mL with placebo. No significant or clinically meaningful improvements were observed in AQLQ or total asthma symptom scores in the FENO-high population versus placebo in STRATOS 2; however, a nominally significant improvement in ACQ-6 was seen (table 3). Moreover, none of the key secondary endpoints differed significantly between tralokinumab and placebo in the all-comers population (table 3) or the FENO-low population (appendix). There were no relevant findings for the other secondary endpoints (appendix).

The safety results from STRATOS 1 and STRATOS 2 were similar and the data for tralokinumab treatment every 2 weeks are reported together (table 4). Safety results for the group receiving tralokinumab every 4 weeks in STRATOS 1 are reported in the appendix. In the STRATOS 1 safety analysis set (all treatment groups), 799 (66.5%) of 1202 participants reported adverse events during the treatment period. 278 (69.8%) of 398 participants in the group receiving tralokinumab treatment every 2 weeks had adverse events compared with 243 (60.8%) of 400 in the combined placebo group. In STRATOS 2, adverse events occurred at a similar rate between the placebo (290 [68.7%] of 422) and tralokinumab (306 [72.0%] of 425) groups. The most frequent adverse events (reported by $\geq 5\%$ of participants) in STRATOS 1 and STRATOS 2 were asthma, headache, and upper respiratory tract infection. The majority of adverse events reported during the treatment period for both trials were mild or moderate in intensity and most were not considered to be related to the investigational drug according to the investigator (table 4). The most frequent adverse events considered to be related to tralokinumab treatment every 2 weeks in STRATOS 1 were injection-site erythema (in 24 [6.0%] of 398 participants), injection-site pain (in 15 [3.8%]), and injection-site reaction (in 16 [4.0%]). In STRATOS 2, the most frequent adverse events considered to be related to tralokinumab were injection-site reaction (in 23 [5.4%] of 425 participants), injection-site erythema (in 15 [3.5%]), and application-site reaction (in six [1.4%]).

In STRATOS 1, 127 (10.6%) of 1202 participants had a serious adverse event during the treatment period (including one death in the group receiving tralokinumab every 2 weeks and one death in the group receiving tralokinumab every 4 weeks). 40 serious adverse events were reported in the group receiving tralokinumab treatment every 2 weeks and 48 in the placebo group. The most common serious adverse event was asthma, although fewer participants receiving tralokinumab every 2 weeks reported this serious adverse event compared with those receiving placebo (12 [3.0%] of 398 vs 25 [6.3%] of 400). Three serious adverse events were considered to be related to the investigational drug: pharyngeal oedema and

	STRATOS 1		STRATOS 2	
	Combined placebo† (n=400)	Tralokinumab every 2 weeks (n=398)	Placebo (n=422)	Tralokinumab every 2 weeks (n=425)
Any adverse event	243 (60.8%)	278 (69.8%)	290 (68.7%)	306 (72.0%)
Any treatment-related adverse event	32 (8.0%)	91 (22.9%)	33 (7.8%)	93 (21.9%)
Any adverse event with outcome of death	0	1 (0.3%)	1 (0.2%)	1 (0.2%)
Any serious adverse event	48 (12.0%)	40 (10.1%)	39 (9.2%)	35 (8.2%)
Adverse events leading to discontinuation	3 (0.8%)	28 (7.0%)	14 (3.3%)	27 (6.4%)
Adverse events with ≥5% frequency in any group (safety population)‡				
Asthma	54 (13.5%)	47 (11.8%)	61 (14.5%)	50 (11.8%)
Nasopharyngitis	36 (9.0%)	43 (10.8%)	6 (1.4%)	9 (2.1%)
Upper respiratory tract infection	36 (9.0%)	26 (6.5%)	29 (6.9%)	29 (6.8%)
Headache	17 (4.3%)	23 (5.8%)	31 (7.3%)	40 (9.4%)
Bronchitis	19 (4.8%)	20 (5.0%)	31 (7.3%)	34 (8.0%)
Injection-site erythema	0	24 (6.0%)	0	15 (3.5%)
Viral upper respiratory tract infection	7 (1.8%)	7 (1.8%)	52 (12.3%)	49 (11.5%)
Injection-site reaction	0	16 (4.0%)	3 (0.7%)	23 (5.4%)

Data are n (%). *Includes adverse events with an onset date on or after the first day of trial treatment and on or before the last day of trial treatment plus dosing frequency.

†The STRATOS 1 placebo treatment group is a combined treatment group (placebo every 2 weeks + placebo every 4 weeks) where the two placebo cohorts were given weights proportional to the number of participants in each cohort. ‡In descending order of 5% or greater frequency in the STRATOS 1 combined placebo group; Medical Dictionary for Regulatory Activities (MedDRA) preferred terms (version 19.1).

Table 4: Overall safety results during the treatment period* for STRATOS 1 and STRATOS 2 in the safety analysis sets

swollen tongue (both in the same participant receiving tralokinumab every 2 weeks), and pneumonia (in one participant receiving placebo). In STRATOS 2, 74 (8.7%) of 847 participants had serious adverse events (including one death in the tralokinumab every 2 weeks group and one death in the placebo group during the treatment period), 39 in the placebo group and 35 in the tralokinumab group. The most frequent serious adverse events were asthma (23 [5.5%] of 422 with placebo vs 17 [4.0%] of 425 with tralokinumab) and pneumonia (three [0.7%] with placebo vs four [0.9%] with tralokinumab). Three serious adverse events were considered to be related to tralokinumab; fatal urosepsis (in one participant), and increased alanine aminotransferase and increased aspartate aminotransferase (both in the same participant).

Across both trials, the number of adverse events leading to discontinuation was higher in participants receiving tralokinumab than in those receiving placebo (appendix). In STRATOS 1, 44 (3.7%) of 1202 participants had adverse events leading to discontinuation (28 [7.0%] of 398 receiving tralokinumab every 2 weeks, three [0.8%] of 400 with placebo). 16 (4.0%) of 398 participants receiving tralokinumab every 2 weeks had injection-related adverse events that led to discontinuation compared with none in the placebo group. The most common adverse event leading to discontinuation with tralokinumab treatment every 2 weeks was injection-site erythema (in six [1.5%] of 398 participants), followed by injection-site reaction (in three [0.8%]). The most common adverse event leading to discontinuation in the STRATOS 2 safety analysis set was injection-site reaction

(in four [0.9%] of 425 participants receiving tralokinumab every 2 weeks vs none receiving placebo).

With regard to other safety topics of special attention, no cases of anaphylaxis attributable to tralokinumab were identified in either trial. Similar rates of severe infections were observed in the tralokinumab and placebo groups. One case of pulmonary tuberculosis occurred in the FENO-high group receiving tralokinumab every 2 weeks in STRATOS 2, but no cases of helminthic or other opportunistic infections were reported during the treatment period. Similar rates of malignancy and cardiovascular or cerebrovascular events were observed between the treatment groups in the trials (data not shown).

No clinically meaningful changes in haematology, clinical chemistry, vital signs, and electrocardiogram (ECG) readings were seen in STRATOS 1 or STRATOS 2. However, more tralokinumab-treated participants had blood eosinophil counts increase from 1500 cells per μL or lower at baseline to more than 1500 cells per μL during treatment than did placebo-treated participants (20 [5.0%] of 398 vs six [1.5%] of 400 in STRATOS 1; 17 [4.0%] of 425 vs six [1.4%] of 422 in STRATOS 2). These increases resolved after treatment cessation (appendix). In STRATOS 1, two participants receiving tralokinumab 300 mg every 4 weeks had adverse events that could have been associated with their increased blood eosinophil counts (>1500 cells per μL). One was a 46-year-old woman who was admitted to hospital with eosinophilic granulomatosis with polyangiitis. This serious adverse event led to discontinuation but was not deemed by the investigator as being attributed to the investigational drug.

The other was a 48-year-old woman diagnosed with allergic alveolitis. This adverse event was not considered by the investigator as being related to the investigational drug and did not lead to investigational drug discontinuation; the participant made a full recovery following a course of corticosteroids. In STRATOS 2 two participants similarly had adverse events associated with eosinophil counts of more than 1500 cells per μL ; a 55-year-old woman in the group receiving tralokinumab every 2 weeks had a skin rash diagnosed as hypersensitivity vasculitis, which was not considered by the investigator to be related to the treatment, and a 51-year-old woman in the placebo group had a serious adverse event of eosinophilic granulomatosis with polyangiitis that was also not considered to be related to treatment, but led to discontinuation of the investigational drug.

In STRATOS 1, four participants died during the trial; one died before randomisation, two died during the treatment period (from infectious diarrhoea [tralokinumab every 2 weeks] and from cerebrovascular disease and asthma [tralokinumab every 4 weeks]), and one participant died during the follow-up period (from cardiac arrest [placebo]). None of the deaths was considered to be related to the investigational drug. In STRATOS 2, five participants died; two died while receiving treatment (one from asthma [placebo], and one from urosepsis and atrial fibrillation [tralokinumab every 2 weeks]), and three participants died after treatment (one from myocardial infarction [placebo], one from large intestinal obstruction, colon cancer, large intestine perforation, peritonitis, septic shock, and multiple organ dysfunction syndrome [placebo], and one from an unknown cause [placebo]). The fatal case of urosepsis was considered by the investigator to be related to tralokinumab treatment every 2 weeks.

Discussion

Asthma is considered to be a heterogeneous disease, with different phenotypes driven by a range of inflammatory mediators.¹⁷ Although the previous tralokinumab phase 2b trial did not meet its primary endpoint of reducing exacerbations in participants with severe, uncontrolled asthma, a subgroup of participants with post-bronchodilator FEV_1 reversibility of 12% or higher who were not taking regular OCS did appear to benefit from treatment, with further improvements seen in participants with high concentrations of biomarkers suggesting increased interleukin-13 pathway activation.¹⁶ The STRATOS 1 and STRATOS 2 trials were designed to assess the efficacy and safety of tralokinumab in a population with the clinical characteristics identified by the phase 2b results, and to ascertain whether there was a subgroup, identified by a biomarker, with an enhanced response to tralokinumab therapy. In both of these phase 3 trials, tralokinumab 300 mg every 2 weeks (or every 4 weeks) did not significantly reduce the AAER compared with placebo in the all-comers population.

The biomarker analyses in STRATOS 1 identified FENO as the preferred biomarker for predicting enhanced response to tralokinumab. In STRATOS 2, the enhanced effect on AAER reduction compared with the all-comers results was neither significant nor clinically meaningful. DPP-4 and periostin did not consistently predict response to tralokinumab therapy, despite being identified as promising biomarkers of increased interleukin-13 activity in the phase 2b trial.¹⁶

Clinically meaningful improvements in lung function were seen with tralokinumab in both the all-comers and FENO-high populations in STRATOS 1, consistent with phase 2b results in which tralokinumab improved pre-bronchodilator FEV_1 in the all-comers population.¹⁶ Although a clinically meaningful increase was also seen in pre-bronchodilator FEV_1 from baseline in the tralokinumab arm of the STRATOS 2 FENO-high population, this outcome was not significant when compared with placebo. The results from phase 3 trials of lebrikizumab, which also targets the interleukin-13 pathway, similarly showed a consistent improvement in FEV_1 in biomarker-positive participants but an inconsistent improvement in exacerbation rates.²⁵ Taken together, these clinical data suggest that drugs targeting the interleukin-13 pathway affect airway smooth muscle tone, which is consistent with previous preclinical data suggesting that interleukin 13 promotes airway hyper-responsiveness and smooth muscle contractility.^{10,25} The findings of the MESOS trial also support this hypothesis. In that study, tralokinumab treatment was associated with improvements in airway physiology but no effect was observed on airway inflammation.¹⁶ By contrast, dupilumab, an anti-interleukin-4 receptor- α monoclonal antibody that targets both interleukin-4 and interleukin-13 signalling, has shown significant reductions in exacerbations in people with uncontrolled, persistent asthma.^{27,28} This difference might be due to the ability of dupilumab to reduce airway inflammation, but there is currently no evidence to support this hypothesis.

The five potential biomarkers of increased interleukin-13 activity chosen for investigation in the STRATOS trials are all markers of type-2 inflammation. Both serum periostin and DPP-4 were included because of the tralokinumab phase 2b results; these biomarkers are thought to be upregulated in response to interleukin 13, and might have a role in airway inflammation in asthma.^{29–31} Results from the STRATOS and lebrikizumab phase 3 trials did not show consistent reductions in asthma exacerbations, and indicate that the ability of periostin to predict an enhanced response to anti-interleukin-13 therapies in asthma has been overestimated.²⁵ Serum IgE is used to determine the appropriate dosing of omalizumab (a biologic indicated for children and adults with severe allergic asthma as per step 5 of the Global Initiative for Asthma [GINA] guidelines);³² in the tralokinumab phase 2b trial, a reduction in AAER and improved lung function was

observed in a subgroup of participants with elevated IgE concentrations (type-2 high participants, defined by >100 IU/mL serum IgE and blood eosinophils ≥ 140 cells per μL).¹⁶ However, serum IgE concentrations were not useful predictors of tralokinumab efficacy in the STRATOS trials. Similarly, blood eosinophil count is frequently used to identify participants with severe asthma who are likely to benefit from anti-interleukin-5 therapies,³³ but eosinophils were not found to be a helpful biomarker for anti-interleukin-13 therapy in STRATOS 1 and STRATOS 2. Finally, FENO has been used as a biomarker in clinical trials for asthma,^{27,34} since increased concentrations might help to identify type-2 inflammation and are associated with an increased risk of exacerbations and enhanced interleukin-13 activity through nitric oxide synthase.^{35–37} Two drugs that have been shown to be effective at reducing asthma exacerbations—dupilumab and tezepelumab—have also been shown to reduce FENO concentrations in clinical trials.^{27,34} The results of the STRATOS trials show that tralokinumab reduces FENO concentrations, with greater reductions seen in people with asthma and elevated baseline FENO concentrations, and confirm that FENO is currently the best predictive biomarker for anti-interleukin-13 therapy.

The safety profile of tralokinumab was acceptable across both STRATOS 1 and STRATOS 2; no new safety signals were seen and there were no signals of concern in the adverse events and serious adverse events of special interest. The most frequent adverse events were balanced across the treatment groups in both trials and the majority were mild or moderate in intensity. The increased rates of adverse events considered to be related to tralokinumab and adverse events leading to discontinuation in STRATOS 1 and STRATOS 2 were partly due to the increased rates of injection-site reactions with tralokinumab compared with placebo.

In STRATOS 1 and STRATOS 2, tralokinumab-treated participants had small increases in blood eosinophil counts from baseline, whereas placebo-treated participants did not; these findings are consistent with those of previous trials of tralokinumab.^{15,16} These changes resolved after treatment, but more tralokinumab-treated participants had blood eosinophil counts increase from less than 1500 eosinophils per μL at baseline to 1500 or more eosinophils per μL during treatment than did placebo-treated participants. Adverse events associated with an increased blood eosinophil count were similar in the tralokinumab and placebo groups. Two of these participants had serious adverse events of eosinophilic granulomatosis with polyangiitis (one on tralokinumab every 4 weeks in STRATOS 1, one on placebo in STRATOS 2). Since the reported cases of this adverse event were similar in both the active drug and placebo groups, we cautiously suggest that a causal association with an anti-interleukin-13 monoclonal antibody cannot be established. However, diligent surveillance of this adverse event must be done in future trials of anti-interleukin-13

monoclonal antibodies in asthma. A similar effect on blood eosinophils was also seen with lebrikizumab.²⁵ Dupilumab has been reported to increase blood eosinophil counts, but transiently and only in people with a baseline blood eosinophil count greater than 300 cells per μL .²⁷ The increase in blood eosinophils observed with anti-interleukin-13 therapy has been hypothesised to be due to reduced recruitment of eosinophils to the lungs from the blood,³⁸ but the results of the MESOS trial suggest that this does not occur.²⁶ Dupilumab is the only biologic under development for treatment of asthma that both reduces exacerbations and increases blood eosinophils.²⁷ Approved treatments for severe asthma, such as corticosteroids and the biologics omalizumab (anti-IgE), benralizumab (anti-interleukin-5 receptor- α), mepolizumab, and reslizumab (both anti-interleukin-5), reduce eosinophil counts during therapy and reduce exacerbation rates in participants with severe asthma.^{39–43} Similarly, phase 2b data from a trial of tezepelumab, which targets thymic stromal lymphopoietin, a cytokine that activates multiple inflammatory pathways, showed a reduction in exacerbations and in blood eosinophil counts in participants with severe, uncontrolled asthma.³⁴

One of the main strengths of the STRATOS trials was the staggered design, allowing identification of a biomarker-positive subgroup in the first trial to be investigated in the second. In comparison with the phase 3 trials of lebrikizumab, which preselected the biomarker and the associated cutoff,²⁵ the sequential design of STRATOS 1 and STRATOS 2 meant it would be less likely that an important biomarker effect would be missed. However, this study design also had some potential limitations. The prevalence of FENO-high participants in STRATOS 2 was 27.4% (229 of 837), which was consistent with STRATOS 1 but lower than originally intended when considering a biomarker-positive population in the trial, and could therefore have affected the power of STRATOS 2. Additionally, as the trials proceeded at the same time, there was no opportunity to enrich the STRATOS 2 population for a FENO-high subgroup once FENO was identified as the predictive biomarker. Similarly, there was no opportunity to amend the design of STRATOS 2 to allow for stabilisation of baseline FENO readings before randomisation. Furthermore, the trial design could have influenced the observed placebo effects in STRATOS 2, potentially compromising the ability to establish a treatment effect on FEV₁ with tralokinumab in the FENO-high subgroup. Elevated FENO concentrations have been shown to reflect poor treatment adherence;⁴⁴ improvements in adherence to concurrent controller medication through frequent monitoring within the clinical trial environment could potentially have contributed to the FEV₁ effect we observed in STRATOS 2 with placebo as well as tralokinumab. However, these placebo effects were not limited to the FENO-high subgroup and were not observed in

STRATOS 1, and are therefore unlikely to be due to greater adherence to controller medication during the trial. A third limitation was the strict inclusion and exclusion criteria used to select the STRATOS 1 and STRATOS 2 populations, which were chosen on the basis of post-hoc analyses of the phase 2b trial that required reversibility at study entry and excluded OCS-dependent participants. As a result, the tralokinumab efficacy observed in the study populations of STRATOS 1 and STRATOS 2 probably does not reflect the efficacy of this drug in a real-world, severe asthma population.⁴⁵

In summary, tralokinumab did not meet the primary endpoint, a reduction in AAER, in either STRATOS 1 or STRATOS 2. Baseline FENO 37 ppb or higher was identified as the optimal biomarker to predict an enhanced response to tralokinumab in STRATOS 1. An enhanced effect in the FENO-high population was confirmed in STRATOS 2, but the benefit to participants was not clinically meaningful.

Contributors

RAP contributed to the design of the trials, interpretation of the data, and oversight of STRATOS 1 as chief investigator. US contributed to the design and conduct of the trials, data collection, literature research, and responsibility for STRATOS 1 as the global trial physician. AP contributed to the design and conduct of the trials, collection and analysis of the data, and responsibility for STRATOS 2 as the global trial physician. PW and KB contributed to the design of the trials, and analysis and interpretation of the data. EP contributed to design of the trials and collection, analysis, and interpretation of the data. GC contributed to the design of the trials, and collection, analysis, and interpretation of the data. CEB contributed to the design of the trials, interpretation of the data, and oversight of STRATOS 2 as chief investigator. All authors contributed to the preparation and review of this report.

Declaration of interests

RAP reports grants and personal fees from AstraZeneca, MedImmune, and Sanofi/Regeneron; personal fees from Novartis, Teva, and Boehringer Ingelheim; and grants from Theratrophix, Amgen, RFIM, Vertex, Bristol Myers Squibb, Genentech, Gilead, and Boston Scientific, outside of the submitted work. US was previously a full-time employee of AstraZeneca. PW and EP are full-time employees of AstraZeneca. AP and KB are full-time employees of AstraZeneca and own shares in AstraZeneca. GC is a full-time employee of AstraZeneca and owns shares and stock options in AstraZeneca. CEB reports consultancy fees (personal) and research funding paid directly to the University of Leicester, UK, from AstraZeneca.

Acknowledgments

This trial was sponsored by AstraZeneca. We thank the health-care providers, research staff, participants, and caregivers who participated in these trials. CEB is supported by a National Institute for Health Research (NIHR) Senior Investigator Award and the Leicester NIHR Biomedical Research Centre. The views expressed are those of the author(s) and not necessarily those of the National Health Service (NHS), the NIHR or the Department of Health. Medical writing support was provided by Sophie Walton (QXV Comms [Macclesfield, UK], an Ashfield Company, part of UDG Healthcare plc), funded by AstraZeneca (Cambridge, UK), in accordance with Good Publication Practice (GPP3) guidelines.

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Supplementary appendix

This appendix formed part of the original submission and has been peer reviewed. We post it as supplied by the authors.

Supplement to: Panettieri Jr RA, Sjöbring U, Péterffy AM, et al. Tralokinumab for severe, uncontrolled asthma (STRATOS 1 and STRATOS 2): two randomised, double-blind, placebo-controlled, phase 3 clinical trials. *Lancet Respir Med* 2018; published online May 20. [http://dx.doi.org/10.1016/S2213-2600\(18\)30184-X](http://dx.doi.org/10.1016/S2213-2600(18)30184-X)

Supplementary appendix

Tralokinumab for severe, uncontrolled asthma: the STRATOS 1 and 2 randomised, placebo-controlled, phase 3 clinical trials

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Study sites

STRATOS 1 was performed at 246 sites in 14 countries (Argentina [n=12], Belgium [4], Bulgaria [15], Columbia [4], Germany [11], Hungary [9], Peru [10] Poland [29], Slovakia [5], South Korea [15], Spain [5], Ukraine [14], USA [106], and Vietnam [7]). STRATOS 2 was performed at 242 sites in 13 countries (Canada [n=15], Chile [6], Czech Republic [6], Italy [10], Japan [48], Mexico [5], Philippines [7], Russia [23], South Africa [6], Taiwan [3], Ukraine [19], United Kingdom [10], and USA [84]).

Inclusion and exclusion criteria for STRATOS 1 and 2

Inclusion criteria

For inclusion in the trials, participants should fulfil the following criteria:

1. Provision of informed consent to any trial specific procedures for participants who are at, or over the age of majority (as per local law). For participants less than the age of majority, in addition to the participant providing informed assent, the participant's legal guardian must also provide their informed consent.
2. Females and males aged from 12 to 75 years, inclusively at time of enrolment (Visit 1). For those countries where local regulations permit enrolment of adults only, participant recruitment will be restricted to those who are ≥ 18 years.
3. Women of childbearing potential (WOCBP) (after menarche), including adolescent females, must use a highly effective form of birth control (confirmed by the investigator). Highly effective forms of birth control include: true sexual abstinence, a vasectomised sexual partner, Implanon™, female sterilization by tubal occlusion, any effective intrauterine device/system (IUD/IUS), Depo-Provera™ injections, contraceptive, and Evra Patch™ or Nuvaring™. WOCBP must agree to use highly effective methods of birth control, as defined above, from enrolment, throughout the trial duration, and within 16 weeks after last dose of investigational product, and have a negative serum pregnancy test result at Visit 1. Women not of childbearing potential are defined as women who are either permanently sterilized (hysterectomy, bilateral oophorectomy, or bilateral salpingectomy), or who are postmenopausal. Women will be considered postmenopausal if they have been amenorrhoeic for 12 months prior to the planned date of randomisation without an alternative medical cause. The following age-specific requirements apply:
 - Women < 50 years old would be considered postmenopausal if they have been amenorrhoeic for 12 months or more following cessation of exogenous hormonal treatment and follicle-stimulating hormone concentrations in the postmenopausal range.
 - Women ≥ 50 years old would be considered postmenopausal if they have been amenorrhoeic for 12 months or more following cessation of all exogenous hormonal treatment.
4. Weight of ≥ 40 and < 150 kg at enrolment (Visit 1).
5. Documented physician-diagnosed asthma for at least 12 months prior to enrolment with the participant having received an asthma controller regimen requiring treatment with medium-to-high dose inhaled corticosteroids (ICS) for at least 6 of the 12 months prior to enrolment (Visit 1). In addition, participants must have used physician prescribed ICS (at a total daily dose ≥ 500 μg fluticasone propionate via dry powder inhaler or equivalent delivered dose) that has been taken as a stable dose for at least 3 months prior to enrolment.
6. Documented treatment with ICS at a total daily dose corresponding to ≥ 500 μg fluticasone propionate dry powder formulation equivalents and a long-acting β_2 agonist (LABA) for at least 3 months prior to Visit 1. The ICS and LABA can be parts of a combination product, or given by separate inhalers. For ICS/LABA combination preparations, the highest strength approved maintenance dose in the local country will be acceptable to meet this ICS criterion.
 - In order to aid the assessment, ICS equivalents for high-dose and moderate-dose fluticasone propionate dry powder inhaler were established by the Global Initiative for Asthma (GINA 2012) guidelines. The Investigator will assess the participant's total daily ICS dose and determine that it corresponds to ≥ 500 μg fluticasone propionate dry powder formulation equivalents. If the participant is on two or more different types of ICS, these can form parts of an addition, and the sum, however approximate, will be assessed.

The below defines the minimally acceptable documentation for subject inclusion:

1. Signed and dated notes from a referring physician, including name and dose of the ICS/LABA inhaler (or names and dosages, if used as separate inhalers).
2. Evidence of prescriptions for ICS/LABA medications that demonstrate coverage for the duration specified in Inclusion criteria 6 and 7.
3. Documented communication (e.g. phone conversation) clarifying that the participant received treatment with ICS/LABA for asthma. The name, dosage, and duration of use for each medication must be recorded. This option should be used only if reasonable attempts to procure participant records have been unsuccessful.
7. Additional maintenance asthma controller medications are allowed according to standard practice of care. These medications must be stable for 3 months prior to enrolment (Visit 1). Furthermore, after randomisation, the participant's background maintenance medication for asthma shall remain unchanged throughout the trial.
8. At Visit 1 the participant must have a morning pre-bronchodilator forced expiratory volume in one second (FEV₁) value <80% (<90% for participants 12 to 17 years of age) of the predicted normal value (PNV). At Visit 2 the participant must have a morning pre-bronchodilator FEV₁ value of ≥40% and <80% value (<90% for participants 12 to 17 years of age) of their PNV. If this is not met at Visit 2, it must be met at Visit 3. Prior to the lung function measurement, the participant should withhold their bronchodilator for the effect duration specific to that agent.
9. A post-bronchodilator reversibility of ≥12% and ≥200 mL in FEV₁ at Visit 2. If not met at Visit 2, it must be met at Visit 3 (randomisation). Before reversibility testing, the participant should withhold their bronchodilator for the effect duration specific to that agent.
10. At least two documented asthma exacerbations in the 12 months prior to the date that informed consent was obtained that required use of a systemic steroid. In the case of participants who are re-screened within 30 days of their screen failure date; the 12 months can be calculated from the date that the first informed consent was obtained.

The below defines what is acceptable to document exacerbations in this Programme:

1. Discharge summaries from a hospital, emergency department, or an urgent care facility indicating that a participant was hospitalised/ treated with systemic steroids for an asthma exacerbation.
2. Signed and dated notes from a referring physician, including information regarding diagnosis and treatment of an exacerbation with systemic steroids.
3. Participants can provide evidence of prescriptions for systemic steroids used during an exacerbation.
4. A documented conversation between the treating/referral physician or nurse/nurse practitioner certifying that a participant was treated for an exacerbation with steroids at their clinic or under their supervision. The dates (month/year) of the exacerbation and verbal confirmation that appropriate prescriptions were provided is necessary. This option should be used only if reasonable attempts to procure participant records have been unsuccessful.

A combination of the above is acceptable to document the two required exacerbations. However, it is necessary for the Investigator to document how they obtained confirmation of the participant's asthma exacerbations. It is the Investigator's responsibility to ensure eligibility for the clinical trial. In cases where the Investigator feels that alternative records to the above constitutes acceptable documentation, the Trial Physician will be contacted for their assessment of eligibility **prior** to enrolment. Every attempt should be made to obtain appropriate source documentation of medical records.

11. ACQ-6 score ≥1.5 at Visit 1 (Week -6).

Prior to randomisation at Visit 3, participants should fulfil the following inclusion criteria:

12. For WOCBP (including all adolescents) only: have a negative urine pregnancy test prior to administration of investigational product.
13. No requirement for additional asthma controller medication including an increase in ICS dose during run-in.

14. Fulfilment of at least one of the following conditions over the 7 days prior to randomisation:
 - 2 days with a daytime or night-time symptom score ≥ 1
 - Reliever (short-acting β_2 agonist) use on >2 days
 - ≥ 1 awakening due to asthma.
15. A morning pre-BD FEV₁ of $\geq 40\%$ and $<80\%$ ($<90\%$ for participants 12 to 17 years of age) of the participant's PNV at the day of randomisation visit, if not met at Visit 2.
16. If not previously achieved at Visit 2, a post-BD reversibility in FEV₁ of $\geq 12\%$ and ≥ 200 mL must be met at Visit 3. Note that theophylline and bronchodilators must be withheld prior to reversibility testing to avoid interference with this assessment.
17. Ability to perform acceptable inhaler, peak flow meter, and spirometry techniques.
18. Show at least 70% compliance with usual asthma controller (i.e. ICS/LABA and any other asthma controller medications) as evidenced by the participant having a minimum of 10 fully compliant dosing days in the 14 days prior to Visit 3 (randomisation) as reported by the participant in the eDiary.
19. Compliance with eDiary assessment schedule:
 - At least 10 days of the 14 days prior to Visit 3 must have complete (morning and evening) eDiary assessments.

For inclusion in the voluntary pharmacogenetic research, participants should fulfil the following criterion:

20. Provision of a signed and dated written informed consent for the pharmacogenetic sample and analysis. If a participant declines to take part in the pharmacogenetic research, there will be no consequence or loss of benefit to the participant. The participant will not be excluded from the other aspects of the trial described in the clinical study protocol, as long as they consent to participate in the trial.

Exclusion criteria

Participants should not enter the trial if any of the following exclusion criteria are met:

1. Clinically important pulmonary disease other than asthma (e.g., active lung infection, chronic obstructive pulmonary disease, bronchiectasis, pulmonary fibrosis, cystic fibrosis, hypoventilation syndrome associated with obesity, lung cancer, alpha 1 anti-trypsin deficiency, and primary ciliary dyskinesia) or ever been diagnosed with pulmonary or systemic disease, other than asthma, that are associated with elevated peripheral eosinophil counts (e.g., allergic bronchopulmonary aspergillosis/mycosis, Churg-Strauss syndrome [eosinophilic granulomatosis with polyangiitis], hypereosinophilic syndrome).
2. Any disorder, including but not limited to, cardiovascular, gastrointestinal, hepatic, renal, neurological, musculoskeletal, infectious, endocrine, metabolic, haematological, psychiatric, or major physical impairment that is not stable in the opinion of the Investigator and could:
 - Affect the safety of the participant throughout the trial.
 - Influence the findings of the trials or their interpretations.
 - Impede the participant's ability to complete the entire duration of the trial.
3. Known history of allergy or reaction to any component of the investigational product formulation.
4. History of anaphylaxis following any biologic therapy.
5. A helminth parasitic infection diagnosed within 6 months prior to enrolment (Visit 1) that has not been treated with, or has failed to respond to, standard-of-care therapy.
6. History of clinically significant infection, including acute upper or lower respiratory infections, requiring antibiotics or antiviral medication within 30 days prior to enrolment (Visit 1) or during the run-in period.
7. Tuberculosis requiring treatment within the 12 months prior to enrolment (Visit 1).
8. Any clinically significant abnormal findings in physical examination, vital signs, ECG, haematology, clinical chemistry, or urinalysis during the run-in period, which in the opinion of the Investigator, may put the participant at risk because of his/her participation in the trial, or may influence the results of the trial, or the participant's ability to complete the entire duration of the trial.

9. History of chronic alcohol or drug abuse within 12 months of the enrolment visit, or a condition associated with poor compliance as judged by the Investigator.
10. Positive hepatitis B surface antigen or hepatitis C virus antibody serology. Participants with a history of hepatitis B vaccination without a history of hepatitis B are allowed to be enrolled.
11. History of any known primary immunodeficiency disorder including a positive human immunodeficiency virus (HIV) test at enrolment, or the participant taking antiretroviral medications as determined by the medical history and/or participant's verbal report.
12. Current tobacco smoking (smoking must have stopped for ≥ 3 months prior to enrolment) or a history of tobacco smoking for ≥ 10 pack-years (one pack year = 20 cigarettes smoked per day for 1 year).
13. History of cancer:
 - Participants who have basal cell carcinoma, localised squamous cell carcinoma of the skin, or in situ carcinoma of the cervix are eligible provided that the participant is in remission and curative therapy was completed at least 12 months prior to enrolment (Visit 1).
 - Participants who have had other malignancies are eligible provided that the participant is in remission and curative therapy was completed at least 5 years prior to enrolment (Visit 1).
14. Use of immunosuppressive medication (including but not limited to: methotrexate, troleandomycin, cyclosporine, azathioprine, systemic corticosteroids including regular treatment with OCS and/or intramuscular long-acting depot corticosteroids, or any experimental anti-inflammatory therapy) within 3 months prior to enrolment (Visit 1).
15. Clinically significant asthma exacerbation, in the opinion of the Investigator, including those requiring use of OCS 30 days prior to the date of enrolment (Visit 1) or during the screening/run-in period.
16. Receipt of immunoglobulin or blood products within 30 days prior to enrolment (Visit 1).
17. Receipt of any marketed or investigational biologic agent (e.g., omalizumab) within 4 months or 5 half-lives prior to the enrolment visit, whichever is longer.
18. Receipt of live attenuated vaccines 30 days prior to the date of randomisation and during the trial, including the follow-up period. Receipt of inactive/killed vaccinations (e.g., inactive influenza) are allowed, provided they are not administered within 5 days before/after any trial visit (in STRATOS 1), or any dosing visit (in STRATOS 2).
19. Receipt of any investigational non-biologic agent within 30 days or 5 half-lives prior to enrolment (Visit 1), whichever is longer.
20. Previous receipt of tralokinumab (CAT-354).
21. Initiation of new allergen immunotherapy or change in existing immunotherapy is not allowed within 30 days prior to enrolment (Visit 1). However, allergen immunotherapy initiated prior to this period may be continued provided there is a span of at least 5 days between the immunotherapy and trial drug administration.
22. Current use of any oral or ophthalmic non-selective beta antagonist (e.g., propranolol).
23. Current use of five-lipoxygenase inhibitors (e.g. zileuton) or roflumilast.
24. Participants that have undergone bronchial thermoplasty.
25. Major surgery within 8 weeks prior to the enrolment visit, or planned in-participant surgery or hospitalisation during the trial period.
26. Alanine aminotransferase (ALT) or aspartate aminotransferase (AST) concentration ≥ 2.5 times the upper limit of normal (ULN) at enrolment.
27. Pregnant, currently breast-feeding, or lactating women.
28. Previous randomisation in the present trial.
29. Concurrent enrolment in another clinical trial where the participant is receiving an investigational product.
30. Involvement in the planning and/or conduct of the trial (applies to both AstraZeneca staff and/or staff at the trial site).

31. Employees of the clinical trial site or any other individuals directly involved with the planning or conduct of the trial, or immediate family members of such individuals.
32. Individuals who are legally institutionalised.

For exclusion from the voluntary pharmacogenetic research:

33. Previous allogeneic bone marrow transplant.
34. Non-leukocyte depleted whole blood transfusion within 120 days of genetic sample collection.

Statistical analysis of key secondary endpoints

The percent change from baseline in pre-BD FEV₁, and change from baseline in ACQ-6 score, AQLQ score and asthma symptom score at Week 52 were compared between each dosing regimen of tralokinumab and placebo using a restricted maximum likelihood-based repeated measures analysis. Fixed categorical effects of treatment group, geographical region, age group, periostin group, visit and treatment-by-visit interaction were included in the models, and number of asthma exacerbations in the year prior to the trial were a fixed covariate in the model. For absolute change from baseline analyses, the baseline value was also included in the model. For analyses of endpoints in the FeNO-high and -low subgroups, a biomarker group and treatment* biomarker group interaction term were added to the model.

Handling of missing data

To minimise the amount of missing data in the trials, participants were encouraged to remain in the trials after premature discontinuation of investigational product and complete visits according to the protocols.

In addition to the primary analyses, sensitivity analyses were performed to cover the range from realistic to plausible worst case assumptions about missing data. The following assumptions were used to impute the missing data for participants who withdrew early from the trials:

- (a) Missing at Random (MAR): Missing counts for a participant was imputed using the observed event rate within the treatment group of that participant
- (b) Dropout Reason-based Multiple Imputation (DRMI): Missing counts were imputed differently depending on the reason for dropout; counts for participants in the tralokinumab arms who dropped out for a treatment-related reason were imputed based on the expected event rate in the placebo arms, whereas the remaining participants who dropped out were imputed assuming MAR. Treatment-related reasons included (1) AEs, (2) death, (3) development of trial-specified reasons to stop active treatments, and (4) severe non-compliance of protocol

The MAR multiple imputation approach was expected to correspond closely to the primary analysis, and was included to allow for comparisons with the Missing Not at Random (MNAR) assumptions (specifically method b) using the same multiple imputation methodology.

The DRMI approach was selected as the most conservative approach based on the fact that placebo participants were receiving standard of care and were not expected to change to a substantially more effective treatment after withdrawal from the trials or trial treatment. For participants receiving tralokinumab who withdrew from the trials due to treatment-related reasons, it was assumed that at worst they would be on the standard of care treatment, i.e. the placebo arm. For participants receiving tralokinumab who withdrew from the trials due to non-treatment-related reasons, it was reasonable to assume they would be similar to those participants who completed treatment.

Adverse events of special interest

Hypersensitivity

In STRATOS 1, a total of 308/1,202 (25.6%) participants experienced AEs of hypersensitivity; 103 of these were in the tralokinumab Q2W group, 101 were in the tralokinumab Q4W group, and 104 were in the placebo group. The most common hypersensitivity AE was asthma, reported in 47/398 (11.8%), 48/404 (11.9%) and 54/400 (13.5%) of the participants in the tralokinumab Q2W, tralokinumab Q4W and placebo groups, respectively. Of the 32 potential hypersensitivity reactions reported in 18 participants, none were considered anaphylaxis reactions. Similarly, in STRATOS 2, 56/425 (13.2%) of the participants in the tralokinumab and 38/422 (9.0%) of the participants in the placebo group suffered hypersensitivity reactions, the most common being asthma (in 3.3% [14/425] and 3.8% [16/422] in the tralokinumab and placebo groups, respectively).

Severe infections

In STRATOS 1, a total of 41/1,202 (3.4%) participants experienced severe infections (defined as life-threatening, requiring hospitalisation, requiring treatment with antiviral medication, intravenous antibiotics or antihelminthic medication, or resulting in permanent discontinuation of the investigational product) during the treatment period; the proportion of participants was similar across treatment groups. Severe herpes zoster infections were reported in 1 participant in the talokinumab Q2W group and 2 participants in the placebo group. Overall, 44/847 (5.2%) participants experienced AEs of severe infection in STRATOS 2, the most frequently reported being influenza (5 participants in each group) and pneumonia (4 participants in each group). Additionally, 1 participant receiving placebo experienced hepatitis A infection. A number of herpes infections were experienced by several participants in the STRATOS 2 talokinumab and placebo groups; oral herpes (2 in each group), herpes zoster (2 receiving talokinumab and 1 receiving placebo), herpes virus infection (1 receiving talokinumab and none receiving placebo), disseminated cutaneous herpes zoster (1 receiving talokinumab and none receiving placebo), and herpes simplex (none receiving talokinumab and 1 receiving placebo). No cases of helminth parasitic, mycobacterial, or invasive fungal infections were reported in STRATOS 1. In STRATOS 2, one participant receiving talokinumab experienced pulmonary tuberculosis, and there were no cases of helminth parasitic or invasive fungal infections reported during the treatment period.

Malignancy

In total, 5 participants experienced new malignancy events in the STRATOS 1 treatment period; 2 of these were in the talokinumab Q2W group (basal cell carcinoma and cervix carcinoma) and 1 was in the placebo group (uterine cancer). During the post-treatment period, 1 participant in STRATOS 1 had an AE of ovarian cancer reported as a new malignancy. In the overall population of STRATOS 2, no participants receiving talokinumab developed a malignancy and 1 participant in the placebo group developed malignancy (rectal cancer).

Major adverse cardiovascular/cerebrovascular events

In STRATOS 1, 7 participants experienced major adverse cardiovascular/cerebrovascular events (MACE); 2 participants receiving talokinumab Q2W (myocardial infarction and stroke, 1 participant each), 1 participant receiving talokinumab Q4W (stroke), and 4 participants in the combined placebo group (myocardial infarction, 3 participants; stroke, 1 participant). In the STRATOS 2 overall population, 2 participants experienced MACE; both myocardial infarction, 1 participant in each treatment group.

Treatment-related adverse events and serious adverse events in STRATOS 1 talokinumab 300 mg Q4W group

The most frequently reported talokinumab-related AEs (>2% of participants) in the STRATOS 1 talokinumab Q4W group were injection site reaction (3.2% [13/404]), injection site erythema (3.0% [12/404]), and injection site pain (2.5% [10/404]).

There were no talokinumab-related SAEs in the STRATOS 1 talokinumab Q4W group.

Talokinumab immunogenicity and pharmacokinetics

There was no obvious relationship between either anti-drug antibodies (ADA) prevalence or ADA incidence and treatment group in either trial (Table S21). However, it should be noted that the number of ADA-positive subjects in each of the treatment cohorts was small ($n < 10$), and thus it is not possible to draw definitive conclusions.

In STRATOS 1, pharmacokinetic (PK) steady-state was achieved for both the talokinumab 300 mg Q2W and Q4W treatment groups by Week 8, with similar geometric mean (coefficient of variation [CV] %) C_{trough} values at Week 8 (56.1 µg/mL [160.6%] and 19.4 µg/mL [111.7%], respectively) and Week 52 (56.3 µg/mL [172.3%] and 18.6 µg/mL [219.3%], respectively). C_{trough} was consistently greater from Week 4 through to Week 52 for the talokinumab 300 mg Q2W group (34.9 µg/mL [199.7%] to 56.3 µg/mL [172.3%], respectively) compared with the talokinumab 300 mg Q4W group (13.2 µg/mL [188.5%] to 18.6 µg/mL [219.3%], respectively). This was due to the shorter dosing interval. Serum C_{trough} values of talokinumab were observed with modest inter-individual variability within each treatment group (geometric CV% ranged from 111.7% to 219.3% across visits and treatment groups) (Table S22).

In STRATOS 2, PK steady-state was achieved by Week 8 in the FeNO-high subgroup with similar geometric mean (CV%) C_{trough} values at Week 8 (55.9 µg/mL [206.5%]) and Week 26 (58.4 µg/mL [145.3%]). Following multiple talokinumab doses, a modest accumulation ratio was observed (2.4, based on geometric mean C_{trough} at Week 26 and Week 2). There was also a high degree of inter-individual variability in talokinumab C_{trough} values

(geometric CV% ranged from 172.5% to 591.3% across visits) with similar degrees of variability observed for the biomarker-negative and all-comers populations (Table S22).

Supplementary tables and figures

Table S1: Stratification factors in STRATOS 1, recorded at time of randomisation

Geographical region	Serum periostin, ng/mL	Age group*	Combined placebo, n (%) (N=400)	Tralo Q2W, n (%) (N=398)	Tralo Q4W, n (%) (N=404)
Asia Pacific	<16·44	Adult	2 (0·5)	2 (0·5)	2 (0·5)
		Adolescent	0	0	0
	≥16·44	Adult	49 (12·3)	49 (12·3)	49 (12·1)
		Adolescent	1 (0·3)	1 (0·3)	0
Central / Eastern Europe	<16·44	Adult	34 (8·5)	34 (8·5)	34 (8·4)
		Adolescent	1 (0·3)	1 (0·3)	0
	≥16·44	Adult	121 (30·3)	121 (30·4)	122 (30·2)
		Adolescent	6 (1·5)	6 (1·5)	7 (1·7)
North America	<16·44	Adult	27 (6·8)	25 (6·3)	26 (6·4)
		Adolescent	0	0	0
	≥16·44	Adult	67 (16·8)	66 (16·6)	67 (16·6)
		Adolescent	1 (0·3)	1 (0·3)	1 (0·2)
South America	<16·44	Adult	4 (1·0)	4 (1·0)	6 (1·5)
		Adolescent	0	0	0
	≥16·44	Adult	68 (17·0)	69 (17·3)	68 (16·8)
		Adolescent	5 (1·3)	5 (1·3)	6 (1·5)
Western Europe / Rest of World	<16·44	Adult	2 (0·5)	3 (0·8)	3 (0·7)
		Adolescent	0	0	0
	≥16·44	Adult	12 (3·0)	11 (2·8)	12 (3·0)
		Adolescent	0	0	1 (0·2)

Q2W, every two weeks; Q4W, every four weeks; Tralo, tralokinumab

*Defined as: Adults, 18–75 years (inclusive); Adolescents, 12–17 years (inclusive)

Table S2: Stratification factors in STRATOS 2, recorded at time of randomisation

Geographical region	Serum periostin, ng/mL	Age group*	FeNO-high (≥ 37 ppb; n=229)		FeNO-low (< 37 ppb; n=598)	
			Placebo, n (%) (n=121)	Tralo Q2W, n (%) (n=108)	Placebo, n (%) (n=290)	Tralo Q2W, n (%) (n=308)
Asia Pacific	<16·44	Adult	0	1 (0·9)	2 (0·7)	1 (0·3)
		Adolescent	0	0	0	0
	$\geq 16\cdot44$	Adult	22 (18·2)	23 (21·3)	49 (16·9)	47 (15·3)
		Adolescent	3 (2·5)	0	1 (0·3)	3 (1·0)
Central / Eastern Europe	<16·44	Adult	4 (3·3)	8 (7·4)	25 (8·6)	20 (6·5)
		Adolescent	0	0	0	0
	$\geq 16\cdot44$	Adult	34 (28·1)	29 (26·9)	90 (31·0)	96 (31·2)
		Adolescent	1 (0·8)	3 (2·8)	5 (1·7)	5 (1·6)
North America	<16·44	Adult	8 (6·6)	4 (3·7)	15 (5·2)	19 (6·2)
		Adolescent	0	1 (0·9)	3 (1·0)	3 (1·0)
	$\geq 16\cdot44$	Adult	20 (16·5)	18 (16·7)	42 (14·5)	46 (14·9)
		Adolescent	4 (3·3)	2 (1·9)	3 (1·0)	4 (1·3)
South America / Mexico	<16·44	Adult	1 (0·8)	1 (0·9)	10 (3·4)	11 (3·6)
		Adolescent	0	0	0	0
	$\geq 16\cdot44$	Adult	11 (9·1)	11 (10·2)	33 (11·4)	34 (11·0)
		Adolescent	3 (2·5)	1 (0·9)	3 (1·0)	6 (1·9)
Western Europe / Rest of World	<16·44	Adult	0	1 (0·9)	3 (1·0)	2 (0·6)
		Adolescent	0	0	0	0
	$\geq 16\cdot44$	Adult	10 (8·3)	5 (4·6)	6 (2·1)	11 (3·6)
		Adolescent	0	0	0	0

FeNO, fractional exhaled nitric oxide ('high' defined as ≥ 37 ppb); Q2W, every two weeks; Tralo, tralokinumab

*Defined as: Adults, 18–75 years (inclusive); Adolescents, 12–17 years (inclusive)

Table S3: Participant demographics and baseline characteristics in the STRATOS 1 tralokinumab Q4W group

	Combined placebo* (N=400)	Tralo Q4W (N=404)
Demographics		
Age, years, mean (SD)	51.4 (14.3)	51.1 (13.9)
Female, n (%)	265 (66.3)	281 (69.6)
Race, n (%)		
White	288 (72.0)	297 (73.5)
Black or African American	14 (3.5)	16 (4.0)
Asian	55 (13.8)	55 (13.6)
Other	43 (10.8)	36 (8.9)
BMI (kg/m ²), mean (SD)	28.8 (6.4)	28.9 (6.1)
Clinical characteristics		
Pre-BD FEV ₁ , L, mean (SD)	1.8 (0.6)	1.7 (0.5)
Pre-BD FEV ₁ , % predicted, mean (SD)	61.5 (13.3)	60.9 (13.8)
Pre-BD FVC, L, mean (SD)	2.8 (0.9)	2.8 (0.8)
FEV ₁ reversibility [†] , %, mean (SD)	23.1 (24.4) [‡]	22.6 (20.6)
Time since asthma diagnosis, years, median (IQR)	16.0 (6, 31)	15.0 (8, 33)
Number of exacerbations in the last 12 months, median (IQR)	2.0 (2, 2)	2.0 (2, 2)
Total asthma symptom score, mean (SD)	2.5 (1.0) [‡]	2.5 (1.0) [§]
ACQ-6 score, mean (SD)	2.6 (0.9) [‡]	2.5 (0.9) [§]
AQLQ score, mean (SD)	4.2 (1.0) [¶]	4.2 (1.0) [¶]
Baseline eosinophil count, cells/μL, mean (SD)	254 (203.8)**	296 (381.4) ^{††}
Baseline FeNO concentration, ppb, mean (SD)	29.7 (28.5) [‡]	29.8 (29.7) ^{‡‡}
Baseline asthma medication		
ICS dosage, n (%)		
Low ^{§§}	3 (0.8)	1 (0.2)
Medium	194 (48.5)	202 (50.0)
High	203 (50.8)	201 (49.8)
LABA, n (%)	400 (100.0)	404 (100.0)

ACQ-6, Asthma Control Questionnaire-6; AQLQ, standardised Asthma Quality of Life Questionnaire; BD, bronchodilator; BMI, body mass index; FeNO, fractional exhaled nitric oxide FEV₁, forced expiratory volume in one second; FVC, forced vital capacity; ICS, inhaled corticosteroids; IQR, interquartile range; LABA, Long-acting beta₂ agonists; Q2W, every two weeks; Q4W, every four weeks; SABA, short-acting beta₂ agonist; SD, standard deviation; Tralo, tralokinumab

*The STRATOS 1 placebo treatment group is a combined treatment group (placebo Q2W + placebo Q4W) where the two placebo cohorts were given weights proportional to the number of participants in each cohort

[†]The post-BD FEV₁ measurement in the reversibility derivation could be the post-BD measurement after 4, 6, or 8 SABA inhalations, depending on when the reversibility assessment was considered complete

[‡]n=399; [§]n=403; [¶]n=398; ^{**}n=378; ^{††}n=393; ^{‡‡}n=395; ^{§§}n=397

^{§§}A minor number of participants were taking low dosages of ICS at baseline, and were recorded as protocol deviations

Table S4: Primary and key secondary efficacy endpoints in the STRATOS 1 tralokinumab Q4W group (Full Analysis Set)

Primary Endpoint	Tralo Q4W vs. placebo*, n	Rate reduction, % (95% CI)	P value
AAER up to Week 52	404 vs. 400	9·8 (–17·2, 30·5)	0·44
Secondary Endpoints	Tralo Q4W vs. placebo*, n	Difference in LS means (95% CI)	P value
Change from baseline at Week 52 in:			
Pre-BD FEV ₁ , %	373 vs. 363	2·10 (–1·58, 5·77)	0·26
AQLQ score	321 vs. 315	0·12 (–0·03, 0·28)	0·12
ACQ-6 score	344 vs. 329	–0·12 (–0·26, 0·01)	0·078
Total asthma symptom score	313 vs. 312	–0·02 (–0·15, 0·12)	0·81

AAER, annual asthma exacerbation rate; ACQ-6, Asthma Control Questionnaire-6; AQLQ, standardised Asthma Quality of Life Questionnaire; BD, bronchodilator; CI, confidence interval; FEV₁, forced expiratory volume in one second; Q2W, every two weeks; Q4W, every four weeks; Tralo, tralokinumab

*The STRATOS 1 placebo treatment group is a combined treatment group (placebo Q2W + placebo Q4W) where the two placebo cohorts were given weights proportional to the number of participants in each cohort

Table S5: Other secondary efficacy endpoints in STRATOS 1 and 2 (Full Analysis Set)

STRATOS 1	Combined placebo* (N=400)	Tralo Q2W (N=398)	Tralo Q4W (N=404)
Time to first exacerbation			
n	400	398	404
Hazard ratio (95% CI)		1.0 (0.8, 1.2)	0.9 (0.7, 1.2)
P value		0.73	0.45
AAER at Week 52 associated with an emergency department/urgent care visit or hospitalisation			
n	32	19	29
AAER (95% CI)	0.1 (0.1, 0.1)	0.0 (0.0, 0.1)	0.1 (0.0, 0.1)
Rate ratio (95% CI)		0.5 (0.3, 1.0)	0.8 (0.5, 1.3)
P value		0.037	0.36
Percentage change from baseline at Week 52 in post-BD FEV₁			
n	342	344	365
Difference in LS means (95% CI), %		4.35 (1.34, 7.35)	3.54 (0.57, 6.51)
STRATOS 2	Placebo (N=417)	Tralo Q2W (N=420)	
Time to first exacerbation			
All-comers			
n	417	420	
Hazard ratio (95% CI)		0.9 (0.8, 1.2)	
P value		0.55	
FeNO-high (≥37 ppb)			
n	121	108	
Hazard ratio (95% CI)		0.8 (0.5, 1.2)	
P value		0.23	
AAER at Week 52 associated with an emergency department/urgent care visit or hospitalisation			
All-comers			
n	46	36	
AAER (95% CI)	0.1 (0.1, 0.2)	0.1 (0.1, 0.1)	
Rate ratio (95% CI)		0.7 (0.4, 1.1)	
P value		0.12	
FeNO-high (≥37 ppb)			
n	16	8	
AAER (95% CI)	0.2 (0.1, 0.3)	0.1 (0.0, 0.1)	
Rate ratio (95% CI)		0.4 (0.2, 1.0)	
P value		0.058	
Percentage change from baseline at Week 52 in post-BD FEV₁			
All-comers			
n	345	370	
Difference in LS means (95% CI), %		2.14 (−0.81, 5.09)	
FeNO-high (≥37 ppb)			
n	98	93	
Difference in LS means (95% CI), %		1.82 (−3.79, 7.43)	

AAER, annual asthma exacerbation rate; BD, bronchodilator; CI, confidence interval; FEV₁, forced expiratory volume in one second; LS, least squares Q2W, every two weeks; Q4W, every four weeks; Tralo, tralokinumab

*The STRATOS 1 placebo treatment group is a combined treatment group (placebo Q2W + placebo Q4W) where the two placebo cohorts were given weights proportional to the number of participants in each cohort

Table S6: European Quality of Life-5 Dimension-5 Level Daily Living Questionnaire results in STRATOS 1 and 2 (Full Analysis Set)

	VAS at baseline		VAS change from baseline at Week 52	
	n	Mean (SD)	n	Mean (SD)
STRATOS 1				
Combined placebo* (N=400)	374	63.2 (16.9)	324	10.1 (18.9)
Tralo Q2W (N=398)	367	62.1 (17.2)	306	10.7 (20.3)
Tralo Q4W (N=404)	376	63.5 (16.3)	319	9.0 (19.0)
STRATOS 2				
All-comers				
Placebo (N=417)	387	65.4 (17.3)	313	11.7 (17.4)
Tralo Q2W (N=420)	390	66.0 (17.8)	317	12.5 (16.7)
FeNO-high (≥ 37 ppb)				
Placebo (n=121)	115	66.0 (18.7)	85	11.6 (17.3)
Tralo Q2W (n=108)	99	63.8 (17.1)	81	14.6 (15.2)

FeNO, fractional exhaled nitric oxide; Q2W, every two weeks; Q4W, every four weeks; SD, standard deviation; Tralo, tralokinumab; VAS, visual analogue scale

*The STRATOS 1 placebo treatment group is a combined treatment group (placebo Q2W + placebo Q4W) where the two placebo cohorts were given weights proportional to the number of participants in each cohort

Table S7: Work Productivity and Activity Impairment Questionnaire and Classroom Impairment Questionnaire results in STRATOS 1 tralokinumab Q2W group and STRATOS 2 (Full Analysis Set)

	Tralo Q2W vs. placebo*, n	WPAI and CIQ percentage impairment/loss at Week 52, mean (SD)
STRATOS 1		
Work productivity loss (employed participants)	112 vs. 118	27·7 (24·1) vs. 31·3 (25·3)
Classroom impairment (participants in school)	11 vs. 15	33·1 (28·0) vs. 32·3 (28·5)
Activity impairment		
Currently employed	120 vs. 127	23·3 (21·3) vs. 27·0 (23·2)
Currently in school	14 vs. 19	29·3 (20·6) vs. 29·0 (23·1)
Not currently employed	203 vs. 206	35·7 (23·2) vs. 37·1 (24·6)
Not currently in school	203 vs. 206	35·7 (23·2) vs. 37·1 (24·6)
STRATOS 2		
All-comers		
Work productivity loss (employed participants)	137 vs. 125	23·4 (23·7) vs. 30·2 (27·1)
Classroom impairment (participants in school)	17 vs. 26	28·0 (31·0) vs. 28·1 (29·8)
Activity impairment		
Currently employed	147 vs. 131	20·7 (19·8) vs. 26·1 (24·9)
Currently in school	22 vs. 29	24·6 (27·4) vs. 27·9 (28·7)
Not currently employed	193 vs. 195	36·1 (25·6) vs. 38·6 (26·2)
Not currently in school	193 vs. 195	36·1 (25·6) vs. 38·6 (26·2)
FeNO-high (≥ 37 ppb)		
Work productivity loss (employed participants)	43 vs. 34	22·5 (24·5) vs. 28·2 (27·4)
Classroom impairment (participants in school)	3 vs. 12	28·9 (34·2) vs. 37·9 (28·7)
Activity impairment		
Currently employed	45 vs. 36	20·9 (18·8) vs. 25·3 (28·6)
Currently in school	5 vs. 13	20·0 (18·7) vs. 33·9 (26·6)
Not currently employed	40 vs. 46	31·8 (23·7) vs. 31·5 (26·4)
Not currently in school	40 vs. 46	31·8 (23·7) vs. 31·5 (26·4)

CIQ, Classroom Impairment Questionnaire; FeNO, fractional exhaled nitric oxide; Q2W, every two weeks; SD, standard deviation; Tralo, tralokinumab; WPAI, Work Productivity and Activity Impairment Questionnaire

*The STRATOS 1 placebo treatment group is a combined treatment group (placebo Q2W + placebo Q4W) where the two placebo cohorts were given weights proportional to the number of participants in each cohort

Table S8: Work Productivity and Activity Impairment Questionnaire and Classroom Impairment Questionnaire results in STRATOS 1 tralokinumab Q4W group (Full Analysis Set)

	Tralo Q4W vs. placebo*, n	WPAI and CIQ percentage impairment/loss at Week 52, mean (SD)
Work productivity loss (employed participants)	116 vs. 118	28·5 (25·1) vs. 31·3 (25·3)
Classroom impairment (participants in school)	14 vs. 15	31·8 (34·3) vs. 32·3 (28·5)
Activity impairment		
Currently employed	119 vs. 127	23·5 (22·6) vs. 27·0 (23·2)
Currently in school	16 vs. 19	27·5 (29·6) vs. 29·0 (23·1)
Not currently employed	221 vs. 206	38·3 (26·4) vs. 37·1 (24·6)
Not currently in school	221 vs. 206	38·3 (26·4) vs. 37·1 (24·6)

CIQ, Classroom Impairment Questionnaire; Q4W, every four weeks; SD, standard deviation; Tralo, tralokinumab; WPAI, Work Productivity and Activity Impairment Questionnaire

*The STRATOS 1 placebo treatment group is a combined treatment group (placebo Q2W + placebo Q4W) where the two placebo cohorts were given weights proportional to the number of participants in each cohort

Table S9: Asthma-related healthcare resource utilisation up to Week 52 by type in STRATOS 1 and 2 (Full Analysis Set)

	Tralo Q2W vs. placebo*	Tralo Q4W vs. placebo*
STRATOS-1		
Ambulance transport, n	5 vs. 16	15 vs. 16
Hospitalisations, [†] days in hospital	270 vs. 482	345 vs. 482
Emergency department visits, n	59 vs. 64	87 vs. 64
Unscheduled outpatient visits, [‡] n	1750 vs. 1705	1786 vs. 1705
Home visits, [§] n	21 vs. 6	5 vs. 6
Telephone calls, n	515 vs. 198	463 vs. 198
Spirometry, n	489 vs. 502	520 vs. 502
Advanced pulmonary function test, n	84 vs. 67	70 vs. 67
STRATOS 2		
All-comers		
Ambulance transport, n	35 vs. 41	–
Hospitalisations, [†] days in hospital	417 vs. 590	–
Emergency department visits, n	87 vs. 99	–
Unscheduled outpatient visits, [‡] n	1798 vs. 1834	–
Home visits, [§] n	59 vs. 44	–
Telephone calls, n	163 vs. 196	–
Spirometry, n	434 vs. 426	–
Advanced pulmonary function test, n	51 vs. 46	–
FeNO-high (≥37 ppb)		
Ambulance transport, n	14 vs. 21	–
Hospitalisations, [†] days in hospital	82 vs. 175	–
Emergency department visits, n	20 vs. 28	–
Unscheduled outpatient visits, [‡] n	513 vs. 579	–
Home visits, [§] n	10 vs. 18	–
Telephone calls, n	51 vs. 76	–
Spirometry, n	148 vs. 151	–
Advanced pulmonary function test, n	16 vs. 20	–

FeNO, fractional exhaled nitric oxide; Q2W, every two weeks; Q4W, every four weeks Tralo, tralokinumab

*The STRATOS 1 placebo treatment group is a combined treatment group (placebo Q2W + placebo Q4W) where the two placebo cohorts were given weights proportional to the number of participants in each cohort

[†]Hospitalisations, intensive care and/or general care

[‡]Visit to specialist, primary healthcare physician and/or other healthcare visit

[§]Home visit by physician and/or other healthcare professional

^{||}Telephone calls to physician and/or nurse

Table S10: Rescue medication use in STRATOS 1 tralokinumab Q2W group and STRATOS 2 (Full Analysis Set)

	Tralo Q2W vs. placebo*, n	Asthma rescue medication use, puffs/day
STRATOS 1		
Baseline, mean (SD)	397 vs. 399	4.1 (3.6) vs. 3.9 (3.5)
Difference in LS means (95% CI) for change from baseline at Week 52	313 vs. 312	-0.1 (-0.5, 0.3)
STRATOS 2		
All-comers		
Baseline, mean (SD)	419 vs. 415	3.8 (3.5) vs. 4.1 (3.8)
Difference in LS means (95% CI) for change from baseline at Week 52	309 vs. 297	-0.2 (-0.6, 0.3)
<i>P</i> value		0.47
FeNO-high (≥ 37 ppb)		
Baseline, mean (SD)	108 vs. 120	4.5 (3.8) vs. 4.5 (4.3)
Difference in LS means (95% CI) for change from baseline at Week 52	79 vs. 81	-1.0 (-1.9, -0.1)
<i>P</i> value		0.036

CI, confidence interval; FeNO, fractional exhaled nitric oxide; LS, least-squares; Q2W, every two weeks; Q4W, every four weeks; SD, standard deviation; Tralo, tralokinumab

*The STRATOS 1 placebo treatment group is a combined treatment group (placebo Q2W + placebo Q4W) where the two placebo cohorts were given weights proportional to the number of participants in each cohort

Table S11: Rescue medication use in STRATOS 1 tralokinumab Q4W group (Full Analysis Set)

	Tralo Q4W vs. placebo*, n	Asthma rescue medication use, puffs/day
Baseline, mean (SD)	403 vs. 399	4·2 (4·6) vs. 3·9 (3·5)
Difference in LS means (95% CI) for change from baseline at Week 52	313 vs. 312	−0·2 (−0·6, 0·2)

CI, confidence interval; LS, least-squares; Q2W, every two weeks; Q4W, every four weeks; SD, standard deviation; Tralo, tralokinumab

*The STRATOS 1 placebo treatment group is a combined treatment group (placebo Q2W + placebo Q4W) where the two placebo cohorts were given weights proportional to the number of participants in each cohort

Table S12: Peak expiratory flow (home lung function) in STRATOS 1 tralokinumab Q2W group and STRATOS 2 (Full Analysis Set)

	Morning PEF Tralo Q2W vs. placebo*, n	PEF, L/min	Evening PEF Tralo Q2W vs. placebo*, n	PEF, L/min
STRATOS 1				
Baseline, mean (SD)	393 vs. 394	236·0 (104·4) vs. 244·7 (112·5)	394 vs. 394	247·2 (108·3) vs. 254·8 (114·5)
Difference in LS means (95% CI) for change from baseline at Week 52	320 vs. 329	6·3 (–3·5, 16·0)	321 vs. 326	7·1 (–2·6, 16·9)
STRATOS 2				
All-comers				
Baseline, mean (SD)	415 vs. 405	257·3 (102·2) vs. 248·2 (101·4)	414 vs. 407	269·3 (103·8) vs. 261·3 (102·9)
Difference in LS means (95% CI) for change from baseline at Week 52	318 vs. 308	3·5 (–6·1, 13·0)	322 vs. 313	3·9 (–5·6, 13·4)
<i>P</i> value		0·48		0·42
FeNO-high (≥37 ppb)				
Baseline, mean (SD)	106 vs. 118	249·5 (107·1) vs. 255·1 (100·5)	106 vs. 119	265·0 (107·0) vs. 272·9 (101·9)
Difference in LS means (95% CI) for change from baseline at Week 52	84 vs. 81	6·2 (–12·1, 24·4)	86 vs. 86	7·8 (–10·3, 26·0)
<i>P</i> value		0·51		0·40

CI, confidence interval; FeNO, fractional exhaled nitric oxide; LS, least-squares; PEF, peak expiratory flow; Q2W, every two weeks; Q4W, every four weeks; SD, standard deviation; Tralo, tralokinumab

*The STRATOS 1 placebo treatment group is a combined treatment group (placebo Q2W + placebo Q4W) where the two placebo cohorts were given weights proportional to the number of participants in each cohort

Table S13: Peak expiratory flow (home lung function) in STRATOS 1 tralokinumab Q4W group (Full Analysis Set)

	Morning PEF		Evening PEF	
	Tralo Q4W vs. placebo*, n	PEF, L/min	Tralo Q4W vs. placebo*, n	PEF, L/min
Baseline, mean (SD)	392 vs. 394	241·9 (104·2) vs. 244·7 (112·5)	392 vs. 394	253·7 (105·5) vs. 254·8 (114·5)
Difference in LS means (95% CI) for change from baseline at Week 52	326 vs. 329	1·8 (–8·0, 11·5)	319 vs. 326	0·6 (–9·1, 10·4)

CI, confidence interval; LS, least-squares; PEF, peak expiratory flow; Q2W, every two weeks; Q4W, every four weeks; SD, standard deviation; Tralo, tralokinumab

*The STRATOS 1 placebo treatment group is a combined treatment group (placebo Q2W + placebo Q4W) where the two placebo cohorts were given weights proportional to the number of participants in each cohort

Table S14: Night-time awakenings due to asthma in STRATOS 1 tralokinumab Q2W group and STRATOS 2 (Full Analysis Set)

	Tralo Q2W vs. placebo*, n	Night-time awakenings due to asthma requiring use of rescue medication, %
STRATOS 1		
Baseline, mean (SD)	397 vs. 400	47·2 (35·8) vs. 47·1 (35·2)
Difference in LS means (95% CI) for change from baseline at Week 52	346 vs. 357	-1·8 (-5·3, 1·7)
STRATOS 2		
All-comers		
Baseline, mean (SD)	420 vs. 416	42·2 (35·5) vs. 44·1 (35·5)
Difference in LS means (95% CI) for change from baseline at Week 52	368 vs. 348	-1·2 (-4·4, 2·0)
<i>P</i> value		0·46
FeNO-high (≥ 37 ppb)		
Baseline, mean (SD)	108 vs. 120	47·0 (35·4) vs. 47·1 (35·0)
Difference in LS means (95% CI) for change from baseline at Week 52	94 vs. 96	-5·0 (-11·2, 1·1)
<i>P</i> value		0·11

CI, confidence interval; FeNO, fractional exhaled nitric oxide; LS, least-squares; Q2W, every two weeks; Q4W, every four weeks; SD, standard deviation; Tralo, tralokinumab

*The STRATOS 1 placebo treatment group is a combined treatment group (placebo Q2W + placebo Q4W) where the two placebo cohorts were given weights proportional to the number of participants in each cohort

Table S15: Night-time awakenings due to asthma in STRATOS 1 tralokinumab Q4W group (Full Analysis Set)

	Tralo Q4W vs. placebo*, n	Night-time awakenings due to asthma requiring use of rescue medication, %
Baseline, mean (SD)	403 vs. 400	43·2 (35·8) vs. 47·1 (35·2)
Difference in LS means (95% CI) for change from baseline at Week 52	357 vs. 357	–2·4 (–5·8, 1·1)

CI, confidence interval; LS, least-squares; Q2Wm every two weeks; Q4W, every four weeks; SD, standard deviation; Tralo, tralokinumab

*The STRATOS 1 placebo treatment group is a combined treatment group (placebo Q2W + placebo Q4W) where the two placebo cohorts were given weights proportional to the number of participants in each cohort

Table S16: Annual asthma exacerbation rate at Week 52 in eosinophil count subgroups in STRATOS 1 and 2 (Full Analysis Set)

	n	AAER (95% CI)	Rate ratio (95% CI)	P value
STRATOS 1				
Eos-high*				
Combined placebo [†]	116	0.8 (0.6, 1.1)		
Tralo Q2W	137	0.7 (0.5, 0.9)	0.8 (0.5, 1.3)	0.42 [‡]
Tralo Q4W	123	0.6 (0.5, 0.8)	0.8 (0.5, 1.2)	0.23 [‡]
Eos-low[§]				
Combined placebo [†]	277	0.5 (0.4, 0.7)		
Tralo Q2W	256	0.5 (0.4, 0.6)	1.0 (0.7, 1.3)	0.80 [‡]
Tralo Q4W	272	0.5 (0.4, 0.7)	1.0 (0.7, 1.4)	0.90 [‡]
STRATOS 2				
Eos-high*				
Placebo	130	0.8 (0.6, 1.1)		
Tralo Q2W	136	1.1 (0.9, 1.5)	1.4 (0.9, 2.1)	0.13
Eos-low[§]				
Placebo	285	0.8 (0.7, 1.0)		
Tralo Q2W	276	0.7 (0.6, 0.9)	0.9 (0.6, 1.2)	0.33

CI, confidence interval; eos, eosinophils; Q2W, every two weeks; Q4W, every four weeks; Tralo, tralokinumab

* ≥ 300 cells/ μ L

[†]The STRATOS 1 placebo treatment group is a combined treatment group (placebo Q2W + placebo Q4W) where the two placebo cohorts were given weights proportional to the number of participants in each cohort

[‡]P values for STRATOS 1 biomarker analyses are nominal and were not adjusted for multiplicity

[§] < 300 cells/ μ L

Table S17: Key secondary efficacy endpoints in the STRATOS 1 and 2 FeNO-low (<37 ppm at baseline) populations (Full Analysis Set)

Change from baseline at Week 52	Tralo Q2W vs. placebo* (n)	Difference in LS means (95% CI)	P value
STRATOS 1			
Pre-BD FEV ₁ , %	268 vs. 269	3.83 (−0.5, 8.1)	0.080 [†]
AQLQ score	241 vs. 230	0.0 (−0.2, 0.2)	0.86 [†]
ACQ-6 score	242 vs. 231	−0.1 (−0.2, 0.1)	0.37 [†]
Total asthma symptom score	242 vs. 243	−0.1 (−0.3, 0.1)	0.22 [†]
STRATOS 2			
Pre-BD FEV ₁ , %	282 vs. 250	3.4 (−1.0, 7.7)	0.13
AQLQ score	242 vs. 230	0.0 (−0.2, 0.2)	0.91
ACQ-6 score	254 vs. 243	0.0 (−0.2, 0.2)	0.97
Total asthma symptom score	215 vs. 223	0.0 (−0.1, 0.2)	0.65

AAER, annual asthma exacerbation rate; ACQ-6, Asthma Control Questionnaire-6; AQLQ, standardised Asthma Quality of Life Questionnaire; BD, bronchodilator; CI, confidence interval; FeNO, fractional exhaled nitric oxide; FEV₁, forced expiratory volume in one second; Q2W, every two weeks; Q4W, every four weeks; Tralo, tralokinumab

*The STRATOS 1 placebo treatment group is a combined treatment group (placebo Q2W + placebo Q4W) where the two placebo cohorts were given weights proportional to the number of participants in each cohort

[†]P values for STRATOS 1 biomarker analyses are nominal and were not adjusted for multiplicity

Table S18: Annual asthma exacerbation rate at Week 52 stratified by baseline serum periostin concentration in STRATOS 1 (Full Analysis Set)

	n	AAER (95% CI)	Rate ratio (95% CI)	P value*
POSTN-high[†]				
Combined placebo [‡]	330	0.6 (0.5, 0.8)		
Tralo Q2W	329	0.6 (0.4, 0.7)	0.9 (0.7, 1.2)	0.33
Tralo Q4W	333	0.5 (0.4, 0.6)	0.8 (0.6, 1.1)	0.17
POSTN-low[§]				
Combined placebo [‡]	70	0.5 (0.3, 0.7)		
Tralo Q2W	69	0.6 (0.4, 1.0)	1.4 (0.7, 2.6)	0.35
Tralo Q4W	71	0.7 (0.5, 1.1)	1.5 (0.8, 2.8)	0.23

CI, confidence interval; POSTN, periostin; Q2W, every two weeks; Q4W, every four weeks; Tralo, tralokinumab

*P values for STRATOS 1 biomarker analyses are nominal and were not adjusted for multiplicity

[†]≥16.44 ng/mL

[‡]The STRATOS 1 placebo treatment group is a combined treatment group (placebo Q2W + placebo Q4W) where the two placebo cohorts were given weights proportional to the number of participants in each cohort

[§]<16.44 ng/mL

Table S19: Overall safety results during the treatment period* in the STRATOS 1 tralokinumab Q4W group (Safety Analysis Set)

	Combined placebo[†] (N=400)	Tralo Q4W (N=404)
Any AE, n (%)	243 (60.8)	278 (68.8)
Any treatment-related AE n (%)	32 (8.0)	55 (13.6)
Any AE with outcome of death, n (%)	0	1 (0.2)
Any SAE, n (%)	48 (12.0)	39 (9.7)
AEs leading to discontinuation, n (%)	3 (0.8)	13 (3.2)
AEs with $\geq 5\%$ frequency in any arm (safety population) [‡] , n (%)		
Asthma	54 (13.5)	48 (11.9)
Nasopharyngitis	36 (9.0)	47 (11.6)
Upper respiratory tract infection	36 (9.0)	48 (11.9)
Headache	17 (4.3)	31 (7.7)
Bronchitis	19 (4.8)	23 (5.7)
Injection site erythema	0	12 (3.0)

AE, adverse event; Q2W, every two weeks; Q4W, every four weeks; SAE, serious adverse event; Tralo, tralokinumab

*Includes AEs with an onset date $\geq$ the first day of trial treatment and $\leq$ (the last day of trial treatment + dosing frequency)

[†]The STRATOS 1 placebo treatment group is a combined treatment group (placebo Q2W + placebo Q4W) where the two placebo cohorts were given weights proportional to the number of participants in each cohort

[‡]In descending order of $\geq 5\%$ frequency in the STRATOS 1 combined placebo arm; MedDRA preferred term (version 19.1)

Table S20: AEs leading to discontinuation in STRATOS 1 and 2 (Safety Analysis Sets)

Any AE leading to discontinuation, n (%)	STRATOS 1			STRATOS 2	
	Combined placebo* (N=400)	Tralo Q2W (N=398)	Tralo Q4W (N=404)	Placebo (N=422)	Tralo Q2W (N=425)
Injection site erythema	0	6 (1·5)	2 (0·5)	0	2 (0·5)
Injection site reaction	0	3 (0·8)	3 (0·7)	0	4 (0·9)
Injection site pruritus	0	2 (0·5)	1 (0·2)	0	0
Injection site extravasation	0	2 (0·5)	0	0	1 (0·2)
Injection site pain	0	2 (0·5)	0	1 (0·2)	0
Injection site rash	0	2 (0·5)	0	0	0
Asthma	1 (0·3)	1 (0·3)	1 (0·2)	2 (0·5)	1 (0·2)
Basal cell carcinoma	0	1 (0·3)	1 (0·2)	0	0
Pulmonary embolism	0	1 (0·3)	1 (0·2)	0	0
Diarrhoea infectious	0	1 (0·3)	0	0	0
Pneumonia	0	1 (0·3)	0	1 (0·2)	0
Basal cell carcinoma	0	1 (0·3)	1 (0·2)	0	0
Cervix carcinoma	0	1 (0·3)	0	0	0
Uterine cancer	1 (0·3)	0	0	0	0
Ischaemic stroke	0	1 (0·3)	0	0	0
Circulatory collapse	0	1 (0·3)	0	0	0
Swollen tongue	0	1 (0·3)	0	0	0
Hepatic function abnormal	0	1 (0·3)	0	0	0
Erythema	0	1 (0·3)	0	0	2 (0·5)
Pruritus	0	1 (0·3)	0	0	2 (0·5)
Rash	0	1 (0·3)	0	0	0
Rash pruritic	0	1 (0·3)	0	0	0
Alopecia	1 (0·3)	0	0	0	0
Administration site reaction	0	1 (0·3)	0	0	0
Injection site hypersensitivity	0	1 (0·3)	0	0	1 (0·2)
Injection site papule	0	1 (0·3)	0	0	0
Injection site swelling	0	0	1 (0·2)	0	0
Injection site urticaria	0	1 (0·3)	0	0	0
Acarodermatitis	0	0	0	1 (0·2)	0
Urosepsis	0	0	0	0	1 (0·2)
Hepatitis A	0	0	0	1 (0·2)	0
Rectal cancer	0	0	0	1 (0·2)	0
Anaemia	0	0	0	0	1 (0·2)
Eosinophilic granulomatosis with polyangiitis	0	0	1 (0·2)	1 (0·2)	0
Eye pruritus	0	0	0	1 (0·2)	0
Cardiac failure	0	0	0	1 (0·2)	0
Cor pulmonale chronic	0	0	0	1 (0·2)	0
Hypertension	0	0	0	1 (0·2)	0
Respiratory failure	0	0	0	1 (0·2)	0
Oropharyngeal pain	0	0	0	1 (0·2)	0
Atelactasis	0	1 (0·3)	0	0	0
Dyspnoea	0	1 (0·3)	0	0	0
Pharyngeal oedema	0	1 (0·3)	0	0	0
Throat irritation	0	1 (0·3)	0	0	0
Wheezing	0	1 (0·3)	0	1 (0·2)	0
Abdominal distension	0	0	0	0	1 (0·2)
Melaena	0	0	0	0	1 (0·2)
Hepatic steatosis	0	0	0	0	1 (0·2)
Liver injury	0	0	0	1 (0·2)	0
Urticaria	0	0	0	1 (0·2)	2 (0·5)
Skin lesion	0	0	0	0	1 (0·2)

Vitiligo	0	0	0	0	1 (0·2)
Myalgia	0	0	0	0	1 (0·2)
Local reaction	0	0	0	0	2 (0·5)
Administration site pruritus	0	0	0	0	1 (0·2)
Application site reaction	0	0	0	0	1 (0·2)
Injection site inflammation	0	0	0	0	1 (0·2)
Puncture site erythema	0	0	0	0	1 (0·2)
Puncture site reaction	0	0	0	0	1 (0·2)
Alanine aminotransferase increased	0	0	0	0	2 (0·5)
Aspartate aminotransferase increase	0	0	0	0	2 (0·5)
Liver function test abnormal	0	0	0	0	1 (0·2)
Liver function test increased	0	0	0	0	1 (0·2)
Transaminases increased	0	0	0	0	1 (0·2)
Oral herpes	0	0	1 (0·2)	0	0
Trachetitis	0	0	1 (0·2)	0	0
Eosinophilia	0	0	1 (0·2)	0	0
Hypothyroidism	0	0	1 (0·2)	0	0
Cerebrovascular disease	0	0	1 (0·2)	0	0
Headache	0	0	1 (0·2)	0	0
Hypoesthesia	0	0	1 (0·2)	0	0
Haematuria	0	0	1 (0·2)	0	0

AE, adverse event; Q2W, every two weeks; Q4W, every four weeks; Tralo, tralokinumab

*The STRATOS 1 placebo treatment group is a combined treatment group (placebo Q2W + placebo Q4W) where the two placebo cohorts were given weights proportional to the number of participants in each cohort

Table S21: Immunogenicity of tralokinumab in STRATOS 1 and 2 (Safety Analysis Set)

	Tralo Q2W vs. placebo*, n	Tralo Q4W vs. placebo*, n
STRATOS 1	373 vs. 374	382 vs. 374
ADA incidence [†] , n (%)	3 (0·8) vs. 3 (0·8)	2 (0·5) vs. 3 (0·8)
ADA positive at baseline, n (%)	4 (1·1) vs. 7 (1·9)	5 (1·3) vs. 7 (1·9)
ADA positive post-baseline, n (%)	3 (0·8) vs. 8 (2·1)	3 (0·8) vs. 8 (2·1)
Persistent ADA positive [‡] , n (%)	2 (0·5) vs. 7 (1·9)	2 (0·5) vs. 7 (1·9)
Transient ADA positive [§] , n (%)	1 (0·3) vs. 1 (0·3)	1 (0·3) vs. 1 (0·3)
Treatment-boosted ADA , n (%)	0 vs. 1 (0·3)	0 vs. 1 (0·3)
Neutralising antibody positive at any visit, n (%)	5 (1·3) vs. 4 (1·1)	5 (1·3) vs. 4 (1·1)
STRATOS 2[¶]	405 vs. 394	–
ADA incidence [†] , n (%)	5 (1·2) vs. 3 (0·8)	–
ADA positive at baseline, n (%)	2 (0·5) vs. 5 (1·3)	–
ADA positive post-baseline, n (%)	5 (1·2) vs. 6 (1·5)	–
Persistent ADA positive [‡] , n (%)	3 (0·7) vs. 6 (1·5)	–
Transient ADA positive [§] , n (%)	2 (0·5) vs. 0	–
Treatment-boosted ADA , n (%)	0 vs. 0	–
Neutralising antibody positive at any visit, n (%)	5 (1·2) vs. 2 (0·5)	–

ADA, anti-drug antibody; Q2W, every two weeks; Q4W, every four weeks; Tralo, tralokinumab

*The STRATOS 1 placebo treatment group is a combined treatment group (placebo Q2W + placebo Q4W) where the two placebo cohorts were given weights proportional to the number of participants in each cohort

[†]Incidence ADA = sum of treatment-induced post-baseline ADA positive and treatment-boosted ADA

[‡]Positive at ≥ 2 post-baseline assessments (with ≥ 16 weeks between first and last positive) or positive at last post-baseline assessment

[§]Having ≥ 1 ADA positive assessment post-baseline but not fulfilling the criteria for persistently positive

^{||}Baseline positive ADA titre boosted 4-fold or greater after drug administration

[¶]Data available for all-comers only

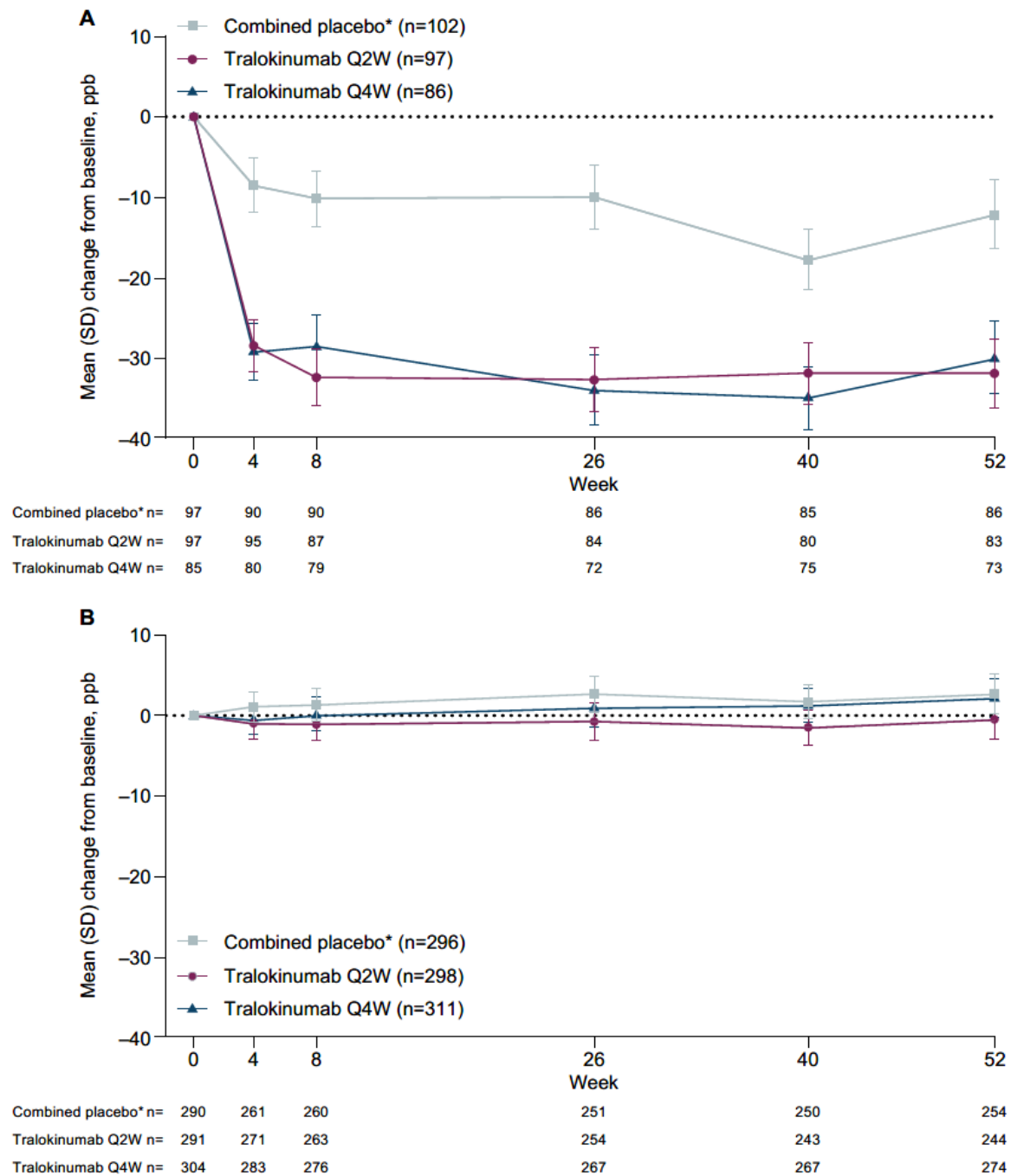
Table S22: Serum concentrations of tralokinumab during the treatment period in STRATOS 1 and 2 (Pharmacokinetics Analysis Set)

Timepoint	Tralo Q2W n (n ≤ LLOQ)	Tralo concentration (trough), µg/mL, geomean (CV%*)	Tralo Q4W n (n ≤ LLOQ)	Tralo concentration (trough), µg/mL, geomean (CV%*)
STRATOS 1				
Baseline	394 (390)	NC	401 (396)	NC
Week 4	351 (10)	34.9 (199.7)	352 (14)	13.2 (188.5)
Week 8	350 (7)	56.1 (160.6)	362 (5)	19.4 (111.7)
Week 26	340 (7)	61.3 (180.1)	357 (9)	34.1 (187.9)
Week 52	328 (7)	56.3 (172.3)	348 (12)	18.6 (219.3)
STRATOS 2				
All-comers				
Baseline	410 (401)	NC	–	–
Week 2	396 (18)	21.7 (248.9)	–	–
Week 8	385 (12)	53.3 (220.3)	–	–
Week 26	373 (10)	50.3 (264.7)	–	–
Week 56 (follow up)	371 (33)	12.5 (671.9)	–	–
FeNO-high (≥37 ppb)				
Baseline	108 (106)	NC	–	–
Week 2	103 (3)	24.0 (172.5)	–	–
Week 8	105 (3)	55.9 (206.5)	–	–
Week 26	99 (1)	58.4 (145.3)	–	–
Week 56 (follow up)	96 (7)	12.4 (591.3)	–	–

CV, coefficient of variation; FeNO, fractional exhaled nitric oxide; geomean, geometric mean; LLOQ, lower limit of quantification; NC, not calculable; Q2W, every two weeks; Q4W, every four weeks, Tralo, tralokinumab

*Calculated from log-transformed data

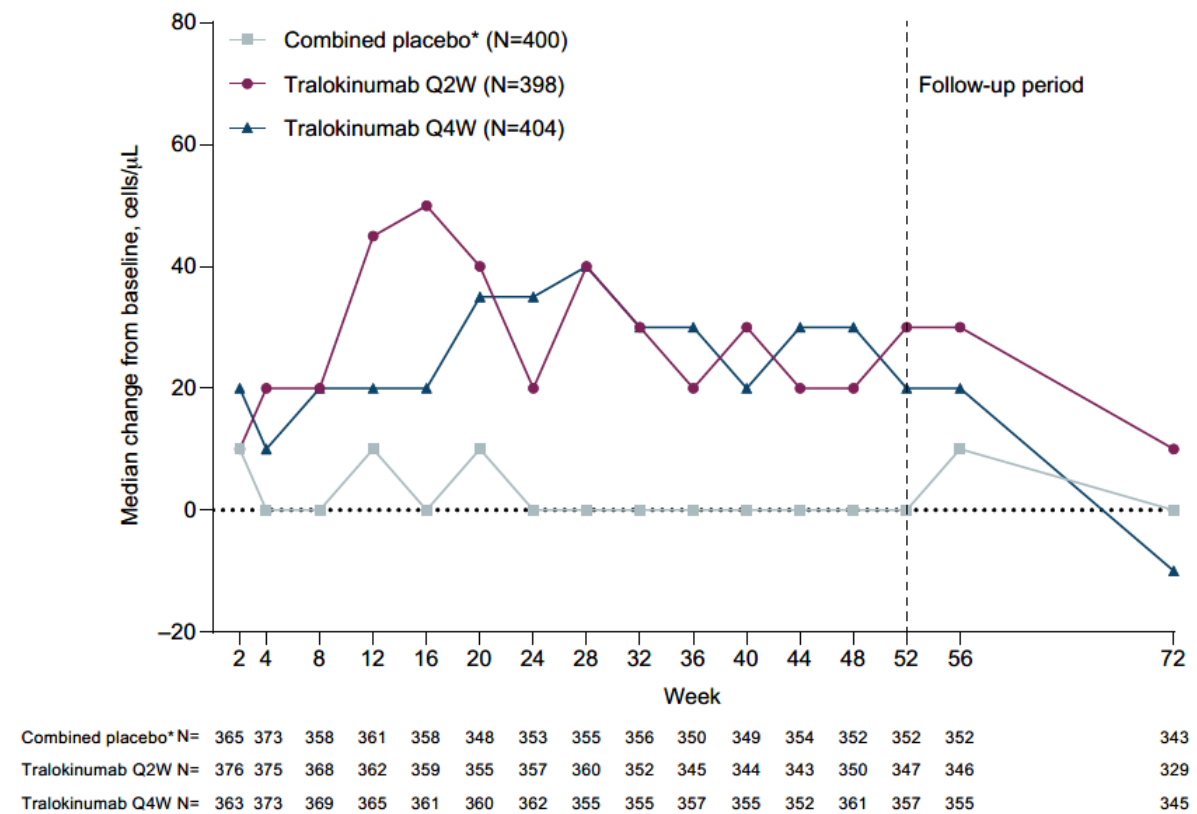
Figure S1: Mean change from baseline in FeNO concentration over time in STRATOS 1 in the (A) FeNO-high (≥ 37 ppb at baseline), and (B) FeNO-low (< 37 ppb at baseline) populations (Full Analysis Set)



FeNO, fractional exhaled nitric oxide; Q2W, every two weeks; Q4W, every four weeks

*The STRATOS 1 placebo treatment group is a combined treatment group (placebo Q2W + placebo Q4W) where the two placebo cohorts were given weights proportional to the number of participants in each cohort

Figure S2: Median change from baseline in blood eosinophil count over time in STRATOS 1 (Full Analysis Set)



Q2W, every two weeks; Q4W, every four weeks

*The STRATOS 1 placebo treatment group is a combined treatment group (placebo Q2W + placebo Q4W) where the two placebo cohorts were given weights proportional to the number of participants in each cohort

Figure S3: Median change from baseline in blood eosinophil count over time in STRATOS 2 (Full Analysis Set)

