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

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Abstract

Background: STRATOS 1 and 2 (NCT02161757, NCT02194699) evaluated tralokinumab, an anti–interleukin (IL)-13 human monoclonal antibody, for the treatment of severe, uncontrolled asthma.

Methods: These randomised, double-blind, parallel-group, placebo-controlled, phase 3 trials enrolled participants aged 12–75 years with severe asthma, inadequately controlled despite inhaled corticosteroids (≥500 µg/day fluticasone or equivalent) plus long-acting $beta_2$ agonist (but not oral corticosteroids). Participants received subcutaneous tralokinumab 300 mg every 2 (Q2W), or 4 (Q4W) weeks, or matching placebo. The primary endpoint for both trials was the annualised asthma exacerbation rate (AAER) reduction at Week 52. STRATOS 1 attempted to identify a biomarker-positive population with enhanced tralokinumab benefit, which was then tested in STRATOS 2.

Findings: In the STRATOS 1 all-comers population, tralokinumab Q2W (N=398) did not significantly reduce AAER versus placebo (N=400; 7·0% reduction [95% CI: −20·8%, 28·4%]; rate ratio [95% CI]: 0·93 [0·72, 1·21] *P*=0·59). Baseline FeNO (≥37 ppb) was identified as the preferred biomarker; in FeNO-high participants, tralokinumab Q2W (n=97) reduced AAER by 44·0% (95% CI: 6·0%, 66·0%; rate ratio [95% CI]: 0·56 [0·34, 0·94] *P*=0·028) versus placebo (n=102), and improved FEV_1 and asthma control. In the STRATOS 2 FeNO-high population, tralokinumab Q2W (n=108) did not significantly improve AAER versus placebo (n=121) (15·8% reduction [95% CI: −33·7%, 47·0%]; rate ratio [95% CI]: 0·84 [0·53, 1·34] *P*=0·47). The safety profile was consistent with previous tralokinumab trials.

Interpretation: Tralokinumab reduced AAER in participants with severe asthma with baseline FeNO ≥37 ppb in STRATOS 1, but not STRATOS 2. These inconsistent effects upon AAER do not support a key role for IL-13 in severe asthma exacerbations.

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Research in context

Evidence before this trial: PubMed was searched for reports of clinical trials investigating anti–interleukin (IL)-13 monoclonal antibodies for the treatment of asthma in humans published between January 1st 2008 and January 1st 2018. We used the search terms "asthma" AND "interleukin-13" AND "antibody" and filtered for clinical trial reports, which yielded 17 results. There were 12 trials reporting results for five biologics that inhibit IL-13 signalling. Lebrikizumab, the only anti–IL-13 biologic with published phase 3 trial results to date, failed to demonstrate a consistent, statistically significant reduction in asthma exacerbations in a biomarker-positive population with uncontrolled asthma.

Added value of this trial: The two clinical trials reported here are the first to assess tralokinumab efficacy and safety in phase 3 trials. In STRATOS 1, tralokinumab 300 mg Q2W or Q4W did not significantly reduce asthma exacerbation rates in an all-comers population of participants with severe, uncontrolled asthma compared with placebo. A biomarker predictive of enhanced tralokinumab efficacy (baseline fractional exhaled nitric oxide [FeNO] ≥37 ppb) was identified based on data from STRATOS 1 and assessed in STRATOS 2. Tralokinumab Q2W was unable to significantly reduce exacerbation rates in the all-comers population (similarly to STRATOS 1) and 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 forced expiratory volume in 1 second 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 current evidence that IL-13 blockade alone is insufficient to reduce asthma exacerbations in people with severe, uncontrolled asthma, but may improve lung function. In contrast, benefits have been observed in the management of severe asthma by targeting IL-13 and IL-4 concurrently.

Introduction

Asthma, a complex, heterogeneous, chronic inflammatory airway disorder, affects approximately 315 million people worldwide.[1] The clinical presentation of asthma can vary widely from exercise-induced bronchospasm to severe disease, which is present in up to 10% of people with asthma.[2] Severe asthma may remain uncontrolled despite treatment with high-dosage inhaled corticosteroids (ICS) plus long-acting beta$_2$ agonists (LABA) and other controller medications.[3] Indeed, people with severe asthma have an increased likelihood of experiencing 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 disease is uncontrolled) consume the majority of asthma-related healthcare resources.[3-5]

In animal models, multiple studies have demonstrated that interleukin-13 (IL-13), a type-2 pleiotropic cytokine, can induce airway hyperresponsiveness, goblet cell metaplasia, and lung eosinophilia, which contribute to the pathophysiology of asthma.[6,7] IL-13 has also been demonstrated to contribute to airway remodelling via transforming growth factor (TGF)-β–mediated collagen deposition.[8,9] Additionally, blockade of IL-13 in ovalbumin-sensitised mice (unlike blockade of the closely related cytokine IL-4) prevents development of airway hyperresponsiveness.[6,10] Subsequent trials in humans support a role for IL-13 in asthma, with bronchial biopsies demonstrating an increased concentration of IL-13 in participants with both atopic and non-atopic disease, compared with healthy individuals.[11-13] Therefore, anti–IL-13 agents may have clinical utility for treatment of severe asthma.

Tralokinumab, an immunoglobulin (Ig) G_4 monoclonal human antibody that potently and specifically neutralises IL-13 by preventing its interaction with the IL-13 receptor α1 and α2 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 (NCT00873860[15] and NCT01402986[16]), although tralokinumab did not improve asthma control or reduce exacerbations in the overall population in these trials. In a *post-hoc* analysis of the phase 2b trial, tralokinumab treatment was associated with a trend towards improvement in the

annualised asthma exacerbation rate (AAER) versus placebo, as well as an enhanced forced expiratory volume in one second (FEV_1) response, in a subgroup of participants with post-bronchodilator (post-BD) FEV_1 reversibility ≥12% and not taking regular OCS.[16] The observations in this subgroup were carried forward to define the participant population for the phase 3 trials. Further *post-hoc* analyses of the phase 2b data suggested participants from this subgroup who also had evidence of IL-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 subgroup with enhanced tralokinumab efficacy to be studied in phase 3 trials.

Tralokinumab was investigated in late stage clinical development in the ATMOSPHERE programme. This consisted of five trials: the pivotal phase 3 clinical trials, STRATOS 1 (NCT02161757) and 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 to assessing the efficacy and safety of tralokinumab treatment for severe asthma. Two pivotal phase 3 trials with identical inclusion and exclusion criteria and endpoints (STRATOS 1 and STRATOS 2) were performed in parallel but with staggered analyses. The first trial, STRATOS 1, assessed the effect of tralokinumab on reducing the AAER in the overall trial (all-comers) population and identified a biomarker subgroup with an enhanced tralokinumab benefit. 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. In this paper we report the findings of the STRATOS 1 and 2 trials.

Methods

Trial designs and participants

These were two randomised, double-blind, parallel-group, placebo-controlled, global phase 3 clinical trials to determine the efficacy and safety of tralokinumab 300 mg in participants with severe, uncontrolled asthma. STRATOS 1 and 2 enrolled participants who were 12–75 years of age with physician-diagnosed asthma for at least a year prior to enrolment, requiring medium–high dosage ICS (total daily dose ≥500 µg fluticasone or equivalent) and a LABA for at least three months prior to Visit 1; the 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 (during which a post-BD FEV_1 reversibility of ≥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.[16]

The STRATOS 1 and 2 trials were conducted 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 from the journal website and https://astrazenecagrouptrials.pharmacm.com/. STRATOS 1 and 2 were registered with ClinicalTrials.gov (STRATOS 1, NCT02161757; STRATOS 2, NCT02194699) and the EU Clinical Trials Register (STRATOS 1, EudraCT 2013-005614-35; STRATOS 2, EudraCT 2013-005615-27).

Randomisation, dose justification, 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 versus adolescents) (Tables S1 and S2). The periostin cut-off for stratification was chosen based on phase 2b results, where participants with periostin concentrations

above the baseline median demonstrated 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 µg fluticasone propionate dry powder or equivalent) and a LABA throughout the treatment period.

In STRATOS 1, participants were randomised 2:1 to tralokinumab 300 mg or placebo administered subcutaneously (SC) every two weeks (Q2W) or every four weeks (Q4W) for 52 weeks. In STRATOS 2, participants were randomised 1:1 to receive tralokinumab 300 mg or placebo SC Q2W. Previous pharmacokinetic and pharmacodynamic modelling analyses indicated that near-maximal improvements in pre-bronchodilator (pre-BD) FEV_1 were seen with tralokinumab 300 mg SC Q2W, justifying its selection for phase 3 trials.[19] Pre-BD FEV_1 was chosen as the endpoint in this modelling analysis as tralokinumab did not significantly reduce AAER in the phase 2b trial.[16] The tralokinumab 300 mg Q4W regimen 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 carried out in blocks using 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 unblinded team member not involved in the management of the participants to maintain blinding. The participants and trial site personnel assessing outcomes were unaware of the treatment allocation.

Outcomes

The primary objective in STRATOS 1 was to assess the effect of tralokinumab Q2W versus placebo on the AAER at Week 52 in the all-comers population. If this objective was met, the effect of tralokinumab Q4W versus placebo on the AAER at Week 52 for the all-comers population was tested. An exploratory objective in STRATOS 1 was to identify a biomarker predictive of enhanced response to tralokinumab to inform the analysis of STRATOS 2. The

pre-defined biomarkers assessed included blood eosinophils, fractional exhaled nitric oxide (FeNO), serum DPP-4 and periostin, and total serum IgE.

After the STRATOS 1 results became available, the primary objective for STRATOS 2 was amended to assess the effect of tralokinumab Q2W versus placebo on the AAER at Week 52 in the biomarker-positive population identified in STRATOS 1 (primary population), and the all-comers population became a secondary population. In both trials, asthma exacerbations were defined as a worsening of asthma that led to use of systemic corticosteroids for ≥3 days, an emergency department visit due to asthma that required systemic corticosteroid use, or hospitalisation due to asthma.

Key secondary objectives assessed in STRATOS 1 and 2 were the percentage change in pre-BD FEV_1 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 objectives for both STRATOS 1 and 2 were: time to first exacerbation; proportion of participants with ≥1 exacerbation; AAER associated with emergency department visits, urgent care visits or hospitalisation; post-BD FEV_1; 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 will focus on the tralokinumab Q2W regimens in STRATOS 1 and 2; tralokinumab Q4W results from STRATOS 1 are included in the supplementary appendix.

In both trials, adverse events (AEs), including serious AEs (SAEs) and AEs 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 collected. An independent Data and Safety Monitoring

Board regularly reviewed unblinded safety data during both trials and monitored the safety of the adolescent and adult participants throughout the double-blind treatment period. An endpoint adjudication committee evaluated, in blinded fashion, all deaths, hospitalisations, emergency department visits, and urgent care visits as to whether they were asthma-related. This committee also reviewed all malignancies and cardiovascular/cerebrovascular events. All AEs identified as occurring within 72 hours of investigational product administration and possibly representing anaphylactic events were reviewed in blinded fashion by an independent allergist using Sampson's criteria.[20]

Statistical analysis

In STRATOS 1, a total sample size of 1,140 was considered 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 Q2W and Q4W groups). In STRATOS 2, a total sample size of 770 participants was considered sufficient. The sample size calculations for both trials used an assumed AAER in the placebo group of 0·8. Assuming a uniform loss of 15% in both trials, these estimates were expected to produce ≥90% power for treatment effects down to 32% and 37% AAER in STRATOS 1 and 2, respectively. At the time the STRATOS 2 protocol was amended to make the FeNO-high subgroup the primary population, it was estimated that, if 25% of studied participants fulfilled the biomarker-positive criteria, a true AAER reduction of 50% would have a power of 80% to demonstrate superiority using a 5% significance level for the biomarker-positive subgroup.

In both trials the AAER was assessed using 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 employed hierarchical testing strategies to provide strong global control of Type I error; these strategies are described in a

separate publication.[18] The statistical methods used to assess the key secondary objectives are provided in the supplementary appendix.

All efficacy analyses for both trials were performed using an intention-to-treat approach based on the Full Analysis Set (FAS). The FAS in both STRATOS 1 and 2 included all participants randomised and receiving any investigational product, and was limited to those who had the potential to receive investigational products for 52 weeks in STRATOS 2. Biomarker-positive participants met the criteria to be included in the FAS and also displayed biomarker concentrations greater than or equal to the cut-off identified in STRATOS 1. In both trials, any participant who received investigational product was included in the Safety Analysis Set and was categorised by the treatment received. The Pharmacokinetic (PK) Analysis Set included all participants in the FAS who received tralokinumab; it included PK blood samples that were assumed not to be affected by factors such as protocol deviations (e.g., disallowed medication, or incorrect study medication received).

A biomarker analysis plan was developed to statistically assess STRATOS 1 in order to identify baseline biomarker(s) likely to predict tralokinumab efficacy and define a biomarker population in which there was a potential enhanced treatment effect of tralokinumab; this 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 based on AAER using negative binomial and generalised additive models, and the Subgroup Identification based on Differential Effect Search (SIDES) algorithm.[21,22] The SIDES analysis was supported by robustness and sensitivity checks (including assessment of consistency with regard to secondary variables) that employed bootstrapping and permutation approaches in order to mitigate risks associated with subgroup identification, such as false discovery, overfitting and overoptimistic belief in the subgroup. The potential predictive properties of the biomarkers were also assessed based on the key secondary endpoints of percent change from baseline in pre-BD FEV_1 and change from baseline in ACQ-6, AQLQ and asthma symptom scores. Methodology for the sample size estimates[18]

has been previously reported; the Statistical Analysis Plan is available on the journal website and https://astrazenecagrouptrials.pharmacm.com/.

Role of the funding source

The funder of the trial contributed to trial design, data collection, data analysis, data interpretation, and writing of the report. All authors had full access to all data and the corresponding author had final responsibility for the decision to submit for publication.

Results

Participant demographics

STRATOS 1 was conducted between 13 June 2014 and 28 February 2017; 2,248 participants were enrolled and 1,669 of these entered the run-in period. Of the 579 participants who did not enter the run-in period, 534 did not meet the inclusion/exclusion criteria. A total of 1,207 participants were randomised; 462 participants failed screening, primarily due to unmet inclusion/exclusion criteria. In total, 1,047 participants (86·7% [1,047/1,207) completed treatment (Figure 2A). STRATOS 2 was conducted between 30 October 2014 and 21 September 2017; 1,696 participants were enrolled, of whom 1,163 entered the run-in. A total of 856 participants were randomised, and 732 participants completed treatment (85·5% [732/856]) (Figure 2B). In total across both trials, 533 participants did not enter the run-in and 307 were not randomised. Participant demographics were similar across the groups in both STRATOS trials (Tables 1, 2 and S3).

STRATOS 1 efficacy results

In STRATOS 1, the primary endpoint was not met in the all-comers population; the AAER reduction at Week 52 with tralokinumab 300 mg Q2W compared with placebo (95% CI) was 7·0% (−20·8%, 28·4%), with a rate ratio (95%CI) of 0·93 (0·72, 1·21), *P*=0·59 (Table 3). As per protocol, the hierarchical testing was stopped and all subsequent results were declared non-significant. There were similar findings for the tralokinumab Q4W group (Table S4).

At Week 52, the percent change from baseline in pre-BD FEV_1 was nominally significant for the tralokinumab Q2W group compared with placebo (difference in least square means [95% CI]): 6·0% (2·3%, 9·7%), *P*=0·0014 (Table 4). This translated to clinically meaningful changes (>100 mL)[23] in FEV_1 between the tralokinumab Q2W group (265 mL) and placebo (153 mL) (Figure 3A). The change from baseline in ACQ-6 score at Week 52 also achieved nominal statistical significance for the tralokinumab Q2W group compared with placebo (difference in least squares mean [95% CI]): −0·2 (−0·3, 0·0), *P*=0·022 (Table 4); this

difference was not clinically meaningful. There were no relevant findings in the other secondary endpoints (Table 4; Tables S5–S15).

STRATOS 1 biomarker analyses

The distribution of each of the five biomarker concentrations was similar at baseline across the treatment groups in the FAS. Initial interaction testing (nominally significant interaction; $P<0{\cdot}10$) suggested that there was no predictive relationship for tralokinumab efficacy with baseline blood eosinophils (Table S16), serum DPP-4, or total serum IgE. Serum periostin (as a continuous variable) demonstrated a nominally significant interaction in the tralokinumab Q4W group ($P=0{\cdot}090$) but not in the tralokinumab Q2W group ($P=0{\cdot}48$). There was a nominally significant interaction effect in both tralokinumab treatment groups for FeNO (as a continuous variable); $P=0{\cdot}038$ and $P=0{\cdot}086$ for the Q2W and Q4W groups, respectively. Further analyses identified a subgroup of participants in the Q2W treatment group with baseline FeNO ≥37 ppb (FeNO-high) as having a nominally significant ($P=0{\cdot}028$) AAER reduction of 44·0% (95% CI: 6·0%, 66·0%), with a rate ratio of (95% CI) 0·56 (0·34, 0·94) (Table 3); there was no significant AAER reduction with tralokinumab in participants with baseline FeNO <37 ppb (FeNO-low) (Table 3).

In the FeNO-high subgroup there was a nominally significant increase from baseline (95% CI) in pre-BD FEV_1 with tralokinumab Q2W treatment versus placebo of 12·8% (5·3%, 20·3%), $P<0{\cdot}001$ (Table 4). This translated to a clinically meaningful improvement in absolute FEV_1 of approximately 340 mL by Week 8 of tralokinumab initiation, representing an approximate 200 mL greater increase from baseline than placebo that was maintained up to Week 52. Nominally significant improvements from baseline were also observed in both AQLQ (apparent within 12–16 weeks) and ACQ-6 (apparent by 26 weeks) scores with tralokinumab Q2W in the FeNO-high subgroup versus placebo; no nominally significant differences in total asthma symptom score were observed at Week 52 (Table 4). There were minimal differences between the treatment arms versus placebo for pre-BD FEV_1, AQLQ, ACQ-6, and total asthma symptom scores for the FeNO-low subgroup (Table S17).

The FeNO-high subgroup demonstrated a clinically meaningful decrease in FeNO concentrations within 4–8 weeks of tralokinumab initiation (Figure S1). At Week 8, the estimated difference in FeNO change from baseline between tralokinumab and placebo was −20·2 ppb (95% CI: –24·5, –15·9; nominal *P*<0·001). Minimal changes in FeNO concentrations were seen in the FeNO-low subgroup at Week 52. Aside from the nominally significant interaction with tralokinumab Q4W, periostin was not able to predict tralokinumab efficacy (Table S18). Based on these analyses, baseline FeNO was the biomarker selected for investigation in STRATOS 2 at a cut-off of 37 ppb (FeNO-high).

STRATOS 2 efficacy results

In STRATOS 2, a significant interaction between FeNO (as a continuous variable) and 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 placebo (AAER reduction [95% CI]: 15·8% [−33·7%, 47·0%]; rate ratio [95% CI]: 0·84 [0·53, 1·34]; *P*=0·47) (Table 3). There was also no difference between treatment arms in reduction of AAER in the all-comers population (AAER reduction [95% CI]: −3·1% [−31·5%, 19·1%]; rate ratio [95% CI]: 1·03 [0·81, 1·31]); *P*=0·80) (Table 3) or the FeNO-low population (AAER reduction [95% CI]: –13·0 % [–50·0%, 15·0%]; rate ratio [95% CI]: 1·13 [0·85, 1·50]; *P*=0·41) (Table 3).

A clinically meaningful numerical improvement in pre-BD FEV_1 from baseline at Week 52 was observed in the FeNO-high subgroup in response to tralokinumab, but this was not statistically significant when compared with placebo because of a large placebo effect; least squares mean difference (tralokinumab vs. placebo [95% CI]): 1·9% (−5·2%, 8·9%), *P*=0·60 (Table 4). This translated to an absolute change in pre-BD FEV_1 from baseline of 320 mL with tralokinumab and 253 mL with placebo. No significant nor clinically meaningful improvements were observed in AQLQ or total asthma symptom scores in the FeNO-high population versus placebo in STRATOS 2; however, significant improvements in ACQ-6 were demonstrated (Table 4). There were also no significant differences between

tralokinumab and placebo in any key secondary endpoints in the all-comers population (Table 4) or FeNO-low population (Table S17). There were no relevant findings in the other secondary endpoints (Table S5–S15).

STRATOS 1 and 2 safety results

The safety results from STRATOS 1 and 2 were similar and the Q2W data are reported together (Table 5). Safety results for the tralokinumab Q4W group in STRATOS 1 are reported in Table S19. In the STRATOS 1 Safety Analysis Set (all treatment groups), 66·5% (799/1,202) of participants reported AEs during the treatment period. A greater percentage of participants experienced AEs in the tralokinumab Q2W group (69·8% [278/398]) than combined placebo (61·3% [245/400]). In STRATOS 2, AEs were experienced at a similar rate between the placebo and tralokinumab groups (68·7% [290/422] and 72·0% [306/425], respectively). The most frequent AEs (reported by ≥5% of participants) in STRATOS 1 and STRATOS 2 were asthma, headache, and upper respiratory tract infection. The majority of AEs reported during the treatment period for both trials were mild or moderate in intensity and most AEs were not considered related to investigational product as judged by the investigator (Table 5). The most frequent AEs considered to be related to tralokinumab Q2W treatment in STRATOS 1 were injection site erythema (5·8% [23/398]), injection site pain (3·8% [15/398]), and injection site reaction (3·8% [15/398]). In STRATOS 2, the most frequent AEs considered to be related to tralokinumab were injection site reaction (4·9% [21/425]), injection site erythema (3·1% [13/425]), and application site reaction (1·4% [6/425]).

In STRATOS 1, 10·6% (127/1,202) of participants experienced an SAE during the treatment period (including those with an outcome of death); 40 and 48 SAEs were reported in the tralokinumab Q2W and placebo groups, respectively. The most common SAE was asthma, but fewer participants in the tralokinumab Q2W group (3·0% [12/398]) reported an SAE of asthma compared with placebo (6·3% [25/400]). Three SAEs were considered investigational product-related; pharyngeal oedema and swollen tongue (both in the same

participant receiving tralokinumab Q2W), and pneumonia (in one participant receiving placebo). In STRATOS 2, 8·7% (n=74/847) of participants experienced SAEs (including those with an outcome of death); 39 participants were in the placebo group and 35 were participants in the tralokinumab group. The most frequent of these were asthma (5·5% [23/422] placebo; 4·0% [17/425] tralokinumab Q2W) and pneumonia (0·7% [3/422] placebo; 0·9% [4/425] tralokinumab Q2W). Three SAEs were considered related to tralokinumab Q2W; fatal urosepsis (in 1 participant), and alanine aminotransferase/aspartate aminotransferase increased (both in the same participant).

Across both trials, there were a greater number of AEs leading to discontinuation in participants receiving tralokinumab than placebo (Table S17). In STRATOS 1, 3·7% (44/1,202) of participants in total experienced AEs leading to discontinuation. In total, 4·0% [16/398] of participants experienced injection-related AEs that led to discontinuation in the tralokinumab Q2W group compared with none in the placebo group. The most common AE leading to discontinuation in the tralokinumab Q2W group was injection-site erythema (1·5% [6/398]), followed by injection-site reaction (0·8% [3/398]). The most common AE leading to discontinuation in the STRATOS 2 Safety Analysis Set (tralokinumab Q2W versus placebo) was injection-site reaction (0·9% [4/425] vs. 0·0% [0/422]).

With regard to other safety topics of special attention, no cases of anaphylaxis attributable to tralokinumab were identified in either trial. There were similar rates of severe infections in the tralokinumab and placebo groups. One case of pulmonary tuberculosis occurred in the FeNO-high tralokinumab Q2W group in STRATOS 2, but there were no cases of helminthic or other opportunistic infections noted during the treatment period. Similar rates of malignancy and cardiovascular/cerebrovascular events were observed between the treatment groups in the trials.

There were no clinically meaningful changes in haematology, clinical chemistry, vital signs, and ECG readings in STRATOS 1 or 2. However, more tralokinumab-treated participants had blood eosinophil counts increase from ≤1,500 cells/μL at baseline to >1,500 cells/μL

during treatment versus placebo (5·0% [20/398] of the tralokinumab-treated versus 1·5% [6/400] of the placebo-treated participants in STRATOS 1; 4·0% [17/420] of the tralokinumab-treated versus 1·4% [6/417] placebo-treated participants in STRATOS 2). These increases resolved after treatment cessation (Figures S2 and S3). In STRATOS 1, there were two cases of AEs with a plausible relationship to increased eosinophil counts in participants in the tralokinumab 300 mg Q4W treatment group who had an increase in blood eosinophil count >1,500 cells/μL. One was a 46-year-old female who was hospitalised with eosinophilic granulomatosis with polyangiitis. This SAE led to discontinuation but was not attributed to the investigational product, as determined by the investigator. The other was a 48-year-old female diagnosed with allergic alveolitis. This AE was not considered by the investigator as related to investigational product and did not lead to investigational product discontinuation, and the participant made a full recovery following a course of corticosteroids. In STRATOS 2 there were also two cases of AEs associated with eosinophil counts >1,500 cells/μL; a 55-year-old female in the tralokinumab Q2W group had a skin rash diagnosed as hypersensitivity vasculitis, which was not related to treatment as determined by the investigator, and a 51-year-old female in the placebo Q2W group had an SAE of eosinophilic granulomatosis with polyangiitis that was also not considered related to treatment, but led to discontinuation of investigational product.

In STRATOS 1, 4 participants died during the trial; 1 participant died before randomisation, 2 participants died during the treatment period (tralokinumab Q2W, infectious diarrhoea; tralokinumab Q4W, cerebrovascular disease and asthma) and 1 participant died during the follow-up period (placebo, cardiac arrest). None of the deaths were considered related to investigational product. In STRATOS 2, 5 participants died; 2 participants died on treatment (asthma in 1 participant [placebo], and urosepsis and atrial fibrillation in 1 participant [tralokinumab Q2W]), and 3 participants died post-treatment (myocardial infarction in 1 participant [placebo], large intestinal obstruction, colon cancer, large intestine perforation, peritonitis, septic shock, and multiple organ dysfunction syndrome in 1 participant [placebo],

and unknown cause of death in 1 participant [placebo]). The fatal case of urosepsis was considered by the investigator to be related to tralokinumab Q2W.

Discussion

The current understanding of asthma suggests that it is 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-BD FEV_1 reversibility ≥12% and not taking regular OCS did appear to benefit from treatment, with further improvements in participants with high concentrations of biomarkers suggesting increased IL-13 pathway activation.[16] The tralokinumab STRATOS 1 and 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 determine if 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 Q2W (or Q4W) did not significantly reduce the AAER versus 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 statistically significant nor clinically meaningful. Interestingly, DPP-4 and periostin did not consistently predict response to tralokinumab therapy, despite these being identified as promising biomarkers of increased IL-13 activity in the previous 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 where tralokinumab improved pre-BD FEV_1 in the all-comers population.[16] Although there was also a clinically meaningful increase in pre-BD FEV_1 from baseline in the tralokinumab arm of the STRATOS 2 FeNO-high population, this did not reach statistical significance when compared with placebo. Similarly, the results from phase 3 trials of lebrikizumab, which also targets the IL-13 pathway, demonstrated a consistent improvement in FEV_1 in biomarker-positive participants but an inconsistent improvement in exacerbation rates.[24]

Taken together, these clinical data suggest that agents targeting the IL-13 pathway affect airway smooth muscle tone, which is consistent with previous preclinical data suggesting that IL-13 promotes airway hyperresponsiveness and smooth muscle contractility.[10,24] 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 upon airway inflammation.[25] In contrast, dupilumab, an anti–IL-4 receptor α monoclonal antibody that targets both IL-4 and IL-13 signalling, has demonstrated significant reductions in exacerbations in people with uncontrolled, persistent asthma.[26,27] It's possible this difference is because dupilumab is able to reduce airway inflammation whilst tralokinumab cannot, but there is currently no evidence that this is the case.

The five potential biomarkers of increased IL-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 IL-13, and may play a role in airway inflammation in asthma.[28-30] Results from the STRATOS and lebrikizumab phase 3 trials did not demonstrate consistent reductions in asthma exacerbations, and indicate that the ability of periostin to predict an enhanced response to anti–IL-13 therapies in asthma has been overestimated.[24] Serum IgE is used to determine the appropriate dosing of omalizumab (a biologic indicated for children and adults with severe allergic asthma [GINA step 5]),[31] and a trend towards AAER reduction 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/μL) in the tralokinumab phase IIb trial.[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–IL-5 therapies,[32] but they were not found to be a helpful biomarker for anti–IL-13 therapy in STRATOS 1 and 2. Finally, FeNO has been used as a biomarker in clinical trials for asthma,[26,33] as increased concentrations may help identify

type-2 inflammation and are associated with an increased risk of exacerbations and enhanced IL-13 activity through nitric oxide synthase.[34-36] Two agents that have shown to be effective at reducing asthma exacerbations have also been shown to reduce FeNO concentrations in clinical trials.[26,33] The STRATOS results demonstrate that tralokinumab reduces FeNO concentrations, with greater reductions in people with asthma and elevated baseline FeNO concentrations, and confirm that FeNO is the best predictive biomarker for anti–IL-13 therapy currently available.

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

In STRATOS 1 and 2, tralokinumab-treated participants had small increases in blood eosinophil counts from baseline, whereas placebo-treated participants did not; these findings are consistent with previous trials of tralokinumab.[15,16] These changes resolved after treatment, but more tralokinumab-treated participants had blood eosinophil counts increase from <1,500 eosinophils/μL at baseline to ≥1,500 eosinophils/μL during treatment. AEs relevant to an increased blood eosinophil count were similar in the tralokinumab and placebo treatment groups. Two of these participants experienced SAEs of eosinophilic granulomatosis with polyangiitis (one on tralokinumab Q4W in STRATOS 1, one on placebo in STRATOS 2). As the reported cases of this AE were the same in both the active drug and placebo arms, it may be cautiously suggested that a causal relationship with an anti–IL-13 mAb cannot be established. However, diligent surveillance of this AE must be performed in future trials in asthma with anti–IL-13 mAbs. A similar effect on blood eosinophils was also seen with lebrikizumab.[24] Dupilumab has been reported to increase blood eosinophil counts, but transiently and only in people with a baseline blood eosinophil count >300 cells/μL.[26] The

increase in blood eosinophils observed with anti–IL-13 therapy has been hypothesised to be the result of reduced recruitment of eosinophils to the lungs from the blood,[37] but the MESOS results have suggested this does not occur.[25] Interestingly, dupilumab is the only developmental biologic agent for the treatment of asthma that both reduces exacerbations and increases blood eosinophils.[26] Approved agents for severe asthma such as corticosteroids and the biologics omalizumab (anti-IgE), benralizumab (anti–IL-5 receptor α), mepolizumab and reslizumab (both anti–IL-5), reduce eosinophil counts during therapy and reduce exacerbation rates in participants with severe asthma.[38-42] Similarly, recent 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.[33]

One of the main strengths of this pair of trials was the staggered design allowing determination of a biomarker-positive subgroup in the first trial to be investigated in the later trial. In comparison with the phase 3 trials of lebrikizumab, which preselected the biomarker and the associated cut-off,[24] The sequential design of STRATOS 1 and 2 meant it would be less likely that an important biomarker effect would be missed. However, this design also had some potential limitations. The prevalence of FeNO-high participants in STRATOS 2 was 27·4% (229/837), which was consistent with STRATOS 1 but lower than originally intended when considering a biomarker-positive population in the trial, and could therefore have impacted the power of STRATOS 2. In addition, as the trials proceeded at the same time, there was no opportunity to enrich the population of STRATOS 2 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 prior to randomisation. Further, the trial design could have influenced the observed placebo effects in STRATOS 2, potentially compromising the ability to establish a treatment effect on FEV_1 with tralokinumab in the FeNO-high subgroup. Elevated FeNO concentrations have been demonstrated to reflect poor treatment adherence;[43] improvements in adherence

to concurrent controller medication through frequent monitoring within the clinical trial environment could potentially have contributed to the FEV_1 effect we observed in STRATOS 2 with placebo as well as tralokinumab. Conversely, these placebo effects were not limited to the FeNO-high subgroup and were not observed in STRATOS 1, so are 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 2 populations, chosen based on the post-hoc analyses of the phase 2b trial that required reversibility at study entry and excluded OCS-dependent patients. As a result, the tralokinumab efficacy observed in the populations of STRATOS 1 and 2 likely did not reflect efficacy of tralokinumab in a real-world, severe asthma population.[44]

In summary, tralokinumab failed to meet the primary endpoint, a reduction in AAER, in either STRATOS 1 or STRATOS 2. Baseline FeNO ≥37 ppb 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.

Author contributions

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.

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Declaration of interests

RAP reports grants and personal fees from AstraZeneca, grants and personal fees from MedImmune, personal fees from Novartis, grants from Theratrophix, grants from Amgen, grants from RFIM, grants from Vertex, grants from Bristol Myers Squibb, grants from Genentech, grants and personal fees from Sanofi/Regeneron, grants from Gilead, grants from Boston Scientific, personal fees from Teva, and personal fees from Boehringer Ingelheim, outside 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 owns 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 University of Leicester from AstraZeneca.

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Tables

Table 1: Participant demographics and baseline characteristics in STRATOS 1

	All-comers		FeNO-high (≥37 ppb)	
	Combined placebo* (N=400)	Tralo Q2W (N=398)	Combined placebo* (n=102)	Tralo Q2W (n=97)
Demographics				
Age, years, mean (SD)	51·4 (14·3)	49·4 (14·3)	46·5 (15·1)	46·3 (13·9)
Female, n (%)	265 (66·3)	252 (63·3)	70 (68·6)	55 (56·7)
Race, n (%)				
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, mean (SD)	28·8 (6·4)	28·4 (6·3)	28·0 (6·2)	27·5 (6·5)
Clinical characteristics				
Pre-BD FEV_1, L, mean (SD)	1·8 (0·6)	1·8 (0·6)	1·9 (0·6)	1·8 (0·6)
Pre-BD FEV_1 % predicted, mean (SD)	61·5 (13·3)	59·8 (12·8)	63·5 (13·8)	59·4 (12·4)
Pre-BD FVC, L, mean (SD)	2·8 (0·9)	2·8 (0·9)	3·0 (0·9)	3·0 (0·9)
FEV_1 reversibility†, %, mean (SD)	23·1 (24·4)‡	22·6 (17·8)§	24·8 (20·7)	24·0 (17·0)
Time since asthma diagnosis years, median (range)	16·0 (1, 73)	15·0 (1, 70)	16·0 (1, 55)	13·2 (1, 52)
Number of exacerbations in the last 12 months, median (range)	2·0 (2, 10)	2·0 (2, 9)	2·0 (2, 10)	2·0 (2, 9)
Total asthma symptom score, mean (SD)	2·5 (1·0)‖	2·5 (1·0)¶	2·5 (1·0)	2·5 (0.9)
ACQ-6 score, mean (SD)	2·6 (0·9)**	2·6 (0·8)	2·6 (0·9)	2.7 (0·8)
AQLQ score, mean (SD)	4·2 (1·0)††	4·2 (0·9)‡‡	4.1 (1.1)§§	4.0 (0.8)‖‖
Baseline eosinophil count, cells/μL, mean (SD)	254 (203·8)¶¶	308 (468·4)¶¶	359 (286·6)***	474 (763·9)
Baseline FeNO concentration, ppb, mean (SD)	29·6 (28·2)**	30·5 (30·6)†††	64·9 (1·9)	69·5 (1·9)
Baseline asthma medication				
ICS dosage, n (%)				
Low‡‡‡	3 (0·8)	1 (0·3)	40 (39·2)§§§	45 (46·4)§§§
Medium	194 (48·5)	204 (51·3)		
High	203 (50·8)	193 (48·5)	62 (60·8)	52 (53·6)
LABA, n (%)	400 (100·0)	397 (99·7)	102 (100·0)	97 (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; FEV_1, forced expiratory volume in one second; FVC, forced vital capacity; ICS, inhaled corticosteroids; LABA, long-acting $beta_2$ agonists; Q2W, every two weeks; Q4W, every four weeks; SABA, Short-acting $beta_2$ 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 FEV_1 post-BD 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=397; ‖n=399; ¶n=397; **n=398; ††n=378; ‡‡n=368; §§n=97; ‖‖n=89; ¶¶n=393; ***n=100; †††n=395

‡‡‡A minor number of participants were taking low dosages of ICS at baseline, and were recorded as protocol deviations

§§§Combined low and medium dosage ICS

Table 2: Participant demographics and baseline characteristics in STRATOS 2

	All-comers		FeNO-high (≥37 ppb)	
	Placebo (N=417)	**Tralo Q2W (N=420)**	**Placebo (n=121)**	**Tralo Q2W (n=108)**
Demographics				
Age, years, mean (SD)	48·0 (15·5)	47·3 (15·6)	45·1 (16·7)	45·1 (15·1)
Female, n (%)	290 (69·5)	276 (65·7)	76 (62·8)	68 (63·0)
Race, n (%)				
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, mean (SD)	27·9 (6·6)*	28·6 (7·1)†	27·2 (7·6)	27·9 (5·9)
Clinical characteristics				
Pre-BD FEV_1, L, mean (SD)	1·8 (0·6)	1·8 (0·6)†	1·8 (0·6)	1·8 (0·6)
Pre-BD FEV_1 % predicted, mean (SD)	61·0 (14·7)	60·8 (13·5)†	62·1 (14·9)	61·1 (12·7)
Pre-BD FVC, L, mean (SD)	2·7 (0·8)	2·8 (0·9)†	2·9 (0·8)	2·9 (0·9)
FEV_1 reversibility‡, %, mean (SD)	25·7 (24·5)	23·4 (17·5)†	27·5 (22·9)	23·1 (17·5)
Time since asthma diagnosis years, median (range)	15·0 (1, 69)	15·0 (1, 71)	15·9 (1, 69)	14·8 (1, 69)
Number of exacerbations in the last 12 months, median (range)	2·0 (2, 19)	2·0 (2, 5)	2·0 (2, 19)	2·0 (2, 5)
Total asthma symptom score, mean (SD)	2·4 (1·0)§	2·3 (0·9)†	2·5 (1·0)‖	2·4 (1·0)
ACQ-6 score, mean (SD)	2·6 (0·9)	2·4 (0·9)	2·7 (1·0)	2·6 (0·9)
AQLQ score, mean (SD)	4·1 (1·0)¶	4·3 (1·0)¶	4·0 (0·9)	4·1 (1·0)
Baseline eosinophil count, cells/μL, mean (SD)	269 (228·2)§	286 (232·9)**	333 (214·7)	353 (252·0)
Baseline FeNO concentration, ppb, mean (SD)	31·7 (27·7)††	29·0 (25·2)*	64.0 (30.8)	61.4 (28.6)
Baseline asthma medication				
ICS dosage, n (%)				
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, n (%)	417 (100·0)	420 (100·0)	121 (100·0)	108 (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; FEV_1, forced expiratory volume in one second; FVC, forced vital capacity; ICS, inhaled corticosteroids; LABA, long-acting $beta_2$ agonists; Q2W, every two weeks; Q4W, every four weeks; SABA, short-acting $beta_2$ agonist; SD, standard deviation; Tralo, tralokinumab

*n=416; †n=419

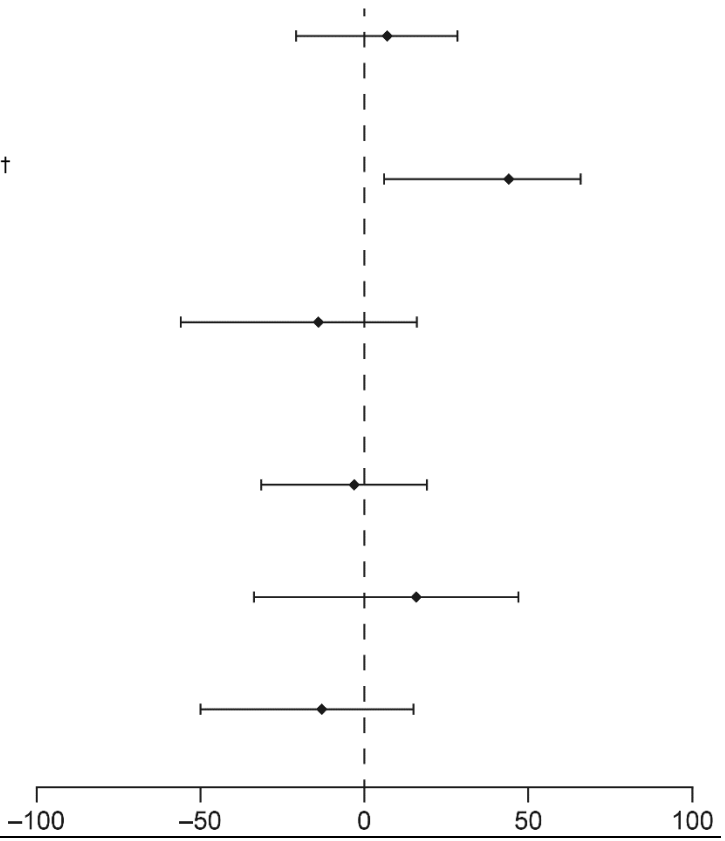
‡The FEV_1 post-BD measurement in the reversibility derivation could be the post-BD measurement after 4, 6 or 8 SABA inhalations, depending on when the reversibility assessment was considered complete

§n=415; ‖n=120; ¶n=394; **n=412; ††n=411

‡‡A minor number of participants were taking low dosages of ICS at baseline, and were recorded as protocol deviations

Table 3: Annual asthma exacerbation rates at Week 52 in STRATOS 1 and 2 (Full Analysis Set)

	n	AAER (95% CI)	Rate ratio (95% CI)	Treatment effect on AAER (95% CI),%	*P* value	Treatment effect on AAER (95% CI), %
STRATOS 1						
All-comers						
Combined placebo*	400	0·6 (0·5, 0·7)	0·93 (0·72, 1·21)	7·0 (–20·8, 28·4)	0·59	
Tralo Q2W	398	0·6 (0·5, 0·7)				
FeNO-high (≥37 ppb)						
Combined placebo*	102	0·9 (0·6, 1·2)	0·56 (0·34, 0·94)	44·0 (6·0, 66·0)	0·028†	
Tralo Q2W	97	0·5 (0·3, 0·7)				
FeNO-low (<37 ppb)						
Combined placebo*	296	0·5 (0·4, 0·6)	1·14 (0·84, 1·56)	–14·0 (–56·0, 16·0)	0·39†	
Tralo Q2W	298	0·6 (0·5, 0·7)				
STRATOS 2						
All-comers						
Placebo	417	0·8 (0·7, 1·0)	1·03 (0·81, 1·31)	–3·1 (–31·5, 19·1)	0·80‡	
Tralo Q2W	420	0·8 (0·7, 1·0)				
FeNO-high (≥37 ppb)						
Placebo	121	1·0 (0·7, 1·3)	0·84 (0·53, 1·34)	15·8 (–33·7, 47·0)	0·47‡	
Tralo Q2W	108	0·8 (0·6, 1·1)				
FeNO-low (<37 ppb)						
Placebo	290	0·8 (0·6, 1·0)	1·13 (0·85, 1·50)	–13·0 (–50·0, 15·0)	0·41§	
Tralo Q2W	308	0·9 (0·7, 1·1)				



CI, confidence interval; 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

†*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

Table 4: Key secondary efficacy endpoints in the STRATOS 1 and 2 all-comers and FeNO-high (≥37 ppb at baseline) populations (Full Analysis Set)

	Change from baseline at Week 52 in:			
	Pre-BD FEV_1, %	**AQLQ score**	**ACQ-6 score**	**Total asthma symptom score**
STRATOS 1				
All-comers				
Tralo Q2W vs. placebo*, n	357 vs. 363	304 vs. 315	324 vs. 329	313 vs. 312
Difference in LS means (95% CI)	6·03 (2·34, 9·73)	0·15 (–0·01, 0·31)	−0·16 (−0·29, –0·02)	−0·09 (−0·23, 0·04)
P value	0·0014	0·061	0·022	0·18
FeNO-high				
Tralo Q2W vs. placebo*, n	87 vs. 92	74 vs. 83	75 vs. 83	71 vs. 68
Difference in LS means (95% CI)	12·80 (5·34, 20·26)	0·53 (0·22, 0·84)	−0·43 (−0·71, −0·16)	−0·05 (−0·34, 0·24)
P value†	0·00079	0·00077	0·0022	0·72
STRATOS 2				
All-comers				
Tralo Q2W vs. placebo, n	384 vs. 358	321 vs. 318	341 vs. 334	297 vs. 309
Difference in LS means (95% CI)	2·95 (–0·73, 6·62)	0·06 (–0·10, 0·22)	–0·08 (–0·21, 0·05)	–0·04 (–0·18, 0·10)
P value	0·12‡	0·45‡	0·24‡	0·58‡
FeNO-high				
Tralo Q2W vs. placebo, n	99 vs. 103	77 vs. 84	85 vs. 86	79 vs. 81
Difference in LS means (95% CI)	1·86 (−5·16, 8·88)	0·27 (–0·04, 0·57)	−0·27 (−0·53, –0·01)	−0·20 (−0·47, 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; BD, bronchodilator; CI, confidence interval; FeNO, fractional exhaled nitric oxide; FEV_1, 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

†*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 5: Overall safety results during the treatment period* for STRATOS 1 and 2 (Safety Analysis Sets)

	STRATOS 1		STRATOS 2	
	Combined placebo† (N=400)	**Tralo Q2W (N=398)**	**Placebo (N=422)**	**Tralo Q2W (N=425)**
Any AE, n (%)	243 (60·8)	278 (69·8)	290 (68·7)	306 (72·0)
Any treatment-related AE, n (%)	32 (8·0)	91 (22·9)	33 (7·8)	93 (21·9)
Any AE with outcome of death, n (%)	0	1 (0·3)	1 (0·2)	1 (0·2)
Any SAE, n (%)	48 (12·0)	40 (10·1)	39 (9·2)	35 (8·2)
AEs leading to discontinuation, n (%)	3 (0·8)	28 (7·0)	14 (3·3)	27 (6·4)
AEs with ≥5% frequency in any arm (safety population)‡, n (%)				
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)

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

*Includes AEs with an onset date ≥ the first day of trial treatment and ≤ (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 ≥5% frequency in the STRATOS 1 combined placebo arm; MedDRA preferred term (version 19.1)

Figure legends

Figure 1: STRATOS 1 (A) and 2 (B) trial designs

Q2W, every two weeks; Q4W, every four weeks; SC, subcutaneous

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Figure 2: Participant disposition in STRATOS 1 (A) and 2 (B)

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

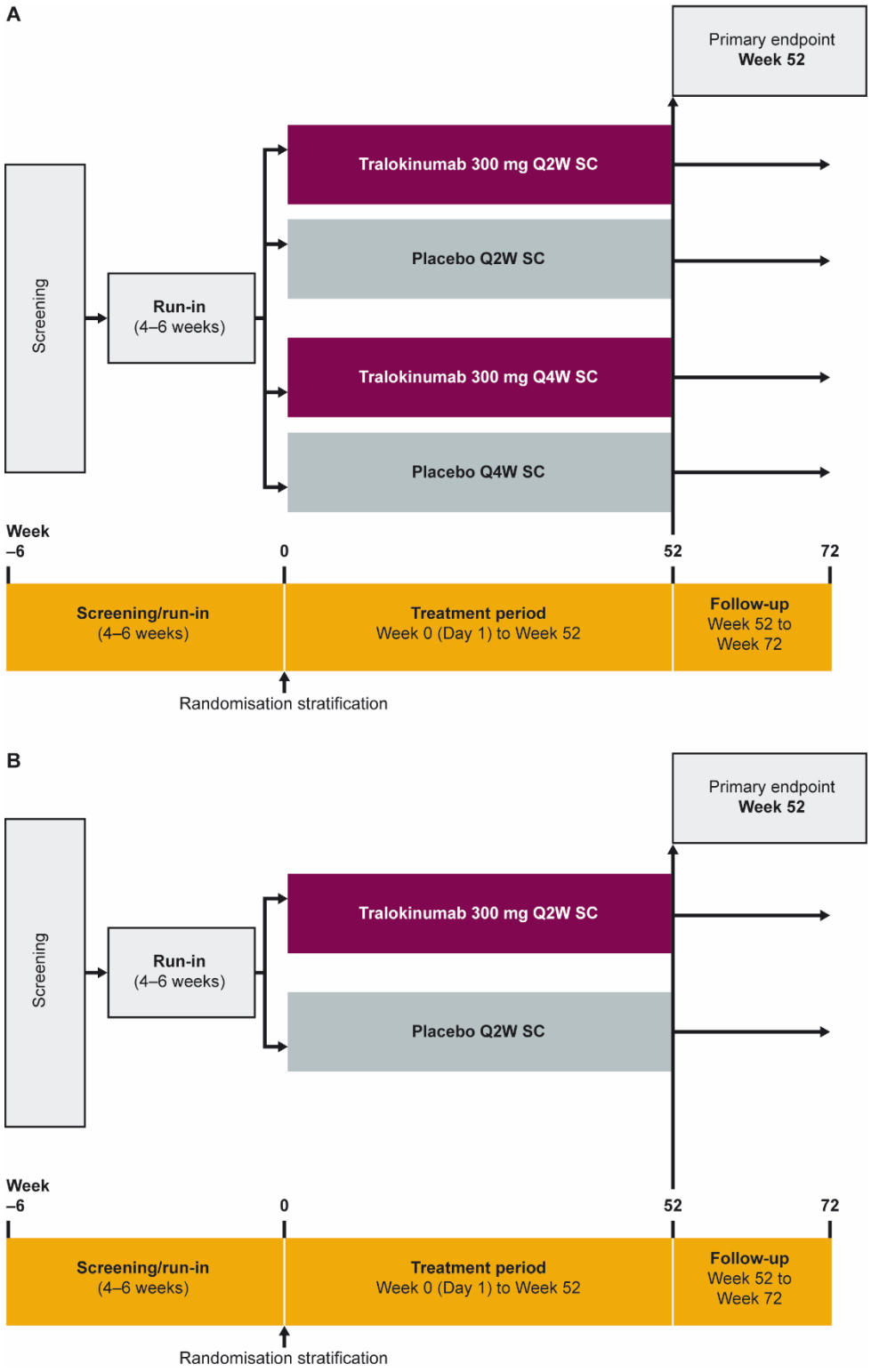
Figure 3: Least squares mean absolute change from baseline in pre-bronchodilator FEV_1 over time in STRATOS 1 in the (A) all-comers, (B) FeNO-high (≥37 ppb at baseline), and (C) FeNO-low (<37 ppb at baseline) populations (Full Analysis Set)†

CI, confidence interval; FEV_1, forced expiratory volume in one second; 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

Figures

Figure 1: STRATOS 1 (A) and 2 (B) trial designs



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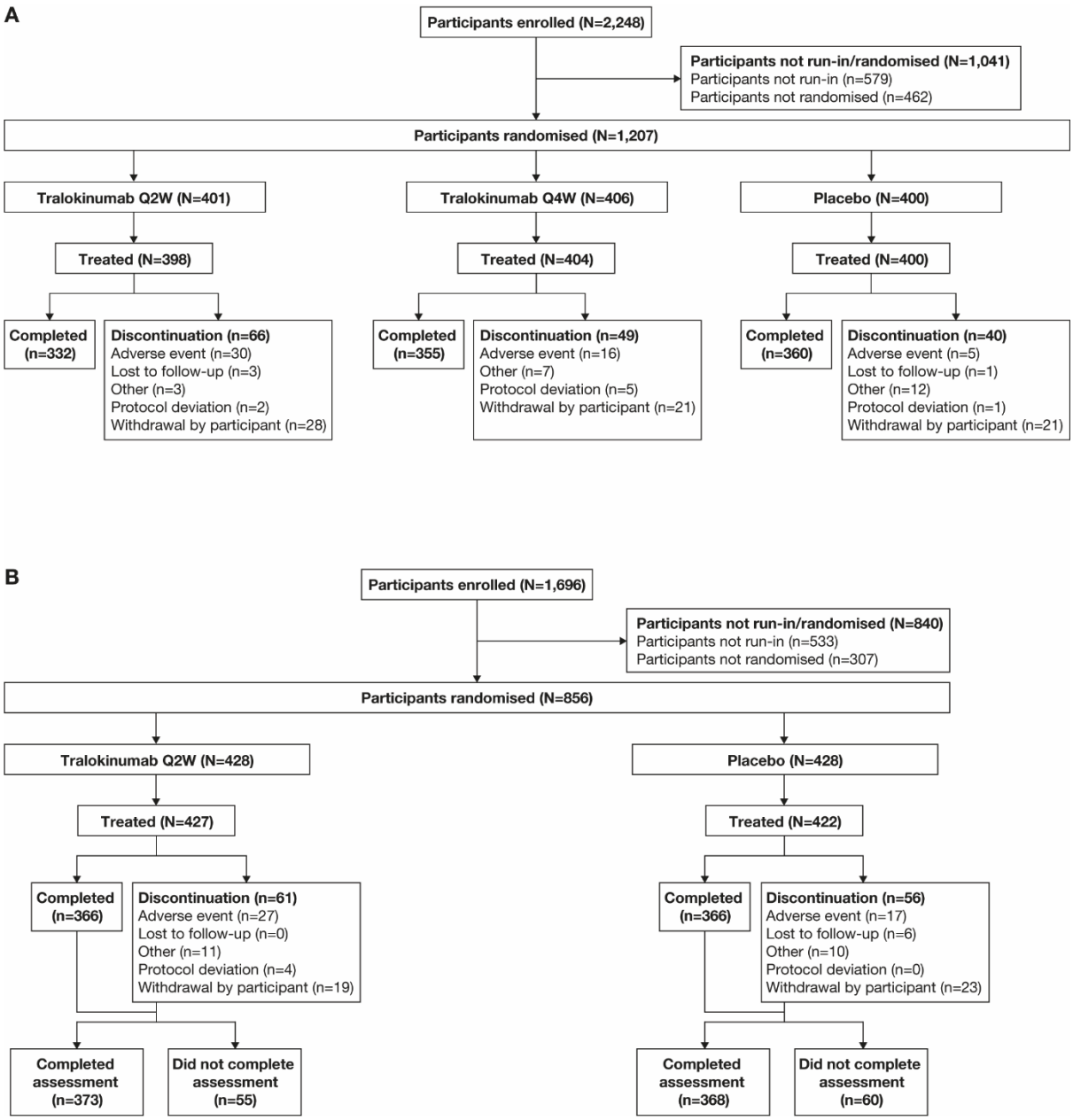

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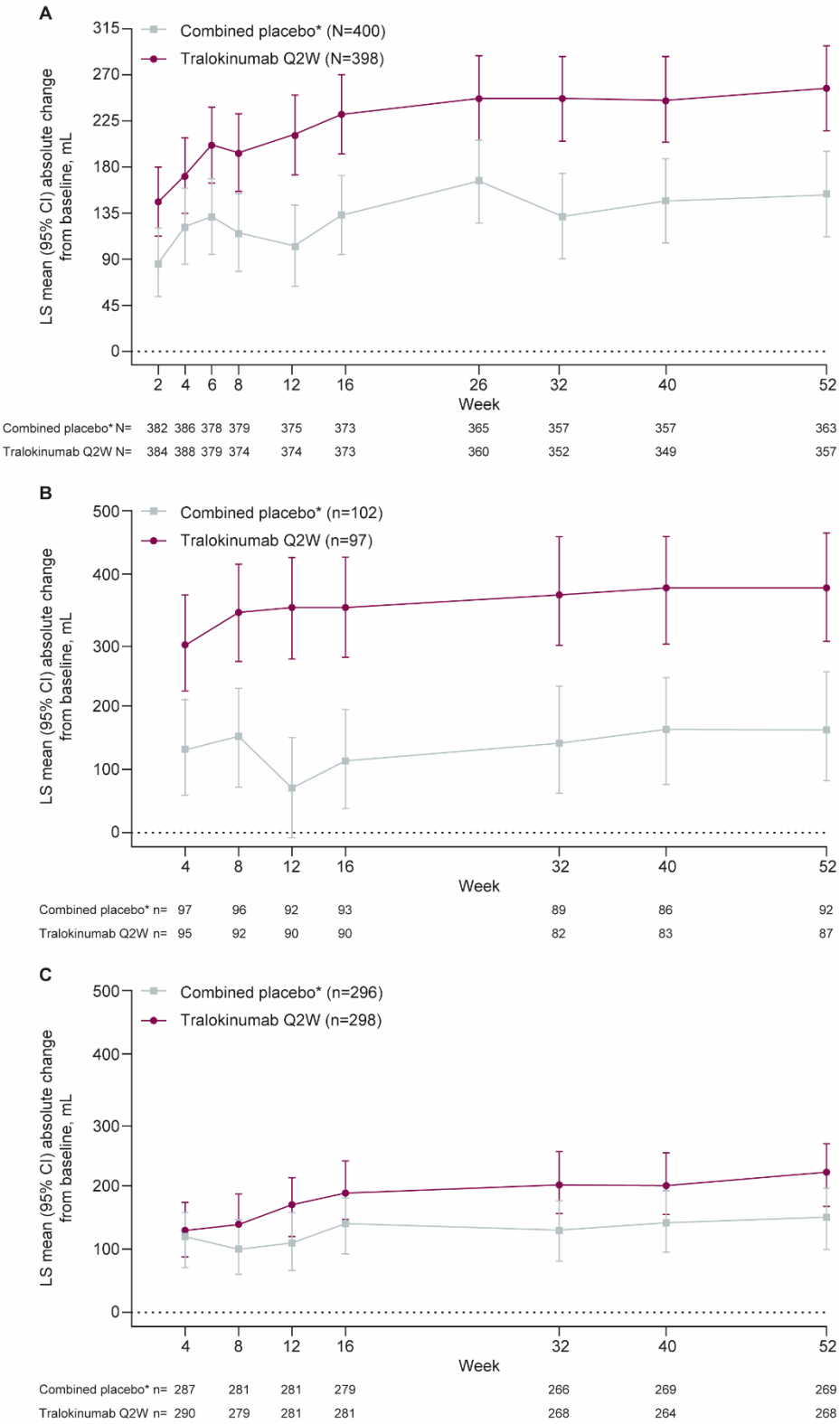

CI, confidence interval; FEV_1, forced expiratory volume in one second; LS, least squares; Q2W, every two weeks

*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