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

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Supplementary Appendix

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1. Eligibility criteria

1.1 Inclusion criteria

For inclusion in the trial, patients must have fulfilled all of the following criteria:

- Written informed consent prior to any trial specific procedures. For patients less than the age of majority, written informed consent was required from parents or legal guardians in addition to the patient. For those countries where local regulations permitted the enrolment of adults only, patient recruitment was restricted to those who were aged ≥18 years.
- Female or male patients aged 12–75 years, inclusively at the time of enrolment (Visit 1).
- Women of childbearing potential and all adolescent females were required to use a highly effective form of birth control (confirmed by the investigator).
    - Highly effective forms of birth control included: true sexual abstinence, a vasectomised sexual partner, Implanon®, female sterilisation by tubal occlusion, any effective intrauterine device/system Depo-Provera™ injections, oral contraceptive, and Evra Patch™ or Nuvaring™.
- Women not of childbearing potential were defined as women who were either permanently sterilised (hysterectomy, bilateral oophorectomy or bilateral salpingectomy) or were postmenopausal. Women were considered to be postmenopausal if they had been amenorrhoeic for 12 months prior to the planned date of randomisation without an alternative medical cause. The following age-specific requirements applied:
    - Women <50 years old were to be considered postmenopausal if they had been amenorrhoeic for 12 months or more following cessation of exogenous hormonal treatment and had follicle stimulating hormone (FSH) levels in the postmenopausal range.
    - Women ≥50 years old were to be considered postmenopausal if they had been amenorrhoeic for 12 months or more following cessation of all exogenous hormonal treatment.
- Weight of ≥40 and <150 kg at enrolment (Visit 1).
- Documented physician-diagnosed asthma for at least 12 months prior to enrolment (Visit 1). In addition, patients should have 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. In addition, patients were required to have used physician-prescribed ICS (at a total daily dose ≥500 µg fluticasone propionate via dry powder inhaler or equivalent delivered dose) that had been taken at a stable dose for at least 3 months prior to enrolment (Visit 1).

- 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.
- Patients were required to have received oral corticosteroids (OCS) therapy for the treatment of asthma for 6 months prior to Visit 1 and be on a stable OCS dose of between ≥7.5 mg and ≤30 mg (prednisone or prednisolone equivalent) daily or daily equivalent for at least 1 month prior to enrolment.
    - Patients with a documented failure of OCS dose reduction within 6 months prior to Visit 1 could omit Visits 2 to 5 and complete a 2-week run-in period prior to Visit 6 (randomisation visit).
    - Failed attempts at OCS-dose reduction were those that resulted in a clinical deterioration or reduced lung function attributed to asthma, demonstrated by documented occurrence of at least 1 of the following:
        - Pre-bronchodilator forced expiratory volume in 1 second (FEV_1) <80% of personal baseline.
        - Morning peak expiratory flow (PEF) <80% of personal baseline.
        - Night-time awakenings increase of >50% of mean personal baseline.
        - Rescue medication use, for example, salbutamol >4 puffs/day above mean personal baseline.
        - Requirement for an OCS burst (large temporary increase) to treat an asthma exacerbation provoked by steroid reduction.
    - Patients without a documented failure of OCS dose reduction within the previous 6 months were required to complete the 2-week run-in period plus the up to 8-week dose optimisation period prior to Visit 6 (randomisation visit).
- Use of additional maintenance asthma controller medications were permitted as per standard practice of care. These medications were required to be stable for 3 months prior to Visit 1. Additionally, the patient's maintenance medication for asthma was to remain unchanged throughout the trial.
- A pre-bronchodilator FEV_1 of <80% (<90% for patients aged 12–17 years) of their predicted normal value.
    - If this criterion was not met at Visit 1, the criterion was required to be met at Visit 2 or Visit 6 (if a patient was not required to undergo dose optimisation).
    - Prior to the lung function assessment, the patient was to withhold theophylline and their bronchodilator for the effect duration specific to the bronchodilator.

- A post-bronchodilator reversibility in FEV_1 of ≥12% at enrolment (Visit 1) or documented reversibility within 6 months prior to Visit 1.
    - For patients with no evidence of a documented reversibility within 6 months prior to Visit 1, or if this criterion was not met at Visit 1, the criterion was required to be met at Visit 2 or Visit 6 (if a patient was not required to undergo dose optimisation).
    - Prior to the lung function assessment, the patient was to withhold theophylline and their bronchodilator for the effect duration specific to the bronchodilator.

1.2 Inclusion criteria prior to randomisation

- A negative urine pregnancy test for women of childbearing potential (including all adolescents).
- No requirement for change in the patients ICS/LABA, other asthma controller medications and/or the requirement to add asthma controller medications during the run-in or run-in/optimisation periods.
- The optimised OCS dose reached at least 2 weeks prior to randomisation for all patients (including patients who proceeded directly to the run-in period and those undergoing dose optimisation).
- Minimum 70% compliance with OCS use.
- Minimum 70% compliance with both the usual asthma controller (i.e. ICS/LABA and any other asthma controller medications).
- Ability to perform acceptable inhaler, peak flow meter and spirometry techniques.
- Minimum 70% compliance with the eDiary assessment schedule.

1.3 Exclusion criteria

Any of the following was regarded as a criterion for exclusion from the trial:

- Clinically important pulmonary disease other than asthma (e.g. active lung infection, chronic obstructive pulmonary disease [COPD], bronchiectasis, pulmonary fibrosis, cystic fibrosis, hypoventilation syndrome associated with obesity, lung cancer, alpha 1 anti-trypsin deficiency and primary ciliary dyskinesia).
- Any disorder, including but not limited to, cardiovascular, gastrointestinal, hepatic, renal, neurological, musculoskeletal, infectious, endocrine, metabolic, haematological, psychiatric, or major physical impairment that was either not stable or could have in the opinion of the

investigator affected the safety of the patient, influenced the findings of the trial or its interpretations or impeded the patient's ability to complete the duration of the trial.

- Known history of allergy or reaction to any component of the investigational product's formulation.
- History of anaphylaxis following any biologic therapy.
- A helminth parasitic infection diagnosed within 6 months prior to the date informed consent was obtained that had not been treated with or had failed to respond to standard of care therapy.
- History of clinically significant infection, including acute upper or lower respiratory infections, requiring antibiotics or antiviral medication within 30 days prior to the date of informed consent.
- Tuberculosis requiring treatment within the 12 months prior to enrolment (Visit 1).
- Any clinically significant abnormal findings in physical examination, vital signs, digital electrocardiogram (dECG), haematology, clinical chemistry or urinalysis during the run-in period, which in the opinion of the investigator could have put the patient at risk or could have influenced the results of the trial or the patient's ability to complete the entire duration of the trial.
- History of chronic alcohol or drug abuse within 12 months of the enrolment visit (Visit 1), or a condition associated with poor compliance as judged by the investigator.
- Positive hepatitis B surface antigen or hepatitis C virus antibody serology.
- History of any known primary immunodeficiency disorder including a positive human immunodeficiency virus test at enrolment (Visit 1) or the patient taking antiretroviral medications.
- Current tobacco smoking (smoking must have stopped for ≥3 months prior to enrolment [Visit 1]) or a history of tobacco smoking for ≥10 pack-years (1 pack-year = 20 cigarettes smoked per day for 1 year).
- History of cancer, except for:
    - Patients who have had basal cell carcinoma, localised squamous cell carcinoma of the skin or in-situ carcinoma of the cervix provided that the patient was in remission and curative therapy was completed at least 12 months prior to the date informed consent was obtained.
    - Patients who have had other malignancies, provided that the patient was in remission and curative therapy was completed at least 5 years prior to the date informed consent was obtained.

- Use of immunosuppressive medication (including but not limited to: methotrexate, troleandomycin, cyclosporine, azathioprine and intramuscular long-acting depocorticosteroids) within 3 months prior to the date informed consent was obtained. Exceptions were made for patients on chronic maintenance OCS for the treatment of asthma.
- Clinically significant asthma exacerbation, including those requiring use of systemic corticosteroids or increase in the maintenance OCS dose within 30 days prior to the date of informed consent or during the enrolment/run-in period or the last 2 weeks of the optimisation period.
- Asthma control reached with an OCS dose of ≤5 mg during the run-in/OCS optimisation period (Visit 2 to Visit 6, for patients undergoing dose optimisation).
- Qualified for 3 consecutive dose reductions at Visit 2 to Visit 4 and continued to meet OCS dose reduction criteria at Visit 5 (for patients undergoing dose optimisation).
- Receipt of immunoglobulin or other blood products within 30 days prior to the date informed consent or assent was obtained.
- Receipt of any approved or investigational biologic agent (e.g. omalizumab) within 4 months or for 5 half-lives prior to the date of randomisation, whichever was longer.
- Receipt of any live attenuated vaccines within 30 days prior to the date of randomisation and during the treatment and follow-up period. Exceptions were made for receipt of inactive/killed vaccinations (e.g. inactive influenza), provided they were not administered within 5 days before/after any trial visit.
- Receipt of any investigational non-biologic agent within 30 days or 5 half-lives prior to informed consent or assent being obtained, whichever was longer.
- Previous receipt of tralokinumab (CAT-354).
- Initiation of any new allergen immunotherapy or change in existing immunotherapy within 30 days prior to the date of informed consent. However, allergen immunotherapy initiated prior to this period could be continued, provided there was a span of at least 5 days between the immunotherapy and administration of the investigational product.
- Use of any oral or ophthalmic non-selective β-adrenergic antagonist (e.g. propranolol) at the time of enrolment.
- Use of 5-lipoxygenase inhibitors (e.g. zileuton) or roflumilast at the time of enrolment.
- Patients who had undergone bronchial thermoplasty.
- Major surgery within 8 weeks prior to the enrolment Visit 1 or planned in-patient surgery or hospitalisation during the trial period.

- Alanine aminotransferase or aspartate aminotransferase level ≥2.5 times the upper limit of normal at enrolment (Visit 1).
- Pregnant, breast-feeding or lactating women.
- Previous randomisation in the present trial.
- Concurrent enrolment in another clinical trial where the patient was receiving an investigational product.
- Involvement in the planning and/or conduct of the trial (applies to both AstraZeneca staff and/or staff at the trial site).
- 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.
- Individuals who were legally institutionalised.

1.4 Restrictions during the treatment period

1.4.1 Asthma medication restrictions

Short-acting β_2-agonists

- Regularly scheduled use of short-acting β_2-agonists (SABA) in the absence of any asthma symptoms was discouraged from enrolment (Visit 1) and throughout the trial duration. Prophylactic use of SABA (e.g. prior to planned exercise) if deemed necessary by the patient and the investigator, was allowed, but was not recorded in the Asthma Daily Diary. Instead, any such use was documented in the medical notes and recorded in the electronic case report form.
- Administration of SABA via a metered dose device was permitted, as needed, for worsening asthma symptoms (i.e. rescue use) and was recorded in the Asthma Daily Diary as number of inhalations.
- Rescue use of SABA administered via jet or ultrasonic nebulisation was allowed; occasions where SABA was administered via nebulisation were recorded separately from metered dose inhaler inhalations in the Asthma Daily Diary.

Short-acting anticholinergics

- Use of short acting anticholinergics (e.g. ipratropium) as a rescue treatment for worsening asthma symptoms outside of managing an asthma exacerbation event was not allowed from enrolment and throughout the trial duration.

LABA

- Use of LABA as a reliever (e.g. Symbicort® maintenance and reliever treatment) was not allowed from enrolment and throughout the trial duration.

Use of theophylline and once-daily bronchodilators

- Use of theophylline and once-daily bronchodilators was allowed at the discretion of the investigator. These drugs were used at a stable dose for at least 3 months before Visit 1. A 48-hour minimum washout period for theophylline or once-daily bronchodilators was required before spirometry.
- To obtain a true pre-bronchodilator (i.e. trough) FEV_1 reading, patients were asked to withhold from taking their usual regular bronchodilator medications and reliever SABA. The patient's usual asthma controller medications could be administered following completion of the pre-bronchodilator spirometry.

Asthma medication restrictions prior to home PEF testing

- Patients were to avoid taking their morning asthma controller medication prior to the morning home PEF testing and were to conduct the evening home lung function testing before taking their evening asthma controller medication. When possible, home PEF testing was to be performed at least 6 hours after the last dose of SABA reliever medication.

Asthma medication restrictions on unscheduled visits

- Asthma medication restrictions on unscheduled visits, where not feasible, could be applied at the discretion of the investigator. Timing of recent controller and reliever SABA use relative to the unscheduled spirometry was noted in the record.

Asthma medication restrictions at site visits with scheduled dECG assessment

- Patients were instructed not to take their usual asthma controller medication before a scheduled dECG assessment. The use of SABA was to be avoided within 6 hours prior to the dECG assessment, use of twice-daily LABA for 12–24 hours and theophylline or once-daily bronchodilators for 48 hours. The medication restriction was waived for the enrolment dECG at Visit 1.

1.4.2 Other medication restrictions

- Use of any off-label medications, for example, medications locally approved for COPD but not for asthma, was not allowed from 30 days prior to Visit 1 and throughout the trial.
- Use of oral or systemic immunosuppressive medication was not allowed (other than prior, stable OCS for the maintenance treatment of asthma).
- Receipt of live attenuated vaccines, within 30 days prior to randomisation and during the treatment and follow-up period, was not allowed. Inactive/killed vaccines (e.g. inactive influenza vaccine) were allowed, provided they were not administered within 5 days before/after any dosing visit.

- Patients were not to receive allergen immunotherapy injection on the same day as the investigation product administration.
- Patients were not to take any other excluded medications: oral or ophthalmic non-selective β-adrenergic antagonist (e.g. propranolol).

1.4.3 Other restrictions

The following restrictions applied while the patient was receiving trial treatment and for the specified times:

- Patients could not undergo bronchial thermoplasty during the entire trial.
- Fertile and sexually active female patients (including adolescent females) were required to use highly effective contraceptive methods throughout the trial and at least for 16 weeks (5 half-lives) after the last administration of the investigational product.
- Patients were required to abstain from donating blood or plasma from the time of informed consent or assent and up to 16 weeks (5 half-lives) after the last dose of the investigational product.

2. Randomisation and blinding

2.1 Randomisation

- Patients were randomised in a 1:1 ratio to receive either tralokinumab 300 mg or placebo every 2 weeks. Each patient received 2 subcutaneous injections of 150 mg tralokinumab at each dosing visit for a total dose of 300 mg or placebo using pre-filled syringes over a 40-week treatment period.
- A fixed block randomisation list was created using an internal AstraZeneca computerised system (GRand). Randomization codes were assigned strictly sequentially in each stratum as subjects became eligible for randomization, using an Interactive Voice/Web Recognition System.
- All patients were stratified at randomization by age group (adults versus adolescents). Adults were also stratified at randomization by baseline OCS dose (≤10 mg versus >10 mg prednisone or prednisolone).
- Randomized patients who discontinued were not replaced. If a patient withdrew from the study, then his/her enrolment/ randomization code could not be reused.

2.2 Blinding

- This was a double-blind trial in which tralokinumab and placebo were visually distinct from each other.

- All the patients, investigators and sponsor staff who were involved in the treatment, clinical evaluation and monitoring of the patients were blinded to the trial.
- Since tralokinumab and placebo were visually distinct, they were handled by an unblinded investigational product manager at the site and were administered by an unblinded investigational site trial team member, who were not involved in the management of the trial patients (could be the same person).
- A blinded AstraZeneca site monitor performed investigational product accountability. If the treatment allocation for a patient became known to the investigator or other study staff involved in the management of patients, or was needed to be known to treat a patient for an AE, the sponsor was notified immediately by the investigator and if possible, before unblinding.
- The packaging and labelling of the investigational product was done in such a way as to ensure blinding for all sponsor and investigational site staff involved in the management of the trial patients.

3. Trial procedures

3.1 Assessment of OCS dose

- During the run-in/OCS optimisation period, the minimum OCS dose, while not losing asthma control, was reached for patients who had undergone dose optimisation. The optimised dose was considered the baseline OCS dose.
- The baseline dose was the dose at randomisation, regardless of whether the patient had undergone dose optimisation. The baseline OCS dose was maintained at the same level from Visit 6 up to Visit 12 (induction phase).
- The dose reduction of the OCS commenced at Visit 12 and if the dose reduction criteria were met, it continued at 4-weekly intervals until Visit 22. During the reduction phase, a minimum stable OCS dose, or complete elimination of the requirement for OCS, while maintaining asthma control was reached for each patient.
- If a patient did not meet the titration criteria, the OCS dose was returned to the previous effective dose (i.e. the higher dose level prior to the titration criterion not being met) and patients were maintained on that OCS dose until end of treatment (Visit 26).
- No adjustments were to be made to the OCS dose after Visit 22 when patients entered the maintenance phase.

3.2 OCS dose titration

- Titration of OCS dose followed the same approach for patients who had not had a documented failure at OCS reduction and entered the optimisation period for a maximum of 8 weeks (Visits 2 to 6) and all patients following the induction phase (Visits 12 to 20). At optimisation period, dose titration began at Visit 2.
- The dose titration during the treatment period began at Visit 12 and ended at Visit 20. Dose reduction at Visit 12 was the only titration visit during the reduction phase that was not based on a protocol-captured set of baseline data.
- Patients who met all of the following criteria were eligible for OCS dose titration (dose reduction):
    - Pre-bronchodilator FEV_1 ≥80% of baseline FEV_1 at the clinic visit.
    - Mean of the morning PEF measures during 14 days prior to visit ≥80% of baseline mean morning PEF measure.
    - Not more than or equal to 50% increase in the proportion of nights with awakenings in the 14-day period prior to the visit compared with baseline.
    - Mean rescue medication use not more than 4 puffs/day above the baseline mean or 12 puffs/day overall in the 14-day period prior to the visit.
    - No asthma exacerbation requiring a burst of systemic corticosteroids since the previous visit.
    - Investigator judged patient's asthma control to be sufficient to allow OCS dose reduction.
- For patients who did not meet the above criteria, further OCS dose reduction was stopped for the duration of the trial and these patients returned to the dose 1 level higher.
- If, in the opinion of the investigator, additional OCS dose reductions were not clinically indicated (due to disease factors that might have affected patient safety), titration could be stopped. The patient was returned to a dose 1 level higher (unless a temporary bolus/burst of steroid was warranted). Further dose reductions could be considered if warranted in the opinion of the investigator.

3.3 Assessment of fractional exhaled nitric oxide

- Fractional exhaled nitric oxide (FeNO) measurements were performed at Visits 1, 6, 12, 18, 22 and 26.
- In patients with a respiratory infection, measurement was delayed until 2 weeks after the infection had resolved.

- Patients could not use their rescue SABA medication (e.g. albuterol/salbutamol) within 6 hours of FeNO measurement.
- FeNO measurements were performed prior to the spirometry measurements using an electrochemical sensor.
- Standard single exhalation technique recommended by the American Thoracic Society (ATS) was followed [1].

3.4 Assessment of asthma exacerbations

- Worsening of asthma was defined as new or increased symptoms and/or signs (i.e. physical examination or lung function) that could be either concerning to the patient (patient-driven) or related to an Asthma Daily Diary alert (diary-driven) and that could lead to any of the following:
    - A temporary bolus/burst of systemic corticosteroids for at least 3 days to treat symptoms of asthma worsening; a single depo-injectable dose of corticosteroids was considered equivalent to a 3-day bolus/burst of systemic corticosteroids.
        - Discontinuation due to an exacerbation after Visit 6 was not mandatory. Patients who experienced an exacerbation during the run-in period were screen failed and were considered for re-screening. Those who experienced an exacerbation after randomisation could remain on the investigative product at the investigators discretion. After the bolus/burst was complete, in the judgment of the investigator, the patient could be returned to the higher OCS dose than the dose that preceded their exacerbation. Further dose reductions could be considered in the opinion of the principal investigator (PI; further reductions followed the scheduled titration).
        - Up titration of OCS dose during optimisation to 1 level higher was not considered an exacerbation.
    - An emergency room or urgent care visit (defined as evaluation and treatment for <24 hours in an emergency department or urgent care centre) due to asthma that required systemic corticosteroids (as per the above).
    - An in-patient hospitalisation (defined as admission to an inpatient facility and/or evaluation and treatment in a healthcare facility for ≥24 hours) due to asthma.

3.5 Spirometry

- Lung function (FEV_1) was measured by spirometry at the trial site using equipment provided by a central vendor.
- All spirometry measurements were performed according to American Thoracic Society/European Respiratory Society (ATS/ERS) guidelines [2].
- All post-randomisation spirometry assessments were performed within ±1.5 hours of the time that the randomisation spirometry was performed.
- The central spirometry vendor reviewed all spirometry results for acceptable technique and selected the best test results based on ATS/ERS recommendations.
- Spirometry recordings considered to be unacceptable by the central spirometry vendor were not used to assess lung function.

3.6 Patient-reported outcomes

Asthma Daily Diary

- The Asthma Daily Diary was completed twice daily (morning on waking and evening prior to going to bed) by patients from the evening of Visit 1 to the morning of Visit 26 using an electronic patient-reported outcome (ePRO) device.
- The twice-daily assessment included morning and evening PEF data, asthma symptoms, rescue medication use, nebuliser treatments, night-time awakenings (due to asthma symptoms) and maintenance medication compliance.
- Asthma symptoms could include, but were not limited to, shortness of breath (dyspnoea), breathlessness, wheezing, coughing, chest tightness and phlegm.
- The investigator/authorised delegate checked the patient's adherence to the Asthma Daily Diary at each visit.
- Asthma symptoms during night-time and daytime were recorded by the patient each morning and evening in the Asthma Daily Diary using a 4-point response scale (0 to 3), where 0 indicated no asthma symptoms. In addition, the morning diary assessment captured night-time awakenings (yes/no) and the use of rescue medication during these awakenings (yes/no).
- Asthma symptom daytime score, night-time score and total score were calculated separately. The total daily symptom score was the sum of the daytime and night-time asthma symptom scores for each day. The total daily symptom score was calculated only when both morning and evening scores were available, otherwise it was set to missing.

Asthma Control Questionnaire-6

- The Asthma Control Questionnaire-6 (ACQ) is a shortened version of the ACQ (omitting FEV_1 measurement) that assesses asthma symptoms (night-time awakenings, symptoms on waking, activity limitation, dyspnoea and wheezing) and rescue SABA medication use during the past week. The questionnaire was completed using the ePRO device.
- Questions were weighted equally and scored on a 7-point scale from 0 (totally controlled) to 6 (severely uncontrolled). The mean ACQ-6 score was the mean of the responses. Mean scores of ≤0.75 indicated well-controlled asthma, scores between 0.75 and ≤1.5 indicated partly controlled asthma and scores >1.5 indicated not well-controlled asthma. Individual changes of at least 0.5 were considered to be clinically meaningful [3].
- The ACQ-6 was first completed by the patient at the trial site at Visit 1, then every 2 weeks throughout the run-in/OCS optimisation period. Patients then completed the ACQ-6 at Visit 6, and following randomisation, patients were asked to complete the ACQ-6 once every 2 weeks throughout the treatment period until the end of treatment visit where the ACQ-6 was completed at the trial site.
- The investigator/authorised delegate checked patient's adherence to the ACQ-6 at each visit.

Asthma Quality of Life Questionnaire standardised for 12 years and older

- The Asthma Quality of Life Questionnaire standardised for 12 years and older (AQLQ) measures health-related quality of life (HRQoL) for patients with asthma aged ≥12 years and older using the ePRO device.
- The questionnaire comprises 4 separate domains (asthma symptoms, activity limitations, emotional function and environmental stimuli). The questionnaire was completed using the ePRO device.
- Patients were asked to recall their experiences during the previous 2 weeks and to score each of the questions on a 7-point scale ranging from 7 (no impairment) to 1 (severe impairment). The overall score was calculated as the mean response to all questions. The 4 individual domain scores (symptoms, activity limitations, emotional function and environmental stimuli) were the means of the responses to the questions in each of the domains. Individual AQLQ total or domain score changes of ≥0.5 were considered to be clinically meaningful.
- The AQLQ was first completed by the patient at the trial site at Visit 1, then every 2 weeks (±1 day) throughout the run-in/OCS optimisation period. Following randomisation (at Visit 6), patients completed the AQLQ and were then asked to complete the questionnaire once

every 4 weeks throughout the treatment period until the end of treatment visit, where the AQLQ was completed at the trial site.

- The investigator/authorised delegate checked patient adherence to the AQLQ at each visit.

4. Statistical analysis of primary, secondary and exploratory endpoints

4.1 General principles

- Summary data were presented by treatment. Categorical data were summarised by the number and percentage of patients in each category. Continuous variables for parametric data were summarised by descriptive statistics including N, mean, standard deviation (SD), median, and range. Minimum and maximum values were reported to the same degree of precision as the raw data unless otherwise stated. Mean, median, SD and confidence intervals (CIs) were reported to 1 further degree of precision.

4.2 Primary and secondary endpoints

- For the primary endpoint, tralokinumab was compared with placebo using an analysis of covariance (ANCOVA) model adjusted for baseline OCS dose as a continuous covariate. For the primary endpoint, the estimated treatment effect (difference in least squares (LS) mean percent reduction in final daily average OCS dose of tralokinumab compared with placebo), corresponding 95% confidence interval (CI) and 2-sided p-value for the difference were calculated. The percent reduction in final daily average OCS dose and the corresponding 95% CI within each treatment group was also calculated. Per the protocol-defined hierarchical testing procedures, if the primary endpoint analysis was not significant, the significance of all subsequent analyses would be declared non-significant.
- For the secondary endpoints (proportion of patients with a prescribed OCS dose of ≤5 mg and those with a ≥50% reduction in prescribed OCS dose), tralokinumab was compared with placebo using a logistic-regression analysis controlling for baseline OCS dose. For these secondary endpoints, the estimated treatment effect between the tralokinumab and placebo groups, corresponding 95% CIs and 2-sided P-values for the differences were calculated. The annual asthma exacerbation rate (AAER) in the tralokinumab group was compared with the placebo group using a negative-binomial model (standard parameterisation approach). For AAER, the estimated treatment effect (i.e. the rate ratio of tralokinumab vs placebo), corresponding 95% CI and the rate ratio were calculated.
- To account for multiplicity, a hierarchical testing strategy was used for the primary and secondary outcomes:

- The difference in the proportion of patients with final OCS dosage ≤5 mg was tested if the p-value for the test of difference in percentage reduction in OCS was <0.05.
- The difference in the proportion of patients with ≥50% reduction was then only tested if both p-values for the tests of difference in percentage reduction in OCS, and difference in the proportion of patients with final OCS dosage ≤5 mg, were <0.05.

4.3 Proportion of patients with a decrease from baseline in their final average OCS dose

- For the proportion of patients with a decreased final OCS dose, change from baseline was classified as decrease in the OCS dosage by specific percentage ranges:
  - 100% reduction (no OCS dose required).
  - ≥90% to <100% reduction.
  - ≥75% to <90% reduction.
  - ≥50% to <75% reduction.
  - >0% to <50% reduction.
  - 0% reduction, i.e. no change in average OCS dose from baseline.
  - Increased OCS dose from baseline.
- The reduction in prescribed daily OCS dose from baseline was calculated descriptively as:
  - *[(Baseline OCS dose – Final OCS dose)/(Baseline OCS dose)] × 100%*

4.4 Percent and least squares mean absolute change from baseline in pre-bronchodilator FEV_1

- Absolute change from baseline was calculated as:
  - (post-randomisation value – baseline value)
- Percentage change from baseline was calculated as:
  - [(post-randomisation value – baseline value)/baseline value] × 100%
- Mixed Model for Repeated Measures (MMRM) was used with change from baseline modelled with treatment group, visit, baseline OCS dose group as fixed effects and number of asthma exacerbations in the past year as a covariate, as well as a treatment group by visit interaction. Restricted Maximum Likelihood (REML) approach within SAS PROC MIXED was used with Kenward-Roger estimate of degrees of freedom and least squares means adjusted for observed covariate distributions.

4.5 Change from baseline in the ACQ-6 and AQLQ

- Change in mean score from baseline at Week 12 and Week 40 for ACQ-6 (including the individual questions) were summarised and analysed using the MMRM approach defined for percent change from baseline in lung function variables. The baseline ACQ-6 mean score was also included in the model.
- The change in score from baseline for AQLQ (including the domain scores) at Week 12 and Week 40 were summarised and analysed using the MMRM approach defined for percent change from baseline in lung function variables. The baseline AQLQ score was also included in the model.
- Least squares means and 95% CIs were presented graphically at each post baseline visit by treatment group.

4.6 Assessment of relationship between baseline FeNO and the treatment effect of tralokinumab on OCS dose reduction and clinical efficacy

- An assessment of the relationship between baseline biomarker (FeNO) and the treatment effect of tralokinumab on OCS dose reduction was undertaken using the following FeNO populations:
    - The **FENO high** population was defined as patients with a baseline FENO ≥37 parts per billion (ppb).
    - The **FENO mid** population was defined as patients with a baseline FENO ≥30 ppb and <37 ppb.
    - The **FENO low** population was defined as those patients with a baseline FENO <30 ppb.

5. Sensitivity analyses (for missing data)

- To assess the robustness of the study to missing data and to address the likelihood that the interpretation of data post discontinuation of investigational products was likely to be confounded by reduced quality of objective confirmation of deterioration, and using subsequent therapies, a number of sensitivity analyses for the primary endpoint and other secondary and exploratory endpoints were explored.
- For the primary and secondary efficacy analysis, imputation methods that were used to assess robustness to missing data included baseline imputation (wherein if a patient withdrew from the study at any point after the baseline assessment and before the Week 40 assessment, the final dose was imputed to be the patient's baseline OCS dose) and average dose imputation (wherein if a patient withdrew from the study at any point after the

baseline assessment and before the Week 40 assessment, the final dose was imputed to be the average daily dose that the patient was taking in the 14 days prior to discontinuation from investigational product or withdrawal from the study [discontinuation from investigational product, if both applied]).

- Results for both imputation methods were consistent with the results of the primary and secondary analyses and did not demonstrate a statistically significant percentage change from baseline in the final daily average OCS dose at Week 40 between tralokinumab and placebo, and regarding the proportion of patients with a final daily average OCS dose of ≤5.0 mg and those with >50% reduction from baseline in final daily average OCS dose at Week 40 (data not shown).

6. Tables

Supplementary Table S1: Patient disposition (All patients analysis)

N (%)	Tralokinumab (N=70)	Placebo (N=70)	Total (N=140)
Patients randomised	70 (100)	70 (100)	140 (100)
Patients who were not randomised			78
Screen failure			71
Development of study-specific withdrawal criteria			2
Protocol deviation			1
Patient withdrawal			3
Other			1
Patients who received treatment	70 (100)	70 (100)	140 (100)
Patients who completed treatment	59 (84.3)	65 (92.9)	124 (88.6)
Patients who discontinued treatment	11 (15.7)	5 (7.1)	16 (11.4)
Adverse event	6 (8.6)	2 (2.9)	8 (5.7)
Lost to follow-up	1 (1.4)	0	1 (0.7)
Patient withdrawal	4 (5.7)	3 (4.3)	7 (5.0)
Patients who discontinued treatment but completed study assessments	4 (5.7)	1 (1.4)	5 (3.6)
Patients who completed the study*	63 (90)	66 (94.3)	129 (92.1)
Patients withdrawn from the study	7 (10)	4 (5.7)	11 (7.9)
Adverse event	2 (2.9)	1 (1.4)	3 (2.1)
Patient withdrawal	4 (5.7)	3 (4.3)	7 (5.0)
Lost to follow up	1 (1.4)	0	1 (0.7)

*Includes patients who completed treatment and patients who discontinued treatment but completed study assessments.
N, total number of patients

Supplementary Table S2: Medical history and other patient baseline characteristics (full analysis set)*

Characteristic	Tralokinumab (N=70)	Placebo (N=70)	Total (N=140)
Age group, n (%)			
≥12 to <18 years	1 (1.4)	0	1 (0.7)
≥18 to <50 years	20 (28.6)	16 (22.9)	36 (25.7)
≥50 to <65 years	38 (54.3)	39 (55.7)	77 (55)
≥65 years	11 (15.7)	15 (21.4)	26 (18.6)
Number of exacerbations resulting in hospitalisation in <12 months, n (%)			
0	44 (62.9)	49 (70)	93 (66.4)
1	16 (22.9)	10 (14.3)	26 (18.6)
2	3 (4.3)	2 (2.9)	5 (3.6)
>2	3 (4.3)	1 (1.4)	4 (2.8)
Asthma medication, n (%)			
ICS	69 (98.6)	70 (100)	139 (99.3)
LABA	70 (100)	70 (100)	140 (100)
LAMA	18 (25.7)	25 (35.7)	43 (30.7)
LTRA	16 (22.9)	22 (31.4)	38 (27.1)
Xanthine derivatives	2 (2.9)	8 (11.4)	10 (7.1)
Other asthma medications	3 (4.3)	9 (12.9)	12 (8.6)
Medical history, n (%)			
Sleep apnoea syndrome	4 (5.7)	10 (14.3)	14(10)
Allergic rhinitis	4 (5.7)	5 (7.1)	9 (6.4)
Atopic dermatitis	0	2 (2.9)	2 (1.4)
Eczema	0	1 (1.4)	1 (0.7)
Perennial rhinitis	0	1 (1.4)	1 (0.7)

*The full analysis set consisted of all patients who were randomised and received any dose of either tralokinumab or placebo irrespective of their protocol adherence and continued participation in the trial.

ICS, inhaled corticosteroids; LABA, long-acting β_2-agonists; LAMA, long-acting muscarinic receptor antagonists; LTRA, leukotriene receptor antagonists; N, total number of patients; n, number of patients.

Supplementary Table S3: Summary of patients with OCS dose optimisation (full analysis set)*		
	Tralokinumab (N=70)	**Placebo (N=70)**
Patients who entered dose optimisation†, n (%)	48 (68.5)	48 (68.5)
Week −8‡	46 (95.8)	44 (91.6)
Week −6‡	15 (31.3)	12 (25)
Week −4‡	1 (2)	2 (4.1)
Week −2‡	2 (4.1)	0
Average dose reduction from entry to optimised dose	1.36 mg	0.99 mg

*The full analysis set consisted of all patients who were randomised and received any dose of either tralokinumab or placebo irrespective of their protocol adherence and continued participation in the trial.

†The number of patients entering the OCS dose optimisation phase were represented as percentage of the total number of patients in each group.

‡The patients achieving optimised OCS dose each week was calculated as a percentage of the total number of patients entering optimisation phase.

N, total number of patients; n, number of patients; OCS, oral corticosteroids.

Supplementary Table S4: Summary of asthma exacerbations (full analysis set)[*]

	Tralokinumab (N=70)	**Placebo (N=70)**
Patients with ≥1 exacerbation, n (%)	47 (67.1)	53 (75.7)
Mean±SD number of exacerbations per patient	1.3±1.50	1.6±1.39
Total days of exacerbations	925	1201
Total days of exacerbations per patient±SD	13.2±16.89	17.2±17.63
Total days of exacerbations/total patient-treatment years	17.37	22.41
Exacerbations requiring hospitalisation or emergency room visit[†], n (%)	7 (10.0)	12 (17.1)

[*]The full analysis set consisted of all patients who were randomised and received any dose of either tralokinumab or placebo irrespective of their protocol adherence and continued participation in the trial.
[†]As assessed by the investigators at trial sites.
N, total number of patients; n, number of patients; SD, standard deviation.

Supplementary Table S5: Proportion of patients with reduction in the final daily average OCS dose at Week 40 from baseline (full analysis set)[*]

	Tralokinumab (N=70)	Placebo (N=70)
Patients with change in OCS dose, n (%)		
Increase	5 (7.1)	5 (7.1)
No change	18 (25.7)	22 (31.4)
>0% to <50% reduction	16 (22.9)	17 (24.3)
≥50% to <75% reduction	8 (11.4)	13 (18.6)
≥75% to <90% reduction	15 (21.4)	6 (8.6)
≥90% to <100% reduction	2 (2.9)	1 (1.4)
100% reduction	6 (8.6)	6 (8.6)
≥25% reduction with a final daily average OCS dose of ≤5.0 mg	32 (45.7)	28 (40)
≤5 mg reduction	43 (61.4)	52 (74.3)

[*]The full analysis set consisted of all patients who were randomised and received any dose of either tralokinumab or placebo irrespective of their protocol adherence and continued participation in the trial.
N, total number of patients; n, number of patients; OCS, oral corticosteroid.

Supplementary Table S6: Summary of FeNO subgroup analysis for efficacy endpoints

Endpoint	All comers		FeNO ≥37 ppb		FeNO <37 ppb	
	Tralokinumab (N=70)	Placebo (N=70)	Tralokinumab (n=23)	Placebo* (n=21)	Tralokinumab (n=47)	Placebo (n=47)
Primary endpoint: Final daily average OCS dose						
Median % reduction	33.3	25	25.0	25.0	33.3	25.0
Mean % reduction, ANCOVA	37.62	29.85	37.73	32.27	37.56	28.62
Treatment effect, % (95% CI)	7.78% (–6.15, 21.70)		5.46% (–20.12, 31.03)		8.94% (–8.28, 26.25)	
Secondary endpoints						
Proportion of patients with final daily average OCS ≤5 mg						
Proportion, %	46.0	40.0	30.4	47.6	53.2	36.2
OR (95% CI)	1.33 (0.65, 2.73)		0.73 (0.19, 2.72)		1.77 (0.73, 4.29)	
Proportion of patients with ≥50% reduction from baseline in final OCS dose						
Proportion, %	44.0	37.0	39.1	42.9	46.8	34.0
OR (95% CI)	1.38 (0.70, 2.74)		1.08 (0.31, 3.74)		1.59 (0.68, 3.70)	
Asthma exacerbations						
AAER	1.84	2.31	1.73	2.19	1.89	2.31
RR (95% CI)	0.80 (0.57, 1.12)		0.79 (0.42, 1.49)		0.82 (0.54, 1.24)	

*No FeNO levels were recorded for 2 patients in the placebo group.

AAER, annual asthma exacerbations rate; ANCOVA, analysis of covariance; CI, confidence interval; FeNO, fractional exhaled nitric oxide; OCS, oral corticosteroids; OR, odds ratio; RR, rate ratio.

Supplementary Table S7: Summary of SAEs (safety analysis population)*		
	Tralokinumab (N=70)	**Placebo (N=70)**
Any SAE, n (%)	9 (12.9)	16 (22.9)
System organ class and preferred term, n (%)		
Respiratory, thoracic and mediastinal disorders (Asthma)	5 (7.1)	8 (11.4)
Infections and infestations	1 (1.4)	2 (2.9)
Bronchitis	1 (1.4)	1 (1.4)
Influenza	0	1 (1.4)
Urinary tract infection	0	1 (1.4)
Neoplasms benign, malignant and unspecified	1 (1.4)	1 (1.4)
Uterine leiomyoma	0	1 (1.4)
Breast cancer Female	1 (1.4)	0
Gastrointestinal disorders (Colitis)	0	1 (1.4)
Renal and urinary disorders (Acute kidney injury)	0	1 (1.4)
Reproductive system and breast disorders (Vaginal prolapse)	0	1 (1.4)
Investigations	1 (1.4)	1 (1.4)
Pulmonary function test abnormal	1 (1.4)	0
Weight decreased	0	1 (1.4)
Injury, poisoning and procedural complaints	1 (1.4)	1 (1.4)
Hand fracture	1 (1.4)	0
Rib fracture	0	1 (1.4)

*The safety analysis population consisted of all patients who received any dose of the interventions.
N, total number of patients; n, number of patients; SAE, serious adverse event.

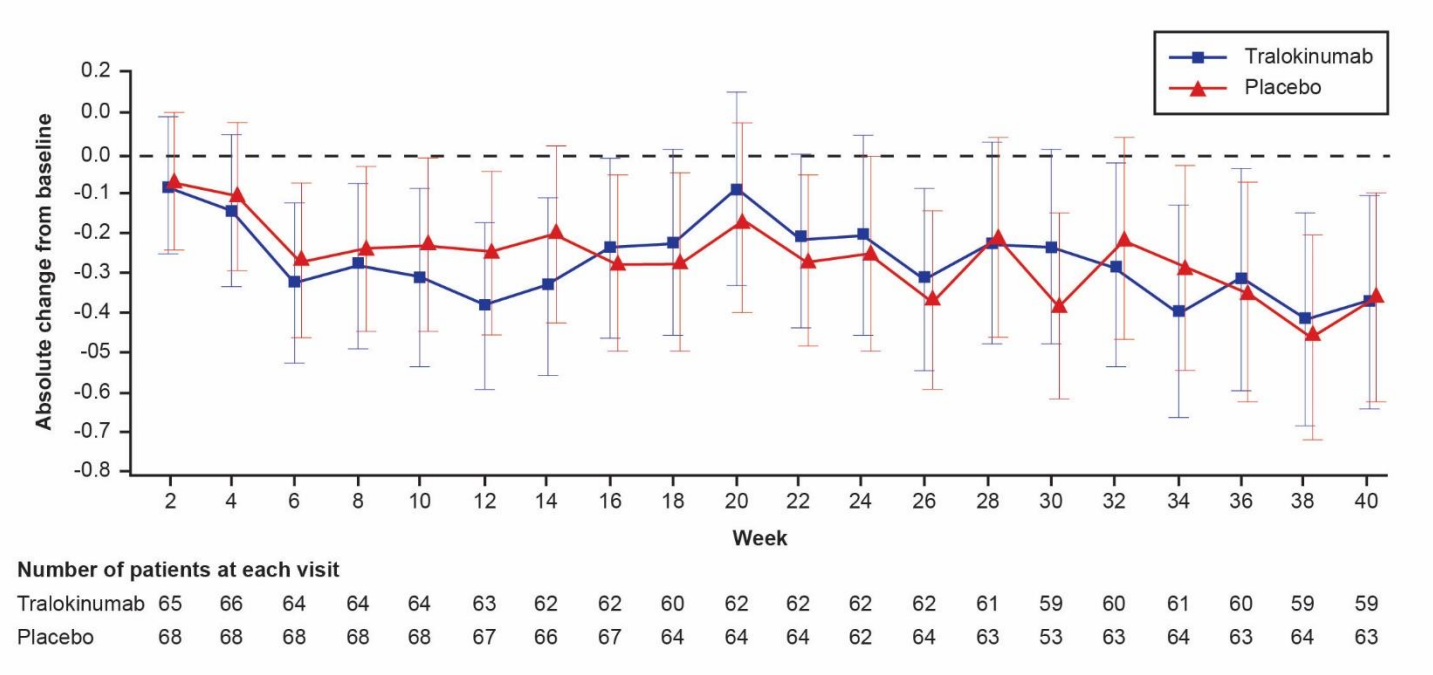
Supplementary Table S8: Summary of AEs reported as severe infections by high level group term, high level term and preferred term (safety analysis population)[*]

High level group term/ High level term/ Preferred term	Tralokinumab (N=70)	Placebo (N=70)
Patients with AE reported as a severe infection, n (%)	6 (8.6)	5 (7.1)
Viral infectious disorders	3 (4.3)	4 (5.7)
Viral infections NEC	2 (2.9)	2 (2.9)
Respiratory tract infection viral	2 (2.9)	1 (1.4)
Viral upper respiratory tract infection	0	1 (1.4)
Herpes viral infections	1 (1.4)	1 (1.4)
Herpes zoster	1 (1.4)	0
Oral herpes	0	1 (1.4)
Influenza viral infections	0	1 (1.4)
Influenza	0	1 (1.4)
Infections - pathogen unspecified	2 (2.9)	2 (2.9)
Infections NEC	1 (1.4)	0
Respiratory tract infection	1 (1.4)	0
Lower respiratory tract and lung infections	1 (1.4)	1 (1.4)
Bronchitis	1 (1.4)	1 (1.4)

[*]The safety analysis population consisted of all patients who received any dose of the interventions.
- Number (%) of patients with AE with severe infections were sorted in descending frequency for high level group term, high level term, and preferred term in patients treated with Tralokinumab.
- Patients with multiple AEs with severe infection were counted once for each high level group term/high level term/preferred term.
- Patients experiencing a severe infection were defined as/resulting in: i) life-threatening, ii) requiring hospitalization, iii) requiring treatment with antiviral medications, intravenous antibiotics or medications for helminth parasitic infections or, iv) a permanent discontinuation of study drug.

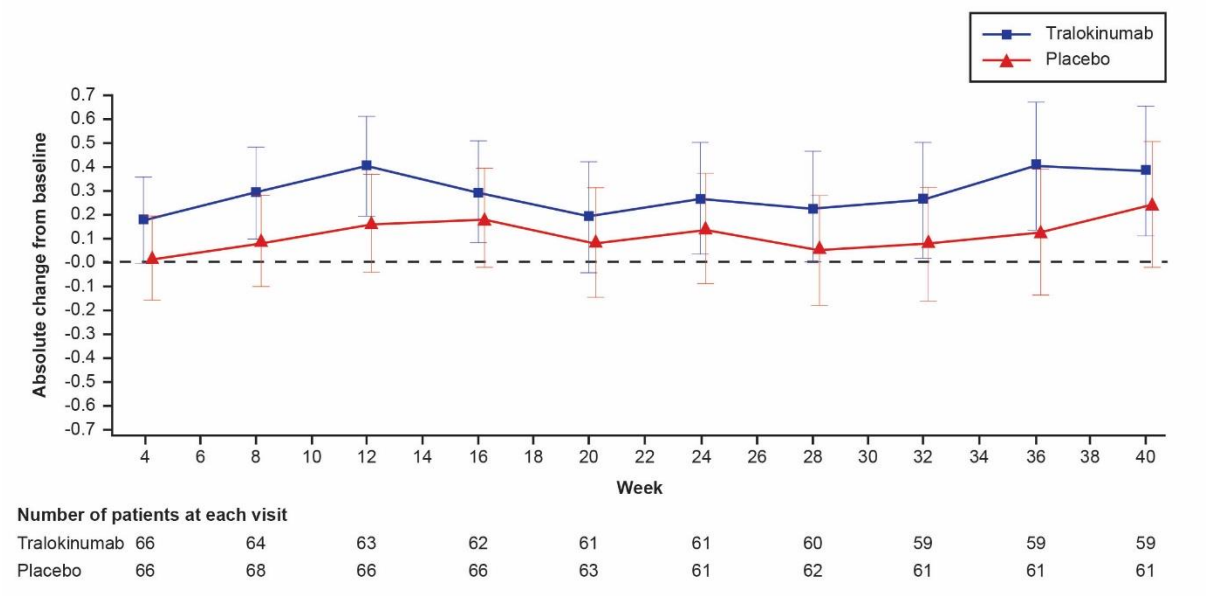
AE, adverse event; N, total number of patients; n, number of patients.

7. Figures



Supplementary Figure S1: Mean change from baseline in ACQ-6 score at Week 40 (full analysis set)

ACQ-6 score was defined as the unweighted mean of the responses to all questions in the questionnaire. If response to any of the questions was missing, the overall score was missing.
LS means and 95% CIs are presented.
The number of patients at each visit in each group is shown below the graph.
ACQ-6, Asthma Control Questionnaire-6; CI, confidence interval; LS: least squares.



Supplementary Figure S2: Mean change from baseline in AQLQ score at Week 40 (full analysis set)

AQLQ score was defined as the unweighted mean of the responses to all questions in the questionnaire. If response to any of the questions was missing, the overall score was missing.
LS means and 95% CIs are presented.
The number of patients at each visit in each group is shown below the graph.
AQLQ, Asthma Quality of Life Questionnaire standardised for 12 years and older; CI, confidence interval; LS, least squares.

8. **References**

1. Dweik RA, Boggs PB, Erzurum SC, et al. An official ATS clinical practice guideline: interpretation of exhaled nitric oxide levels (FENO) for clinical applications. Am J Respir Crit Care Med 2011; 184: 602-615.
2. Miller MR, Hankinson J, Brusasco V, et al. Standardisation of spirometry. Eur Respir J 2005; 26: 319-338.
3. Juniper EF, Bousquet J, Abetz L, et al. Identifying 'well-controlled' and 'not well-controlled' asthma using the Asthma Control Questionnaire. Respir Med 2006; 100: 616-621.