CLINICAL INVESTIGATION

TROPOS: designing a clinical trial to evaluate the oral corticosteroid-sparing effect of a biologic in severe asthma

In a Phase IIb study, administration of tralokinumab, an anti-IL-13, fully human monoclonal antibody, to patients with severe uncontrolled asthma treated with high-dose inhaled corticosteroid (ICS) and long-acting β2-agonists (LABA) significantly improved lung function. Since many patients with severe asthma using ICS-LABA only achieve symptom control with add-on oral corticosteroids (OCS), an unmet need for OCS-sparing treatment strategies exists. This Phase III, randomized, double-blind, parallel-group, placebo-controlled TROPOS (NCT02281357) study will evaluate the OCS-sparing potential of tralokinumab in patients with severe asthma requiring continuous ICS-LABA and chronic maintenance OCS. After an initial screening/assessment period, patients will be randomized to tralokinumab or placebo for 40 weeks (12-week induction, 20-week OCS reduction and 8-week maintenance phases); patients will be followed-up for 14 weeks.

Keywords: anti-IL-13 monoclonal antibody • biologic • clinical trial design • IL-13 • oral corticosteroids • severe asthma • tralokinumab

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Asthma affects approximately 300 million people worldwide and its prevalence continues to rise, both in developing countries and in some western countries [1]. Of this population, 5–10% of patients have severe asthma [2], which is defined by a requirement for treatment with high-dose inhaled corticosteroids (ICS) and a long-acting inhaled β2-agonist (LABA), with or without additional medications, to control symptoms and prevent exacerbations [1]. Although the proportion of patients with severe uncontrolled asthma is small, this population accounts for the greatest proportion of healthcare costs in asthma [3].

Patients with severe asthma who cannot achieve symptom control on ICS-LABA alone are often prescribed maintenance oral corticosteroids (OCS) as an additional asthma controller [1]. However, sustained use of OCS is associated with significant side effects, including growth retardation in children, as well as osteoporosis, diabetes, cardiovascular adverse events, weight gain, muscular weakness, bruising and cataracts [4]. Consequently, therapies which reduce the need for OCS exposure in patients with severe uncontrolled asthma are urgently needed. Biologics are one such alternative therapy. Unlike OCS, biologic agents can be precisely targeted against factors that contribute to disease severity, such as inflammation-promoting interleukins.

Tralokinumab is a fully human monoclonal antibody that specifically blocks signal transduction via IL-13, a central mediator implicated in the key pathological features of asthma, by preventing its interaction with the IL-13 receptor [5–8]. Multiple observations suggest that the ICS and OCS used to treat asthma will affect the IL-13 axis. Mechanistically, dexamethasone has been shown to inhibit IL-13 production via a glucocorticoid receptor-mediated inhibition of c-Jun phosphorylation and induced by JNK [9]. Elevated levels of Th2 cytokines have been reported in nasal lavage samples from patients with allergic rhinitis induced by grass pollen [10,11]. Administration of fluticasone propionate (100 µg twice daily

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[b.i.d.], intranasal route) [10] or budesonide (100 μg b.i.d., intranasal route) [11] reduced clinical symptoms and IL-13 levels. In a study of patients with mild-to-moderate asthma [12], patients with high levels of Th2 cytokines treated with inhaled fluticasone showed improvements in clinical features while those patients with low levels of Th2 cytokines did not. IL-13 overexpression has been detected in sputum and bronchial biopsy samples from patients with severe asthma that is uncontrolled despite treatment with ICS [13]. IL-13 expression has been shown to be attenuated in patients with asthma who are clinically responsive to corticosteroids [13]. In the BIOAIR study, which included patients with mild and severe asthma, serum levels of the IL-13 biomarker, periostin, were significantly reduced by oral prednisolone [14]. Furthermore, although there was no difference in baseline periostin levels between patients with mild and severe disease, greater baseline concentrations of periostin tended to be associated with response to steroid treatment [14]. Taken together, these findings demonstrate that either ICS or OCS may attenuate the IL-13 axis in patients with inflammatory lung disease and moreover suggest that targeted therapy directed to IL-13 signaling might provide OCS-sparing benefits in patients with asthma.

In a Phase IIb study in patients with uncontrolled severe asthma, tralokinumab 300 mg administered every 2 weeks did not significantly reduce the annual asthma exacerbation rate, but was associated with improved lung function (improvement from baseline in forced expiratory volume in 1 s [FEV_1]) in the overall population [15]. Exploratory *post hoc* analyses showed significant improvements in FEV_1, exacerbations and asthma symptoms, as assessed by the asthma control questionnaire-6 in a subpopulation of patients who demonstrated reversibility to bronchodilators on study entry (reversibility ≥12% and ≥200 ml in FEV_1), not receiving chronic OCS, and with baseline levels of periostin or DPP-4 above median at baseline. The beneficial effect of tralokinumab appeared to have been attenuated in patients who were chronically using OCS. However, these *post hoc* analyses should be interpreted cautiously because of the small number of patients; a larger study is warranted.

The possible benefit of tralokinumab in treating patients with severe persistent asthma, and who require chronic OCS therapy, is an important issue because of the clinical need. The Phase III clinical development program for tralokinumab includes two pivotal trials, both of which exclude patients receiving chronic OCS. Consequently, it was deemed most appropriate to study this group separately in the tralokinumab Phase III program and investigate whether treatment with tralokinumab may allow reduction of OCS dosage. This Phase III study (TROPOS, NCT02281357) [16] will assess the OCS-sparing effects of tralokinumab versus placebo in patients with severe asthma.

Study design

TROPOS is a Phase III, randomized, double-blind, parallel-group, multicenter, placebo-controlled study in patients with severe asthma who require continuous treatment with ICS-LABA, and chronic treatment with maintenance OCS therapy. Approximately 120 patients will be randomized from 50 participating study sites in the USA and Europe (Belgium, France, Germany and the Netherlands). After the initial enrollment (visit 1) and confirmation of entry criteria, subjects will enter either a 2-week run-in period (if there has been a documented failure of OCS dose reduction within 6 months prior to visit 1) or a 2-week run-in period plus an 8-week optimization period to establish a minimum effective dose of the prescribed OCS (established by dose titration every 2 weeks). Patients who fulfill the eligibility criteria will be randomized to enter a 40-week treatment period with two follow-up safety visits at weeks 44 and 54 (Figure 1). Subjects will be maintained on their currently prescribed ICS plus LABA and any additional controller medication, without change, from enrollment, throughout the run-in/optimization and treatment periods.

The study is designed to ensure that patients are receiving the optimal OCS dose prior to entering the 40-week treatment period. Any patient who had a clinically documented failure of OCS dosage reduction within the 6 months prior to visit 1, indicated by a reduction in lung function or deterioration in asthma control (according to appropriate clinical criteria), will (after confirmation with the sponsor study physician) be deemed to be on the optimal OCS dose. These patients will proceed directly to the treatment period after a 2-week run-in period. The intent of this approach is to minimize the unnecessary risks of an OCS dose-reduction process, if recently performed and failed. Patients who have not failed OCS dosage reduction in the 6 months prior to visit 1 will be required to complete the OCS optimization period. During the OCS optimization period, patients will remain on their current ICS-LABA treatment, while their OCS dosage is titrated down at 2-week intervals according to a prespecified titration schedule. The minimum effective OCS dosage reached during this phase, prior to randomization, will be used when the patient commences the 40-week treatment period and will be considered as their baseline OCS dosage for the final analysis.

The 40-week treatment period will be divided into three phases. During the induction phase (weeks 0–12) patients will remain on their established asthma control-

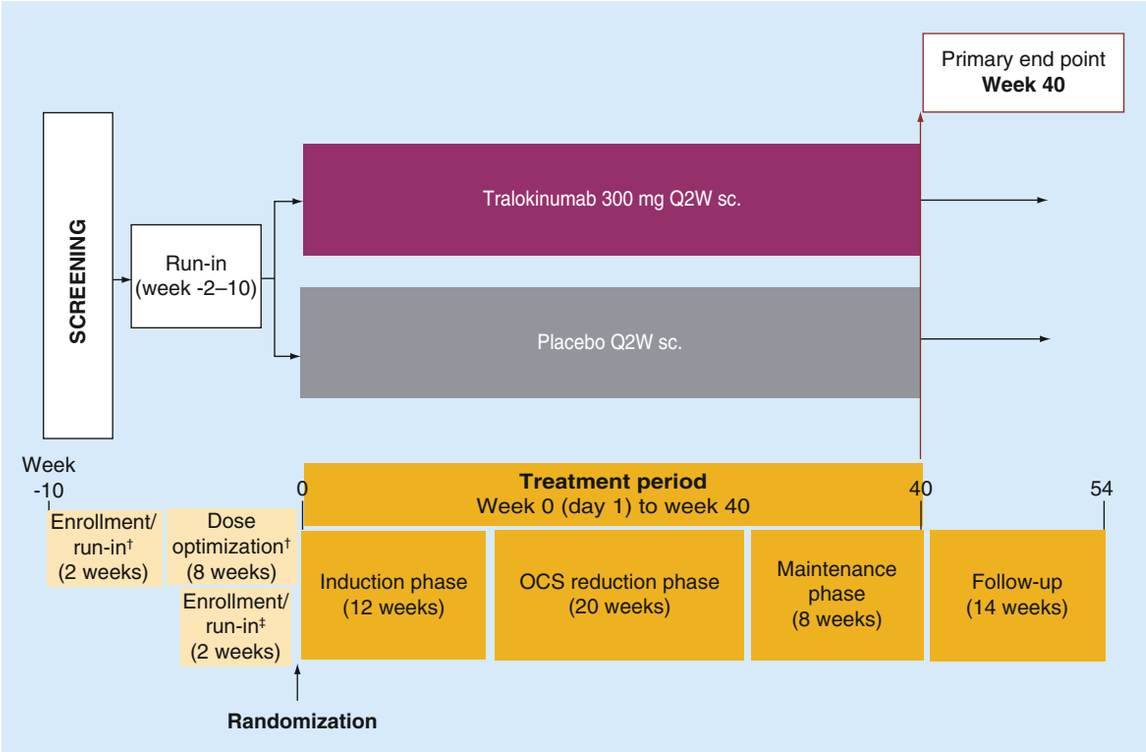

Figure 1. TROPOS study design.
†Subjects undergoing optional dose optimization (can be omitted if the patient has undergone dose adjustment).
‡Subjects with documented failure of OCS reduction within 6 months prior to visit 1.
CS: Oral corticosteriods; Q2W: Every 2 weeks; sc.: Subcutaneously.

ler medications and continue with their baseline OCS dosage, with concomitant administration of study drug (either tralokinumab or placebo). In the OCS reduction phase (weeks 12–32), the OCS dosage will be decreased at 4-week intervals, again according to a prespecified titration schedule. For the final phase, maintenance (weeks 32–40), patients continue on the stable OCS dosage achieved during the reduction phase (which may be zero), unless an asthma exacerbation occurs. The follow-up period consists of two visits at weeks 44 and 54 to complete the safety follow-up assessments.

During the OCS dose optimization and the OCS dose-reduction periods, each dose reduction may only proceed if the patient meets the following criteria: for each of the 14 days prior to the clinic visit, the patient must have had morning peak expiratory flow ≥80% of their baseline mean value; ≤50% increase from baseline in nighttime awakening; mean rescue medication use not more than four puffs/day above baseline mean or 12 puffs/day overall and no asthma exacerbations requiring a burst of systemic corticosteroids. Additionally, the patient must demonstrate FEV_1 ≥80% of baseline and ≥40% of the predicted volume at the clinic visit. Finally, the investigator must also judge that the patient's asthma control is sufficient to allow OCS dose reduction.

Eligible patients will be randomized in a 1:1 ratio, stratified by baseline OCS dosage and age group (adults [≤10 mg vs >10 mg prednisone or prednisolone] vs adolescents), to receive either tralokinumab 300 mg (150 mg/ml) or placebo every 2 weeks during the treatment period, administered subcutaneously as two 1 ml injections. Patients will continue their regular ICS-LABA asthma controller therapy regimen without change, throughout the study.

This study is sponsored by AstraZeneca. Written informed consent will be obtained from all patients before initiation into the study. The study will comply with the Declaration of Helsinki, the International Conference on Harmonisation guidelines, local ethics committee needs, applicable regulatory requirements and the AstraZeneca policy on Bioethics and Human Biological Samples.

Objectives & outcome measures

Efficacy evaluations

The primary objective of this study is to evaluate the efficacy of tralokinumab compared with placebo in reducing the need for OCS maintenance dosage in patients with asthma requiring chronic treatment with maintenance OCS in addition to ICS-LABA. This will be assessed by the percentage change from baseline

in the average OCS dose at week 40, without loss of asthma control. The secondary objectives are to assess the effect of tralokinumab on the proportion of these patients with a prescribed OCS maintenance dosage ≤5 mg at the end of the treatment period, and the proportion with at least 50% reduction in prescribed OCS maintenance dosage, both compared with placebo. For assessment of the primary and secondary efficacy objectives, the baseline OCS dosage is taken as the dosage at randomization, regardless of whether the patient has undergone dosage optimization.

Exploratory assessments

The TROPOS study will also investigate a number of exploratory outcome measures (Box 1).

Safety evaluations

During the study, the safety and tolerability of tralokinumab will be evaluated by monitoring of adverse events and serious adverse events, vital signs, digital electrocardiogram, clinical chemistry, hematology and urine analysis, plus physical examinations. Potential immunogenicity will also be assessed by the incidence rate of antidrug antibodies and characterization of their neutralizing potential.

Biomarker evaluations

Blood samples will be collected and may be analyzed to assess the relationship between exploratory biomarkers and disease activity, effects of tralokinumab, clinical outcomes and toxicity. The main biomarkers that will be measured are periostin, DPP-4, blood eosinophils, total serum IgE and fractional exhaled nitric oxide, but other exploratory blood biomarkers may also be analyzed. Patients' consent will be obtained for the use of donated biological samples for nonexploratory analysis purposes.

Pharmacokinetic evaluations

Pharmacokinetic parameters to be assessed include C_{trough} at steady state.

Inclusion & exclusion criteria

Key inclusion and exclusion criteria are shown in Box 2. Prior to randomization, all patients must additionally demonstrate a minimum of 70% compliance with their OCS use, with their regular asthma controller regimen (ICS-LABA plus any other asthma controller medications) and with the eDiary assessment schedule. Adherence to both OCS and controller medications will be assessed by eDiaries.

Statistical considerations

The sample size estimation was based on a targeted difference in the percentage reduction in OCS dosage between the tralokinumab and placebo groups of 50%. Based on previous OCS reduction studies, an estimate of 80% was used for the standard deviation. Using these parameters, and assuming a type I error rate of 5% and at least 90% power, at least 55 patients are required per treatment group. To allow for patient attrition, the target number of randomized patients is 120.

To account for multiplicity, a hierarchical testing strategy will be used for the primary and secondary outcomes. The difference in the proportion of patients with final OCS dosage ≤5 mg will only be tested if the p-value for the test of difference in percentage reduction in OCS is <0.05. The difference in the proportion of patients with ≥50% reduction will then only be 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, are <0.05.

Sensitivity analyses will be performed to assess both the effect of missing data and deviations from the assumptions underlying the primary analysis.

Discussion & conclusion

Tralokinumab is a fully human monoclonal antibody of the IgG4λ subclass targeted against IL-13 [6,8], which prevents the interaction of IL-13 with both IL-13Rα1 and IL13-Rα2. Extensive *in vitro*, animal and human experimental work has suggested that IL-13 plays an important role in the pathogenesis of asthma. A Phase IIb trial demonstrated that tralokinumab significantly improves FEV_1 in patients with severe uncontrolled asthma [15]. *Post hoc* analyses of this study suggest that the greatest benefit with tralokinumab may be seen in patients with reversible airway obstruction, with high levels of IL-13-associated biomarkers, and who are not receiving chronic OCS treatment. However, these analyses were based on a small number of patients, and therefore should be interpreted with caution.

The tralokinumab clinical development program, consisting of two pivotal Phase III trials in patients with severe asthma: STRATOS 1 (NCT02161757) [24] and STRATOS 2 (NCT02194699) [24], has excluded patients without reversible airway obstruction and who are receiving chronic OCS. Consequently, this program will not address the important clinical question of how best to manage the asthma patient receiving OCS. As there is evidence that cessation of OCS in patients with asthma with an active IL-13 axis may result in increased IL-13 expression [Medimmune, Data on File], there may be a rationale for using an anti-IL-13 agent in these patients to enable OCS reduction. Since precision biologic therapy appears a reasonable OCS-sparing approach in patients with severe asthma, the separate Phase III TROPOS clinical trial has been

Box 1. Exploratory outcome measures.

Outcomes & assessments and/or definitions

- Oral corticosteroids exposure
  - Area under the dose curve
  - Proportion of patients that have decreased their daily average oral corticosteroids dosage by specific percentage ranges (100, 50–99, 1–49 and 0% from baseline)
- Asthma exacerbation rate
  - Asthma exacerbation is defined as:
    - A worsening of asthma symptoms requiring a temporary burst of systemic corticosteroids for at least 3 days
    - An asthma-related emergency room or urgent care visit that required systemic corticosteroids
    - An inpatient hospitalization due to asthma
- Lung function
  - Parameters assessed include:
    - Percentage change from baseline pre-bronchodilator forced expiratory volume in 1 s
    - Forced vital capacity
    - Forced expiratory flow between 25 and 75% of forced vital capacity
- Asthma symptoms and control
  - Change from baseline in the biweekly mean daily asthma symptom score (combined daytime and nighttime score as captured in the Asthma Daily Diary) [17]
  - Rescue medication use (captured using the eDiary)
  - Morning and evening home peak expiratory flow
  - Nighttime awakening due to asthma.
  - Asthma Control Questionnaire-6 scores [18,19]
- Health-related quality of life
  - Standardized Asthma-Related Quality of Life Questionnaire for 12 Years and Older [20]
  - European Quality of Life – 5 Dimensions – 5 Level questionnaire [21]
- Asthma-specific resource utilization
  - Unscheduled physician visits or phone calls
  - Use of additional asthma medications
- Productivity loss due to asthma
  - Work productivity and Activity Impairment Questionnaire [22] and Classroom Impairment Questionnaire [23] scores

designed to specifically address whether tralokinumab treatment will achieve this objective.

The TROPOS study incorporates several important methodological components. Firstly, to ensure that patients are receiving the lowest appropriate OCS dose at baseline, this study incorporates a novel OCS dose-optimization approach. Regular reassessment of OCS dose is recommended by asthma management guidelines [1]; if a patient has had a reduction in OCS dose as part of their asthma care that resulted in clinical deterioration in the 6 months prior to study oasis:entry, this can be accepted as evidence that the patient's OCS dose is currently optimal. A further attempt at OCS dose reduction would represent an undue safety concern in these patients. However, if OCS dose reduction has not taken place in the previous 6 months as part of standard clinical care, then a standardized 8-week OCS dose-optimization period is included, during which the OCS dose is gradually reduced.

Another important feature of the study design is the 12-week induction phase. This was incorporated into the TROPOS study design to ensure maximal effect on FEV_1, based on previous findings from the tralokinumab clinical development program in patients with severe asthma [15,25]. Previous studies to evaluate the OCS-sparing effects of ICS in asthma have incorporated OCS dose-reduction periods of various durations into their methodologies; however, use of an induction period has been less widely used [26–28].

The use of an OCS dose-optimization period followed by an induction period is similar in design to a recent study of an anti-IL-5 humanized monoclonal antibody (the SIRIUS study) in patients with eosinophilic asthma, which demonstrated OCS-sparing effects [29]. This study used a shorter induction period than TROPOS (0–4 weeks vs 12 weeks, respectively), and also differed from the present study in that the optimization period was mandatory, with no option to omit optimization for any patients with recent failure of OCS dosage reduction. Additionally, in the SIRIUS study, the OCS dosage was reduced at weekly intervals over 2–8 weeks, while TROPOS uses a 2-weekly dose-reduction schedule over 8 weeks,

Box 2. Key inclusion and exclusion criteria.

Key inclusion criteria

- Female or male, aged 12–75 years inclusive, weight ≥40 kg and <150 kg at enrollment
- Documented physician-diagnosed asthma for ≥12 months prior to enrollment with the patient requiring treatment with medium-to-high dose inhaled corticosteroids (total daily dose ≥500 µg fluticasone propionate dry powder or equivalent delivered dose) for ≥6 months prior to enrollment
- Documented treatment with inhaled corticosteroids (total daily dose corresponding to ≥500 µg fluticasone propionate dry powder formulation equivalents) and a long-acting β2-agonist for ≥3 months prior to enrollment
- Received oral corticosteroids for treatment of asthma for 6 months prior to visit 1 and on stable oral corticosteroids dose ≥7.5 mg to ≤30 mg (prednisone or prednisolone equivalent) daily for ≥1 month prior to enrollment
- Predicted normal value for morning pre-bronchodilator forced expiratory volume in 1 s ≥40% and <80% (<90% for patients 12–17 years)
- Post-bronchodilator reversibility in forced expiratory volume in 1 s of ≥12% and ≥200 ml at enrollment, or documented reversibility ≤6 months prior to enrollment
- Additional maintenance asthma controller medications are permitted according to standard practice of care, but must be stable for 3 months prior to enrollment and remain unchanged throughout the study

Key exclusion criteria

- Clinically important pulmonary disease other than asthma, associated with elevated peripheral eosinophil counts
- Clinically significant infection requiring antibiotics or antiviral medication ≤30 days prior to date of informed consent
- Clinically significant asthma exacerbation ≤30 days prior to informed consent or during run-in period
- Asthma control reached at oral corticosteroids dose ≤5 mg during run-in or oral corticosteroids optimization period
- For patients undergoing dose optimization, qualified for three consecutive dose reductions at visits 2–4 and who continue to meet dose-reduction criteria at visit 5
- Any clinically significant abnormal findings during the run-in period
- History of cancer, hepatitis B or C, or HIV
- Current tobacco smoking or history of tobacco smoking for ≥10 pack-years
- Pregnant or breastfeeding
- Previous receipt of tralokinumab
- History of anaphylaxis following any biologic therapy

thus allowing more time for assessment of the effect of each OCS dose reduction. Moreover, TROPOS was powered to detect tralokinumab-associated OCS reduction over placebo after 40 weeks of treatment, thus demonstrating robust longer term efficacy compared with that reported in the 24-week SIRIUS study [29], or the ICS studies mentioned above (12–26 weeks) [26–28].

The exploratory objectives of the TROPOS study include assessment of the relationship between biomarkers of IL-13 activity and the effect of tralokinumab on OCS dose reduction. Measurement of these biomarkers of IL-13 activity, particularly periostin and DPP-4 [15,30], will allow reciprocal evaluation of this relationship: baseline biomarker levels may predict the extent of OCS dose reduction, and OCS dose reduction may itself impact biomarker levels. A robust relationship between these factors could facilitate identification of the subset of patients who are most likely to benefit from tralokinumab treatment or OCS dose reduction, potentially allowing patients to benefit from more personalized, targeted asthma therapy. In summary, due to the adverse events associated with long-term OCS use, OCS-sparing therapies are urgently needed for patients who require long-term OCS to maintain asthma control. The Phase III TROPOS study will evaluate the clinical benefits of tralokinumab in this important patient population.

Future perspective

We are entering an era of personalized healthcare in respiratory diseases such as asthma. Recent advances in the understanding of the complex pathophysiology of asthma have enabled the development of precision therapies that target specific inflammatory pathways. These new therapies offer alternatives for patients whose symptoms remain uncontrolled despite current standard of care treatments. In addition, precision therapies may facilitate a reduced dependence on OCS in order to maintain adequate levels of control. Biomarkers may help guide which patients will benefit most from specific treatment approaches.

Financial & competing interests disclosure

WW Busse reports personal fees from Novartis, Pfizer, Roche, GlaxoSmithKline, AstraZeneca, Genentech, Boston Scientific, Circassia and ICON; and grants from NIH-NIAID and NIH-NHLBI, outside the submitted work. M Wang, J Gibson, M Gottlow, G Colice and M Braddock are all employees of AstraZeneca. G Colice has also been a consultant, advisor and speaker for Teva, Boehringer-Ingelheim and Dey Pharma. This study is sponsored by AstraZeneca. The authors have no other relevant affiliations or financial involvement with any organization or entity with a financial interest in or financial conflict with the subject matter or materials discussed in the manuscript apart from those disclosed.

The authors thank J Gamage, from QXV Communications, an Ashfield business, part of UDG Healthcare plc, who provided medical writing support funded by AstraZeneca.

Executive summary

Background

- Many patients with severe asthma find that their symptoms are poorly controlled or uncontrolled, despite treatment with high-dose inhaled corticosteroid and long-acting β2-agonists and maintenance oral corticosteroids (OCS).
- Reduction of OCS exposure is a key challenge for treatment of patients with severe uncontrolled asthma.
- New biologics in clinical development for severe asthma may have OCS-sparing properties.
- Tralokinumab is a fully human monoclonal antibody that inhibits multiple IL-13-mediated effects on a variety of cell types involved in inflammation; previous studies have shown that it is effective in improving lung function in patients with asthma.

Study rationale

- Treatment with adjunctive tralokinumab may allow patients to reduce their maintenance OCS dosage without worsening their asthma symptoms.

Study design

- TROPOS (NCT02281357) is a Phase III, randomized, double-blind, parallel group, multicenter, placebo-controlled study in patients with asthma who require continuous treatment with inhaled corticosteroid and long-acting β2-agonists, and chronic treatment with maintenance OCS therapy.
- The TROPOS study will investigate whether adjunctive tralokinumab allows reduction of maintenance OCS dosage.

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• **Describes the identification of periostin as a surrogate biomarker for eosinophillic airway inflammation in asthma. This contributed to the use of periostin as a surrogate biomarker in subsequent Phase II studies of tralokinumab, and its inclusion as a potential surrogate biomarker within the TROPOS study described here.**