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Tralokinumab for severe, uncontrolled asthma

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LAY SUMMARY

Asthma is a long-term condition that affects the lungs and breathing. People with asthma have symptoms such as coughing, wheezing, chest tightness and breathlessness. Some people have symptoms despite trying various treatments or may suffer from more sudden 'asthma attacks'. Severe asthma attacks can lead to hospitalisation, and on rare occasions can be life threatening.

Tralokinumab is a new drug that could help people with severe asthma that remains uncontrolled despite other treatments. It is injected under the skin every two weeks. An advanced-stage clinical trial is currently exploring whether tralokinumab will be more effective in a particular subgroup of people with asthma, and could be targeted towards this patient population. If licensed, tralokinumab could provide a new treatment option for people with uncontrolled asthma, as it works differently compared to other currently available treatments.

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TARGET GROUP

Severe asthma; uncontrolled despite inhaled corticosteroids and long-acting β2-agonist; in adults and adolescents – add-on therapy

TECHNOLOGY

DESCRIPTION

Tralokinumab (CAT-354; LP-0162) is a recombinant anti-IL-13 human immunoglobulin-G4 monoclonal antibody. Tralokinumab blocks the binding and signalling of IL-13 to its receptors. IL-13 is a signalling protein that plays a key role in the pathogenesis of asthma. When IL-13 binds to receptors (IL-13Rα1 and IL-13Rα2) found on cells in the airways, this can lead to inflammation, airway hypersensitivity and structural changes. The IL-13 pathway therefore has been considered to represent a potentially effective target for asthma therapy.[1]

Tralokinumab is in clinical trials as an add-on therapy for severe asthma that remains uncontrolled despite the patient having received inhaled corticosteroids (ICS) and a long-acting β2-agonist (LABA). AstraZeneca's second pivotal phase III trial (STRATOS 2) focuses on a subgroup of patients with an elevated biomarker associated with increased IL-13 activity, who the company suggests may have an enhanced response to tralokinumab.[2] [3] In the STRATOS 1 and STRATOS 2 phase III trials, 300mg of tralokinumab was administered as a subcutaneous injection, every two weeks for a year.[4]

In addition to the STRATOS trials, AstraZeneca's ATMOSPHERE clinical trial programme in asthma also includes TROPOS (phase III trial in adult and adolescent patients with severe asthma who require continuous treatment with ICS plus LABA, and chronic treatment with maintenance oral corticosteroid therapy) and MESOS (phase II trial in adults with uncontrolled asthma requiring continuous treatment with ICS, with or without other asthma controllers).[2]

Tralokinumab does not currently hold a marketing authorisation for any indications. In addition to asthma, it is also under development for the treatment of atopic dermatitis, and was previously under development for ulcerative colitis and idiopathic pulmonary fibrosis.[5]

INNOVATION and/or ADVANTAGES

Tralokinumab has a different mechanism of action compared to treatments that are currently available. The drug will target severe cases of uncontrolled asthma with specific biological and clinical features, and has been expected to be a part of a shift toward personalised medicine in asthma treatment.[6]

DEVELOPER

AstraZeneca UK Ltd (MedImmune)

AVAILABILITY, LAUNCH or MARKETING

Tralokinumab is currently in phase III clinical trials.

PATIENT GROUP

BACKGROUND

Asthma is a long-term inflammatory disorder of the airways. Its symptoms include breathlessness, chest tightness, wheezing, sputum production, airflow obstruction, hyper-responsiveness of airways, and cough (particularly at night). Symptoms vary in frequency and severity, from intermittent and mild, to frequent and severe. Asthma can impair a person's quality of life, with symptoms leading to fatigue, as well as absence from school or work. Psychological problems, such as depression, are up to six times more common in asthma patients compared to the general population, particularly in people with severe and difficult-to-control asthma.[7]

Most cases of asthma can be well controlled with inhaled corticosteroids and long-acting beta-agonists; however, a proportion of patients do not respond to these treatments and attain at best limited disease control. Severe, uncontrolled asthma is defined by at least one of the following:
1) Poor symptom control (Asthma Control Questionnaire [ACQ] >1.5 or Asthma Control Test [ACT] <20);
2) Frequent severe exacerbations (two or more bursts of systemic corticosteroids in the previous year);
3) Serious exacerbations (at least one hospitalization, intensive care unit stay, or mechanical ventilation in the previous year); and
4) Airflow limitation (forced expiratory volume in 1 s [FEV1] <80% predicted).

This patient cohort represents a considerable healthcare and financial burden, as people may experience frequent exacerbations and require admission to a hospital. Although severe asthma only accounts for approximately 10 to 15% of asthmatics, this cohort may utilise up to 50% of overall healthcare costs for asthma. Although new biological agents and disease biomarkers (aiding targeting of treatment) have provided novel avenues in asthma treatment, only a proportion of severe asthmatics respond to such targeted treatment due to the heterogeneity of the condition.[8]

CLINICAL NEED and BURDEN OF DISEASE

Although the proportion of patients with severe uncontrolled asthma is relatively small, this population accounts for the greatest proportion of healthcare costs in asthma.[9] According to Asthma UK, about 5% of the asthmatic cohort have a medical diagnosis of severe asthma, with about 250,000 adults and children in the UK being diagnosed with severe asthma.[10]

In 2015, 1,302 deaths from asthma were registered in England and Wales. This was the highest number of deaths in asthma in over ten years, and a 17% increase in the number of asthma related deaths from the previous year (1,114 in 2014).[11] In 2015/16, there were 68,426 hospital admissions for asthma (ICD-10 code: J45) in England, resulting in 145,022 bed days and 92,872 finished consultant episodes.[12]

PATIENT PATHWAY

RELEVANT GUIDANCE

NICE GUIDANCE

- NICE technology appraisal in development. Asthma (eosinophilic) - reslizumab (after inhaled corticosteroids) (ID872). Expected publication date TBC.
- NICE technology appraisal in development. Benralizumab for treating inadequately controlled asthma (1129). Expected publication date TBC.
- NICE technology appraisal. Mepolizumab for treating severe refractory eosinophilic asthma (TA431). January 2017.
- NICE technology appraisal. Omalizumab for treating severe persistent allergic asthma (review of technology appraisal guidance 133 and 201) (TA278). April 2013.
- NICE technology appraisal. Inhaled corticosteroids for the treatment of chronic asthma in children aged 12 years and over (TA138). March 2008.
- NICE technology appraisal. Inhaled corticosteroids for the treatment of chronic asthma in children under the age of 12 years (TA131). November 2007.
- NICE technology appraisal. Inhaler devices for routine treatment of chronic asthma in older children (aged 5-15 years) (TA38). March 2002.
- NICE technology appraisal. Guidance on the use of inhaler systems (devices) in children under the age of 5 years with chronic asthma (TA10). August 2000.
- NICE clinical guideline in development. Asthma – diagnosis and monitoring (GID-CGWAVE0640). Expected publication date October 2017.
- NICE clinical guideline in development. Asthma management (GID-CGWAVE0743). Expected publication date October 2017.
- NICE quality standard. Quality standard for asthma (QS25). February 2013.
- NICE diagnostics guidance. Measuring fractional exhaled nitric oxide concentration in asthma: NIOX MINO, NIOX VERO and NObreath (DG12). April 2014.
- NICE interventional procedure guidance. Bronchial thermoplasty for severe asthma (IPG419). January 2012.

NHS ENGLAND and POLICY GUIDANCE

- NHS England. 2013/14 NHS Standard Contract For Respiratory: Severe Asthma (Adult). A14/S/b.

OTHER GUIDANCE

- Scottish Intercollegiate Guidelines Network and British Thoracic Society. British guideline on the management of asthma: A national clinical guideline (SIGN 141). October 2014.
- Scottish Intercollegiate Guidelines Network. Managing asthma in adults: a booklet for patients and their families and carers. December 2011.
- NHS quality improvement (Scotland) service guidance. Asthma services for children and young people: clinical standards. March 2007.

CURRENT TREATMENT OPTIONS

There is no cure for asthma, therefore treatment aims to control symptoms while minimising the adverse reactions to treatment. Current guidelines from the British Thoracic Society (BTS) and Scottish Intercollegiate Guidelines Network (SIGN) recommend a stepwise approach to treatment aligned with the pathway of the Global Initiative for Asthma (GINA):

- Step 1 (for mild intermittent asthma) of the GINA pathway recommends using inhaled short-acting beta2 agonists occasionally.
- Step 2 recommends introducing inhaled corticosteroids at 200 to 800 micrograms per day in people aged 12 years and over and at 200 to 400 micrograms per day in children aged 5 to 12 years.
- Step 3 recommends adding an inhaled long-acting beta2 agonist and, if control remains inadequate, increasing the dosage of inhaled corticosteroids to 800 micrograms per day in adults and adolescents and to 400 micrograms per day in children. If a person's asthma does not respond to an inhaled long‑acting beta2 agonist, a leukotriene receptor antagonist (oral), a theophylline (oral) or a slow‑release beta2 agonist (oral) may be considered instead.
- Step 4 recommends increasing the dosage of inhaled corticosteroids to up to 2000 micrograms per day in adults and adolescents and up to 800 micrograms per day in children. As with step 3, adding a leukotriene receptor antagonist, a theophylline or an oral beta2 agonist may also be considered. Before moving to step 5, clinicians should refer people whose asthma is inadequately controlled to specialist care.
- Step 5 recommends daily corticosteroid tablets at the lowest dose that provides adequate control, alongside high-dose inhaled corticosteroids. Treatments that can minimise the use of corticosteroid tablets may also be considered. The adverse effects of long-term oral corticosteroids are significant and include adrenal suppression, glucose intolerance, decreased bone mineral density, cataracts and glaucoma, and growth failure in children.[7]

NICE technology appraisal also recommended the use of omalizumab (Xolair) for severe persistent asthma as an add-on to optimise standard therapy in people aged six years and over who need continuous or frequent treatment with oral corticosteroids (defined as four or more courses in the previous year).[7]

EFFICACY and SAFETY

Trial	STRATOS 1; tralokinumab vs. placebo; NCT02161757; D2210C00007; phase III
Sponsor	AstraZeneca
Status	Partial results published in a company press release. Listed in the trial registry as ongoing, not recruiting.
Source of Information	Trial registry,[4] company press release[2]
Location	EU (not incl UK), USA, other countries
Design	Randomised, double-blind, placebo-controlled trial
Participants	N=1,231; aged 12 to 75 years; physician-diagnosed asthma; documented treatment with ICS at a total daily dose corresponding to ≥500µg fluticasone propionate dry powder formulation equivalents and a LABA

Schedule	300 mg administered every 2 weeks, for 52 weeks
Follow-up	72 weeks
Primary Outcomes	Asthma exacerbation rate reduction (AERR)
Secondary Outcomes	Percent change from baseline to Week 52 in pre-dose/pre-bronchodilator forced expiratory volume in 1 second; Change from baseline to Week 52 in daily asthma symptom score; Change from baseline to Week 52 in Asthma Quality of Life Questionnaire for 12 Years and Older total score; and 14 other secondary outcomes.
Key Results	Tralokinumab, an anti-interleukin-13 (IL-13) human monoclonal antibody, did not meet its primary endpoint of a significant reduction in the annual asthma exacerbation rate (AAER) in the overall population of severe, uncontrolled asthma patients, compared with placebo in STRATOS 1, the first of two pivotal Phase III trials. In a planned analysis, a clinically-relevant reduction in AAER was observed in a sub-population of patients with an elevated biomarker associated with increased IL-13 activity. This sub-group of patients will now be the focus for the future analysis of STRATOS 2, the second ongoing pivotal Phase III trial.
Adverse effects (AEs)	The safety and tolerability findings in STRATOS 1 were consistent with those observed in previous trials with tralokinumab.
Expected reporting date	-

Trial	STRATOS 2; tralokinumab vs. placebo; NCT02194699; D2210C00008; phase III
Sponsor	AstraZeneca
Status	Reported as ongoing, results not yet published.
Source of Information	Trial registry[13]
Location	EU (incl UK), USA, Canada, and other countries
Design	Randomised, double-blind, placebo-controlled trial
Participants	Estimated N=770 to 856; aged 12 to 75 years; physician-diagnosed asthma; documented treatment with ICS at a total daily dose corresponding to ≥500µg fluticasone propionate dry powder formulation equivalents and a LABA
Schedule	300 mg administered every 2 weeks, for 52 weeks
Follow-up	72 weeks
Primary Outcomes	Asthma exacerbation rate reduction (AERR)
Secondary Outcomes	Percent change from baseline to Week 52 in pre-dose/pre-bronchodilator forced expiratory volume in 1 second; Change from baseline to Week 52 in daily asthma symptom score; Change from baseline to Week 52 in Asthma Quality of Life Questionnaire for 12 Years and Older total score; and 13 other secondary outcomes.
Key Results	-
Adverse effects (AEs)	-
Expected reporting date	Final data collection date for primary outcome measure was May 2016. Results are expected imminently, in the second half of the year.

Trial	TROPOS; tralokinumab vs placebo; NCT02281357; phase III
Sponsor	AstraZeneca
Status	Ongoing, not recruiting
Source of Information	Trial registry,[14] published protocol[9]
Location	EU (not incl UK), USA, Ukraine
Design	Randomized, double-blind, placebo-controlled trial
Participants	N=140; ages 12 to 75; physician-diagnosed asthma; documented treatment with ICS at a total daily dose corresponding to ≥500µg fluticasone propionate dry powder formulation equivalents and a LABA
Schedule	300 mg dose of tralokinumab administered subcutaneously every 2 weeks, for 40 weeks (12-week induction, 20-week OCS reduction and 8-week maintenance phases)
Follow-up	n/a
Primary Outcomes	Percent change from baseline in the daily, average, OCS dose at week 40 post randomization while not losing asthma control.
Secondary Outcomes	Difference between tralokinumab vs. placebo in the proportion of subjects with final daily average OCS dose ≤5 mg at Week 40 post randomization. Difference between tralokinumab vs. placebo in the proportion of subjects with ≥50% reduction in average daily OCS dose at Week 40 post randomization.
Key Results	-
Adverse effects (AEs)	-
Expected reporting date	Estimated primary completion date: September 13, 2017.

ESTIMATED COST and IMPACT

COST

The cost of omalizumab, another monoclonal antibody recommended by NICE for asthma treatment, ranges from approximately £1,665 per patient per year (excluding VAT) for a 75 mg dose administered every 4 weeks to approximately £26,640 per patient per year (excluding VAT) for a 600 mg dose (the maximum recommended dose in the summary of product characteristics) administered every two weeks. Costs may vary in different settings because of negotiated procurement discounts.[7]

IMPACT – SPECULATIVE

IMPACT ON PATIENTS AND CARERS

☒ Reduced mortality/increased length of survival

☒ Reduced symptoms or disability: *a potential improvement in quality of life and a reduced rate of asthma exacerbations*

☐ Other

☐ No impact identified

IMPACT ON HEALTH and SOCIAL CARE SERVICES

☐ Increased use of existing services

☒ Decreased use of existing services

☐ Re-organisation of existing services

☐ Need for new services

☐ Other

☐ None identified

IMPACT ON COSTS and OTHER RESOURCE USE

☐ Increased drug treatment costs

☐ Reduced drug treatment costs

☐ Other increase in costs

☐ Other reduction in costs

☒ Other: *uncertain cost*

☐ None identified

OTHER ISSUES

☐ Clinical uncertainty or other research question identified

☒ None identified

REFERENCES

[1] Walsh, G. (MedScape). An Update on Biologic-based Therapy in Asthma. *Immunotherapy*. 2013; 5(11):1255-1264. Available from: http://www.medscape.com/viewarticle/817432_4 [Accessed 26 July 2017]

[2] AstraZeneca. *AstraZeneca provides update on STRATOS 1 Phase III trial of tralokinumab in severe, uncontrolled asthma*. 10 May 2017. Available from: https://www.astrazeneca.com/media-centre/press-

releases/2017/astrazeneca-provides-update-on-stratos-1-phase-iii-trial-of-tralokinumab-in-severe-uncontrolled-asthma-100517.html [Accessed 26 July 2017]

[3] Fierce Biotech. *AstraZeneca asthma drug misses endpoint in phase 3.* Available from: http://www.fiercebiotech.com/biotech/astrazeneca-asthma-drug-misses-endpoint-phase-3 [Accessed 26 July 2017]

[4] ClinicalTrials.gov. *A Phase 3 Study to Evaluate the Efficacy and Safety of Tralokinumab in Adults and Adolescents with Uncontrolled Asthma (STRATOS1).* Available from: https://clinicaltrials.gov/ct2/show/NCT02161757 [Accessed 26 July 2017]

[5] Global Data. *Tralokinumab.* Available from: https://pharma.globaldata.com/ProductsView.aspx?ProductType=0,1&ProductID=1176 [Accessed 26 July 2017, log-in required]

[6] Global Data. *PharmaPoint: Asthma – Global Drug Forecast and Market Analysis to 2023*. Available from: https://pharma.globaldata.com/Reportsview.aspx?DocID=40927 [Accessed 26 July 2017, log-in required]

[7] NICE technology appraisal. *Omalizumab for treating severe persistent allergic asthma (review of technology appraisal guidance 133 and 201) (TA278).* April 2013. Available from: https://www.nice.org.uk/guidance/ta278/ [Accessed 26 July 2017]

[8] Low K, Bardin PG. Targeted Therapy for Severe Asthma: Identifying the Right Patients. *Molecular diagnosis & therapy*. 2017 Jun 1; 21(3):235-47.

[9] Busse WW, Wang M, Gibson J, Gottlow M, Braddock M, Colice G. TROPOS: designing a clinical trial to evaluate the oral corticosteroid-sparing effect of a biologic in severe asthma. *Clinical Investigation*. 2015 Aug; 5(8):723-30.

[10] Asthma UK. *Severe Asthma*. Available from: https://www.asthma.org.uk/advice/severe-asthma/what-is-severe-asthma/ [Accessed 26 July 2017]

[11] Asthma UK. *Asthma deaths in England and Wales hit highest peak for 10 years*. 13 July 2016. Available from: https://www.asthma.org.uk/about/media/news/asthma-deaths-in-england-wales-hit-10-year-peak/ [Accessed 26 July 2017]

[12] NHS Digital. Hospital Admitted Patient Care Activity, 2015-16. Available from: http://www.content.digital.nhs.uk/catalogue/PUB22378 [Accessed 28 March 2017]

[13] ClinicalTrials.gov. *A Phase 3 Study to Evaluate the Efficacy and Safety of Tralokinumab in Adults and Adolescents with Uncontrolled Asthma (STRATOS2).* Available from: https://clinicaltrials.gov/ct2/show/NCT02194699 [Accessed 26 July 2017]

[14] ClinicalTrials.gov. *Phase 3 Study to Evaluate the Efficacy & Safety of Tralokinumab in Adults & Adolescents with OCS Dependent Asthma (TROPOS).* Available from: https://clinicaltrials.gov/ct2/show/NCT02281357 [Accessed 26 July 2017]