

# Nocturnal temperature-controlled laminar airflow device for adults with severe allergic asthma: the LASER RCT

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## Scientific summary

### **The LASER RCT**

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# Scientific summary

## Background

Asthma affects > 5.4 million people in the UK, with nearly 500,000 experiencing severe symptoms and frequent exacerbations that are inadequately controlled with available treatments. The burden of severe asthma on the NHS is enormous, accounting for 80% of the total asthma cost (£1B), with frequent exacerbations and expensive medications generating much of this cost. More than 70% of severe asthmatic patients are sensitised to common aeroallergens and the level of exposure determines symptoms; those exposed to high allergen levels are at increased risk of exacerbations and hospital admissions. Significant allergen exposure also occurs at night, when airborne particles are carried by a persistent convection current established by the warm body, transporting allergens from the bedding area to the breathing zone. The temperature-controlled laminar airflow (TLA) device is effective at reducing this nocturnal allergen exposure. This trial sought to determine whether use of the TLA device when compared with placebo would lead to improvements in asthma control, inflammation and lung function and reductions in severe exacerbations in adults with severe allergic asthma.

## Objective

To assess whether or not home-based nocturnal TLA treatment can effectively reduce asthma-related morbidity over a 1-year period in a real-life group of people with poorly controlled, severe allergic asthma.

## Trial definition

A multicentre, randomised, double-blind, placebo-controlled, parallel-group trial of the effectiveness of a TLA device (Airsonett®; Airsonett AB, Ängelholm, Sweden) in adults with poorly controlled, severe allergic asthma.

## Methods

### Participants

Participants were adults (aged 16–75 years) with severe, poorly controlled, exacerbation-prone asthma despite high-intensity treatment [as defined by American Thoracic Society (ATS)/European Respiratory Society (ERS) 2013 guidance] who were sensitised to a perennial indoor aeroallergen.

### Intervention

The intervention was nocturnal home-based TLA treatment using an Airsonett device, in addition to standard care, in accordance with the national British Thoracic Society/Scottish Intercollegiate Guidelines Network guidelines for the management of asthma in adults. The device is CE (Conformité Européenne) marked for use in asthma.

## Trial outcomes

### Primary outcome

The primary outcome was the frequency of severe asthma exacerbations occurring within the 12-month follow-up period. Severe asthma exacerbations were defined in accordance with ATS/ERS guidelines as a worsening of asthma requiring systemic corticosteroids [ $\geq 30$  mg of prednisolone or equivalent daily (or  $\geq 50\%$  increase in dose if on a maintenance dose of  $\geq 30$  mg of prednisolone)] for  $\geq 3$  days. Courses of corticosteroids separated by  $\geq 7$  days were treated as separate severe exacerbations. Post hoc analyses of worsening of asthma requiring  $\geq 10$  mg of prednisolone or equivalent daily for  $\geq 3$  days were also carried out.

## Secondary outcomes

Secondary outcomes included changes in asthma control, lung function and asthma-specific and global quality of life for participants, adherence to the intervention, device acceptability, health-care resource use and costs, and cost-effectiveness.

### *Randomisation and blinding*

Participants were randomised 1 : 1 to TLA therapy or placebo using a validated computer randomisation program with a minimisation algorithm to ensure balanced allocation of participants across the two treatment groups for clinical site, prevalent compared with incident cases and the following prognostic factors at baseline: severe exacerbation frequency in the previous 12 months, use of maintenance oral corticosteroids and pre-bronchodilator forced expiratory volume in 1 second (FEV<sub>1</sub>).

### *Sample size calculation*

Based on an estimated rate of two severe asthma exacerbations per participant over the 12-month period in the placebo group, determined from landmark trials of asthma, it was calculated that a minimum of 222 participants (111 per group) would be required to provide 80% power (at a 5% two-sided significance level) to detect a clinically meaningful 25% reduction in the average severe exacerbation rate in the group using the TLA device. This sample size was based on a Poisson regression model with the treatment group as the covariate and a 10% overall dropout rate. A review of comparative interventions of proven efficacy in severe asthma gave effect sizes ranging from 21% to 63%, with a mean of 41%. Given that this was a pragmatic trial in which the intervention was expected to be less effective than in an efficacy trial, a deliberately more conservative effect size of 25% was chosen. This represented, on average, one less severe exacerbation per participant every 2 years.

### *Monitoring and ethics*

The trial was approved by the Health Research Authority: National Research Ethics Service (NRES) Committee South Central – Berkshire Research Ethics Committee [reference 14/SC/0092, Integrated Research Approval System (IRAS) project ID 148386].

## Results

### *Patient numbers*

In total, 489 patients were consented for screening between May 2014 and January 2016 across 14 trial centres in England and Northern Ireland, of whom 249 were excluded or failed both phases of screening and 240 were randomised ( $n = 185$  from existing clinics and  $n = 50$  from other sources); 119 participants were allocated to treatment and 121 were allocated to placebo.

A total of 202 participants (84.0%) reported use of the device for at least 9–12 months and 30 participants (12.5%) reported use of the device for < 6 months after randomisation. Of 87,840 study days reported from 240 participants, a steroid dose was reported on 58,251 days (66.3%) from the trial records and a total of 344 severe exacerbations were recorded during the trial. Carer recruitment for the trial was low and so further analyses were not performed.

### *Baseline characteristics*

The mean baseline percentage predicted FEV<sub>1</sub> was 69.2%, the mean baseline fraction of exhaled nitric oxide (FeNO) was 37.5 parts per billion (p.p.b.) [standard deviation (SD) 35.8 p.p.b.] and the mean severe exacerbation frequency in the previous 12 months was 3.9 per year (SD 2.9 per year). In total, 58 (24%) participants were on maintenance oral corticosteroids.

### *Primary outcome*

There was a significant reduction in severe exacerbations in both groups from baseline to completion of the trial: from 4.3 (SD 3.7) to 1.48 (SD 2.03) per year in the placebo group and from 3.5 (SD 1.8) to

1.39 (SD 1.57) per year in the active group. An intention-to-treat mixed-effects model with a negative binomial distribution was used to estimate the difference in effects of treatment and placebo. The mean rate of severe exacerbations was not significantly different between the groups, with a risk ratio of 0.92 [95% confidence interval (CI) 0.66 to 1.27;  $p = 0.616$ ]. Sensitivity analyses including alternative sources of reported exacerbations (e.g. exacerbations recalled at a follow-up visit or a combination of dated reports and those recalled at a follow-up visit, rather than dated reports only) did not reveal any further differences between treatment groups for the primary outcome.

### Secondary outcomes

There were no significant differences in the secondary outcomes related to lung function (pre- or post-bronchodilator FEV<sub>1</sub>) except for a reduction in mean daily peak expiratory flow (PEF) [difference 14.7 (SD 7.35) l/minute; 95% CI 0.32 to 29.1 l/minute;  $p = 0.045$ ] in favour of the active device; there were no significant differences in asthma control (as concluded from the 7-Point Asthma Control Questionnaire and Asthma Control Diary) or airway inflammation (as measured by FeNO). There were no significant safety concerns in either group.

Qualitative analyses in both the pilot and at the end of the trial showed high levels of acceptability of the device.

### Economic evaluation

Use of the TLA device yielded higher levels of generic and disease-specific health-related quality of life (HRQoL), with the results showing statistically significant higher HRQoL at some intermediary follow-up visits. Given that TLA use was not associated with any reduction in health-care use, these increases in HRQoL were not sufficient to offset the annual costs associated with use of the TLA device, which resulted in an incremental cost per quality-adjusted life-year (QALY) gained that was higher than the £20,000 per QALY gained threshold used by the National Institute for Health and Care Excellence (NICE) to determine cost-effectiveness.

## Conclusions

### Main findings

The TLA device has previously been shown to be beneficial in patients with allergic asthma, with improvements in asthma control and HRQoL. In this multicentre, randomised, placebo-controlled trial, no consistent benefits of the device over placebo were seen for severe exacerbation frequency (despite assessment of severe exacerbations from a variety of sources), asthma control or airway inflammation. There were some improvements in HRQoL at the 6-month follow-up and in PEF, but the magnitude of these differences was not sufficient to make the device cost-effective.

### Limitations

Despite using multiple sources of recording of severe exacerbations, a significant number of participants failed to record levels of prednisolone in their daily diaries, which may have led to an overall under-reporting of exacerbations and rendered the trial inconclusive. The magnitude of this effect is unknown as the majority of missing doses occurred at levels that were low, when participants were likely to have remained well and exacerbation free.

### Clinical and research implications

The types of patients who may benefit from the TLA device, and the reasons for the large reduction in exacerbation frequency in severe asthma in trials incorporating other methods of recording exacerbations, requires further exploration.

## **Trial registration**

This trial is registered as ISRCTN46346208.

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