Airsonett® Air4 Temperature controlled Laminar Airflow (TLA) treatment for patients with severe persistent allergic asthma and moderate-to-severe atopic dermatitis

The clinical information in this document is intended for healthcare professionals, administrators, and other stakeholders responsible for the treatment, planning, or financing of healthcare for patients with allergic diseases, in the public and private sectors.

Airsonett®
A Breath of New Life

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Overview

AirsonettAir4	The Airsonett Temperature controlled Laminar Airflow (TLA) technology has been evaluated in controlled clinical studies and case series. The Air4 devices (Airsonett AB, Ängelholm, Sweden) are approved according to Medical Device Regulation (MDR EU 2017/745). CE-marked Class I. In the USA, Airsonett Air4 is a Class II medical device under Classification Regulation 21 CFR 880.5045, Product Code: FRF.
Mechanismof action	Airsonett Air4 TLA technology and TLA-treatment uses air filtration technology in combination with vertical Temperature controlled Laminar Airflow technology to remove airborne particles and allergens from the breathing zone. The TLA-treatment has demonstrated, in the breathing zone, a reduction (≥99.5%) of particles with a size range relevant to allergens that can cause allergic symptoms in sensitized individuals (Gore RB[1,2].); Spilak [3]). The technology provides a sustained overnight particle reduction which is maintained over the device lifetime by means of a six-month filter exchangeprogram. The device particle reduction efficiency is independent of bedroom size.
Clinical Outcomes	Nocturnal treatment with TLA has in clinical asthma studies shown attenuation of inflammation in the airways, reduced asthma symptoms and improved asthma related quality of life (QoL), when used in addition to recommended pharmacotherapy in children and adults with persistent allergic asthma [4-8]. Patients uncontrolled on GINA step 4–5 treatments were shown to benefit the most. Significant effects on symptoms and quality of life (QoL) were reached in 3–6 months with sleep as an early indicator within one month [6]. This patient population also had fewer severe asthma exacerbations and less related health-care utilization [7, 8, 9]. Pilot-data indicates that TLA can replace expensive biologic therapy (omalizumab) without loss in efficacy [10]. In initial pilot studies, TLA has also shown effect on moderate to severe atopic dermatitis (AD) by improving QoL and reducing symptoms and pharmacologic therapy [11-13]. There have been no reports of device-related serious adverse events in any of the asthma or AD clinical studies, neither on the recuring Post Market Surveillance activities. Present data also indicate that TLA treatment is cost-effective in the more uncontrolled severe asthma patients. The incremental cost-effectiveness ratio (ICER)was around £10,000 to 20,000 per Quality-Adjusted Life Year (QALY)[8, 14], which is within the NICE-acceptable range (<£30,000 per QALY gained (NICE)). In summary: TLA is a non-invasive, non-pharmacological treatment with demonstrated efficacy and cost-effectiveness with a favorable safety profile.
Indication Licensed Intended Purpose	Alleviation of symptoms of allergy induced diseases such as allergic asthma and atopic dermatitis. Airsonett Air4 provides a reduction of airborne particle exposure (e.g., airborne allergens) by means of Temperature controlled Laminar Airflow (TLA). The device is intended for home use. Nocturnal treatment with TLA is recommended to adults and children with uncontrolled allergic asthma, who have not reached acceptable effect on GINA step4–5 pharmacologic treatment. TLA is also recommended to children with moderate to severe AD with concomitant asthma [15]. TLA-treatment is intended for long-term treatment. The need for continued therapy is to be assessed on a 6-month basis as determined by physician assessment of the patient's level of control. The prevalence is high for both asthma and AD (about 6-7% in adults but much higher in children, between 16-38 % pending on country or region) [16,17]. The medical need is also high especially in more severe disease. The current treatment options for patients with uncontrolled severe asthma are oral corticosteroids and immunosuppressants, having

	side effects or biologics, associated with high costs. In this severe asthma segment, it is estimated that 80% of expenditure on asthma is consumed by 20% of people whose asthma is more severe [18]. The current treatment option for moderate to severe AD is similar to asthma i.e. treatments with safety concerns or high costs.
Independent Expert Reviews	Several national bodies have reviewed and recommend TLA treatment for uncontrolled severe allergic asthma [19-22]. The Swedish pediatric association also recommend, TLA for AD with concomitant asthma [15]. The Healthcare Improvement Scotland hasalso found TLA being cost-effective [22]. Academic experts have also reviewed the efficacy, tolerability, and cost-effectiveness of TLA treatment in asthma and their recommend the deviations are in line with the national bodies [23-25].

Airsonett Air4

Intended purpose
Alleviation of symptoms of allergy-induced diseases such as allergic asthma and atopic dermatitis. Airsonett Air4 provides a reduction of airborne particle exposure (e.g. airborne allergens) by means of Temperature controlled Laminar Airflow (TLA). The device is intended for home use.

Precaution
TLA-treatment is to be used in addition to regular pharmaceutical treatments. TLA-treatment is used for regular treatment, not for acute relief or emergency treatment. This means patients should use TLA every night in combination with prescribed medication. Always consult prescribing doctor before changing or reducing medications.

Pregnancy, breast-feeding and small children
Experience from using Airsonett Air4 during pregnancy, breast-feeding and in small children is limited. However, Airsonett Air4 does not supply any substances that can affect the pregnancy, breast-feeding or small children.

Usage
Airsonett Air4 is installed next to the bed with the air nozzle above the breathing zone. Effectiveness is dependent on following instructions for use. Airsonett Air4 should be used every night in combination with prescribed medication. Sporadic use of Airsonett Air4 reduces the effectiveness. Treatment time is as minimum 5 of the week's days (7) and at least 6 consecutive hours during treatment/night based

on studies. The device comes with a timer function that will turn on/off the device every night, if preferred. Overall, Airsonett Air4 is easy to use.

Safety

Taking the intended use and indication of TLA treatment into consideration, Airsonett AB concludes that for all listed claims the clinical safety and performance data demonstrate conformity with the General Safety and Performance Requirements of Annex 1, MDR 2017.

Operating conditions

TLA treatment shall not be used outside of the following environmental conditions: Temperature range +5°C to +40°C, relative humidity range 15% to 90% and atmospheric pressure 700-1060hPa.

Budget and Service Impact

Airsonett Air4 should be prescribed by specialists with no additional home testing required. Airsonett or trained distributor, offer to arrange the delivery and support of the device installation according to the instruction manual in the patients' homes and to educate patients on its use. The device is easily installed by following the instruction provided in the parcel with the device at delivery. The company does not anticipate that additional staff and resource use will be required with the use of the device. There are two different possibilities to get an Airsonett Air 4, one is purchase and another one is to rent.

Present data indicate that TLA treatment is cost-effective in a more uncontrolled patient group with an ICER (Incremental Cost-Effectiveness Ratio) of around £10,000 to 20,000 per QALY (Quality-Adjusted Life-Year), which is within the NICE-acceptable range (<£30,000 per (QALY) gained).

Brief Facts

- Height: 119–139 cm (can be adjusted depending on type of bed up to bunkbed)
- Base unit: Length: 54 cm Width: 34 cm
- Energy consumption: Equivalent to a 60 W light bulb
- Sound level: ≤38 dB(A)
- Exchange of air in the breathing zone: >400 times/h
- Weight: 23 kg

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TLA: Rationale, technology, and effectiveness

Rationale: Exposure to allergen and other reactive particles in the breathing zone, may lead to inflammations.

Asthma is associated with a chronic inflammation of the airways often driven by exposure to the allergen(s) the patient is allergic to. Asthmatics are also sensitive to exposure to irritant particles. Asthma patients are particularly vulnerable during the night, mainly driven by symptoms such as cough and breathlessness, which may affect sleep quality.

Atopic Dermatitis (AD) is a typical disease of type 2 immune responses. The disease is mainly driven by exposure to the allergen. Similar to asthma patients, AD patients are particularly vulnerable during the night, mainly driven by itching, a symptom, which may affect sleep quality.

Rhinitis is also associated with inflammation, which is mainly driven by allergens. As for asthma and AD, patients with rhinitis are affected during night and especially the sleep quality is disturbed by nasal blockage.

The three diseases may also occur in the same patient, e.g., in severe uncontrolled allergic asthma up to 80% of the patients could have rhinitis as co-morbidity.

Sleeping with asthma, AD and/or rhinitis. While sleeping in the bed, the airways and skin are close to pillows, mattresses, and duvets, which can be a significant reservoir of allergens such as house dust mite, dog and cat. While sleeping in the bed, the nocturnal exposure to allergens and other airborne particles is increased by the body convection flow [21,26]. The body convection flow is a persistent convection current established by the temperature difference between the warm air surrounding a human body and the ambient room temperature (Figure 1). These convection currents appear particularly prominent around the head, where they concentrate allergens and irritant particles from the bed area to the breathing zone. A reduction of this concentration around the patient would benefit these allergic patients.

Figure 1. The body convection flow.

TLA technology and effectiveness

TLA treatment uses a unique and patented technology Temperature-controlled Laminar Airflow (TLA) to control a flow of filtered clean air towards the breathing zone. The filtered air is slightly cooled before released from the air supply unit. Thereafter the air flow gently descends with gravity and displaces away the warmer air flow, containing the particle- and allergen-rich air from the breathing zone. This leads to, at least 99.5% of particles ≥0.5 µm are blocked from reaching the patient's breathing zone during sleep. The TLA-treatment allows airways and immune system to rest and recover during the night. The TLA treatment device is installed next to the bed with the air nozzle above the breathing zone and should be used every night. This will protect the patient from allergens and irritating particles throughout the night.

Figure 2. TLA-generated laminar air flow enveloping the breathing zone.

The TLA technology for home use is based on the same principle as temperature laminar airflow flow systems (uni-directional flow) in surgical theatres which provides zones of clean air which prevent bacteria-carrying particles from contaminating the surgical site during surgery. TLA for home use also concentrates the laminar airflow over the breathing zone to prevent allergens and other particles to expose the subject in bed during night. The TLA principle is to create a laminar airflow with as little turbulence as possible to avoid ambient contaminated air to be mixed in and to displace contaminants coming from the bed environment (e.g., house dust mite allergens). TLA is thus independent of the room size in contrast to a residential air cleaner which uses the full room volume as a "mixing/dilution chamber". When comparing the breathing zone particle reduction efficiency of TLA with an air cleaner the difference is 100-fold in favor for TLA [3]. This may explain the difference in clinical outcome where clinical trials have found no evidence of symptom relief from the use of residential air cleaners in asthmatic or atopic dermatitis patients [24,27]. Even if the mechanisms are unknown, TLA has potential effect to restoration of the skin-barrier [28].

Table 1 presents technical trials performed with the TLA technology. All particle measurements were performed in accordance with the standard ISO 14644-1 (Cleanrooms and associated controlled environments) in operation, i.e., with a subject in bed, with the measurement point just above the

forehead of the subject in bed. The measurement point is within the equivalent exposure environment as inhaled by the subject in bed and the trials presented in table 1 compare breathing zone particle exposure with and without TLA intervention.

The trials have been repeated in a climate chamber with a thermal manikin, in a controlled environment with subjects and in home environments with subjects. The results demonstrate a consistent breathing zone particle reduction of >99.5% over all particle size ranges and the magnitude of reduction correlates positively with the particle exposure rate without TLA intervention. I.e., TLA reduces nocturnal particle exposure by >99.5% corresponding to e.g., traffic pollution (nano particles <0.1µm), cat/dog allergens (>0.5µm) and house dust mite allergens (>5µm). Spilak et al (3) have shown that TLA treatment device with TLA reduces particles >0.5µm 100-fold better than Air cleaners.

Table 1. TLA efficacy data on breathing zone particle reduction

TLA studies on breathing zone particle reduction measured in operation according to standard ISO14644-1 (Cleanrooms and associated controlled environments). Percentage reduction for TLA vs no intervention.				
Particle size range	Spilak et al, [3] Climate chamber with manikin – TLA vs Air cleaner	Gore RB et al, [1] Controlled environment in n=5 subjects	Gore RB et al, [2] Home environments in n=12 subjects	Bakshi et al, [29] Inner city home environments in n=6 subjects
<0.1µm (nano particles)	NM*	NM	NM	>99.5% (>1000-fold)
≥0.5µm (pet dander 1-5µm)	>99.5% (>1000-fold) 100-fold vs Air cleaner	>99.5% (>3000-fold)	>99.5% (>14500-fold)	NM
≥5µm (House dust mite allergens 5-20µm)	NM	>99.5% (>4500-fold)	>99.5% (>2600-fold)	NM

* NM = Not Measured

Prevalence in allergic diseases

Asthma Prevalence

According to the Global Asthma Report 2018 [30]

- Asthma is one of the most common non-communicable diseases. It affects around 339 million people in all regions of the world. It causes a high global burden of death and disability, with around 1,000 people dying each day from asthma, and is in the top 20 causes of years of life lived with disability.
- In Europe, about 30 million children and adults less than 45 years old have asthma.
- In western Europe, the prevalence of asthma increased in the latter part of the 20th century, but it now appears to be levelling off in many countries; the UK and Ireland have some of the highest rates of asthma in the world.
- Adults with asthma include those who have had asthma since childhood, those in whom it apparently resolved but has subsequently recurred and those who have developed asthma de novo in adult life. [16]
- Appropriate management of asthma can enable people to enjoy a good quality of life. [31]

Severe allergic asthma is recognized as an area of high unmet need. These patients are at high risk of exacerbations, suffer from daily symptoms and an impaired quality of life.

The current treatment options available for patients with severe persistent asthma uncontrolled with high dose inhaled corticosteroids in combination with other controller therapies are limited to:

- Treatments with significantly less beneficial side effect profile (e.g., oral corticosteroids and immunosuppressants); and/or;
- Treatments associated with high costs (e.g., Biologics). It is estimated that 80% of expenditure on asthma is consumed by 20% of people whose asthma is more severe. [18]

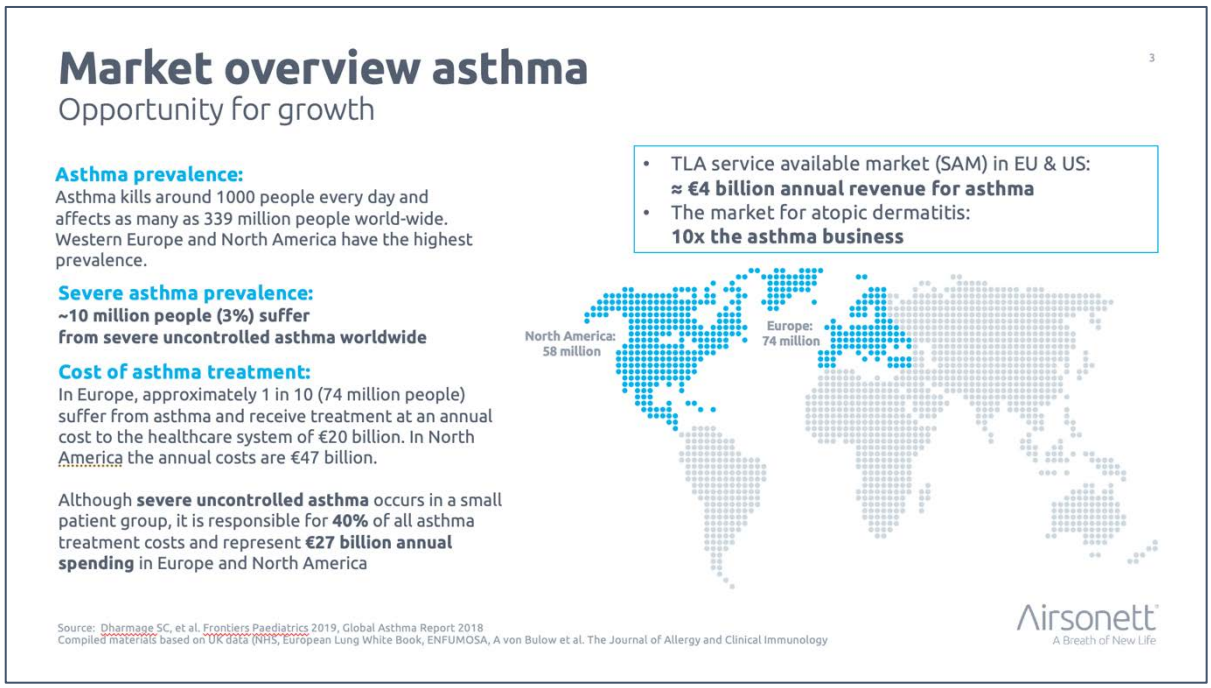


Figure 3. Global Market Overview Asthma

Atopic Dermatitis Prevalence

According to the global skin position paper 2018 [32]

- AD is the most common form of eczema. It is currently an incurable, chronic immune-mediated systemic disease with a debilitating effect on 2–10% of adults worldwide and with 15–30% for children in industrialized countries [27, 33-36]
- Early onset of eczema is associated with an increased risk of sensitization of inhalant allergens. In the BAMSE cohort, 62% of children sensitized to inhalant allergens between 4 and 16 years had co-occurrence of asthma, rhinitis, or eczema. [37]
- Moderate-to-severe atopic dermatitis is characterized by painful lesions over large or sensitive parts of the body that can include skin dryness, cracking, redness, crusting and oozing [38]. Intense and persistent itching is one of the most debilitating symptoms, causing long-lasting, extreme pain.
- More than 60% of moderate-to-severe patients reporting itch at least 12 hours a day [36].
- Moderate-to-severe AD had more persistent disease and higher prevalence of rhinitis and asthma compared to participants with mild disease. Children with AD have an increased risk to develop allergic asthma and allergic rhinitis [16,27,36,37].

The current treatment options available for patients with moderate to severe uncontrolled disease are, ointments, high dose corticosteroids ointments in combination with other controller therapies are limited to:

- Treatments with significantly less beneficial side effect profile (e.g., oral corticosteroids and immunosuppressants); and/or;
- Treatments associated with high costs (e.g., Biologics).
- Treatment in hospitals with lights, baths, and staff/time demanding resources.

Clinical Program

Research hypothesis

The evaluation of the clinical performance of the TLA-treatment was based on the hypothesis that the highly significant reduction of allergens and airborne particles achieved by the TLA-treatment in the breathing zone during sleep, would further reduce allergic reactions such as inflammation and symptoms and thus improve health-related quality of life QoL in patients suffering from perennial allergic asthma and patients suffering from AD.

Four common and important asthma outcomes were chosen to demonstrate the effectiveness of adding the TLA-treatment to regular conventional pharmacotherapy on allergic reactions:

- Fractional Nitric Oxide concentration in exhaled breath (FENO; NIOX MINO™) was chosen to acquire an objective measure of the effect on airway inflammation.
- The Asthma Quality of Life Questionnaire (AQLQ) was chosen to measure improved QoL, and alleviation of asthma symptoms as perceived by the patient. For adults and adolescence, the mini- AQLQ was used and for children <12 years of age the Pediatric QQLQ (PAQLQ) was used.
- Asthma Control Test (ACT) and Asthma Control Questionaries (ACQ) were used to access the patient's asthma symptoms.
- Severe exacerbations were chosen because patients having acute exacerbations are at risk, and repeated exacerbations may affect the long-term prognosis. In addition, severe exacerbations are costly, both for health care and society.

Three important AD outcomes were chosen to demonstrate the effectiveness of adding the TLA-treatment to regular conventional pharmacotherapy on allergic reactions:

- Scoring Atopic Dermatitis (SCORAD) was chosen as being a common AD outcome in clinical trials. The scoring system also includes subcomponents (extent and intensity criteria for lesions, and subjective symptoms composed of pruritus and sleep loss scores), which may reveal interesting information about TLA-treatment in AD.
- Investigator Global Assessment (IGA) was chosen because it is recommended by health agencies. It should however be mentioned that it is a questioned outcome as not being properly validated and sensitive to record differences.
- Dermatitis Quality of Life Index (DQLI) was chosen as an instrument recording how AD affects the patient's life quality. The index is also developed for adults, children, infants, and family.
- Eczema Area and Severity Index (EASI) score was chosen as a tool to measure the extent (area) and severity of atopic eczema. Area score is recorded for each of the four regions of the body when applicable. The area score is the percentage of skin affected by eczema for each body region.

Results in Clinical Studies in asthma and atopic dermatitis

Asthma studies	
22-week Pilot Study: **Pedroletti** [4]	Pedroletti C et al. Clinical effects of purified air administered to the breathing zone in allergic asthma: A double-blind randomized cross-over trial. Respir Med 2009; 103:1313-9 ClinicalTrials.gov: NCT00987064
1-year Pivotal Study: **Boyle** [5,54]	Boyle RJ et al. Nocturnal temperature controlled laminar airflow for treating atopic asthma: a randomized controlled trial. Thorax 2012; 67:215-221 Bjermer L et al. Time to onset of improvement in Quality of Life from temperature-controlled Laminar Airflow (TLA) in severe allergic asthma. Respir Med 2019; 147:19-25 ClinicalTrials.gov: NCT00986323
1-year Pivotal Study: **Kapoor** [37]	Kapoor et al. Nocturnal temperature-controlled laminar airflow device for adults with severe allergic asthma: the Laser RTC. Health Technol. Assess. 2019 Jun;23(29):1-140. Doi:10.3310/hta23290
Meta-analysis of two 1-year pivotal studies **Chauhan** [4]	Chauhan et al Effect of nocturnal Temperature-controlled Laminar Airflow on the reduction of severe exacerbations in patients with severe allergic asthma: a meta-analysis. Europe Clinical Resp Journal, 8:1, 1894658, DOI: 10.1080/20018525.2021.1894658 hhtps://doi.org/10.1080/20018525.2021.1894658
Post-hoc analysis on severe exacerbations, QoL and Health Economy. **Chauhan** [8]	Chauhan AJ, Eriksson G, Storrar W, Brown T, Peterson S, Radner F, D'Cruz LG, Miller P, Bjermer Temperature-controlled Laminar Airflow (TLA) in symptomatic severe asthma - a post hoc analysis of severe exacerbations, quality of life and health economics. L.BMC Pulm Med. 2022 Nov 9;22(1):407. doi: 10.1186/s12890-022-02205-6.PMID: 36352399 Miller et al. The cost-effectiveness of Temperature-controlled Laminar Airflow (TLA in uncontrolled severe asthma Abstract SLMF 20210504
6-month open-label, controlled study **Wang**[7]	Wang CH et al. A nocturnal temperature controlled laminar flow device (TLA) maintains good control of severe allergic asthma (SAA) after withdrawal of Omalizumab therapy. Abstract 10036; ERS 2017
12-month observational study **Schauer** [9,14]	Schauer et al. Improved asthma control in patients with severe persistent allergic asthma after 12 months of nightly temperature-controlled laminar airflow (TLA): An observational study with retrospective comparisons. Eur Clin Respir J. 2015;2. Brazier P et al Economic analysis of temperature controlled laminar airflow (TLA) for the treatment of patients with severe persistent allergic asthma. BMJ Open Resp Res: 2016;3:e000117. Doi:10.1136/bmjresp-2015-000117

Atopic Dermatitis studies	
A pilot study in Children Söderman [11]	Söderman, et al. Case reports of the effectiveness of temperaturecontrolled laminar air flow therapy on allergen- induced atopic dermatitis. EACCI Congress abstract 2012
A 12-month proof-of-concept Gore C [12]	Gore C et al. To evaluate the effect of the temperature-controlledlaminar airflow (TLA) treatment in children/adolescents with severe atopic dermatitis. Clin Exp Allergy 2018 May;48(5):594-603.doi: 10.1111/cea.13105. Epub 2018 Mar 13
An observational study in Adults Traidl [13]	S Traidl, S et al. Temperature-controlled laminar airflow in adultatopic dermatitis patients – an observational study. J Eur Acad Dermatol Venereol 2021 Jul 9. doi: 10.1111/jdv.17507

Summary of the results of the clinical studies in asthma and atopic dermatitis

TLA effect in Asthma

Treatment with TLA in addition to regular treatment with inhaled steroids, resulted in reduced airway inflammation (study Pedroletti and Boyle), improved asthma symptoms (study Bjermer, Chauhan, Schauer and Wang) and quality of life (study Pedroletti, Boyle, Bjermer, Chauhan and Schauer). Asthma patients having symptoms despite step 4 treatment had the greatest effect of the treatment (study Boyle, Bjermer, Chauhan, Schauer and Wang). Effect of TLA on symptoms and quality of life could be detected within 3 months while sleep turned out to be an earlier indicator of effect (1 month) (study Bjermer).

In this symptomatic severe population TLA treatment reduced the frequency of exacerbations as well as fewer patients reported need of acute care and hospital admission (study Boyle, Chauhan, Wang and Schauer). TLA maintained asthma control after discontinuation of omalizumab (study Wang). One study (Kapoor) failed to show positive effects for TLA. This is most likely a result of an underpowered study with frequent missing data and a high placebo effect. These limitations may render the study inconclusive as the authors stated.

The clinical studies confirmed the pre-specified hypothesis that using TLA treatment to minimize nocturnal exposure to allergens and other airborne irritants can reduce airway inflammation and asthma symptoms as well as improving asthma-related quality of life when used in addition to regular pharmacotherapy in children and adults with persistent allergic asthma. Patients uncontrolled on GINA step 4–5 treatment were shown to benefit the most. This patient population also experienced less severe exacerbations and required less healthcare resources.

TLA effect in Atopic Dermatitis

Treatment with TLA, in addition to conventional treatment have been investigated in children in two small uncontrolled studies (Söderman, Gore). In study Traidl, TLA was tested for the first time in 8 AD patients with positive results in clinical improvements (QoL, symptoms and medication reduction). Study Gore C demonstrated an effect of TLA in 15 children with AD treated for 12 months. The primary variables SCORAD and IGA were significantly reduced, as was reduction of topical corticosteroids. The observational study (Traidl) is the first study with TLA in adult patients with AD to show efficacy in objective, subjective and In-vitro results. The results are promising and a randomized, double-blinded placebo-controlled study is ongoing to confirm the effect of TLA in AD.

TLA Safety in Asthma and Atopic Dermatitis

As a non-invasive, non-pharmacological treatment, Airsonett Air4, delivering clean air, has an inherent beneficial safety profile. In two randomized, placebo-controlled 12-month asthma studies, the frequency and type of adverse reactions reported were comparable in 552 patients receiving active treatment and placebo treatment [5, 39]. The safety profile in atopic dermatitis was also tolerable, as shown in two small studies. The adverse reactions in 100 patients with atopic dermatitis and concomitant asthma were comparable to 78 patients receiving placebo [5, 39].

No device-related serious adverse events have been reported in any of the clinical studies or in European Post Market Surveillance activities.

TLA and health economy

Severe Exacerbations and patient's quality of life are of great economic importance to health, especially in the uncontrolled severe asthmatic patients. Present therapy in uncontrolled patients on step 4/5-treatment includes oral steroids and immunosuppressive drugs (with risk of safety problems) and newer biologics (proven efficacy but not proven cost-effectiveness).

Based on health care expenditure in the observation study by Schauer et al. [9] an English expert team, led by Professor John o. Warner, did a health economic analysis [23]. The analysis was based on German data but English medical costs. The results showed that TLA treatment in patients with severe allergic asthma uncontrolled on treatment step 4–5, would lead to an ICER on £8,998/ Quality- Adjusted Life-Year (QALY). In Kapoor et al [38] TLA failed to demonstrate cost-effectiveness. However, the study had limitations and could have been inconclusive. A sub analysis of the study (Chauhan (Miller) [8]) revealed that more symptomatic patients with severe allergic asthma showed cost-effectiveness.

ICER was around £20,000. Present data indicate that TLA treatment is cost-effective in this more uncontrolled patient group with an ICER of around £10,000 to 20,000 per QALY, which is within the NICE-acceptable range (<£30,000 per Quality-Adjusted Life-Year (QALY) gained).

Conclusion

The prevalence of allergic diseases such as Asthma, Rhinitis and AD are high and the burden for patients and society is significant. The treatment option is mainly pharmacologic as avoidance of allergens in the treatment has hitherto not achieved significant benefit despite the strong evidence that exposure to aeroallergens both increases severity of disease and impairs quality of life. There is a huge unmet need.

An avoidance alternative is nocturnal TLA treatment.

The device is placed by the bed with the air supply above the head of the patient. Filtered room air is cooled by 0.5-1.0 degrees Centigrade, which descends over the patient, while in bed. The supply of clean laminar airflow in the breathing zone hinders the body convection flow of allergens and other irritant particles by ≥99.5% to reach the patient in bed. TLA treatment has been shown to be 100 times more effective than traditional air cleaners in reducing airborne particles in the breathing zone. Nocturnal treatment with TLA has in clinical asthma studies shown attenuation of inflammation in the airways, reduced asthma symptoms and improved asthma related quality of life (QoL), when used in addition to recommended pharmacotherapy in children and adults with persistent allergic asthma. Patients uncontrolled on GINA step 4–5 treatments were shown to benefit the most. Significant effects on symptoms and quality of life (QoL) were reached in 3–6 months with sleep as an early indicator within one month. This patient population also had fewer severe asthma exacerbations and less related health-care utilization. Pilot-data indicate that TLA can replace expensive biologic therapy (omalizumab) without loss in efficacy. A post hoc study in rhinitis and initial uncontrolled studies in AD indicate effect of TLA in two other allergic diseases. No foreseeable clinical performance and safety risk of TLA treatment were identified with regards to its intended use when the instructions provided in the Instruction for Use, subsections; Intended use.

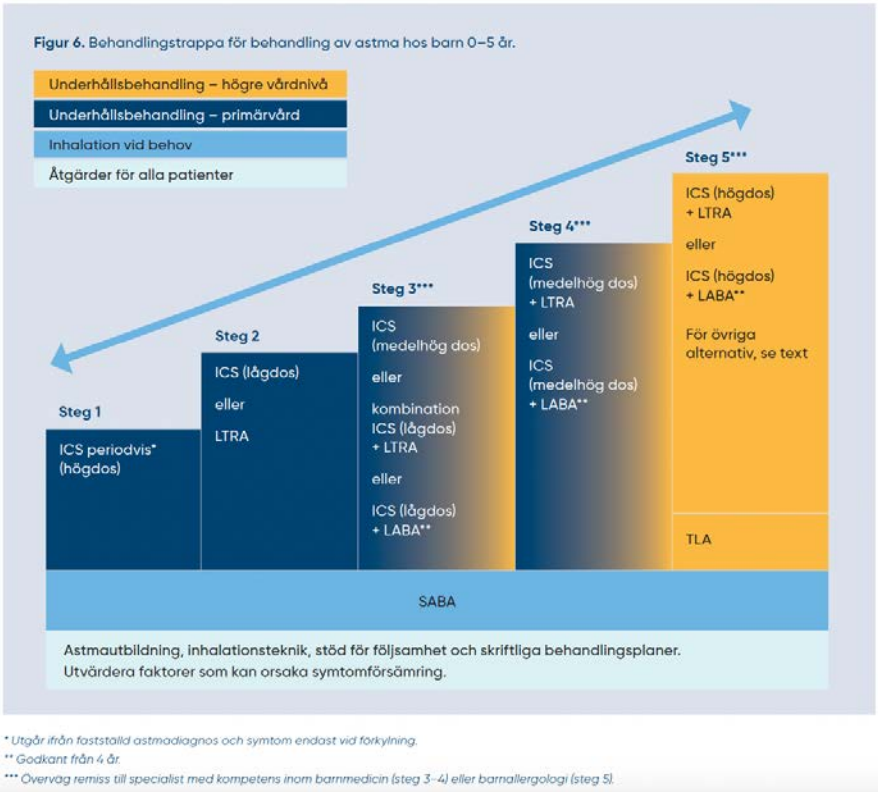
The effect of TLA on airborne particle exposure and clinical outcomes such as improved symptoms, quality of life and reduction of exacerbations, supports the EU and US Instructions for Use. The results are also in line with recommendations in national guidelines and by experts in the field i.e., TLA is an effective and cost-effective add-on treatment in symptomatic severe allergic disease such as asthma. Evidence is growing for effect also in moderate-to-severe AD and rhinitis.

TLA treatment with demonstrated efficacy and safety, is non-invasive, are without any pharmacological side effects and no added risk for interacting with pharmaceutical treatments. TLA-treatment has also demonstrated cost- effectiveness in asthma.

Expert recommendation

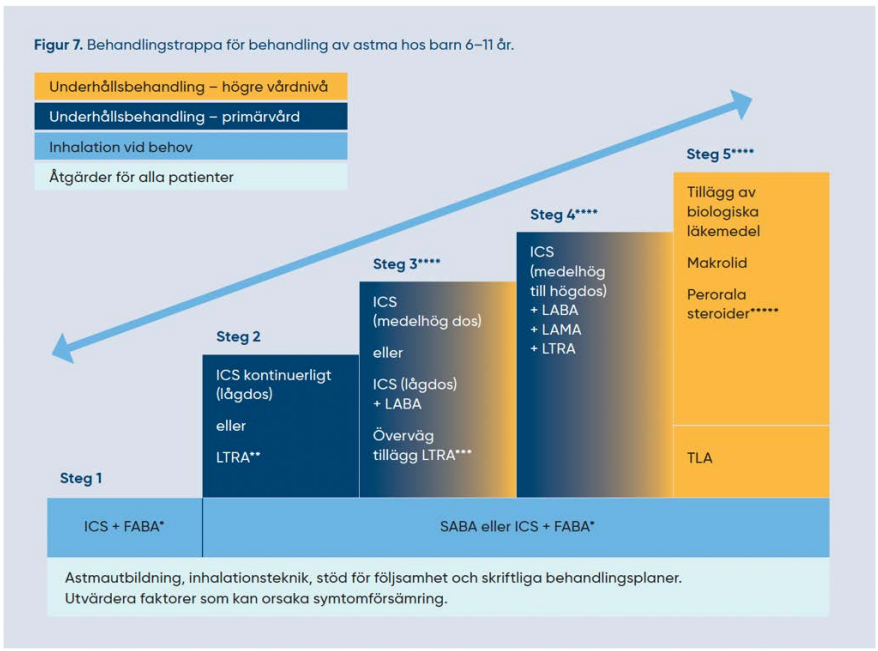
Recommendations/guidelines by independent expert groups

1. National institute for Health and care excellence. NICE [21] reviewed TLA-technology as an add-on treatment for children with severe persistent allergic asthma, which, in spite of high intensity drug therapy, remains uncontrolled. This includes patients who have reached the BTS/SIGN step 4 or higher and that would otherwise be considered for treatment with oral steroids, biologics or bronchial termoplasti. NICE 2014
2. Healthcare Improvement Scotland [22] considered that the clinical and economic evidence as presented by the company showed that Airsonett® was clinically and cost effective, as add-on treatment to standard of care. Healthcare Improvement Scotland
3. The Swedish National Board of Health and Welfare [20] recommended TLA for "allergic, severe, uncontrolled asthma despite treatment step 4 in adults and children ≥6 years (Recommendation 5). National guidelines for the treatment of asthma and chronic obstructive pulmonary disease (COPD). The Swedish National Board (2020)
4. The Swedish National Product Agency (Läkemedelsverket) [19] Page 26–42 Treatment guidelines. Non-pharmacological treatment with TLA, generating a laminar flow of filtered air, to create an allergen-free breathing zone during the night. The treatment can be an alternative to other add-on treatments for patients with perennial severe allergic asthma. Läkemedelsbehandling vid astma (lakemedelsverket.se)
5. Swedish pediatric association, [15] BLFA chapter 10. "Underhållsbehandling av astma". In step 5 in the treatment recommendations for poorly controlled step-4 patients, one or more of the following add-on treatments should be considered at step 5. The recommended pharma and other treatments included in step 5 are biological as anti-IgE and Anti-Il5, oral corticosteroids, azithromycin and Airsonett. Airsonett is recommended for severe allergic asthma with perennial airway allergy, regardless of if the allergy is IgE- or cellular-mediated. Evaluation of the treatment effect should be done after 3 months. Treatment with Airsonett TLA can be especially valuable for combinations of severe asthma and difficult-to-treat eczema, as the treatment affects both conditions favorably. https://aol.barnlakarforeningen.se/wp-content/uploads/sites/24/2020/07/d10_underhallsbeh_astma.pdf
6. Warner JO. [23] Use of temperature-controlled laminar airflow in the management of atopic asthma: clinical evidence and experience. Ther Adv Respir Dis 2017;11:181-188
7. von Boven [24] Frank E et al. Effectiveness of the Air Purification Strategies for the Treatment of Allergic Asthma: A Meta-Analysis Clinical Allergy – Research Article Int Arch Allergy Immunol 2020 Published online
8. Warner JO. [25] et al. ALLERGY PREVENTION – REALITY OR NOT? Current Allergy & Clinical Immunology I October/December 2020 I Vol 33, No ¾
9. The Swedish Dental and Pharmaceutical Benefits Agency (TLV) [40] considers treatment with TLA to be cost-effective given the data available, provided that the patient corresponds to the indication. The patient should preferably be referred to a specialist doctor/allergist for individual assessment. https://www.tlv.se/download/18.467926b615d084471ac33936/1510316400090/Slutrapport_medicinteknik_141217.pdf



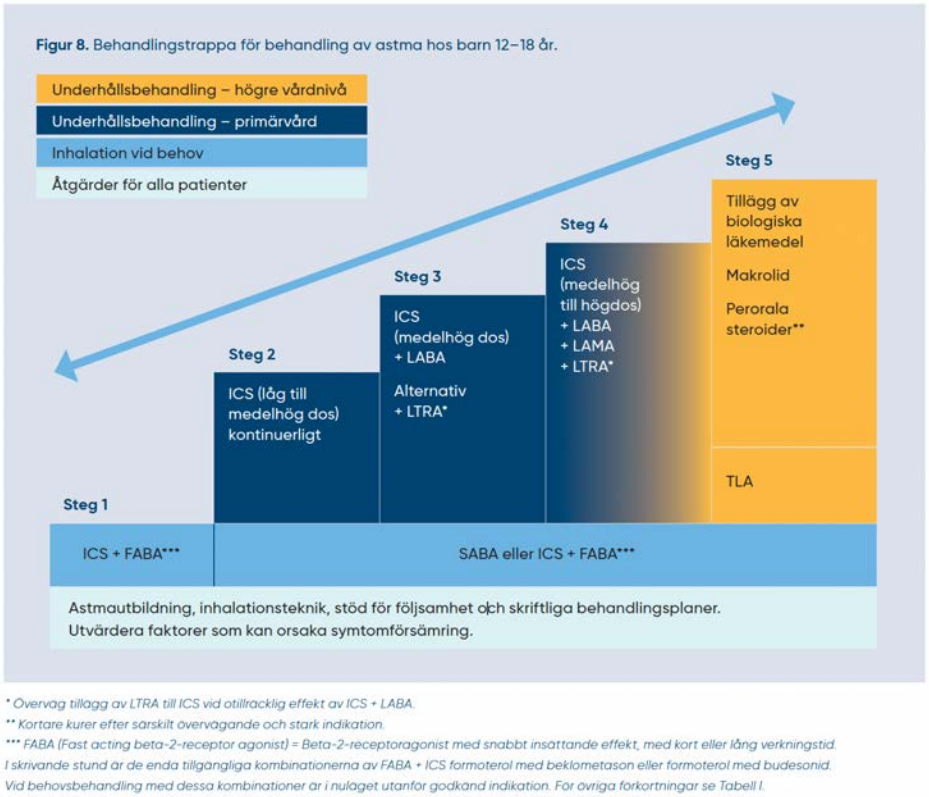
* Utgår ifrån fastställd astmadiagnos och symtom endast vid förkylning.
** Godkänt från 4 år.
*** Överväg remiss till specialist med kompetens inom barnmedicin (steg 3–4) eller barnallergologi (steg 5).

Figure 4. Excerpt Asthma Treatment guidelines, children 0-5 years, The Swedish Medical Products Agency



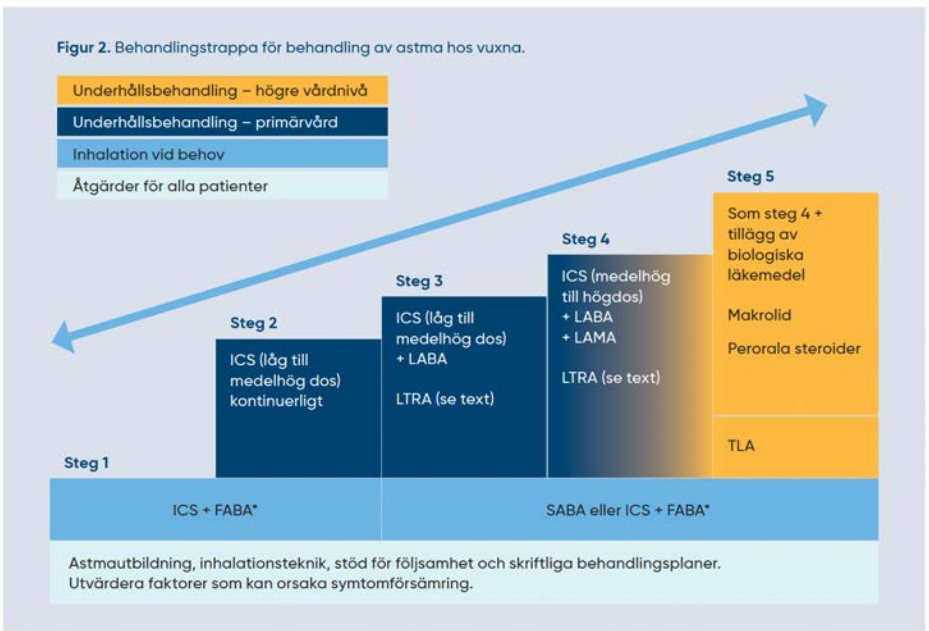
* FABA (Fast acting beta-2-receptor agonist) = Beta-2-receptoragonist med snabbt insättande effekt, med kort eller lång verkningstid. I skrivande stund är de enda tillgängliga kombinationerna av FABA + ICS formoterol med beklometason eller formoterol med budesonid. Vid behovsbehandling med dessa kombinationer är i nuläget utanför godkänd indikation. För övriga förkortningar se Tabell I.
** ICS har bättre effekt än LTRA, framför allt hos barn med allergisk laggning.
*** Överväg tillägg av LTRA till ICS vid otillräcklig effekt av ICS och LABA.
**** Överväg remiss till specialist med kompetens inom barnmedicin (steg 3–4) eller barnallergologi (steg 5).
***** Kortare kurer efter särskilt övervägande och stark indikation.

Figure 5. Excerpt Asthma Treatment guidelines, children 6-11 years, The Swedish Medical Products Agency



* Överväg tillägg av LTRA till ICS vid otillräcklig effekt av ICS + LABA.
** Kortare kurer efter särskilt övervägande och stark indikation.
*** FABA (Fast acting beta-2-receptor agonist) = Beta-2-receptoragonist med snabbt insättande effekt, med kort eller lång verkningstid. I skrivande stund är de enda tillgängliga kombinationerna av FABA + ICS formoterol med beklometason eller formoterol med budesonid. Vid behovsbehandling med dessa kombinationer är i nuläget utanför godkänd indikation. För övriga förkortningar se Tabell I.

Figure 6. Excerpt Asthma Treatment guidelines, children 12-18 years, The Swedish Medical Products Agency



* FABA (Fast acting beta-2-receptor agonist) = Beta-2-receptoragonist med snabbt insättande effekt, med kort eller lång verkningstid. I skrivande stund är de enda tillgängliga kombinationerna av FABA + ICS, formoterol med beklometason eller formoterol med budesonid. Vid behovsbehandling med dessa kombinationer utan underhållsbehandling är i nuläget utanför godkänd indikation. För övriga förkortningar se **Tabell I.**

Figure 7. Excerpt Asthma Treatment guidelines, Adults, The Swedish Medical Products Agency

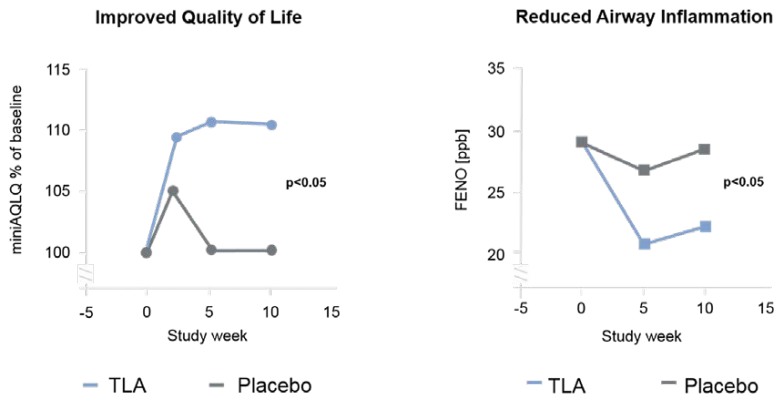
Results from the clinical studies

A 22-week Pilot Study, Pedroletti et al [4]	
Objective:	To demonstrate the efficacy of TLA treatment when used in addition to regular pharmacotherapy to reduce allergic reactions in a population of subjects with mild to moderate persistent allergic asthma.
Design:	Randomized, controlled, double-blind, cross-over study in 22 patients with mild to moderate persistent allergic asthma who received 10 + 10 weeks treatment with the Airsonett TLA device and placebo device (with 2 weeks wash-out period).
Patient Population:	*Key inclusion criteria* • Patients 12–33 years with diagnosed asthma • Perennial allergy demonstrated by a positive skin prick test to at least one of the following allergens: cat, dog, house dust mites and/or mold • Daily medication with inhaled corticosteroid equivalent to ≥400µg/day of inhaled budesonide *Key exclusion criteria* • Current smoker • Participation in another allergen avoidance program or in a drug trial
Primary Endpoint:	Difference in quality of life between active versus placebo treatment as assessed by change in miniAQLQ score over 10 weeks.
Key Secondary Endpoints:	Difference in airway inflammation between active versus placebo treatment as assessedby change in FENO over 10 weeks.

Clinical Outcomes:

The mean improvement in overall miniAQLQ score in the group treated with the Airsonett TLA device was significantly greater than in the placebo group (mean difference = 0.54; SEM ±0.28, p<0.05) after 10 weeks of treatment. FENO was significantly reduced by 6.4 ppb (SEM ±2.50, p<0.05) after 10 weeks of Airsonett TLA treatment as compared with placebo.

Nocturnal TLA treatment provided a statistically and clinically significant improvement asthma-related quality of life (AQLQ) and significant reduction in airway inflammation (FENO).



Airsonett
A Breath of New Life

A 12-month Pivotal Study Boyle et al [5]	
Objective:	To demonstrate the effectiveness and safety of the Airsonett TLA device when usedin addition to regular pharmacotherapy to reduce allergic reactions in a population ofsubjects with poorly controlled persistent allergic asthma over 12 months.
Design:	312 patients with moderate to severe poorly controlled persistent allergic asthma were enrolled in this randomized (2:1 ratio), double-blind, placebo-controlled, parallel-group study conducted in 19 European asthma clinics in 6 countries over 12 months.
Patient Population:	*Key inclusion criteria* • Patients (7–70 years) with diagnosed asthma • Allergy to cat, dog and/or house dust mite demonstrated by specific IgE level • ≥0.70kU/L or positive skin prick test • Daily maintenance dose of at least ICS ≥200µg/day of budesonide or ≥100µg/day of fluticasone since at least 6 months • Partly uncontrolled asthma according to GINA 2006 • Mini-AQLQ/PAQLQ score of ≤5.5 *Key exclusion criteria* • Current smoker (Non-smoker is defined as abstinent since >1 year). Children: Parents' indoor smoking. • ICS ≥1200µg/day of budesonide or 1000µg/day of fluticasone
Primary Endpoint:	Difference between TLA treatment and placebo in the proportion of patients with an increase of ≥0.5 points* in the miniAQLQ score and the corresponding pediatric PAQLQ score ("responders") after one year of treatment.
Key Secondary Endpoints:	Change in FENO, asthma symptoms and quality of sleep, and exacerbation rates.

Clinical Outcomes:

The primary efficacy analysis demonstrated a significant difference in AQLQ responder rate between active (143 of 189, 76%) and placebo (56 of 92, 61%) groups after 12 months – absolute difference 14.8% (OR: 1.99; 95% CI 3.1 to 26.5, p=0.02). This was also true for the pediatric subgroup (<12 years; absolute difference 16.8%; OR:7.63, p=0.04. The absolute differences in AQLQ responder rates corresponds to Numbers Needed to Treat (NNT; 1/absolute difference in responder rates) values of 6.8 (ITT) and 6.0 (<12 years).

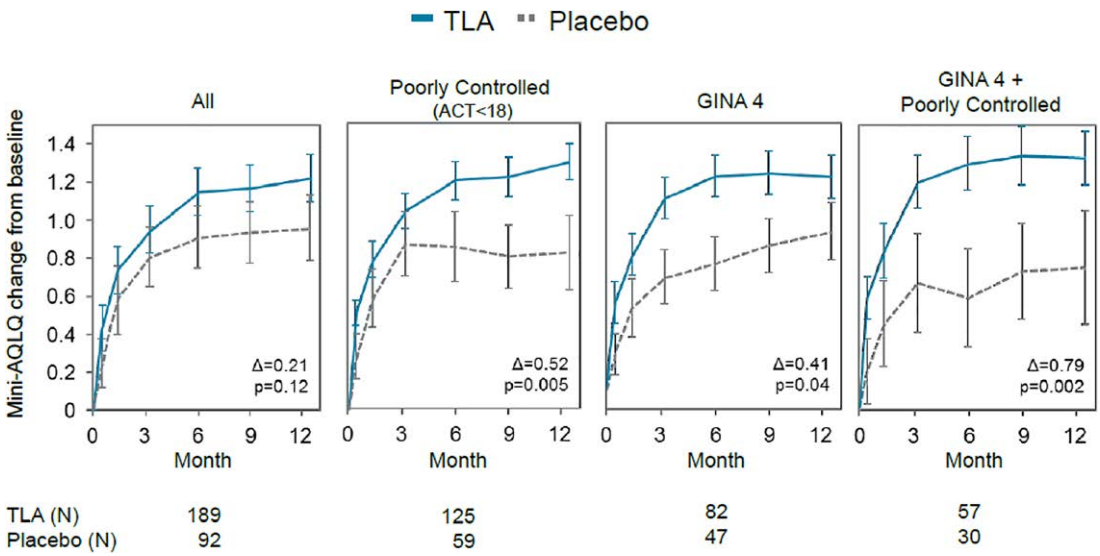
A pre-specified subgroup analysis based on asthma severity and asthma control showed that patients with more severe disease (based on high intensity treatment such as GINA step 4 at baseline) and uncontrolled asthma (based on an ACT <18 at baseline) identifies the patients that will benefit the most (absolute difference TLA vs placebo 25.4%; OR=4.74; p=0.009). In this subgroup the NNT can be calculated to 3.9.

Although this study was not primarily designed to evaluate the effect of the Airsonett TLA device on asthma exacerbation rates, and in general the patients showed relatively low rates of severe asthma exacerbations (approx. 0.2 exacerbations/year). A subgroup analysis based on markers of increased exacerbation risk (such as ACT<18 and/or GINA 4 treatment intensity or ACT<18 and GINA 4 combined with sensitivity to multiple allergens at baseline) showed a clear trend towards a reduced exacerbation risk with TLA treatment vs. placebo in patients with increased exacerbation risk. Safety: In total, 153 (74%) patients in the active and 79 (75%) in the placebo group suffered an adverse event, and 32 (17%) patients in the active and 14 (15%) in the placebo group a serious adverse event. None were treatment related. Further details are given in the online supplementary material.

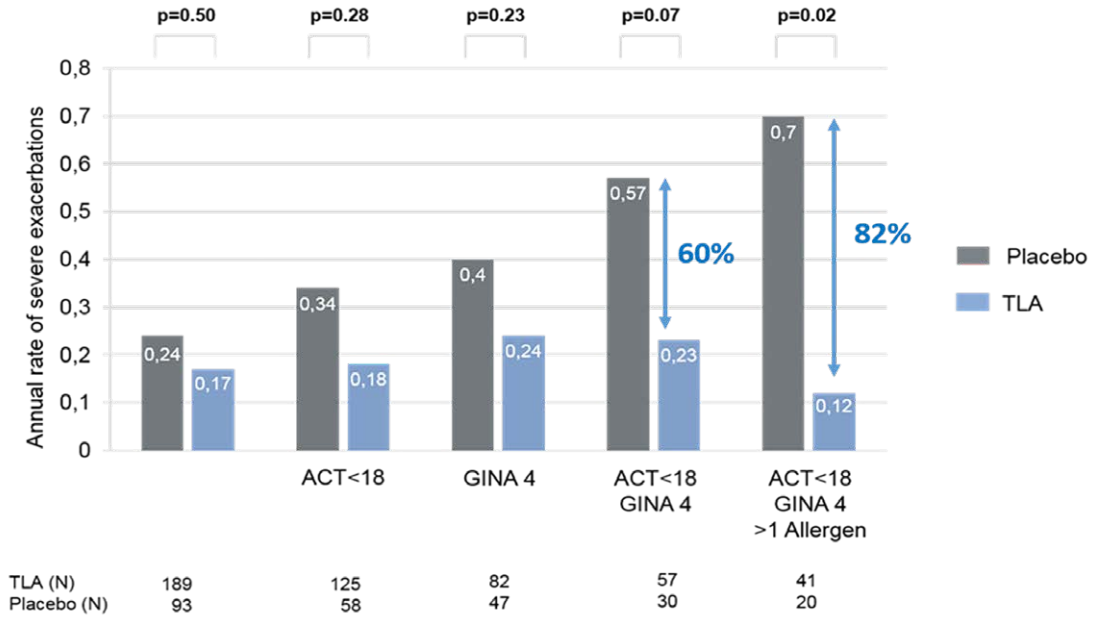
* The minimal important difference of quality-of-life score per item has been defined to be 0.5 points for the overall asthma-specific quality of life score as well as for the individual domains. [16]

Study Boyle, continued

Patients with uncontrolled allergic asthma despite BTS step 4 treatment showed both a statistically significant and clinically meaningful improvement in Asthma related Quality of Life.



Post-hoc analysis showed a significant reduction of exacerbations in patients with uncontrolled allergic asthma despite BTS step 4 treatment sensitized to >1 allergen.



Safety:

The adverse event reporting was very similar in the Airsonett TLA group and the placebo group. Serious adverse events occurred in 17% of the participants in the Airsonett TLA device group and 15% in the placebo group, none of which were considered treatment related.

A 12- months pivotal study (Time-to-onset) Bjermer et al [6]	
Objective:	To study the effect of TLA-treatment in addition to regular chronic pharmacologic therapy on patients with uncontrolled persistent allergic asthma over 12 months.
Design:	312 patients with moderate to severe poorly controlled persistent allergic asthma were enrolled in this randomized (2:1 ratio), double-blind, placebo-controlled, parallel-group study conducted in 19 European asthma clinics in 6 countries over 12 months.
Patient Population:	*Key inclusion criteria* • Patients (7–70 years) with diagnosed asthma • Allergy to cat, dog and/or house dust mite demonstrated by specific IgE level • ≥0.70kU/L or positive skin prick test • Daily maintenance dose of at least ICS ≥200µg/day of budesonide or ≥100µg/day of fluticasone since at least 6 months • Partly uncontrolled asthma according to GINA 2006 • Mini-AQLQ/PAQLQ score of ≤5.5 *Key exclusion criteria* • Current smoker (Non-smoker is defined as abstinent since >1 year). Children: Parents' indoor smoking. • ICS ≥1200µg/day of budesonide or 1000µg/day of fluticasone
Primary Endpoint:	Time to onset (TTO) for AQLQ total in the patient group with uncontrolled severe allergic asthma i.e. the indicated patient group for TLA.
Key Secondary Endpoints:	Time to the efficacy of the sub-domains of the AQLQ and Sleep in the group with uncontrolled severe asthma. Time to effect for AQLQ in all patients, symptomatic patients and GINA 4 patients. Time to onset for decreases in FENO.

Clinical Outcomes:

Patients with uncontrolled asthma treated according to GINA step 4 reported a statistically significant and clinically relevant ((≥0.5) improvement in overall AQLQ scores (0.57; p = 0.009) after 3 months of

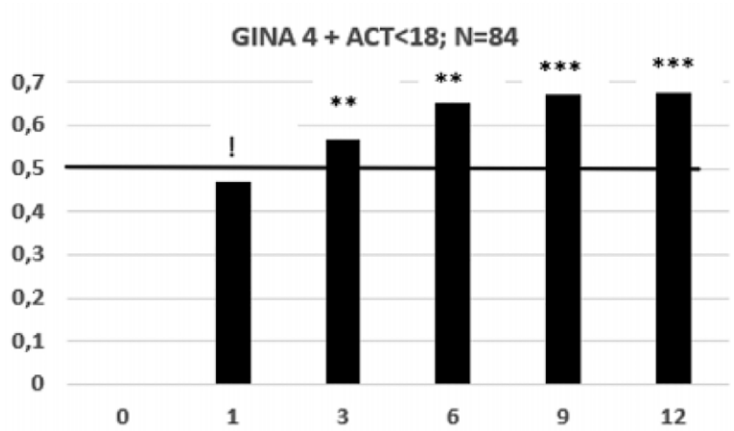
treatment with TLA as compared to placebo. The shortest time to response was on sleep quality and for the environmental domain, which was recorded within one month. TTO for the emotional and symptom domains were within 3 months (0.66 0.64; p = 0.020, respectively; p = 0.014) and 6 months for "activity domain"

(0.47; p = 0.036). Patients in GINA 4 and patients with symptoms (ACT <18) also showed significant effects on overall AQLQ but the difference between TLA and placebo was less.

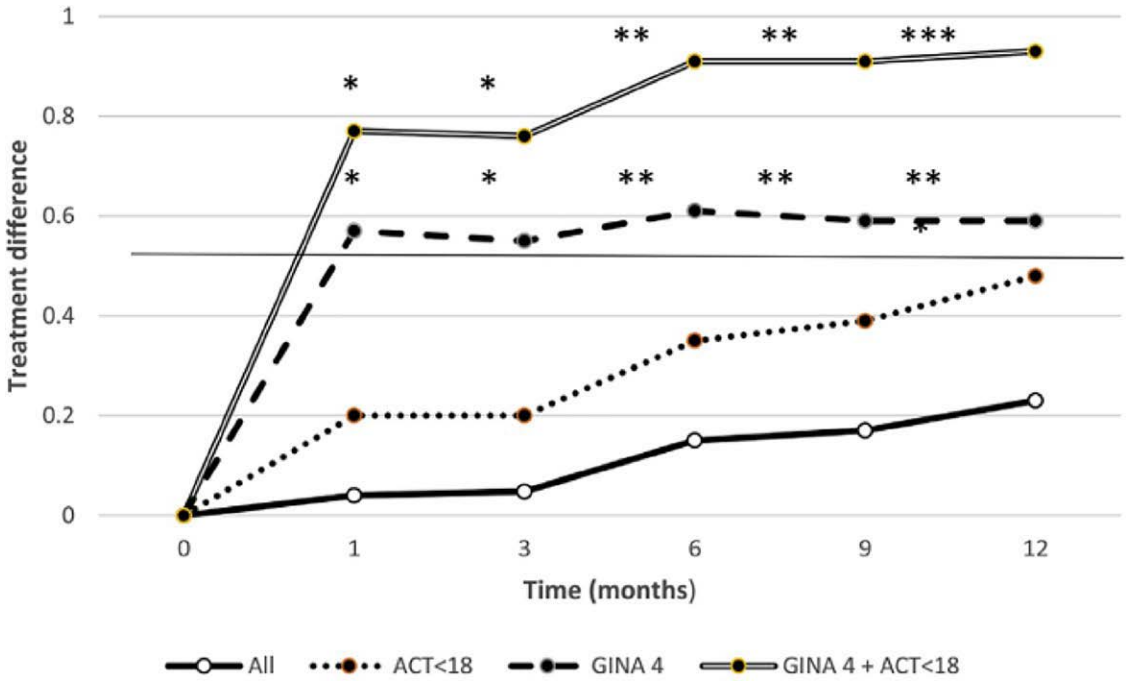
Patients with abnormally high values for FENO at baseline (>45 ppb; N=77) had a statistically significant decrease in FENO (0.32; p= 0.024) already after 1 month of treatment with TLA compared to placebo. The treatment difference persisted at 12 months ((0.24; p = 0.038)).

Study Bjermer, continued

Effect over time on AQLQ total for patients with uncontrolled severe asthma.



Differences in Sleep quality over time between TLA and placebo for the three subdomains and all patients.



Nocturnal avoidance of allergens using TLA resulted in a statistically significant and clinically relevant improvement in overall AQLQ scores within 3 months. Questions regarding sleep quality and emotion can give a first indication of response; already in the first month of TLA-treatment.

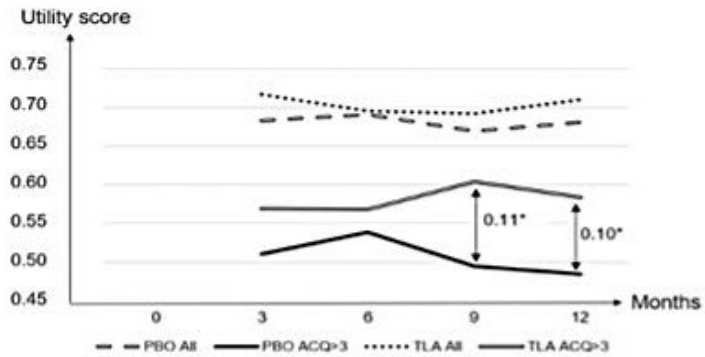
A 12- month Pivotal Study Kapoor et al [39]	
Objective:	To demonstrate the effectiveness and safety of TLA treatment used to reduce severe exacerbations in a population of subjects with poorly controlled persistent allergic asthma over 12 months.
Design:	Patients with moderate to severe poorly controlled persistent allergic asthma wereenrolled in a randomized, double-blind, placebo-controlled, parallel-group study conducted in 14 asthma clinics in the UK over 12 months.
Patient Population:	*Key inclusion criteria* • Patients (16–75 years) with diagnosed asthma • Diagnosis of asthma for > 6 months, • Severe asthma (high dose ICS and or stable OCS • Poorly controlled asthma (2 or more severe exacerbations previous year and ACQ>1) • Sensitization to one or more perennial indoor aeroallergens • Adherence *Key exclusion criteria* • Current smoker (Non-smoker is defined as abstinent since > 6 months • Clinically significant comorbidities • Treatment with omalizumab, use of oxygen and thermoplasty
Primary Endpoint:	To determine whether or TLA treatment reduces the frequency of severe asthma exacerbations (defined as an acute deterioration in asthma requiring treatment with systemic corticosteroids).
Key Secondary Endpoints:	Asthma control and quality-of-life Health-care utilisation
Clinical Outcomes: 240 patients were randomized. The rate of severe exacerbations did not differ between groups (active 1.39, placebo 1.48, risk ratio 0.92 p = 0.61). No differences could be detected in secondary outcomes, except for a reduction in PEF. TLA was well tolerated and comparable to the safety of placebo. Health economy observed no difference between the groups in quality-adjusted life-years gained over 1 year was observed, as the increases in quality of life were not sufficient to offset the annual costs associated with use of the TLA device. The study failed to show positive effects for TLA. This is most likely a result of an underpowered study with frequent missing data and a high placebo effect. These limitations may render the study inconclusive. Safety: The numbers of adverse events were similar in both groups and none of the serious adverse events was device-related following causality assessment. Five adverse events (in four patients) were considered to be probably related to the device, all in the placebo group.	

Study Chauhan 2022: A 12-month Pivotal Study (Sub-group) (Miller 2019) et al [5]	
Objective:	To demonstrate the effectiveness and safety of TLA treatment to reduce severe exacerbations in the more symptomatic patients of subjects with severe persistent allergic asthma over 12 months.
Design:	Patients with more uncontrolled severe persistent allergic asthma were extracted from a randomized, double-blind, placebo-controlled, parallel-group study over 12 months (38).
Patient Population:	*Key inclusion criteria* • Patients (16–75 years) with diagnosed asthma • Diagnosis of asthma for > 6 months, • Severe asthma (high dose ICS and or stable OCS • Poorly controlled asthma (2 or more severe exacerbations previous year and ACQ>1) • Sensitization to one or more perennial indoor aeroallergens • Adherence *Key exclusion criteria* • Current smoker (Non-smoker is defined as abstinent since > 6 months • Clinically significant comorbidities • Treatment with omalizumab, use of oxygen and thermoplasty
Primary Endpoint:	To demonstrate an effect on severe asthma exacerbations (defined as an acute deterioration in asthma requiring treatment with systemic corticosteroids) in the more uncontrolled patients with severe allergic asthma.
Key Secondary Endpoints:	Quality of Life (AQLQ)

Clinical Outcomes:

93 to 137 patients were included in the analyses, dependent baseline covariate used. Total AQLQ improved 0.31 (p=0.085) and 0.33 (p=0.034) score units with AQLQ and EQ5D-VAS, respectively, as covariates. Severe exacerbations showed a 33% (p=0.083) and 31% (0.073) reduction, in favour of TLA in the ACQ>3 and EQ5D-VAS≤65 sub-groups respectively. These results for severe exacerbations and quality of life are consistent with a similar patient population in another 12-month study (Study B1). The difference in EQ5D-5L utility scores between TLA and placebo was significant (0.10, p=0.046) resulting in an incremental cost-effectiveness ratio (ICER) of around £20,000, which is within the NICE-acceptable range (<£30,000 per Quality-Adjusted Life-Year (QALY) gained), i.e. TLA treatment was cost-effective in this more uncontrolled patient group.

Utility scores by timepoint from the full study and the sub-group ACQ7>3: MMRM analyses using baseline values as co-variant.



Study C2, continued

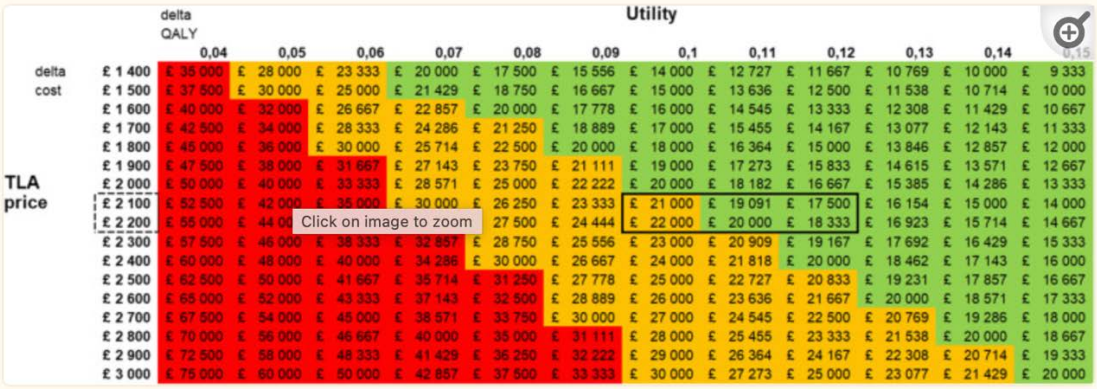


Fig. 4

Cost-effectiveness grid over the incremental cost-effectiveness ratio (ICER) estimates for TLA from the ACQ7 > 3 sub-group. The utility scores for TLA at 9 and 12 months are shown on the Delta QALY-axis. In addition, the TLA price is shown on the Delta cost-axis resulting in cost-effectiveness (ICER) for TLA of about £17,000–£22,000 (black rectangle), which is below the acceptable recommended threshold for NICE, i.e., <£30,000

Two 12 months Pivotal Studies (Meta-analysis 2021) Chauhan et al [4]	
Objective:	To investigate the effect of TLA on severe exacerbations and quality-of-life among patients with more symptomatic severe allergic asthma when two 1-year studies [1, 5] were pooled for a meta-analysis of individual patient data.
Design:	Patients with more uncontrolled severe persistent allergic asthma were extracted from two randomized, double-blind, placebo-controlled, parallel-group study over 12 months (Study B1 and C1).
Patient Population:	*Key inclusion criteria* • Patients (7–75 years) with diagnosed asthma • Diagnosis of asthma for > 6 months, • Severe asthma (GINA 4/5) • Poorly controlled asthma (ACQ>1 or ACT<18)) • Sensitization to one or more perennial indoor aeroallergens • Adherence *Key exclusion criteria* • Current smoker (Non-smoker is defined as abstinent since > 6 months • Clinically significant comorbidities • Treatment with omalizumab, use of oxygen and thermoplasty
Primary Endpoint:	To demonstrate an effect on severe asthma exacerbations (defined as an acute deterioration in asthma requiring treatment with systemic corticosteroids) in the more uncontrolled patients with severe allergic asthma.

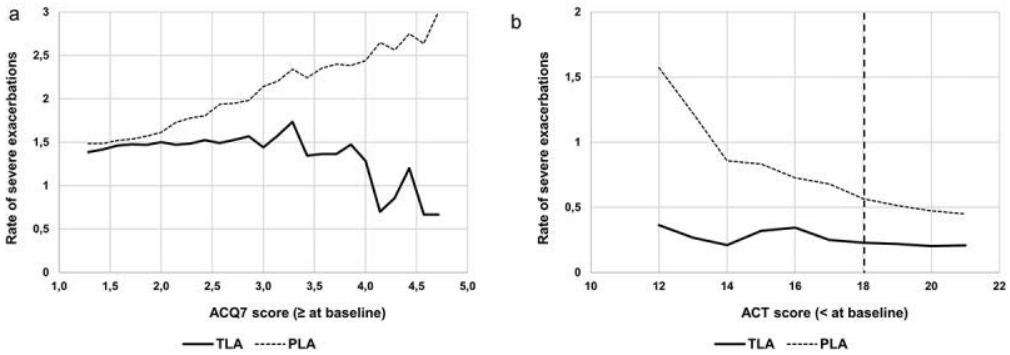
Key Secondary Endpoints:	Quality of Life (AQLQ-responders)

Clinical Outcomes:

179 patients with more symptomatic severe asthma at baseline (ACT<18 or ACQ>3), had a significant mean 41% reduction in severe exacerbations (p=0.015) in favor of TLA. Higher ACQ cut points of 3.5-4.5 resulted in significant reductions of 48-59%. More uncontrolled patients based on AQLQ total and AQLQ symptom ≤3.0 at baseline also showed a significant reduction in severe exacerbations for TLA vs. placebo ((47% (p=0.037) and 53% (p=0.011), respectively). The meta-analysis also confirmed a significant difference in AQLQ- responders (MCID ≥0.5; 74% vs. 43%, p=0.04). These beneficial effects support the national management recommendations for TLA treatment in patients with symptomatic severe allergic asthma.

Descriptive presentation of the rate of severe asthma exacerbations over 12 months in Study A and Study B2 by baseline ACQ7 and ACT-scores for TLA-treated (solid line) and placebo-treated (dotted line) patients. (a): Baseline ACQ7 score in Study A. (b): Baseline ACT score in Study B2.

Abbreviations: ACQ, Asthma Control Questionnaire; ACT, Asthma Control Test; TLA, Temperature-controlled Laminar Airflow; PLA, placebo. Notes: Dashed vertical line represents ACT = 18, the prespecified cut-off in Study B2.



Airsonett
A Breath of New Life

Study D, continued

Rate ratios for severe asthma exacerbations in the pooled dataset for different cut-off levels of baseline ACQ7/ACT scores, total AQLQ score, and AQLQ symptom domain score.

	TLA (n)	TLA (n_{ex})	Rate TLA	PLA (n)	PLA (n_{ex})	Rate PLA	RR (95% CI)	p-value
ACQ7/ACT interval								
>4.5 and <18	62	19	0.31	42	50	1.19	0.41 (0.18–0.94)	0.036
>4.0 and <18	71	31	0.44	55	78	1.42	0.46 (0.24–0.86)	0.016
>3.5 and <18	83	48	0.58	67	100	1.49	0.52 (0.31–0.86)	0.012
>3.0 and <18	100	75	0.75	79	122	1.54	0.59 (0.38–0.90)	0.015
>2.5 and <18	118	106	0.90	102	147	1.44	0.73 (0.50–1.06)	0.096
AQLQ interval								
Total AQLQ score								
≤ 2.5	20	11	0.55	19	41	2.16	0.33 (0.13–0.71)	0.014
≤ 3.0	33	31	0.94	32	68	2.13	0.53 (0.29–0.70)	0.037
≤ 3.5	51	49	0.96	55	92	1.67	0.63 (0.37–0.72)	0.083
AQLQ symptoms domain only								
≤ 2.5	17	12	0.71	30	71	2.37	0.37 (0.16–0.79)	0.011
≤ 3.0	42	37	0.88	46	94	2.04	0.47 (0.26–0.84)	0.011
≤ 3.5	66	67	1.02	62	102	1.65	0.70 (0.43–1.12)	0.132

Abbreviations: TLA, Temperature-controlled Laminar Airflow; PLA, placebo; RR, Rate ratio; ACQ, Asthma Control Questionnaire; ACT, Asthma Control Test; AQLQ, Asthma Quality of Life Questionnaire

A 48 weeks omalizumab-sparing study Wang al et [10]	
Objective:	To study the effectiveness of TLA-treatment over 48 weeks in patients with allergicasthma, which was controlled at omalizumab and then ended with omalizumab.
Design:	Randomized, controlled study involving 23 patients with severe allergic asthma, who were controlled on omalizumab for 6 months before inclusion. At randomization omalizumab was withdrawn and patients were treated with TLA or placebo for 48 weeks but were treated with or without a TLA for 48 weeks.
Patient Population:	Patients with asthma were treated with inhaled steroid long-acting beta-agonist anti-IgE preparations (omalizumab) at study entry.
Primary Endpoint:	Time to first severe exacerbation (Cox-regression).
Key Secondary Endpoints:	• Number of exacerbations (Fischer's test) • Lung function • Asthma control test (ACT) • FENO

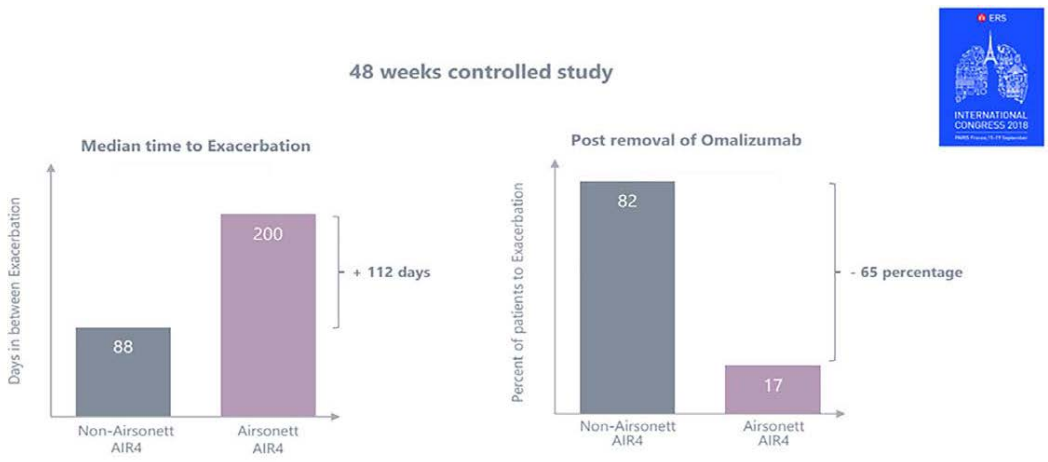
Clinical Outcomes:

Time to first exacerbation was significantly longer for TLA treated patients (200 days) compared with patients not treated with TLA (88 days, p = 0.0005). The number of exacerbations was also significant in favor of TLA (2/12 = 17%) vis-à-vis without TLA (9/11 = 82%, p = 0.0001). Patients treated with TLA had stable FEV1, ACQ and FENO, while those not treated with TLA had deterioration in FEV1 and ACT and increased FENO. Reduction of allergen/particles with TLA maintains control of asthma after discontinuation of omalizumab and can be an alternative to patients with uncontrolled severe asthma requiring the addition of anti-IgE therapy

Clinical Trials/Results

Maintain good control after withdrawal of Omalizumab therapy.

- TLA treatment significantly increase time between exacerbations while at the same time reducingthe need for usage of Omalizumab treatment.



C.H. Wang et al., Thorac Medicine, Chang Gung Memorial Hospital.

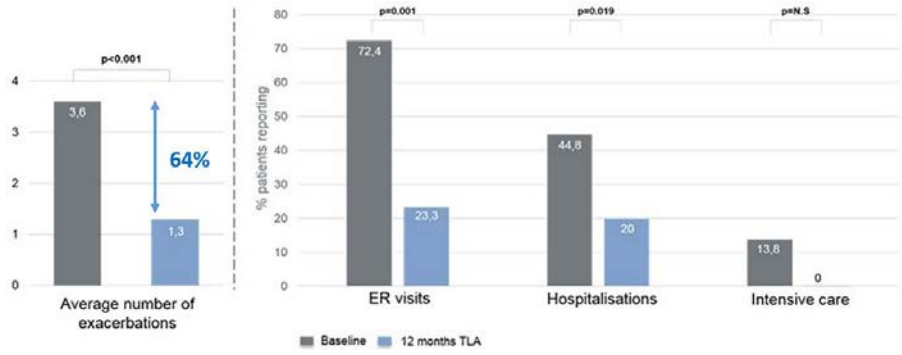
A 12-month Observational Study Schauer [9]	
Objective:	To demonstrate the effectiveness of TLA treatment when used during real-life conditions in addition to regular pharmacotherapy by reducing severe exacerbations and improving asthma control in patients with severe allergic asthma during 12 months.
Design:	Multicenter, pre- and post- retrospective observational study in patients with severe allergic asthma who received add-on treatment with the TLA device for 12 consecutive months.
Patient Population:	*Key inclusion criteria* • 30 patients with diagnosed severe persistent allergic asthma. • 7–80 years (mean age was 28, and 50% were <18 years at baseline). • History of at least one episode of severe exacerbation were included. All patients were treated with inhaled corticosteroids, ten patients (33%) were on regular treatment with oral corticosteroids (OCS) and 13 (43%) were treated with anti-IgE monoclonal antibodies at the beginning of the study
Primary Endpoint:	The primary objective of the study was to evaluate the intra-individual change in asthma control after 12 months of Airsonett TLA device use: • the number of severe exacerbations • the need of asthma-related ER, hospital, or ICU admission
Key Secondary Endpoints:	Need of Health Care utilization Asthma Control Test (ACT). Lung function Use of OCS

Clinical Outcomes:

30 patients completed measurements at baseline and 4 months and 27 patients the 12-month visit. Treatment with the Airsonett TLA device significantly improved asthma control over 12 months as shown by:

- A significant reduction in severe exacerbation frequency from 3.6 to 1.3 (p<0.001).
- A reduction in the proportion of patients requiring asthma exacerbation related healthcare utilization as demonstrated by:
- Asthma Control Test (ACT) scores were significantly improved from 14.1 to 18.5 (p<0.0001) with a clinically meaningful difference (≥ 3 points) compared with baseline.
- FEV1 improved significantly from 1.9 to 2.3 L (p<0.01).
- Number of patients treated with oral steroids decreased during the study from 10 to 6 patients Safety: No safety reported

Airsonett TLA device significantly reduced exacerbations and related healthcare utilization.



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An economic analysis of TLA, Brazier [14]	
Objective:	To quantify the health economic value of TLA technology in the UK, based on published evidence in a 12-months observational study.
Design:	Multicenter, pre- and post- retrospective observational study in patients with severe allergic asthma who received add-on treatment with the TLA device for 12 consecutive months.
Patient Population:	*Key inclusion criteria* • 30 patients with diagnosed severe persistent allergic asthma. • 7–80 years (mean age was 28, and 50% were <18 years at baseline). • History of at least one episode of severe exacerbation were included. All patients were treated with inhaled corticosteroids, 33% were on regular treatment with oral corticosteroids (OCS) and 43% were treated with anti-IgE monoclonal antibodies at the beginning of the study.
Primary Endpoint:	The primary objective of the study was to evaluate the intra-individual change in asthma control after 12 months of Airsonett TLA device use: • Need of Health Care utilization • The need of asthma-related ER, hospital or ICU admission
Key Secondary Endpoints:	Need of Health Care utilization Asthma Control Test (ACT). Lung function Use of OCS
Health economic outcome: 30 patients completed measurements at baseline and 4 months and 27 patients the 12-month visit. A cost-benefit analysis (Cost Utility Analysis) was carried out including an incremental cost- effectiveness ratio (ICER) and a cost per life year gained (QALY) quality. The results showed that TLA treatment, patients with severe allergic asthma uncontrolled in treatment step 4–5, would lead to: • an ICER of £8,998/QALY. • two hospital admissions (via A&E or general admission) or one ICU admission less per year, which means cost savings for Health Care.	

Cost-effectiveness outcomes:	
• **Total savings =** cost per episode × reduction in episodes	- £46,039
• **Savings per person =** total savings/30 study participants	- £1,535
• **Incremental cost per person =** TLA (Airsonett) cost £2,088 – savings per person £1,535	£553
• **Incremental cost-effective ratio (ICER)** = Incremental cost (£553)/incremental QALY gain (0.0615)	£8,998/QALY

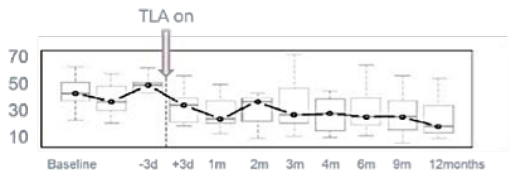
An pilot study in Children Söderman et al [11]	
Objective:	To investigate if TLA could have an effect on allergen-induced atopic dermatitis.
Design:	Children with severe allergic atopic dermatitis slept under the TLA device for at least3 months.
Patient Population:	*Key inclusion criteria* • Patients (5–16) with diagnosed severe atopic dermatitis.
Primary Endpoint:	Clinical improvement
Key Secondary Endpoints:	Quality-of-life, Symptoms, sleep and medication reduction
Clinical Outcomes: 8 children were included in the study. All eight children achieved a good improvement and 5/8 patients turned completely free from AD symptoms and could reduce their treatment to moisturizers only. 3/8 patients reduced treatment to moisturizers and intermittent use of mild topical corticosteroids. Quality of life was significantly improved and none of the subjects reported to have any sleep disturbance. Symptom improvements and consequent medication reductions were achieved within one month in a majority of the cases. Short period without TLA treatment led to exacerbations of AD symptoms.	

An 12-month proof-of-concept study Gore [12]	
Objective:	To evaluate the effect of the temperature-controlled laminar airflow (TLA) treatment in children/adolescents with severe atopic dermatitis
Design:	A single-centre, open-label study in patients with long-standing, severe AE. A run-in period of 6–10 weeks was followed by a 12-month treatment with overnight TLA.
Patient Population:	*Key inclusion criteria* • Patients (2–16 years) with diagnosed severe atopic dermatitis • Sensitization to ≥1 perennial inhalant allergen • High medication requirement
Primary Endpoint:	To assess disease severity over time with two atopic dermatitis questionnaires: SCORAD-Index and IGA (Investigator Global Assessment-)
Key Secondary Endpoints:	Child/family dermatology quality of life and family impact questionnaires (CDQLI, FDQLI, DFI),Patient-oriented eczema measure (POEM) Medication requirements Healthcare contacts.

Clinical Outcomes:

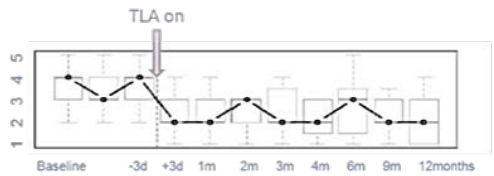
15 children were recruited and all, but one completed the 12 months. A significant reduction in AE severity was ascertained by SCORAD and IGA (P < .001). SCORAD was reduced from a median of 34.9 at baseline to 17.2 at the final visit, and IGA improved significantly from 4 to 2. We observed a significant improvement in FDQLI) and DFI but not CDQLI or POEM. Compared to 6-month period prior to enrolment, there was a significant reduction at six months after the start of the intervention in potent topical corticosteroids (P = .033). Addition of TLA treatment to standard pharmacological treatment may be an effective add-on to the management of difficult-to-control atopic dermatitis. Safety: One patient reported lack of efficacy after 6 months. Two patients reported non-serious adverse events (initial trouble with by-sound and co-sleeping with parent.

Total SCORAD



- The minimal clinically important difference for SCORAD has been defined as 8.7

Investigator Global Assessment



- IGA 0-5 Scale
  0=clear, 1=almost clear, 2=mild disease, 3=moderate disease, 4=severe disease and 5=very severe disease

Study, continued

*Results of Friedman test for primary and secondary end points (*significant at p<0.1, **significant at p<0.05,* ***significant at p<0.01, ****significant at p<0.001)

	Friedman test p-values
PRIMARY END POINTS	
SCORAD Total	0.000**
Investigator Global Assessment	0.000**
SECONDARY END POINTS	
SCORAD Objective	0.000****
SCORAD Subjective	0.003***
SCORAD Subjective Pruritus/Itch	0.018**
SCORAD Sleep Loss	0.037**
CDLQI	0.129
POEM	0.604
FDLQI	0.000****
DFI	0.000****

An observational study in adults with AD Traidl [13]	
Objective:	To examine the clinical and immunological effect of TLA in adult patients with AD.
Design:	A single-center, single-arm observational proof-of-concept study, investigating the effect of add-on treatment with TLA in patients with moderate to severe AD (Figure a).
Patient Population:	Patients were >18 years of age with a moderate to severe AD characterized by SCORAD ≥20, Eczema Area Severity Index (EASI) ≥8 or EASI score per body region of the head-neck region ≥ 1 with an erythema score of ≥2.
Primary Endpoint:	Assess disease severity after 3 months with scoring AD (SCORAD) and Local Eczema intensity (local SCORAD) and Eczema Area Severity Index (EASI) -questionnaires.
Key Secondary Endpoints:	The Physician global assessment (PGA) together with patient assessed dermatology life quality index (DLQI). Invitro parameters, such as CD 4+/8+ and HDMspecificth1 and 17.

Clinical Outcomes:

After 3 months of intervention, scoring AD (SCORAD; 41,96 ± 9,78 vs. 34,15 ± 9,69, P =0,037), local eczema intensity of the head-neck region (local SCORAD; 8.0 ±1,7 vs. 6,4 ±2,5 P= 0,037 and Eczema Area Severity Index (EASI; 10,01 ±3,94 vs. 8,41 ±3,76, P= 0,038) improved significantly (Figure b/c).

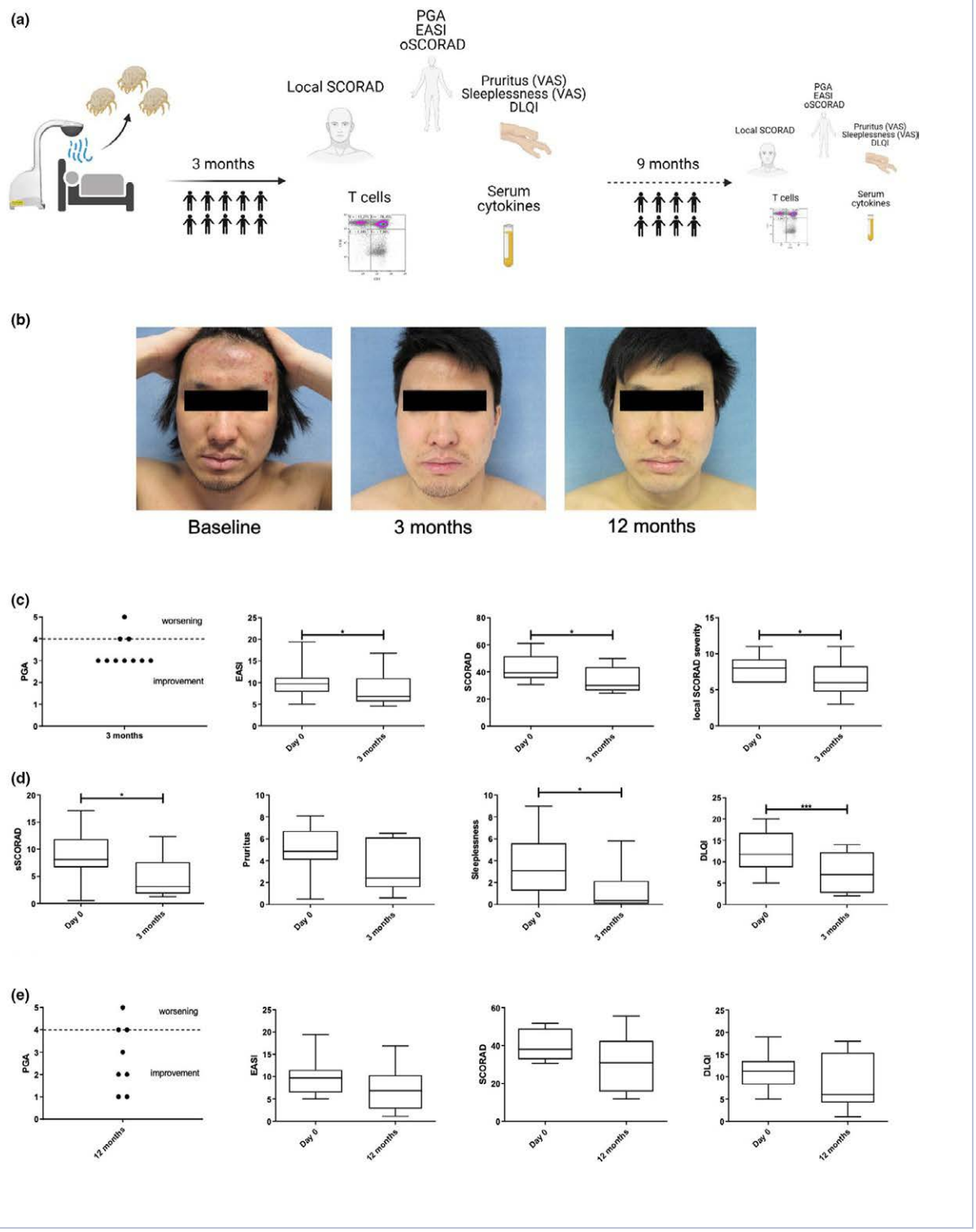
The physician global assessment (PGA) displayed an improvement in seven of ten patients. Patient-assessed dermatology life quality index (DLQI; 12.55 ± 4.78 vs. 7.45 ± 4.66, p= .001), subjective SCORAD symptoms (8.58 ± 4.47 vs. 4.86 ± 4.01, p = .038), including sleeplessness (3.52 ± 2.86 vs. 1.37 ± 2.16, p = .038) were also significantly ameliorated (figure b/c). Skin-homing CD4+ T cells (p = .018), and CD8+ T cells (p = .037) were significantly decreased after 3 months of TLA usage.

After 12 months, five of eight patients showed an improvement measured by PGA, of which four had an improvement of over 50%. HDM-specific Th1 (p = .014) and Th17 (p = .039) cells were significantly reduced extent in the circulation after 12 months.

This study is the first to demonstrate beneficial effects of TLA on HDM sensitized adults AD patients regarding objective (SCORAD), subjective (DQLI) and in vitro parameters.

Study Traidl, continued

Figure a–e.



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About Airsonett

Airsonett® is a Swedish medical device company that leads the way in the development of non-pharmacologic treatment of allergic diseases such as asthma and atopic dermatitis.

Airsonett Air4 is a non-invasive device for treatment in the home, based on the patented Temperature-controlled Laminar Airflow technology (TLA). Treatment with the Airsonett Air4 significantly reduces allergens and other airborne irritants from the patient's breathing zone during rest and sleep.

Airsonett Air4 is a CE marked class 1 medical device that meets the requirements according to MDR 2017/745, intended to be used for the alleviation of symptoms of allergy-induced diseases such as allergic asthma and eczema. It adheres to relevant EU directives regarding design, function, safety and health requirements and has undergone rigorous clinical research as well as health-economic studies. Airsonett Air4 holds a 510(k) cleared class II approval from FDA.

The company's main shareholders are SEB Venture Capital, Industrifonden, Magnus Lundberg and Fåhraeus Startup and Growth.

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