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SINGLE TECHNOLOGY ASSESSMENT:
Bronchial thermoplasty for the treatment of severe ashma

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Responsible	Camilla Stoltenberg, Director-General
Authors	Hagen, Gunhild, *health economist, Norwegian Institute of Public Health* Smedslund, Geir, *researcher*, *Norwegian Institute of Public Health* Denison, Eva, *researcher, Norwegian Institute of Public Health* Kvist, Beate Fagerlund, *health economist, Norwegian Institute of Public Health* Næss, Gunn Eva, *librarian, Norwegian Institute of Public Health*
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Innhold

Key messages

Asthma is a chronic inflammatory illness affecting the airways. Severe asthma is defined as "asthma that is uncontrolled despite maximal optimised therapy and treatment of contributory factors, or that worsens when high dose treatment is decreased". Patients suffering from severe treatment-resistant asthma currently have few available treatment options, for these patients, bronchial thermoplasty (BT) may be an alternative. BT is a device-based treatment option that uses temperature-controlled radio frequency energy to reduce the amount of airway smooth muscle within the airway wall.

Overall, the current evidence base for bronchial thermoplasty indicates no clear and well documented positive health effect on the most important outcomes. This single-technology assessment shows that:

- The effect of BT on mortality is uncertain
- The risk of hospitalization increased during the BT treatment (first 12 weeks).
- There was no difference in hospital admissions between BT and sham/control after 12 months.

The clinical effectiveness data doesn't demonstrate a clear difference between BT and control on the rate of exacerbations, hospitalisations, or visits to general practitioner or emergency room. As the central drivers of the suggested health economic model were thus found to be insufficiently documented, the submitted model was not further assessed. Absolute shortfall and severity are not estimated as cost effectiveness is not documented in a cost per QALY analysis. It is estimated that 1258 Norwegian patients with severe asthma may be eligible for bronchial thermoplasty each year. According to the manufacturer, the budget impact when treating 1258 patients with BT would require about 100 million NOK during the first year.

Title:
Bronchial thermoplasty for the treatment of severe ashma:
A single technology assessment.

Type of publication:
Single technology assessment based on manufacturer's submission

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Doesn't answer everything:
No organisational, juridical, or ethical considerations

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External content experts:
Lehmann, Sverre, MD, Head of Dept., Department of Thoracic Medicine, Haukeland University Hospital

Tollåli, Terje, MD, Head of Dept., Department of Pulmonary Medicine, Nordland Hospital

Carlsen, Espen Aabol, MD, Department of Pulmonary Medicine, Nordland Hospital
Nordland Hospital

Hovedbudskap

Astma er en kronisk inflammatorisk sykdom som påvirker luftveiene. Alvorlig astma er definert som "astma som er ukontrollert til tross for maksimal optimalisert behandling og behandling av medvirkende faktorer, eller som forverres når høydosebehandling reduseres". Pasienter som lider av alvorlig behandlingsresistent astma har begrensede behandlingsalternativer. For disse pasientene kan bronkial termoplastikk (BT) være aktuelt. Under BT brukes temperaturstyrt radiofrekvensenergi for å redusere mengden glatt muskulatur i luftveiene.

Den samlede dokumentasjonen for BT viser foreløpig ingen klar helsegevinst på de viktigste kliniske utfallene. Denne hurtige metodevurderingen viser at:

- Effekten av BT på dødelighet er usikker
- Det var økt risiko for sykehusinnleggelse i BT-gruppen i behandlingsperioden (første 12 uker)
- Det var liten eller ingen forskjell i antall sykehusinnleggelser etter 12 måneder,

Det foreligger ikke kliniske effektdata som viser en klar forskjell mellom BT og kontroll målt på antall forverringer, sykehusinnleggelser eller besøk hos fastlege eller legevakt. Ettersom de sentrale driverne for den innsendte helseøkonomiske modellen således ble funnet å være utilstrekkelig dokumentert vurderte vi ikke den innsendte modellen videre. Alvorlighetsgrad er ikke beregnet ettersom ikke kostnadseffektivitet er dokumentert gjennom en kostnad-per-QALY-analyse. Det anslås at 1258 norske pasienter med alvorlig astma kvalifiserer for bronkial termoplastikk hvert år. Ifølge produsent vil budsjettpåvirkningen ved behandling av 1258 pasienter med BT være rundt 100 millioner kroner det første året.

Tittel:
Bronkial termoplastikk til behandling av alvorlig astma:
en hurtig metodevurdering

Publikasjonstype:
Hurtig metodevurdering basert på innsendt dokumentasjonspakke

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Svarer ikke på alt:
Ingen vurdeing av organisatorske, juridiske eller etiske forhold

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Hvem står bak publikasjonen?
Folkehelseinstituttet har levert rapporten på oppdrag fra Bestillerforum for nye metoder

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Når ble litteratursøket utført?
Søk etter studier ble avsluttet i september 2020.

Eksterne fageksperter:
Sverre Lehmann, avdelingsleder, Lungeavdelingen, Haukeland Universitetssykehus

Terje Tollåli, avdelingsleder, Lungeavdelingen, Nordlandssykehuset

Espen A. Carlsen, overlege, Lungeavdelingen, Nordlandssykehuset

Preface

The Division for Health Services in the Norwegian Institute of Public Health was commissioned by the National System for Managed Introduction of New Health Technologies within the Specialist Health Service in Norway to conduct a single health technology assessment of bronchial thermoplasty with the Alair™ System for patients with severe asthma. In a single-technology assessment, the technology (a pharmaceutical or a device) is assessed based on documentation submitted by the company owning the technology, or their representatives. The submission used in this single technology assessment of the Alair™ System was submitted by Boston Scientific.

The HTA unit of the Norwegian Institute of Public Health (NIPH) receives and evaluates the submitted documentation with regard to effect and safety (important clinical outcomes), resource use and assumptions made in the analysis and models submitted by the manufacturer. NIPH does not develop separate health economic models within the scope of a single technology assessment. If applicable, NIPH can obtain additional information from the manufacturer or independently retrieve updated information to make own calculations of relative effect, costs, cost-effectiveness, severity and budgetary consequences.

Project group
Hagen, Gunhild, *health economist,*
Smedslund, Geir, *researcher*
Denison, Eva, *researcher*
Kvist, Beate Fagerlund, *health economist*
Næss, Gunn Eva, *librarian*

Clinical experts
Sverre Lehmann, MD, Head of Dept., Department of Thoracic Medicine, Haukeland University Hospital
Terje Tollål, MD, Head of Dept., Department of Lung Medicine, Nordland Hospital
Espen A. Carlsen, MD, Department of Lung Medicine, Nordland Hospital

Conflicts of interest
Sverre Lehmann declares that Boston Scientific paid for an internship in Manchester to learn the BT method, and sponsored a trip to Paris (airport meeting with international experts on BT). Other authors and experts involved in this report state they have no conflict of interest to declare.

Norwegian Institute of Public Health assumes final responsibility for the content of this report. The aim of this report is to support well-informed decisions in health care that lead to improved quality of services. The evidence should be considered together with other relevant issues, such as clinical experience and patient preference.

Progress log

Suggestion submitted	04.11.2016
STA commissioned	12.12.2016
Valid submission acknowledged	06.11.2020
Start-up meeting with experts	23.11.2020
Report sent for expert review	02.06.2021
Report sent to manufacturer	02.07.2021
Feedback from technology manufactory	07.07.2021
Report submitted	09.07.2021

Kåre B. Hagen
Director of reviews and Health Technology Assessments

Kjetil G. Brurberg
Department director

Gunhild Hagen
Project leader

Introduction

Disease

Asthma is a chronic inflammatory illness affecting the airways. Symptoms include cough, shortness of breath, wheezing and chest tightness. Typically, asthma is characterised by episodes of breathing difficulty and other symptoms followed by periods when the patient is symptom free. Severe asthma is defined as "asthma that is uncontrolled despite maximal optimised therapy and treatment of contributory factors, or that worsens when high dose treatment is decreased" (1).

Mainstay treatment is inhaled corticosteroids (ICS). Episodes or asthma attacks may be controlled by relief medication (5) or may require emergency room visits and/or hospitalisations if one is not able to get symptoms under control. Many different environmental and other factors may trigger asthma attacks, among these are cold air, vigorous exercise, allergy, airway infection and pollutants.

Burden of asthma on patients and society

Asthma poses a large burden on affected patients in terms of loss of quality of life, absence from school or work, hospitalisations or emergency room visits and increased mortality (2).

Severe asthma poses large costs on society. A Swedish study recently estimated the total annual cost per patient to be €6,500 from a societal perspective (i.e., including both health care costs and cost of work absenteeism) (3). Of the €6,500, hospitalisations and cost of pharmaceutical treatment contributes to on average € 1,000 and €800 respectively. From a healthcare perspective, hospitalisations and cost of pharmaceuticals are the main cost drivers in severe asthma, however, from a societal perspective, work absenteeism and early retirement are the largest contributors to the total cost. Asthma patients also have a lower health related quality of life as measured by the EQ-5D than the general population (4), additionally, asthma leads to many lives lost (2).

Treatment options

Asthma treatment follows a stepwise approach, first line treatment is currently inhaled corticoid steroids (ICS) in combination with either a long-acting beta$_2$-agonist (LABA) or with a short acting beta$_2$-agonist (SABA) (5). If a patient seldom has symptoms, medicine can be taken as needed. If the patient does not respond, daily administration may be needed, and dosage of ICS may be increased. If still no control of symptoms is achieved, long-acting muscarinic antagonist (LAMA) may be added and a higher dosage of ICS may be further increased. For severe treatment resistant asthma (c.f. definition above), testing of the type of asthma (phenotype) is relevant as choice of further treatment will depend on patient characteristics (1, 6, 7). Peroral glucocorticoid steroids may be added to gain symptom control.

For patients that have eosinophilic inflammation, several new medications have entered the marked in recent years (6). This also applies to allergic asthma (7). These medications are effective for these subsets of severe asthma patients. For uncontrolled asthma patients who do not suffer eosinophilic inflammation or allergic asthma, treatment options are limited. One treatment alternative for these patients could be bronchial thermoplasty (1, 5, 7, 8).

Bronchial thermoplasty (BT)

This section is copied directly from manufacturer submission:

"The Alair™ System received the European CE Mark and the US FDA approval in 2010."(9)

"Excessive and inappropriate constriction of airway smooth muscle (ASM) is recognized as a predominant feature of asthma.

BT with the Alair™ System is a non-pharmacologic, device-based treatment option for patients with asthma. BT uses temperature-controlled radio frequency (RF) energy to reduce the amount of ASM within the airway wall. Excessive ASM mass is recognized as a predominant feature of asthma.

The Alair™ BT System is indicated for:

- (FDA-approved) the treatment of severe persistent asthma in patients 18 years and older whose asthma is not well controlled with ICS and LABAs.

- (CE-marked) the treatment of asthma in patients 18 years and older.

The Alair™ BT System consists of the Alair™ Catheter and the Alair™ Controller System, as described below:

Alair™ Catheter

The Alair™ Catheter Model ATS 2-5 ("Catheter") is provided sterile and is a *single-use only*, disposable device. The Catheter delivers energy from the Controller to the desired site in the airway and relays temperature feedback to the Controller. The Alair™ Catheter Model ATS 2-5 is designed to be used with the Alair™ RF Controller Model ATS 200.
Alair™ Controller System:

Alair™ RF Controller

The Alair™ RF Controller Model ATS 200 ("Controller") is designed to provide controlled delivery of RF energy to the Alair™ Catheter. The Controller delivers low-power, temperature-controlled RF energy to the airway at a predetermined temperature setting for a predetermined time period.

Footswitch

The Controller is supplied with a footswitch that allows the operator to start and stop the delivery of RF energy.

Patient Return Electrode

The patient return electrode is used to complete the return path for the electrical current. The Controller is designed to be used with a gel-type patient return electrode that is compliant with the applicable portions of IEC 60601-2-2:2006 and/or CE marked.

A complete BT course of treatment consists of 3 separately scheduled Hospital procedures covering different regions of the lung separately. Treatment sessions are designed to address different lobes of the lung with the right lower lobe treated during the first bronchoscopy, the left lower lobe treated during the second bronchoscopy, and both the right and left upper lobes treated in the third and final bronchoscopy. BT is usually performed with the patient under sedation or general anaesthesia.

During each subsequent session, previously treated airways are evaluated visually by bronchoscopy to ensure adequate healing of previously treated segments before proceeding with further treatment. If previously treated areas have not healed, consideration should be given to postponing treatment.

Following this inspection, the bronchoscope is navigated to the region of the lung that is to be treated and the bronchoscopist plans the order in which the airway segments are to be accessed and treated. The bronchoscopist then navigates to the most distal region of the first airway to be treated, positioning the bronchoscope with the targeted treatment site in clear bronchoscopic view. The catheter is then introduced into the working channel of the bronchoscope and advanced until the distal end is in bronchoscopic view. Once at the targeted region, the electrode array is expanded until the four electrode wires firmly contact the airway wall, being careful not to over-expand the electrodes as this may result in distortion of the electrode array.

Proper contact of the electrodes with the airway wall should be confirmed visually. With the electrode array properly positioned and expanded, the bronchoscopist initiates energy delivery by pressing and releasing the controller footswitch. The controller automatically delivers energy according to pre-set treatment parameters programmed into the controller.

The bronchoscopist should continue to apply contiguous and not overlapping activations throughout accessible airways distal to the main stem bronchi down to 3mm in diameter. This process is repeated along the entire length of the targeted airways.

A systematic approach from distal to proximal, working methodically from airway to airway across the region of lung being treated is recommended to ensure that all accessible airways are carefully identified and treated once and only once. The use of a 'map' of the airways to plan and track the progression of the treatment for each session is recommended."(9)

Number of patients likely eligible for thermoplasty

In Norway, we expect that in an adult population of approximately 3,000,000 persons, 5 % will have asthma (2, 10) and 5% of them will suffer a severe, treatment resistant asthma (8, 11). These assumptions indicate that 7,500 persons could be eligible for advanced treatment. Boston Scientific has in the submitted documentation package estimated the number of patients to be 6,291 (9).

Of the patients with severe treatment resistant asthma, between 500 and 2,000 patients are likely to be eligible for treatment with IL-5 inhibitors (12). Of the remaining, some would likely respond to anti IgE treatment, anti IL-5 treatment or anti IL-4 treatment, the remaining could be considered for BT (8). The manufacturer has assumed that 20% would be candidates for BT, i.e., 1,258 patients, our medical experts estimate the number to be approximately 1,000 patients. Several of the necessary assumptions are very uncertain, including percentage of patients likely to suffer from severe treatment resistant asthma and percentage of these that are likely to respond to the new medications. As illustrated in Figure 2, the number of patients also depend on which patient groups are considered for BT.

For the very severe cases that do not respond to IL-5, IL-4 or IgE inhibitors, bronchial thermoplasty has been proposed as a last resort. These patients currently have few other treatment options.

Patient perspective on severe asthma

A 2019 study investigated the patient perspective on severe asthma among patients in Sweden and Denmark (13). This study included a web survey and in-depth interviews, 93 patients participated in the web survey and 33 in the interviews.

In the survey, 5% reported to have good asthma control, 17% to be partly controlled and 77% to be uncontrolled. The majority of patients were treated with a combination of inhaled corticosteroids and LABA (76%), 44 of the 93 included patients used oral corticosteroids daily. Most patients were treated by their general practitioner (59%), 9% were treated by an allergist, 25% pulmonologist and 8% by other health professionals.

All patients participating in the interviews reported to suffer limitations in daily activities due to their asthma, 30% of interviewed participants also reported longer sick leaves due to asthma symptoms. Many of the interviewed patients reported some sort of psychological effect of their asthma, i.e. anxiety, feeling of panic if rescue medication was not available and fear of suffocating.

What do international treatment guidelines recommend?

Global Initiative for Asthma (GINA): bronchial thermoplasty should be used only in research, in a specialty centre, in selected patients, «Bronchial thermoplasty should be performed in adults with severe asthma only in the context of an independent Institutional

Review Board approved systematic registry or a clinical study, so that further evidence about effectiveness and safety of the procedure can be accumulated". (5)

The National Asthma Education and Prevention Program: bronchial thermoplasty should be used only in research, in selected patients, "Bronchial thermoplasty is not recommended as part of standard care; if used, it should be part of an ongoing research effort." More specifically, the recommendation regarding use of bronchial thermoplasty reads: "

- In individuals aged 18 years or older with persistent asthma, the expert panel conditionally recommends against bronchial thermoplasty (conditional recommendation, low certainty of evidence).
- Individuals aged 18 years or older with persistent asthma who place a low value on harms (short-term worsening symptoms and unknown long-term adverse effects) and a high value on potential benefits (improvement in quality of life, a small reduction in exacerbations) might consider bronchial thermoplasty."(14)

However, guidelines from different countries and organisations differ. NIPH is aware that BT is recommended for some patients in e.g., Australia and in the UK (15). An overview of various guidelines has been presented by Nasim and Vivek, showing that different organisations have made different judgements and trade-offs with regards to the evidence base for clinical effectiveness and the need to offer an alternative to patients with severe asthma (16).

Literature search

Assessment of submitted literature search

An assessment of the literature search of the submission file for Bronchial Thermoplasty was done in February 2021. Checklists based on "Review of Information Retrieval in the Draft Assessment by a Dedicated Reviewer (Information Specialist)"(17), a standard operating procedure from EUnetHTA, were used. The assessment was performed by librarian Gunn Eva Næss and peer-reviewed by librarian Elisabet Hafstad, both employed at the Norwegian Institute of Public Health (NIPH).

Summary description of the search from the submission file: The search done by the company uses the NICE IPG635-search which has been searched up to 22.08.2018 (15). The updated search was performed 02.09.2020. Databases searched are Cochrane Library, Medline, Embase and HTA. Delimitations for study design was not done as a part of the search strategy. The population was patients with asthma, and the intervention Bronchial Thermoplasty.

Elements	Details
Databases and trial registries searched	Cochrane Library, Medline, Embase, HTA.
Search date	02.09.2020
Keywords/ PICO elements	Asthma, Bronchial Thermoplast*, Alair, Bronchoscopy, Airway Remodeling, Bronchus Muscle
Inclusion criteria	Clinical studies, articles with relevance to the safety and/or efficacy
Exclusion criteria	Abstracts with no clinical outcomes, conference abstracts, non-English-language articles
Date restrictions	22.08.2018-02.09.2020 (update from NICE IPG635)
Other search limits or restrictions	

Our overall assessment is that the literature searches in the bibliographic databases are satisfactory, and are reported thoroughly. In order to be more certain that all relevant studies have been identified, we suggest additional searches in the study registers Clinical Trials and the WHO International Clinical Trials Registry Platform.

The possible weakness in the search strategy by not searching for ongoing trials was tested by performing a search in the databases Clinical Trials and the WHO International Clinical Trials Registry Platform (WHO ICTRP). The number of hits was 139 unique references. Two researchers reviewed the search results, but no additional relevant studies were identified.

Below is the search strategy that we created in the two mentioned databases for ongoing studies:

Clinical Trials

Search:
(Asthma OR Bronchial OR Thermoplast OR Thermo OR Alair OR Bronchoscop) AND
(airway remodel OR airway muscle) = 100 hits

WHO ICTRP

Search:
alair OR bronchial thermoplasty OR airway remodeling OR asthma AND thermoplasty OR asthma AND remodeling = 84 hits

Clinical effectiveness

Methods

Description of the documentation

The documentation mainly relies on a report from the National Institute of Health and Care Excellence (NICE) (18) which included two systematic reviews; a Cochrane review from 2014 by Torrego et al. (19) and a systematic review by Zhou et al. from 2016, published in Journal of Asthma (20). Both reviews included three randomized controlled multicenter multi-country trials labelled AIR, AIR 2 and RISA. Torrego et al. completed the literature search in January 2014, while Zhou et al. searched until June 2014. There are five-year follow-ups of the patients who had been treated with BT for all three randomized trials. In addition, the manufacturer carried out a "Targeted literature review" to identify studies published after the search dates of Torrego et al. and Zhou et al. (Table 1).

Table 1. Summary of the documentation for effect and safety of BT.

<table>
<tr><th colspan="6">Documentation included in NICE report IPG635 (18)</th></tr>
<tr><td colspan="3">Systematic review Torrego et al (19)</td><td colspan="3">Systematic review Zhou et al (20)</td></tr>
<tr><td>AIR (21)</td><td>RCT
AIR2 (22)</td><td>RISA (23)</td><td>AIR (21)</td><td>RCT
AIR2 (22)</td><td>RISA (23)</td></tr>
<tr><td colspan="3" rowspan="2"></td><td>RCT
AIR 5-year (24)</td><td>Case-series
AIR2 5-year (25)</td><td>Case-series
RISA 5-year (26)</td></tr>
<tr><td colspan="6">Other studies included in NICE report IPG635 (18)</td></tr>
<tr><td colspan="6">1 non-randomized controlled study (27)
1 registry study (28)
1 case-series (22, 25)</td></tr>
<tr><td colspan="6">Documentation included in «Targeted literature review» conducted by Boston Scientific</td></tr>
<tr><td colspan="6">1 prospective cohort study (29)</td></tr>
</table>

We asked the clinical experts to list and rank the most important outcomes. We describe the documentation for each outcome and whether the results show comparison between groups or within groups across follow-up assessment points. The primary outcomes assessed by Torrego et al. were quality of life, asthma exacerbations and adverse events. Zhou et al did not explicitly describe primary outcomes but stated that "Outcomes of interest assessed after BT included spirometric data, adverse respiratory events, emergency room (ER) visits and hospitalization for respiratory illness».

Risk of bias in the three randomized trials

Risk of bias assessment by Torrego et al. shows that AIR 2 is the study with the lowest risk of bias (Figure 1). This is because participants personnel, and outcome assessors were blinded (comparison with a sham procedure) while the two other studies were not blinded. The AIR2 study was also the largest study.

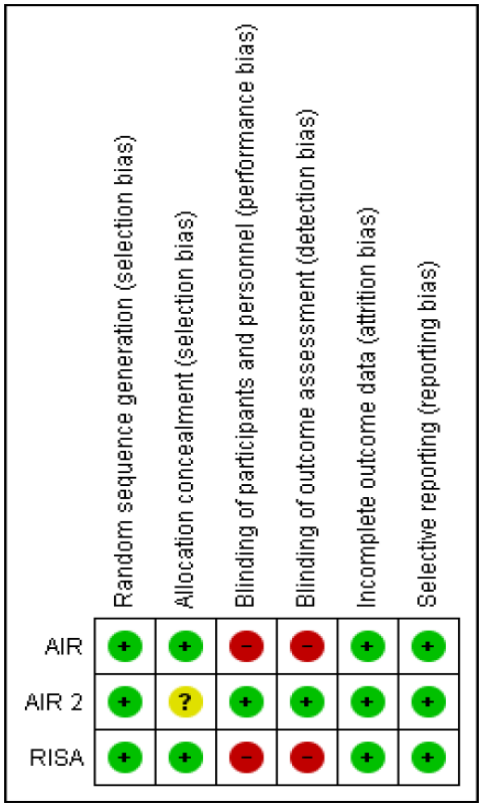

Figure 1. Risk of bias in the three randomized trials.

Comparisons in the three randomized trials

The AIR and RISA studies compared BT with treatment as usual, which in both studies was medical management, while the AIR2 study compared BT with a sham procedure.

Results

Table 2 shows the documentation for effect and safety of BT for the most important outcomes as suggested by the clinical experts. There were no reported deaths in any study. BT was associated with more hospitalizations during the first 12 weeks, but there was no significant difference for the first 12 months. Moderate exacerbations were more frequent in the BT group during the first 12 months, but most events occurred during the first day and were resolved during the first week. Health-related quality of life measured with the AQLQ was 0.31[1] higher in the BT group (95 % CI from 0.10 to 0.53), but this is less than the minimal clinically important difference (MCID) of 0.5 (30-32). Asthma control was measured with ACQ, and the difference of 0.16 was less than the MCID of 0.5 (33).

Table 2. Summary of the documentation for effect and safety of BT based on all study designs (outcomes ranked by importance)

Outcome	Documentation	Results before-and-after	BT versus control
Outcomes with critical importance			
1 Mortality	162 patients in 5-year follow-up based on: RCT AIR1, Thomson 2011 (24); Case-series Pavord 2013 (26), Wechsler 2013 (25), Castro 2010 (22), Langton 2020 (29).	No deaths reported.	No deaths reported.
2 Serious asthma exacerbation: Hospitalization and/or emergency room visit. Immediate help during the treatment period	Systematic review with 3 RCTs, n=429, Torrego et al (2014)(19). Follow-up mean 12 weeks (treatment period)		Hospitalizations first 12 weeks: RR: 3.5 (1.26 to 9.68). Significantly more hospitalizations among patients who received BT.
	Systematic review with 3 RCTs, n=429, Torrego et al (2014) (19). Follow-up mean 12 months (post-treatment period)		Hospitalizations first 12 months: RR: 1.12 (0.44 to 2.85).

[1] In Analysis 1.1 in Torrego, the figure is 0.28. We were not able to explain the difference. We constructed our forest plot by entering the exact numbers for N, mean and SD from Torrego in Review Manager 5.4.1, and the calculations were slightly different.

Outcome	Documentation	Results before-and-after	BT versus control
	Systematic review with 6 studies, (3RCT and 3 follow-up studies, n=249) Zhou et al (2015) (20). N=249 (1 year); N=216 (5 year).	Hospitalization at 1-5-year follow-up: RR 1,47 (0,69 to 3,12) Emergency room visits at 1-5-year follow-up: RR 1,06 (0,77 to 1,46).	
	Prospective cohort, n=91, Langton (2020)(29).	Readmission within 30 days after BT: 6/126 procedures = 4,7 %.	
Important, but not critical outcomes			
3 Moderate asthma exacerbation: often defined as need for systemic treatment with corticosteroids and/or antibiotics	Systematic review with 3 RCTs, n=429, Torrego et al (2014) (19). Follow-up mean 12 months (post-treatment period)		Adverse events: RCT AIR 2: n=288: 85 % in BT group, 76 % in control group; AIR: RCT n=112: 407 in BT group, 106 in control group; RISA: RCT n=32: 136 in BT group, 57 in control group. Most events occurred day 1 after BT and were resolved within 7 days.
	Systematic review with 6 studies, (3RCT and 3 follow-up studies, n=249) Zhou et al (2015) (20). N=249 (1 year); N=216 (5 year).	Airway irritation, including worsening asthma symptoms (wheezing, chest discomfort, cough, and chest pain) and upper respiratory tract infections; Most respiratory adverse events occurred within 1 day of the procedure and resolved within 7 days. 1-5-year, RR = 3.41, 95% CI: 2.96–3.93.	
	Case-series UK BTS Difficult Asthma Registry, n=131, (28), follow-up 1-year, 2-years.	Asthma exacerbation during the treatment period was reported in 9% (11/128) of patients.	
4 Reduced respiratory function: spirometry.	Case-series UK BTS Difficult Asthma Registry, n=131, (28), follow-up 1-year, 2-years.	FEV1: only reported as one of several asthma related symptoms, not described what proportion of the 15% reported.	
5 Health related quality of life (AQLQ)	Torrego et al (2014) (19) 3 RCT, n=429. Follow-up mean 12 months.		Mean AQLQ ranged across control groups from 5.1 to 5.7. Mean AQLQ in the intervention groups was 0.31

Outcome	Documentation	Results before-and-after	BT versus control
			higher (0.10 to 0.53 higher)
6 Asthma control (ACQ)	Torrego et al (2014) (19) 3 RCT, n=429. Follow-up mean 12 months.		Mean change in ACQ ranged across control groups from -0.55 to -0.01. Mean ACQ change intervention groups was 0.16 lower (0.44 lower to 0.11 higher)
7 Sick leave from work/school	Torrego et al (2014) (19) 3 RCT, n=429.		The AIR 2 trial reported that the decrease in severe exacerbations experienced by participants in the bronchial thermoplasty group resulted in fewer days lost from work or other activities because of asthma compared with participants who received the sham intervention (1.32 ± 0.36 days/y vs 3.92 ± 1.55 days/y).
Outcomes of low importance			
8 Mild asthma exacerbation: increased use of bronchodilators and inhaled corticosteroids	Torrego et al (2014) (19) 3 RCT, n=429.		Participants in BT group decreased from 0.35 ± 0.32 exacerbations per participant/wk at baseline to 0.18 ± 0.31 at 12 months follow-up, compared with an increase in the control group from baseline 0.28 ± 0.31 exacerbations per participant/wk to 0.31 ± 0.46 at 12 months follow up. The difference between groups was statistically significant.
Documentation of undefined importance			
Infection	Case-series UK BTS Difficult Asthma Registry, n=131, (28), follow-up 1-year, 2-years.	Infection in the treatment period: 6 %.	
Symptoms related to the BT procedure	Case-series UK BTS Difficult Asthma Registry, n=131, (28), follow-up 1-year, 2-years.	Bronchospasm, dry cough, chest twinges, tightness, discomfort	

Outcome	Documentation	Results before-and-after	BT versus control
		or pain) were reported in 13% (16/128) of patients.	

Figure 3 shows results for hospitalizations during the treatment period (19). The meta-analysis showed that there were significantly more patients in the BT group who were hospitalized, and in all three studies there were more hospitalizations in the BT group.

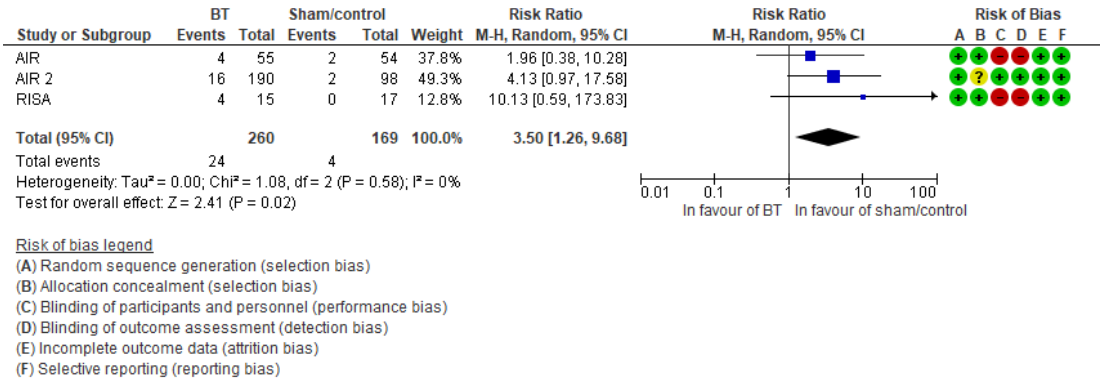

Figure 3. Hospitalizations during the treatment period

Figure 4 shows the number of hospitalizations during the first 12 months (19). There were no differences between the groups, and in AIR 2 there were fewer hospitalizations in the BT group, even though the difference was not significant.

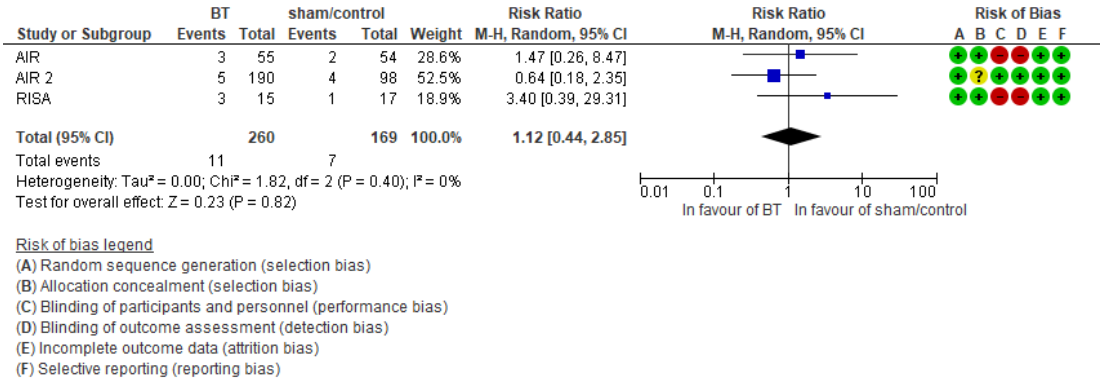

Figure 4. Hospitalizations during the first 12 months

Figure 5 shows health-related quality of life after 12 months (19). Overall, the results favour the BT group, but in the RISA and AIR 2 studies the differences are not significant. The outcome used was Asthma Quality of Life Questionnaire (AQLQ) ranging from 1 to 7 (best). Mean difference is about 0.3 points, which is somewhat lower than the suggested threshold (i.e. 0.5) for clinical significance (35).

Figure 6 shows asthma control at 12 months (19). In AIR and RISA, there were significantly better asthma control in the BT group when the studies are pooled, while for AIR 2 there was no difference. The meta-analysis showed a better asthma control for BT, but the difference was not significant.

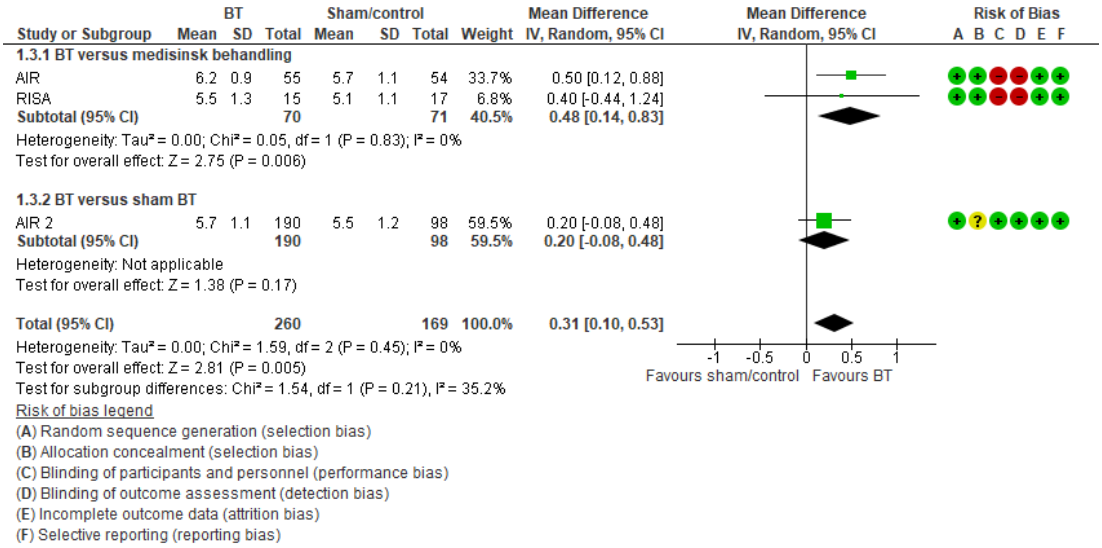

Figure 5. Health-related quality of life after 12 months

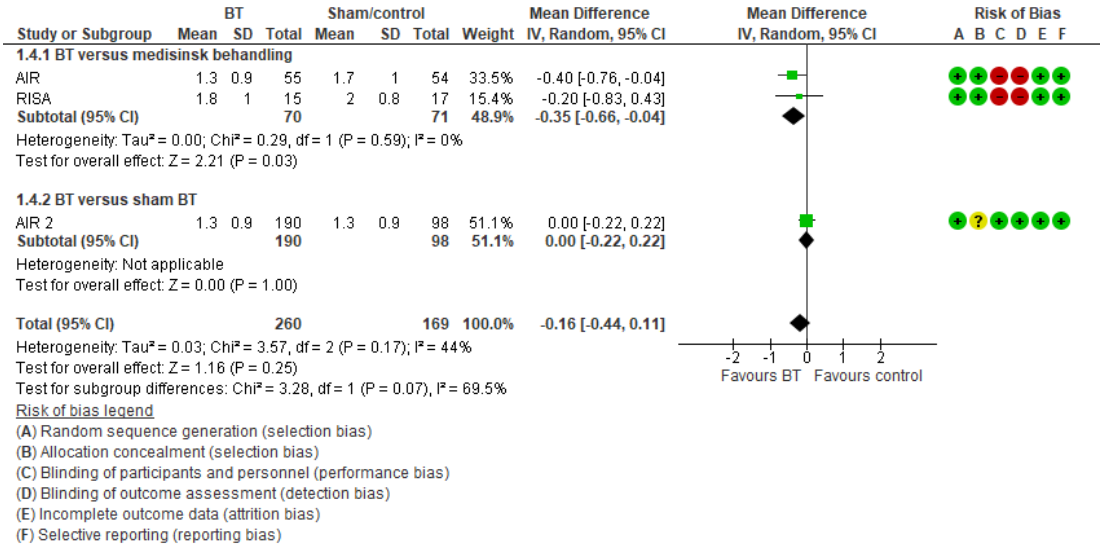

Figure 6. Asthma control (ACQ) after 12 months

Figure 7 shows the use of rescue medication at 12 months (19). There is no significant difference in any of the studies, and neither in the pooled analysis.

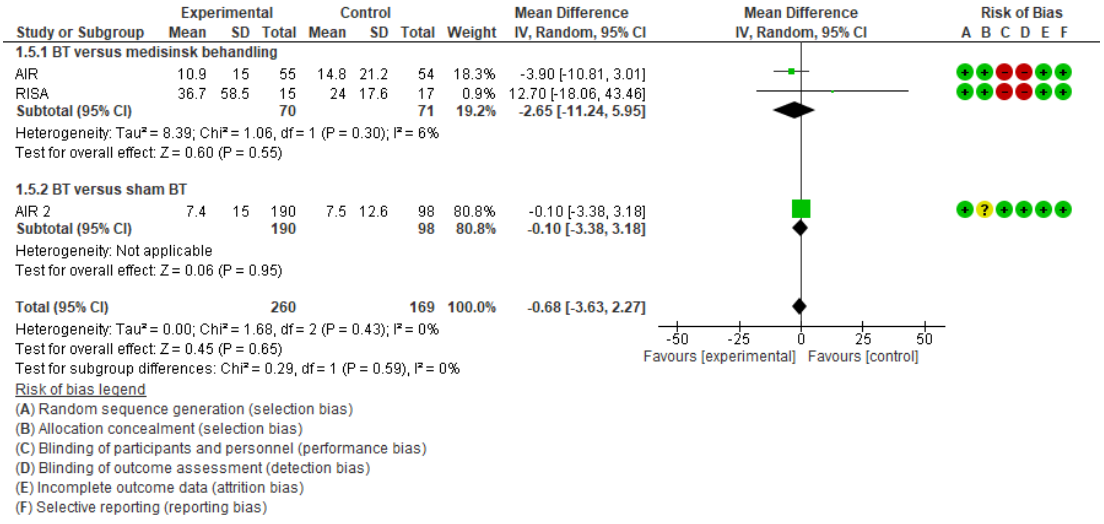

Figure 7. Use of rescue medication at 12 months.

Zhou (20) shows follow-up data for 1 and 5 years, but there were only 249 and 216 patients who had been followed up to these time points, respectively. And we know nothing about the 169 patients in the control group. Figure 8 shows the incidence of hospitalizations at five years versus one year (20). The data suggest that there is no significant difference in hospitalization between the two time points.

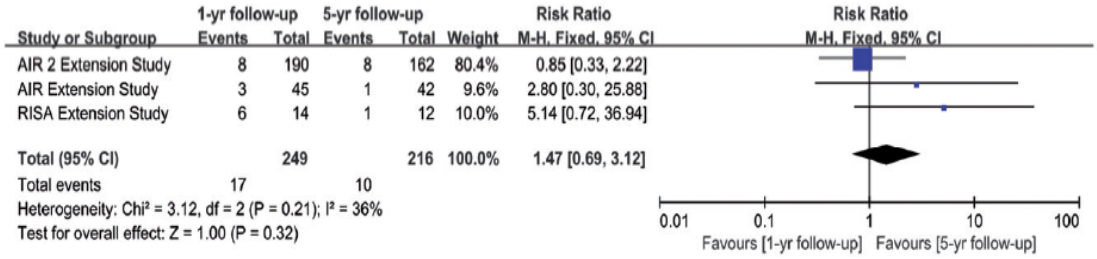

Figure 8. Incidence of hospitalizations at five years versus one year.

Figure 9 shows the number of emergency room visits at five years versus one year (20). The data suggest that there is no significant difference in visits between the two time points. Figure 10 the frequency of adverse respiratory events at five years versus one year (20). The data suggest that there were significantly fewer events at the five-year follow-up.

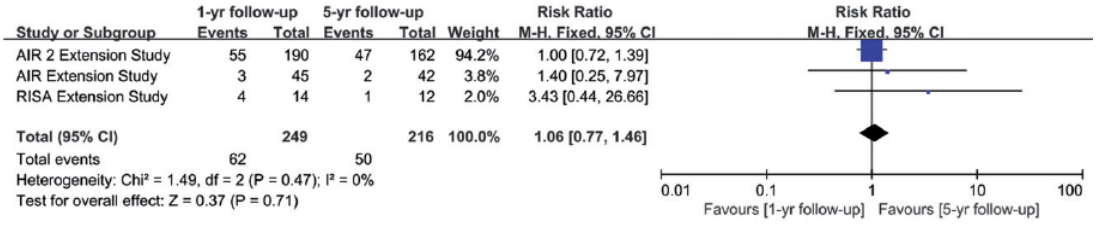

Figure 9. Number of emergency room visits at five years versus one year.

Figure 10. Frequency of adverse respiratory events at five years versus one year.

Summary

Available data on mortality are uncertain. There are no reports about deaths in the three randomized studies, but there were only 429 patients in total in the data material. Because bronchial thermoplasty is an intervention that is used in a very small patient group, it is difficult to acquire reliable estimates for mortality.

Regarding hospitalization, there was increased risk in the BT group during the treatment period (first 12 weeks), but there was no difference during the first 12 months. The BT group was followed for 5 years, and 5-year hospitalization was non-significantly lower after 5 years than after 1 year. For emergency room visits, there were no differences in the BT group between 1-year and 5-year follow-ups. It should be noted that there were few hospitalizations overall (18 out of 429 patients were hospitalized

during the first 12 months). The studies also excluded patients with frequent exacerbations in the past. Because there were more hospitalizations in the BT group during the first 12 weeks and no difference during the first 12 months, this indicates that there were less hospitalizations in the BT group during the period between 12 weeks and 12 months.

During the treatment period, there were more respiratory adverse events in the BT group than in sham/control for all three RCTs. Most adverse events occurred one day after treatment and were resolved within 7 days. During the follow-up period, the frequency of respiratory adverse events was significantly lower after 5 years than after 1 year.

The health-related quality of life was higher in the BT group after 12 months follow-up. Asthma control was not different between the BT and sham/control group after 12 months.

In the AIR 2 trial, days missed from work or other activities was lower in the BT group than in the sham group.

Health economic evaluation

Methods for evaluating submitted cost-effectiveness models

The primary objectives of health economic modelling are to provide a mechanism to determine the relative cost-effectiveness of the specified health intervention(s) compared to standard treatment using the best available evidence. A model analysis may further assess the most important sources of uncertainty surrounding the results.

To make comparisons across different types of treatments and multiple health outcomes, economic models typically measure health outcomes in terms of quality-adjusted life years (QALYs), a variable designed to capture both life extension and health improvement. QALYs, by definition, take on a value of 1 for perfect health and 0 at death.

The output of a cost-effectiveness model is expressed as an incremental cost-effectiveness ratio (ICER), which can be thought of as the extra cost of obtaining an extra life-year in perfect health. The ICER is defined as:

$$Cost_{Intervention} - Cost_{Comparator} \Big/ QALY_{Intervention} - QALY_{Comparator}$$

There is no single correct way to build an economic model to estimate the cost-effectiveness of a specific health intervention. Modelling requires consulting with clinical experts to gain an understanding of normal disease progression, and to determine, based on the research question, the relevant treatment population, relevant comparator; and important health outcomes and adverse events connected to treatment. This information informs the basic model structure, and also determines which clinical effect data is most important to retrieve. Once the model structure is in place, systematic searches and evidence grading are used to provide the most reliable risk information

for the model, but also to collect all of the relevant cost and quality of life data that is needed for cost-effectiveness calculations.
A model is rarely meant to capture every potential detail of the treatment landscape; rather the goal is to include enough detail to provide a realistic view of the most significant pathways in disease progression, given the research question(s) one is trying to answer.

Evaluating any given health economic model is primarily about whether:

- the clinical effect data used in the model are of adequate quality and whether they are aligned with the clinical effectiveness part of the report
- treatment comparator is reasonable given the research question
- baseline epidemiological data reflect the population in which the analysis is being performed
- resource use and costs reflect the conditions of the healthcare system in question
- there has been sufficient sensitivity and scenario analyses to determine the degree and sources of uncertainty in the model results
- the model displays external and internal validity

Checklists are available to help researchers systematically examine these issues. We proceed by first describing the health economic model used in the manufacture's submission.

Submitted health economic model

Description of model

The company has submitted a health economic model, i.e. a Markov model consisting of different health states and events (Figure 2). The model is structured around asthma exacerbations and resulting hospital admittances and visits to a general practitioner and/or emergency room.

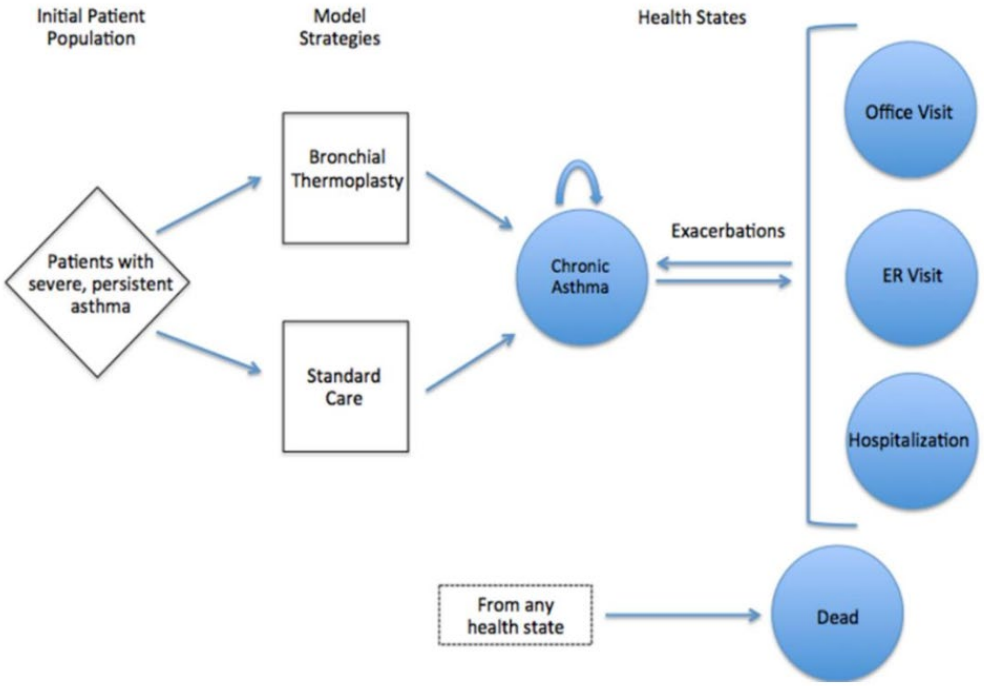

Figure 11 Illustration of the submitted model

The clinical input parameters driving the difference between the BT and the control group is the rate of exacerbations. Rates of exacerbations are collected from the AIR2 trial. Rate of exacerbations from the AIR2 trial are then used to predict hospital visits etc. using data from an epidemiological study (TENOR), i.e. probabilities for these visits are not gathered from clinical trial data (Table 3).

Table 3 Clinical input parameters in submitted model

Parameter		Base case	Reference
SC exacerbation rate	Physician visits	0.74	AIR2 trial (55)
	ER visits	1.19	
	Hospitalization	0.06	TENOR study (56)
BT exacerbation relative risk (weeks 0-13)	Physician visits	1.55	AIR2 trial (55)
	ER visits	0.67	TENOR study (56)
	Hospitalization	4.90	
BT exacerbation relative risk (weeks 14+)	Physician visits	0.77	AIR2 trial (55)
	ER visits	0.17	TENOR study (56)
	Hospitalization	0.26	
Mortality due to asthma exacerbations requiring hospitalization		0.011	Sullivan et al. 2009 (57)

Assessment of model

The clinical effectiveness part of this assessment found no difference between BT and control on rate of exacerbations. The clinical effectiveness part of this report further did not find a direct effect of BT on hospitalisations and visits to a general practitioner and/or emergency room. Seeing that this central driver of the model is not found to be well documented based on the current evidence, the submitted model has not been further assessed.

From a health economic perspective, we recommend a reassessment of the cost-effectiveness of BT at a time when the effect of BT on exacerbations or directly on hospitalisations and other health care resources has been further investigated.

Submitted budget impact analysis

The company has submitted a budget impact analysis. The main analysis assumes reductions in hospitalisations, office visits and emergency room visit in year 2-5. As described in the previous section, NIPH does not accept this assumption based on the current evidence base and hence will not present the whole analysis.

We do however accept the assumptions made when calculating a potentially eligible population of 1 258 patients per year, i.e. 20% of target population as described in Table 4.

Table 4 Assumptions made when estimating the number of eligible patients

Target population	Value	Source
Norwegian inhabitants	5 295 619	Statistics Norway (65)
Proportion of adult population in Norway	79%	Statistics Norway (65)
Rate of severe asthma among general population	0.15%	Abrahamsen R, et al (66)
Target population	6 291	

The company further assumes “As an add-on treatment to SC, BT added approximately 70944 kr to SC for the first year.” “For the budget impact when treating 1258 severe asthma patients with BT in Norway, this would require about 100 million NOK during the first year.

Absolute shortfall and disease severity

This report assesses BT in light of the Norwegian priority setting criteria: health benefits, resource use and disease severity. This implies that health benefits and resource use should be assessed against the severity of the condition. The absolute shortfall and the severity of the condition can have an impact on whether the costs are considered reasonably proportionate to the health benefit of the treatment. The severity criterion in a quantified format, however, only becomes relevant when considering the cost-effectiveness of the intervention. In the case of BT, the intervention was not established to be more effective than the comparator on the outcomes driving the cost-effectiveness model, hence cost effectiveness could not be assessed. We recommend that the cost-effectiveness of BT and the severity of severe treatment-resistant asthma are reassessed once new data on the effectiveness of BT becomes available.

Discussion

We have summarized the documentation for effect and safety of bronchial thermoplasty for severe asthma. We used the single technology assessment submitted to us by the manufacturer, Boston Scientific (unpublished). The published material they referred to was in the Interventional procedures guidance [IPG635] by the National Institute of Health and Care Excellence (NICE) in the UK (18). The NICE report included three randomized controlled trials called AIR, AIR 2 and RISA. There are publications on all three trials with 5-year outcomes. We asked our expert panel to rank the most important outcomes, and we have presented the results from these outcomes.
Our expert panel advised us to make a distinction between effects and safety during the treatment period and during the follow-up. Initial worse outcomes might be more than compensated by better long-term outcomes.

Before we conclude, there are some methodological questions that should be addressed. The primary study by AIR 2 Trial Study Group (25) has a long author list. Almost all of the authors state conflicts of interest, and a number of the authors specifically note that they have received grants, lecture payments etc. from Boston Scientific. Although scientists typically claim that they are not affected by payments from manufacturers, the evidence shows otherwise. A Cochrane review by Lundh et al. (34) concluded that "Sponsorship of drug and device studies by the manufacturing company leads to more favorable efficacy results and conclusions than sponsorship by other sources. Our analyses suggest the existence of an industry bias that cannot be explained by standard 'Risk of bias' assessments."

Apart from the conflicts of interest aspect, the AIR 2 trial is the largest study with the lowest risk of bias according to Torrego et al. assessments using the Cochrane risk of bias tool. It is a strength that AIR 2 used a sham BT procedure. The other two trials

were open-labeled. This is an argument for trusting the results of AIR 2 the most. **Mortality** is the most important outcome. There are no reported deaths in the studies. Because of low numbers of patients, the risk of death is uncertain, and treatment should probably commence as part of studies in order to get more precise estimates.

1. **Serious asthma exacerbations.** Even though the BT group had more hospitalizations during the treatment period, there was no difference after 12 months. After 5 years, there was no increase in the BT group. For the 5-year outcome there is no control group, but there is reason to believe that the asthma patients would deteriorate over time without treatment. The fact that they were reasonably stable can be taken as an indication that the treatment was at least not harmful. However, a problem with the five-year follow-up reported by Zhou et al is that participants contributed data twice in the same analysis, which is known as a "unit-of-measurement" error. This reduces our confidence in the results.
2. **Moderate asthma exacerbations.** Although it seems that the BT procedure causes some initial exacerbations, these complications mostly resolve within a week.
3. **Reduced respiratory function**. There were insufficient data on this outcome.
4. **Health-related quality of life.** There seems to be a positive effect of BT after 12 months.
5. **Asthma control (ACQ).** There are no important differences in asthma control after one year between the BT group and the sham/control group.
6. **Sick leave from work/school**. We have only data from the AIR 2 trial, but BT seems to reduce days absent from work and other activities.
7. **Mild asthma exacerbation.** We have only data from the AIR trial (n=112), but the change in number of mild exacerbations per week from baseline to 12 months was in favor of BT, and the difference was statistically significant.

Overall, the beneficial effects are not clearly demonstrated. However, bronchial thermoplasty also shows no clear negative effects or safety concerns.

BT is only performed on a very small patient group for which there are few other treatment alternatives.

Implication of results on practice

The current evidence base for bronchial thermoplasty indicates no clear and well documented positive health effect on important outcomes. There are however some indications that the intervention may be beneficial.

NIPH acknowledges that the relevant patient population has few treatment options and that severe treatment resistant asthma poses a large burden on affected patients and on the health care system.

The current evidence based may not be considered sufficiently robust to support adoption of bronchial thermoplasty in routine clinical practice. If this is the case, one possibility would be to open for the use of the procedure as a part of ongoing research effort followed by a reassessment as new data become available. This strategy would be in line with many international guidelines, but NIPH is aware that some guidelines also recommend the use of BT for selected patients.

Seeing that randomised trials may be difficult to conduct in the most relevant patient population, clinical centres should closely monitor patients receiving BT and enter data about treatment effects and safety into clinical registries.

Conclusion

The evidence for health benefits of BT in the treatment of severe asthma is uncertain. Data on mortality is lacking, BT seems to be associated with increased risk of respiratory adverse events and hospitalization during the treatment period (i.e. first twelve weeks), but there is no difference in hospital admissions between BT and control after twelve months, Case series suggest the number of hospitals admissions following BT remains stable or decreases between one and five year follow-up, but this is based on very low quality evidence. Asthma control was not different between BT and control, but the health-related quality of life was higher in the BT group at twelve months follow-up. Most respiratory adverse events that occurred following BT occurred one day after treatment and resolved within seven days.

The submitted health economic model was based on data on rate of exacerbations from the AIR2 trial which are then used to predict hospital visits etc. using data from an epidemiological study. The clinical effectiveness part of this report further did not find a direct effect of BT on hospitalisations and visits to a general practitioner and/or emergency room. Seeing that this central driver of the model is not found to be well documented based on the current evidence, the submitted model was not further assessed. Absolute shortfall and severity were not estimated as cost effectiveness is not documented in a cost per QALY analysis

It is estimated that 1258 Norwegian patients with severe asthma may be eligible for bronchial thermoplasty each year. According to assumptions made by the company, the budget impact when treating 1258 patients with BT would require about 100 million NOK during the first year.

References

1. Difficult to Treat and Severe Asthma: Global Initiative for Asthma (GINA); 2019 [cited 2021 03.05]. Available from: https://ginasthma.org/wp-content/uploads/2019/04/GINA-Severe-asthma-Pocket-Guide-v2.0-wms-1.pdf.
2. Prevalence and attributable health burden of chronic respiratory diseases, 1990-2017: a systematic analysis for the Global Burden of Disease Study 2017. Lancet Respir Med. 2020;8(6):585-96.
3. Jansson SA, Backman H, Andersson M, Telg G, Lindberg A, Stridsman C, et al. Severe asthma is related to high societal costs and decreased health related quality of life. Respir Med. 2020;162:105860.
4. Doz M, Chouaid C, Com-Ruelle L, Calvo E, Brosa M, Robert J, et al. The association between asthma control, health care costs, and quality of life in France and Spain. BMC Pulm Med. 2013;13:15.
5. Global Initiative for Asthma. Global Strategy for Asthma Management and Prevention 2020 [cited 2021 27.04]. Available from: https://ginasthma.org/.
6. Fajt ML, Wenzel SE. Asthma phenotypes and the use of biologic medications in asthma and allergic disease: the next steps toward personalized care. J Allergy Clin Immunol. 2015;135(2):299-310; quiz 1.
7. Blaiss MS, Castro M, Chipps BE, Zitt M, Panettieri RA, Jr., Foggs MB. Guiding principles for use of newer biologics and bronchial thermoplasty for patients with severe asthma. Ann Allergy Asthma Immunol. 2017;119(6):533-40.
8. Côté A, Godbout K, Boulet LP. The management of severe asthma in 2020. Biochem Pharmacol. 2020;179:114112.
9. Bronchial thermoplasty system for treating severe asthma. Single Technology Assessment (documentation submitted by manufacturer). Boston Scientific; 2020.
10. Tema: Hva er forekomsten av astma, allergisk rhinitt og atopisk eksem blant barn, unge og voksne? Kort sammendrag på norsk av foreløpige resultater: Norwegian Institute of Public Health; [cited 2021 29.04]. Available from: https://www.fhi.no/contentassets/bfc671b851e84e848ef6228ed1df9c4e/notat-om-forekomsten-av-astma-allergisk-rhinitt-og-atopisk-eksem-blant-barn-unge-og-voksne.pdf.
11. Peters SP, Ferguson G, Deniz Y, Reisner C. Uncontrolled asthma: a review of the prevalence, disease burden and options for treatment. Respir Med. 2006;100(7):1139-51.
12. Hurtig metodevurdering for legemidler finansiert i spesialisthelsetjenesten. Benralizumab (Fasenra) til behandling av alvorlig eosinofil astma: Statens legemiddelverk; 2018 [cited 2021 03.05.2021]. Available from: https://nyemetoder.no/Documents/Rapporter/Benralizumab_%20Fasenra%20-%20hurtig%20metodevurdering.pdf.
13. Papapostolou G, Tunsäter A, Binnmyr J, Telg G, Roslind K. Patient perspectives on living with severe asthma in Denmark and Sweden. Eur Clin Respir J. 2020;8(1):1856024.
14. Cloutier MM, Dixon AE, Krishnan JA, Lemanske RF, Jr., Pace W, Schatz M. Managing Asthma in Adolescents and Adults: 2020 Asthma Guideline Update From the National Asthma Education and Prevention Program. Jama. 2020;324(22):2301-17.

15. Bronchial thermoplasty for severe asthma. Interventional procedures guidance [IPG635]: National Institute of Health and Care Excellence (NICE); [updated 19 December 2018 cited 2021 25.05]. Available from: https://www.nice.org.uk/guidance/ipg635.
16. Nasim F, Iyer VN. Bronchial thermoplasty-an update. Ann Thorac Med. 2018;13(4):205-11.
17. Standard Operating Procedure (SOP): Review of Information Retrieval in the Draft As-sesment by a Dedicated Reviewer (Information Specialist). . Unpublished: EUnetHTA 2018.
18. National Institute of Health and Care Excellence. Bronchial thermoplasty for severe asthma: Interventional procedures guidance [IPG635]. London: NICE; 2018.
19. Torrego A, Sola I, Munoz AM, Roque IFM, Yepes-Nunez JJ, Alonso-Coello P, et al. Bronchial thermoplasty for moderate or severe persistent asthma in adults. Cochrane Database Syst Rev. 2014(3):CD009910.
20. Zhou JP, Feng Y, Wang Q, Zhou LN, Wan HY, Li QY. Long-term efficacy and safety of bronchial thermoplasty in patients with moderate-to-severe persistent asthma: a systemic review and meta-analysis. J Asthma. 2016;53(1):94-100.
21. Cox G, Thomson NC, Rubin AS, Niven RM, Corris PA, Siersted HC, et al. Asthma control during the year after bronchial thermoplasty. N Engl J Med. 2007;356(13):1327-37.
22. Castro M, Rubin AS, Laviolette M, Fiterman J, De Andrade Lima M, Shah PL, et al. Effectiveness and safety of bronchial thermoplasty in the treatment of severe asthma: a multicenter, randomized, double-blind, sham-controlled clinical trial. Am J Respir Crit Care Med. 2010;181(2):116-24.
23. Pavord ID, Cox G, Thomson NC, Rubin AS, Corris PA, Niven RM, et al. Safety and efficacy of bronchial thermoplasty in symptomatic, severe asthma. Am J Respir Crit Care Med. 2007;176(12):1185-91.
24. Thomson NC, Rubin AS, Niven RM, Corris PA, Siersted HC, Olivenstein R, et al. Long-term (5 year) safety of bronchial thermoplasty: Asthma Intervention Research (AIR) trial. BMC Pulm Med. 2011;11:8.
25. Wechsler ME, Laviolette M, Rubin AS, Fiterman J, Lapa e Silva JR, Shah PL, et al. Bronchial thermoplasty: Long-term safety and effectiveness in patients with severe persistent asthma. J Allergy Clin Immunol. 2013;132(6):1295-302.
26. Pavord ID, Thomson NC, Niven RM, Corris PA, Chung KF, Cox G, et al. Safety of bronchial thermoplasty in patients with severe refractory asthma. Ann Allergy Asthma Immunol. 2013;111(5):402-7.
27. Chupp G, Laviolette M, Cohn L, McEvoy C, Bansal S, Shifren A, et al. Long-term outcomes of bronchial thermoplasty in subjects with severe asthma: a comparison of 3-year follow-up results from two prospective multicentre studies. Eur Respir J. 2017;50(2).
28. NICE. Analysis of unpublished data from the UK BTS Difficult Asthma Registry was commissioned by NICE MTEP as project reference IP675 from Newcastle and York External Assessment Centre (EAC), completed 31/03/2017. The work is intended for imminent submission to academic publication by representatives of NY EAC, NICE, BTS and the IP675 project steering group.; 2017.
29. Langton D, Sha J, Guo S, Sharp J, Banks C, Wang W, et al. Bronchial thermoplasty versus mepolizumab: Comparison of outcomes in a severe asthma clinic. Respirology. 2020;25(12):1243-9.
30. Juniper EF, Svensson K, Mörk A-C, Ståhl E. Modification of the asthma quality of life questionnaire (standardised) for patients 12 years and older. Health Qual Life Outcomes. 2005;3:58-.
31. Wyrwich KW, Ireland AM, Navaratnam P, Nolte H, Gates DF, Jr. Validation of the AQLQ12+ among adolescents and adults with persistent asthma. Qual Life Res. 2011;20(6):903-12.

32. Wyrwich KW, Khan SA, Navaratnam P, Nolte H, Gates DF, Jr. Validation and agreement across four versions of the asthma control questionnaire in patients with persistent asthma. Respir Med. 2011;105(5):698-712.
33. Juniper E, O'Byrne P, Guyatt G, Ferrie P, King D. Development and validation of a questionnaire to measure asthma control. European Respiratory Journal. 1999;14(4):902-7.
34. Lundh A, Lexchin J, Mintzes B, Schroll JB, Bero L. Industry sponsorship and research outcome. Cochrane Database Syst Rev. 2017;2:MR000033.
35. Juniper EF, Guyatt GH, Willan A, GriHith LE. Determining a minimal important change in a disease-specific quality of life questionnaire. Journal of Clinical Epidemiology 1994;47(1):81-7.

Appendix

Checklist for peer review of the literature search in the submission file

Name of submission file:
Bronchial thermoplasty system for treating severe asthma

Part one: Checklist for general aspects of information retrieval

1.	**Search in bibliographic databases**	**Yes**	**No**
a)	Did the submitted documentation report the bibliographic databases searched?	X	
b)	Did the submitted documentation search the following bibliographic databases:		
	• MEDLINE/ PubMed	X	
	• Embase	X	
	• Cochrane Database of Systematic Reviews (Cochrane Reviews)		X
	• Cochrane Central Register of Controlled Trials (CENTRAL)	X	
	• Specific databases related to subject (e.g. PsycINFO, Pedro, etc.)		X
	• Other databases? Please specify (Epistemonikos, etc.)?	X*	
c)	Was the total hits and search date reported from the bibliographic databases?	X	
d)	Did the submitted documentation apply general limitations (e.g. languages, year of publication)?	X	
e)	If general limitations (e.g. languages, year of publication) were applied, was appropriate justification provided?	X	
f)	Comment: *= HTA database		
2.	**Search in study registries**	**Yes**	**No**
a)	Did the submitted documentation report the study registries searched?		X
b)	Did the submitted documentation search the following study registries:		
	• ClinicalTrials.gov		X
	• WHO ICTRP Search Portal		X
c)	Was the total hits and search date reported from the study registries?		X

d)	Did the submitted documentation apply general limitations (e.g. languages, year of publication)?		X
e)	If general limitations (e.g. languages, year of publication) were applied, was appropriate justification provided?		X
f)	Comment: No study registries were searched		
3.	**Study selection**	**Yes**	**No**
a)	Did the submitted documentation report that the screening steps (in title/ abstracts and full text) were performed by two persons independently of one another?	X	
b)	If this was not the case, was there any mentioning of why/ why not?		
c)	Comment:		
4.	**Search strategies for bibliographic databases**	**Yes**	**No**
a)	If relevant: In cases where more PICO's than one was included, did the submitted documentation conduct and document one search strategy for each PICO?	*	
b)	Do the search strategies reflect the limitations mentioned in the methods chapter (e.g. inclusion criteria, languages considered and year of publication)?	X	
c)	In the bibliographic databases, was the search documented in such a way that it can be easily reproduced?	X	
d)	Comment: *= not relevant		
5.	**Search strategies for study registries**	**Yes**	**No**
a)	If relevant: In cases where more PICO's than one was included, did the submitted documentation conduct and document one search strategy for each PICO?	*	
b)	In the study registries, was the search documented in such a way that it can be easily reproduced?	*	
c)	Comment: *= not relevant		

Part two: Checklist PRESS (Peer Review of Electronic Search Strategies) 2015, Guideline Evidence-Based Checklist

6.	**Translation of the research question**	**Yes**	**No**
a)	Does the search strategy match each PICO's?	X	
b)	Are the search concepts clear?	X	
c)	Are there too many or too few PICO's elements included?		X
d)	Are the search concepts too narrow or too broad?		X
e)	Does the search retrieve too many or too few records? (Number of hits should be shown per line).		X
f)	Are unconventional or complex strategies explained?	X	
	Comment:		
7.	**Boolean and proximity operators (these vary based on search service)**	**Yes**	**No**

a)	Are Boolean or proximity operators used correctly?	X	
b)	Is the use of nesting with brackets appropriate and effective for the search?	X	
c)	If NOT is used, is this likely to result in any unintended exclusions?		X
d)	Could precision be improved by using proximity operators (e.g. adjacent, near, next) or phrase searching instead of AND?		X
e)	Is the width of proximity operators suitable (e.g. might adj5 pick up more variants than adj2)?	X	
	Comment:		
8.	**Subject Headings (database specific)**	**Yes**	**No**
a)	Are the subject headings relevant?	X	
b)	Are any relevant subject headings missing; e.g. previous index terms?		X
c)	Are any subject headings too broad or too narrow?		X
d)	Are subject headings exploded where necessary and vice versa?	X	
e)	Are major headings ("starring" or restrict to focus) used? If so, is there adequate justification?	X	
f)	Are subheadings missing?		X
g)	Are subheadings attached to subject headings? (Floating subheadings may be preferred).	X	
h)	Are floating subheadings relevant and used appropriately?	X	
i)	Are both subject headings and terms in free text (see the following) used for each concept? Text word searching (free text)		X
	Comment:		
9.	**Text word searching (free text)**	**Yes**	**No**
a)	Does the search include all spelling variants in free text (e.g. UK vs. US spelling)?	X	
b)	Does the search include all synonyms or antonyms (e.g. opposites)?	X	
c)	Does the search capture relevant truncation (ie, is truncation at the correct place)?	X	
d)	Is the truncation too broad or too narrow?		X
e)	Are acronyms or abbreviations used appropriately? Do they capture irrelevant material? Are the full terms also included?	X	
f)	Are the keywords specific enough or too broad? Are too many or too few keywords used? Are stop words used?		X
g)	Have the appropriate fields been searched; for example, is the choice of the text word fields (.tw.) or all fields (.af.) appropriate? Are there any other fields to be included or excluded? (database specific)?	X	
h)	Should any long strings be broken into several shorter search statements? Spelling, syntax, and line numbers.		X
	Comment:		
10.	**Spelling, syntax and line numbers**	**Yes**	**No**

a)	Are there any spelling errors?		X
b)	Are there any errors in system syntax; for example, the use of a truncation symbol from a different search interface?		X
c)	Are there incorrect line combinations or orphan lines (ie, lines that are not referred to in the final summation that could indicate an error in an AND or OR statement)?		X
	Comment:		
11.	**Limits and filters**	**Yes**	**No**
a)	Are all limits and filters used appropriately and are they relevant given the research questions/ PICO's?	X	
b)	Are all limits and filters used appropriately and are they relevant for the database?	X	
c)	Are any potentially helpful limits or filters missing? Are the limits or filters too broad or too narrow? Can any limits or filters be added or taken away?		X
d)	Are sources cited for the filters used?		X
	Comment:		

Part three: Checklist for checking search strategies for study registries (PRESS for study registries)

12.	**Documentation of search strategies**	**Yes**		**No**	
a)	Did the submitted documentation show a separate search strategy for each registry?			X	
13.	**Name of study registry**	**CT.gov**		**ICTRP**	
a)	Date of the last search	*dd/mm/yyyy*		*dd/mm/yyyy*	
b)	Did the submitted documentation show the following items: name of study registry, internet address, date of the last search, search strategy, number of results?	NR = Not relevant		NR = Not relevant	
14.	**Reproducibility and comprehensiveness of search results**	**CT.gov Yes/no**		**ICTRP Yes/no**	
a)	Is the number of hits reproducible?	NR	NR	NR	NR
b)	If the above deviation is large, please limit the search results to the last date of the search conducted by the submission file senders. Then answer: is the number of hits reproducible now?	NR	NR	NR	NR
c)	Did the submitted documentation list a registry entry for each study from the study pool?	NR	NR	NR	NR
d)	Do the search blocks for the intervention and indication contain enough synonyms?	NR	NR	NR	NR
e)	Did the submitted documentation use the basic search function on the main page?	NR	NR	NR	NR
f)	Did the submitted documentation employ Boolean operators correctly?	NR	NR	NR	NR

g)	Did the submitted documentation dispense with parentheses?	NR	NR	NR	NR
h)	Does the strategy include other search blocks than population, intervention or study type?	NR	NR	NR	NR

Part four: Supplementary searches by NIPH

To assess the completeness of the evidence base, NIPH will:

1) rerun the study registry searches from the submission file and screen the results for trials identified in the submission file as well as potentially missing relevant trials, OR

2) modify the submission file strategies and then rerun the searches and screen the results for trials identified in the submission file as well as potentially missing relevant trials

Complete search strategy for ClinicalTrials.gov:

(Asthma OR Bronchial OR Thermoplast OR Thermo OR Alair OR Bronchoscop) AND (airway remodel OR airway muscle) = 100 hits

Complete search strategy for WHO ICTRP:

alair OR bronchial thermoplasty OR airway remodeling OR asthma AND thermoplasty OR asthma AND remodeling = 84 hits

15.	Summary of part four	Yes	No
a)	Are relevant studies missing in the submission file?		X

If the answer is yes, we think that these studies should be included:
Not relevant

Part five: Summary

16.	Total summary	Yes	No
a)	As a whole, is the search approved by the information specialist from NIPH?	X	

Our overall assessment is that the literature searches in the bibliographic databases are satisfactory, and are reported thoroughly. In order to be more certain that all relevant studies have been identified, we suggest additional searches in the study registers Clinical Trials and the WHO International Clinical Trials Registry Platform.

The possible weakness in the search strategy by not searching for ongoing trials was tested by performing a search in the databases Clinical Trials and the WHO International Clinical Trials Registry Platform. The number of hits was 139 unique references. Two researchers reviewed the search results, but no additional relevant studies were identified.

Summary of peer review:

Name and date of the information specialist conducting this peer review:

Name:	Date:
Gunn Eva Næss	10.05.2021

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P.O.B 4404 Nydalen
NO-0403 Oslo
Phone: + 47-21 07 70 00
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