



Australian Government

Medical Services Advisory Committee

## Public Summary Document

### ***Application No. 1384 – Bronchial thermoplasty for the treatment of severe persistent asthma***

**Applicant:** Boston Scientific

**Date of MSAC consideration:** MSAC 63<sup>rd</sup> Meeting, 1-2 April 2015

Context for decision: MSAC makes its advice in accordance with its Terms of Reference, see at [www.msac.gov.au](http://www.msac.gov.au)

#### **1. Purpose of application and links to other applications**

An Assessment Report requesting Medical Benefits Schedule (MBS) listing of bronchial thermoplasty (BT) for severe persistent asthma was received from Boston Scientific by the Department of Health in October 2014.

#### **2. MSAC's advice to the Minister**

After considering the available evidence presented in relation to safety, clinical effectiveness and cost-effectiveness of bronchial thermoplasty (BT), MSAC did not support public funding for BT for the treatment of severe persistent asthma because of uncertainties with the patient population, its place in the clinical management of severe persistent asthma, its clinical effectiveness and resulting uncertain cost-effectiveness.

#### **3. Summary of consideration and rationale for MSAC's advice**

MSAC noted that this application is for use of bronchial thermoplasty to treat uncontrolled severe asthma despite treatment and adherence with optimised asthma therapy (OAT). OAT is defined as the maximal inhaled therapy including high-dose inhaled corticosteroid (ICS) combined with a long-acting beta agonist. Bronchial thermoplasty is a minimally invasive procedure involving the delivery of controlled radiofrequency energy to the walls of distal airways through a single use catheter and 4 expandable electrodes introduced using a bronchoscope under moderate sedation. It was noted that a complete course of treatment comprises three procedures with the intent that it is a single, once per lifetime treatment.

The patient population for the application included adult patients (older than 18 years) with severe asthma whose asthma symptoms are not well controlled despite OAT. It was noted that confirmation required that asthma symptoms were not due to comorbidities, persistent

environmental exposures, psychological factors, poor medication compliance and poor inhaler technique.

MSAC accepted BT as an alternative option to maintenance treatment with low-dose oral corticosteroids (MOCS), humanised monoclonal antibody omalizumab (OM) or best supportive care/optimised asthma therapy alone (BSC/OAT) for people with uncontrolled, severe, non-allergic and allergic asthma. However, alternative clinical management algorithms were suggested, where patients with uncontrolled severe allergic asthma may transition between individual and mutually exclusive treatments.

Safety comparisons between BT and BSC/OAT were based on 3 randomised controlled trials (RCTs), AIR, AIR2 and RISA. Trial data indicated that BT was associated with increased mild to moderate respiratory adverse events and increased frequency of unscheduled office visits and hospitalisations during treatment. However, after BT there was a decrease in respiratory adverse events and decrease in unscheduled office and emergency department visits and hospitalisations. MSAC was concerned that the sham control in the trials may favour BT as the sham could have a worse safety profile than no intervention.

MSAC noted that there was no comparative evidence on the safety of BT and MOCS; however, due to the well-documented adverse side effects of long-term oral corticosteroid use there is a claim of superior safety for BT compared to MOCS.

While there are few adverse events related to OM use, these adverse events have the potential to continue for as long as the patient remains on OM therapy. MSAC was concerned by the sparse reporting of safety data in OM trials, differences in the nature of treatments, durations of randomised treatment follow-up and approaches to safety outcomes.

Overall, MSAC was concerned about the uncertainty of the clinical claims for the superior safety of BT compared with MOCS or OM.

MSAC noted that the clinical efficacy claim, based on the AIR2 and RISA RCTs, for BT plus ongoing OAT compared to OAT alone for the treatment of uncontrolled severe asthma is one of superiority and non-inferior safety in the longer term. However, MSAC expressed a number of concerns with the AIR2 trial including:

- the use of Asthma Quality of Life Questionnaire (AQLQ) as a primary outcome
- whether the results were due to more intensive treatment
- use of Bayesian statistics
- uncertainty around the degree of benefit ascribed to thermoplasty itself
- uncertainty around whether improved asthma management may be responsible for a large degree of improvement in AQLQ
- similar profiles of patients willing to be re-treated in sham and BT groups indicating that the effects may not be treatment related
- small sample sizes
- issues with treatment adherence
- lack of objective, quantitative data
- uncertainty regarding a potential improvement in behaviour because of observation (“Hawthorne effect”).

MSAC was concerned about the lack of extended follow-up of control patients in the RISA study, a smaller, open-label RCT which included a slightly broader population than AIR2, including subjects with more frequent symptoms and poorer lung function.

Due to the lack of direct evidence comparing BT with OM, efficacy comparisons were indirect using 5 RCTs, of which two were placebo-controlled and three used 'no treatment' as the comparator. MSAC expressed concerns regarding the differing inclusion criteria across trials resulting in inclusion of patients with higher degree of severity in OM trials compared to AIR2. Therefore, MSAC could not confirm non-inferiority of BT to OM.

MSAC noted that no relevant RCTs were identified to compare the relative efficacy of BT and MOCS, as add-on therapy to OAT for managing uncontrolled severe asthma. Therefore a 'pragmatic approach' which conservatively assumes equivalent efficacy between BT and MOCS was proposed; however, MSAC was concerned that this assumption of equivalence was not justified.

Economic evaluation was based on a cost utility analysis with a 10 year time horizon using a stepped approach. MSAC was uncertain about the utility weights used through the modelling with missing data and exacerbation of events as well as application of elevated asthma-related mortality rates to the model. MSAC noted that this would likely result in overstating the value for money offered by BT and increase the ICER for BT. The estimated cost of BT was originally calculated at \$1,126 per patient however, in the pre-ESC response the Applicant revised the MBS Benefit amount to \$770.85.

MSAC noted a number of financial uncertainties with this application based on uncertainties surrounding:

- anticipated caseload capacity
- whether the 'very high uptake' scenario would be exceeded
- number of associated consultations
- whether an anaesthetist would need to be present for the procedure
- whether there is any benefit with less than three BT sessions
- whether there will be a potential shift from a public to a private setting.

MSAC was concerned with a number of additional uncertainties such as whether the treatment effect would be reduced if delay between procedures was extended; whether usage outside the intended population would occur and whether specification of the maximum number of 3 claims per patient per lifetime can be managed in practice.

#### **4. Background**

The Medical Services Advisory Committee (MSAC) has not previously considered an application requesting MBS listing of BT.

#### **5. Prerequisites to implementation of any funding advice**

The Applicant's bronchial thermoplasty system is listed on the Australian Register of Therapeutic Goods (ARTG) for the treatment of asthma in patients 18 years and older.

BT will be performed according to a standardised protocol by appropriately qualified and trained respiratory specialists (bronchoscopists and pulmonologists) at public and private facilities that are equipped to perform bronchoscopy (bronchoscopy/endoscopy suite) and handle respiratory emergencies.

## 6. Proposal for public funding

The MBS item is intended to cover the service performed by an appropriately qualified and trained specialist performing the BT procedure. The Applicant claims that the procedure does not require professional physician assistance.

Table 1: Proposed MBS item descriptor

	Category 3 –Therapeutic Procedures
MBS ##### BRONCHIAL THERMOPLASTY for delivery of thermal energy to the airway wall as a means of reducing excess airway smooth muscle in patients with uncontrolled and severe asthma	
(a) the patient to whom the service is provided: (i) is currently being treated with and adherent to maximal inhaled therapy which includes high-dose inhaled corticosteroid combined with long-acting beta-2 agonist, unless contraindicated or not tolerated AND (ii) their asthma symptoms are uncontrolled despite this treatment,	
(b) the service is performed by a specialist or consultant physician with appropriate training in bronchial thermoplasty	
To be claimed a maximum of three times in the patient's lifetime.	
Multiple services rule (Anaes.)	
Fee:\$1,126.60 Benefit: 75% = \$844.95	

Source: Table 6, p12 of the Assessment Report

MSAC noted that in the pre-ESC response the Applicant revised the MBS Benefit amount to \$770.85.

To be eligible for BT a patient must have stable asthma symptoms without an increase in rescue inhaler usage and no recent exacerbations or infections in the 4 weeks preceding the procedure. If a patient meets these criteria, he or she should receive prednisone at 50 mg/day for the 3 days before the procedure.

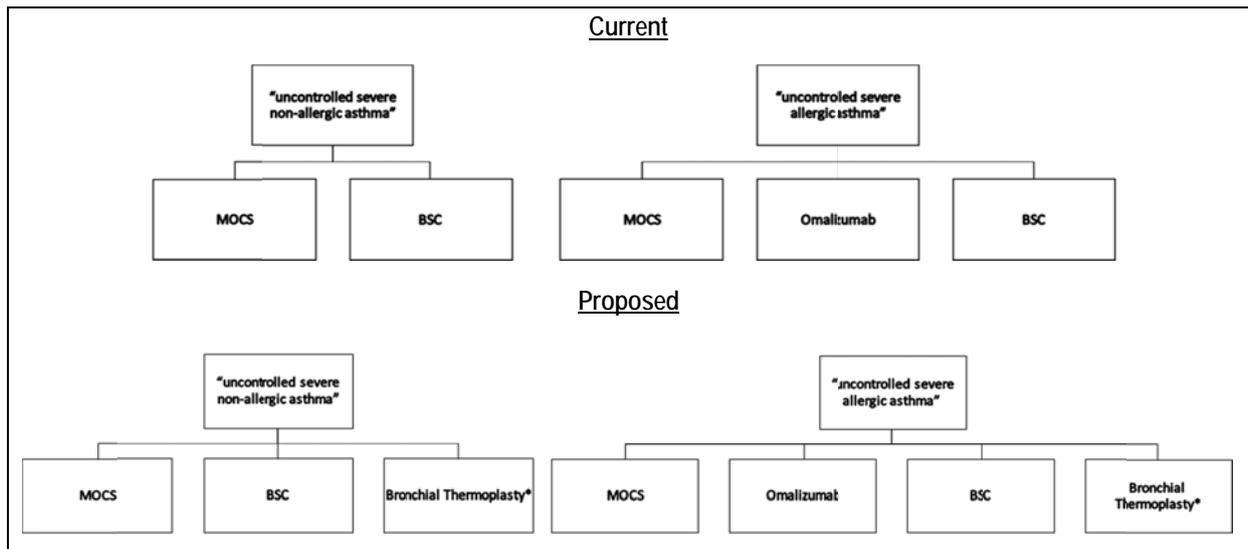
## 7. Summary of Public Consultation Feedback/Consumer Issues

No consumer statement was provided in the assessment.

## 8. Proposed intervention's place in clinical management

The clinical management algorithm for the intended use of BT and for current practice is presented in Figure 1. These algorithms are for the onward clinical management of patients with uncontrolled, severe asthma, which are based on local and international guidelines for the treatment of severe asthma (NACA 2014; GINA 2014).

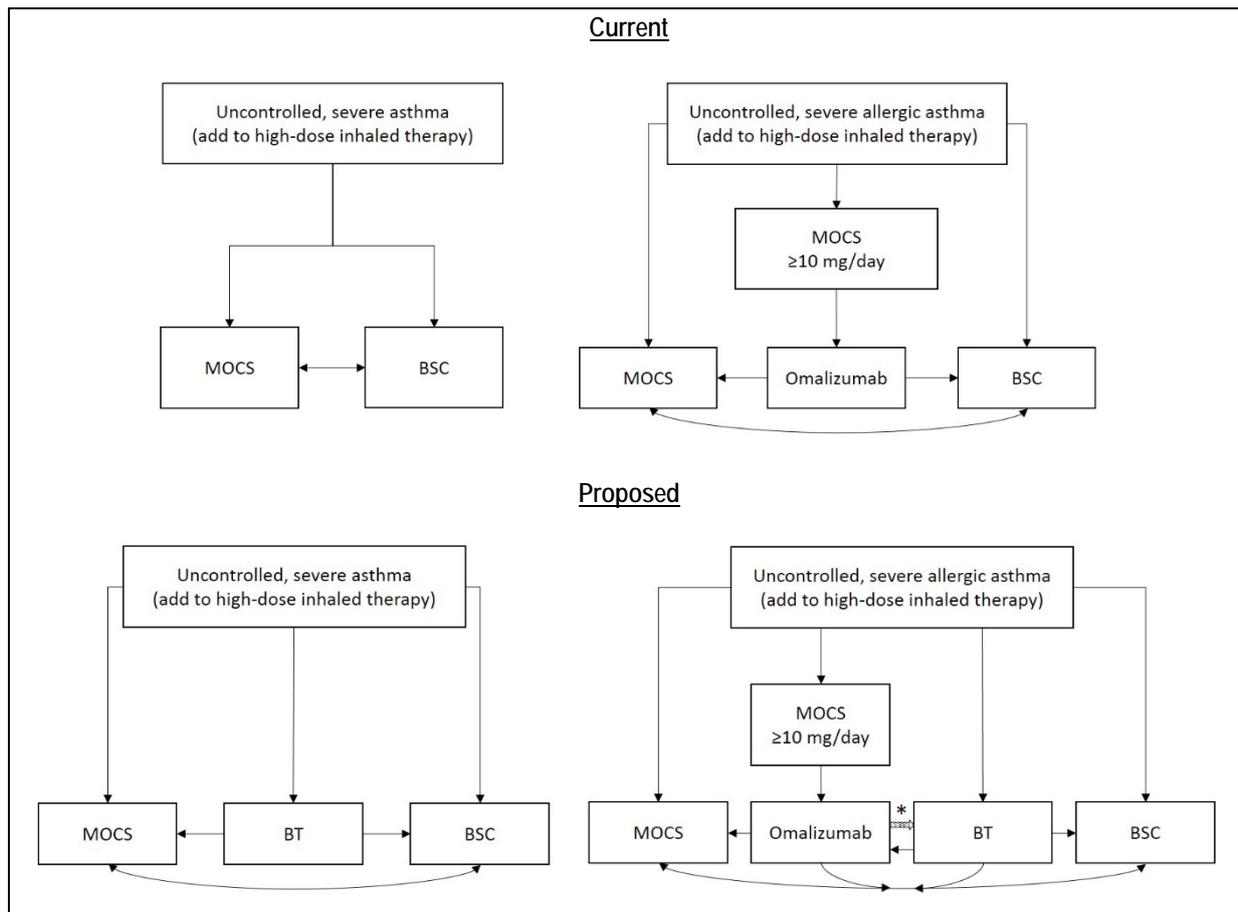
Figure 1 Current and proposed clinical management algorithms



Source: Assessment Report, p16.

- Abbreviations: BSC, best supportive care; MOCS, maintenance oral corticosteroids
- \* Bronchial thermoplasty (three procedures) is intended as a single, once-per-lifetime treatment.
- Note: Uncontrolled severe asthma is defined as asthma symptoms not well controlled despite optimised asthma therapy which comprises adherence to maximal inhaled therapy, including ICS (budesonide 1600 µg/day or fluticasone 1000 µg/day or equivalent), plus LABA (at least salmeterol 50 µg bid or formoterol 12 µg bid or equivalent), unless contraindicated or not tolerated, after ruling out non-asthma-related causes, avoidable aggravating factors, poor medication compliance and bad inhaler technique.
- Note: The algorithm does not preclude the possibility that patients may recycle back through any of the available therapies (except BT in the proposed algorithm).

Figure 2 Alternative algorithms showing the ability of patients to switch therapies, and depicting the pre-requisite of failed MOCS to access PBS-subsidised omalizumab



Abbreviations: BSC, best supportive care; BT, bronchial thermoplasty; MOCS, maintenance oral corticosteroids.

\* All treatments are add-on therapies and can be accessed simultaneously, except that BT cannot be accessed while patients are on PBS-subsidised OM, for which continuation criteria (sustained asthma control) are inconsistent with eligibility criteria for BT.

Note: All patients commence and continue on high-dose ICS/LABA, unless add-on treatments allows a reduction in these medications. BT is a once-only treatment, whereas all other treatments can be attempted multiple times.

BT is a minimally invasive medical procedure that aims to improve asthma control by reducing excessive airway smooth muscle mass, thereby reducing airway hyper-responsiveness and airflow obstruction. The procedure involves the application of controlled radiofrequency energy to the walls of the distal airways using a single-use catheter with expandable electrodes that is introduced into the airways through a bronchoscope under moderate sedation.

The patient population that is proposed to benefit from the use of BT as a service on the MBS are those with persistent (uncontrolled) asthma despite treatment with, and adherence to, optimised asthma therapy (OAT), defined as maximal inhaled therapy which includes high-dose inhaled corticosteroid (ICS) combined with a long-acting  $\beta_2$  agonist, unless contraindicated or not tolerated. The Assessment Report clarifies what is intended by 'maximal inhaled therapy', providing a definition that is consistent with the Pharmaceutical Benefits Schedule (PBS) wording of the Authority Required restriction for omalizumab (OM) for the treatment of uncontrolled severe allergic asthma.

## 9. Comparator

Asthma patients are anticipated to remain on OAT throughout the BT treatment period and as required after treatment (Assessment Report, p12). The Assessment Report makes no specific claims of any therapies being prescribed less frequently should BT be included on the MBS. However, patients may avoid other currently available add-on therapies to ICS if they instead elect to receive the 'one-off' BT course of treatment and achieve adequate symptom control. The Assessment Report and the Protocol nominate three interventions as the appropriate main comparators for BT:

- best supportive care;
- maintenance with oral corticosteroids (MOCS), typically prednisolone, which is listed on the PBS General Schedule; and
- OM, which is administered by subcutaneous injection in the out-patient clinic setting.

OAT is present as background therapy for each of these comparisons.

The proposed clinical management algorithms were presented in the Critique and presented the add-on therapies as alternative options of equivalent priority.

## 10. Comparative safety

### Comparison versus best supportive care

BT is associated with a transient increase in respiratory adverse events peri-procedure, accompanied by an increased frequency of unscheduled physician office visits and hospitalisations for respiratory adverse events. Overall, most adverse events experienced by subjects receiving BT were mild to moderate in severity. There was no increase in the rate of respiratory adverse events attributed to subsequent BT treatment sessions. In contrast, post-treatment, BT was associated with a lower frequency of respiratory adverse events accompanied by fewer unscheduled physician office visits, emergency visits and hospitalisations.

### Comparison versus MOCS

The adverse side effects of long-term exposure to oral corticosteroids are well documented. On this basis, without comparative evidence in patients with uncontrolled severe asthma, the Assessment Report makes a claim of superior safety for BT compared to MOCS.

### Comparison versus OM

While subjects undergoing BT may face a transient increase in respiratory adverse events (and associated unscheduled physician office emergency visits and hospitalisations) peri-procedure, the risks apply only to the treatment period which is relatively short and a once per life event. After the treatment phase is over, the trial data show the risk of experiencing most adverse events is generally comparable in BT and control subjects, with some adverse events, including asthma, being less frequent in the subjects who received BT. While treatment-related adverse events may be few for patients receiving OM, these have the potential to continue for as long as the patient remains on therapy.

### Pre-modelling studies:

The pre-modelling studies are included in the Assessment Report and identify the relevant translation issues.

## **11. Comparative effectiveness**

### **Comparison versus best supportive care**

The clinical efficacy claim for BT plus ongoing OAT compared to OAT alone for the treatment of uncontrolled severe asthma is one of superiority, and non-inferior safety in the longer term. The clinical claim is based on two randomised controlled trials (RCTs) of BT in patients with uncontrolled severe asthma, with post-treatment follow-up periods of one year. Five-year follow-up extension studies provide evidence for long-term efficacy and safety in BT subjects.

AIR2 is a double-blind, sham-controlled trial and constitutes the pivotal evidence for BT. RISA is a smaller, open-label RCT that provides supportive information. The RISA trial included a slightly broader population than AIR2 in that it permitted entry of subjects with more frequent symptoms and poorer lung function. The recommendations for the conduct of BT might caution against performing the procedure in some of these patients.

In AIR2, statistical significance (using a Bayesian analysis) was not demonstrated for the primary outcome, a change from the baseline in Asthma Quality of Life Questionnaire (AQLQ), but was achieved in the per-protocol analysis (but not when analysed using a Frequentist approach).

A responder analysis of the proportion of AIR2 subjects that improved their baseline AQLQ score by at least 0.5 points showed a statistically significant difference between the BT and sham bronchoscopy groups in favour of BT.

None of the outcomes designated as secondary outcomes in the AIR2 clinical study report (CSR) show statistically significant differences between groups. With the exception of pre- and post-bronchodilator FEV1 (% predicted), each of the secondary outcomes demonstrated a large sham effect.

A statistically significant difference between groups, favouring BT, was demonstrated by Bayesian analysis for emergency department (ED) visits over both the entire study period and the post-treatment period (referred to as 'other variable' in the CSR).

### **Comparison versus MOCS**

The Applicant did not identify any relevant RCTs with which to compare the relative efficacy of BT and MOCS, as add-on therapy to OAT, for the management of uncontrolled severe asthma. The Assessment Report claims to take a "pragmatic approach" and conservatively assumed equivalent efficacy between BT and MOCS, given that MOCS treatment is likely to be intermittent and/or given at a suboptimal dose.

### **Comparison versus OM**

No direct trials of BT versus OM were identified. An indirect comparison was therefore attempted using the five identified RCTs of OM, of which two were placebo-controlled and three used 'no treatment' as the comparator. However, inclusion criteria differed across the studies resulting in substantial differences between the BT and OM trial populations.

## **12. Economic evaluation**

Three comparators are independently considered in the current economic evaluation according to the clinical claim made for each of the comparators in Section B, as summarised in Table 1.

The Assessment Report presents a stepped economic evaluation for the comparison between BT+OAT and OAT alone, based on direct randomised trials, and implements a modelled evaluation using variables reported in Section C. The modelled cost-utility analysis (CUA) is presented as the base case economic evaluation to justify the notion that BT represents a value-for-money technology for the management of severe uncontrolled asthma. This allows for the transformation and extrapolation of the trial data discussed in Section C to capture the QALY and cost implications of BT+OAT versus the comparator treatments (OAT alone and MOCS+OAT). A cost-minimisation analysis has been conducted for the comparison between BT+OAT and OM+OAT.

Table 1 Comparisons considered in the current economic evaluation to support the MBS listing of BT and type of economic evaluation for each comparison

Comparator	Therapeutic claim and type of economic evaluation	Comments
OAT alone	Superior efficacy and non-inferior safety, as informed by AIR2 and RISA.  Modelled CUA with a 10-year time horizon (base case).	AIR2 is the primary source of clinical information. The model determines the QALY/cost implications of exacerbations of varying severity (requiring physician visit, ED or hospitalisation).
MOCS + OAT	Non-inferior efficacy and superior safety.  Modelled CUA with a 10-year time horizon (base case).	No quality comparative evidence is identified.  The non-inferiority efficacy claim is a pragmatic assumption. Although there is uncertainty around this claim due to absence of any evidence being presented in the Assessment Report.  Long-term use of OCS is well documented to have potentially serious adverse events. The cost/QALY implications are quantified by the model.  The model also examines the potential impacts of treatment cessation of OCS due to the safety concern.
OM (only relevant to allergic asthma patient population) + OAT	Non-inferior efficacy and superior safety.  Cost comparison based on a cost-minimisation analysis.	The presented cost comparison takes a conservative approach by foregoing the superior long-term safety of BT over OM.

Source: Table 123, p276 of the Assessment Report

Abbreviations: BT, bronchial thermoplasty; CUA, cost-utility analysis; ED, emergency department; MOCS, maintenance oral corticosteroid, OAT, optimised asthma therapy; OCS, oral corticosteroids; OM, omalizumab; QALY, quality-adjusted life year.

Table 3 summarises the steps taken in the economic evaluation provided in the Assessment Report. Note that the stepped evaluation is presented as a secondary analysis in the Assessment Report for the comparison between BT+OAT and OAT alone.

Table 3 Steps in the economic evaluation

Step	Description
Step 1	Trial-based analysis (primary outcome); ICER in terms of additional costs per patient experiencing AQLQ change $\geq 0.5$ over 12 months
Step 2	Trial-based analysis as informed by the AIR2 5-year extension study; ICER in terms of additional costs per case of severe exacerbation avoided
Step 3	Modelled 5-year analysis; ICER in terms of additional costs per additional QALY
Step 4	Modelled 10-year analysis; ICER in terms of additional costs per additional QALY

Source: Table 134, p291 of the Assessment Report

Abbreviations: AQLQ, Asthma Quality of Life Questionnaire; ICER, incremental cost-effectiveness ratio; QALY, quality-adjusted life year

The primary goal of the economic model was to estimate the total number of exacerbations experienced by patients using each treatment strategy under consideration, and determine the quality of life (QoL) and economic implications of the exacerbation events over a 10-year period. Patient characteristics at baseline, such as average age and disease severity, are informed by the characteristics of patients in the pivotal trial.

At treatment initiation, patients begin in the ‘chronic asthma without exacerbations’ health state. During each two-week model cycle, patients could transition to another health state (i.e. ‘experience an asthma exacerbation’ or ‘die’). Each asthma exacerbation could result in an in-office visit, ED visit or hospitalisation and the treatment setting impacts the costs as well as QoL decrements associated with exacerbation. The rates of each such event differ by the treatment they receive, as informed by the available clinical evidence presented.

Patients can die at any time point in the model and from one of two causes. After experiencing exacerbation requiring ED visit or hospitalisation, patients are at risk of asthma-related mortality. As discussed above, there are doubts about the way mortality risks were applied to the model. It would appear that these should only be applied to those who are hospitalised. The effect of this is investigated in the Critique and shown to have a substantial negative impact on the cost-effectiveness of BT. While in the chronic asthma health state, patients are also at risk of dying from non-asthma-related causes, as informed by the Australian life table.

Table 2 below summarises the results for BT+OAT versus both OAT alone and MOCS+OAT. These results account for the changes that were made to the analyses during the Critique. It is noted that the estimates provided in the critique differ markedly from those provided in the Assessment Report (ICERs of \$28,435 in the analysis against OAT alone and \$41,831 in the analysis against MOCS+OAT). The differences in approach and data applied are discussed throughout the Critique. The most notable, however, is the difference in the application of asthma-related mortality risks. This has a profound impact on the results, by impacting heavily on the QALYs accrued through the modelled period. The end consequence is that the results of the economic model are outside the range that is typically considered to represent good value for money.

Table 2 Incremental cost per additional QALY calculated by the model

Estimated cost/QALYs	Comparator arm		
	BT+OAT	OAT alone	MOCS+OAT
Estimated costs	\$32,113	\$17,241	\$16,959
- Incremental costs (for BT+OAT)	-	\$14,872	\$15,154
Estimated QALYs	6.8720	6.6182	6.7024
- Incremental QALYs (for BT+OAT)	-	0.2538	0.1696
Incremental cost-effectiveness ratio <sup>a</sup>	-	\$58,594	\$89,347

Source: Table D.5.8 of the Critique. See Table 133, p289 of the Assessment Report for comparison with original ICERs.

Abbreviations: BT, bronchial thermoplasty; MOCS, maintenance oral corticosteroids; OAT, optimal asthma therapy; QALY, quality-adjusted life year

Note: All costs/outcomes discounted at 5% per annum.

<sup>a</sup> Cost-effectiveness of BT+OAT compared to comparator arm.

A key area of uncertainty in the analyses can be found in the exacerbation rates applied to the model. As discussed in the Assessment Report, there are several alternative sets of data available. As a consequence, the impact of utilising different data was examined in sensitivity analyses.

Other sensitivity analyses were undertaken using both OAT alone and MOCS+OAT as the comparator. The results of these are presented in the Critique. The model was shown to be most sensitive to utility assumptions and least sensitive, generally speaking, to cost inputs.

In regards to the economic evaluation, three issues raised in the Critique were identified by the Applicant’s preMSAC response as sources of disagreement, namely:

- Potential uncertainty arising from the way in which missing utility data were handled (Applicant maintains that changes to the original model to account for missing utility data would be unwarranted).
- Re-estimation of the asthma-related mortality rate applied to the economic model (the revised Applicant estimate of 1.8% of hospitalisations is likely to be an overestimate, and the true mortality rate in the patient population of interest is likely to fall between 0.8% and 1.8%).
- Re-estimation of the risk associated with use of maintenance with oral corticosteroids (MOCS) with alternate risk rates suggested by Applicant and the Critique).

The Applicant responded to these issues with a re-specification of the model proposed in the Critique. This re-specification reduced the incremental cost-effectiveness ratios (ICERs) associated with BT such that they were estimated to lie between those proposed in the original Application and those proposed in the Critique (Applicant re-specification incremental cost per QALY ratios of \$49,218 versus OAT or \$53,403 versus OCS).

Incremental cost per additional QALY calculated by the model (incorporating changes made during the evaluation process)

Estimated cost/QALYs	Comparator arm		
	BT+OAT	OAT alone	MOCS+OAT
Estimated costs	\$30,325	\$17,196	\$17,835
- Incremental costs (for BT+OAT)		\$13,129	\$12,490
Estimated QALYs	6.8680	6.6012	6.6341
- Incremental QALYs (for BT+OAT)		0.2668	0.2339
ICER BT vs comparator		\$49,218	\$53,403

### 13. Financial/budgetary impacts

Epidemiological data suggests that the prevalence of confirmed, uncontrolled, severe asthma is roughly 50,000 patients in Australia. However, despite a sizeable patient pool, the actual usage of BT will be limited by the caseload capacity to perform the procedure. The Applicant claims that there are currently five centres in Australia (two private and three public) that are equipped to perform BT, each treating 10 patients a year. The Applicant anticipates that the number of private and public centres would grow to 20 over the first five years of an MBS listing (12 public and 8 private), with each centre expected to perform up to 48 procedures each year.

Under this caseload/uptake scenario, and assuming that only private centres generate cost implications to the MBS, the cost to the MBS of the proposed item is estimated to be approximately \$141,000 in Year 1 (48 patients), increasing to \$433,000 in Year 5 (128 patients), at the original proposed Schedule fee of \$1,126.60. When combined with additional MBS costs due to specialist consultations and anaesthetist attendances, the total MBS cost is estimated to be approximately \$185,000 in Year 1, increasing to \$568,000 in Year 5.

MSAC noted that these estimates do not include the cost of the specialised catheter used for BT (approximately \$9,000 for a course of three treatments per patient). These costs would grow from \$432,000 (Year 1) to \$1.15M (Year 5) but would not be borne by the MBS. The Applicant’s pre-MSAC response proposed a reduction in price of the catheters to \$8,250 for a course of three treatments.

MSAC noted that the Applicant in their pre-ESC response also provided a revised MBS fee of \$770.85 for the catheter and several MBS cost scenarios:

**Table 2 Estimated MBS costs of the proposed procedure at 85% benefit, revised**

<b>Caseload scenarios</b>	<b>Year 1</b>	<b>Year 2</b>	<b>Year 3</b>	<b>Year 4</b>	<b>Year 5</b>
<b><i>Base case scenario (as proposed in the Protocol)</i></b>					
BT procedural costs, original	\$131,300	\$199,576	\$267,852	\$336,128	\$403,354
<i>BT procedural costs, revised to account for additional 7.2%</i>					
- at original fee	\$154,409	\$234,239	\$314,070	\$393,900	\$475,957
- at revised fee of \$770.85	\$102,114	\$154,907	\$207,700	\$260,494	\$314,760
<b><i>High uptake scenario</i></b>					
BT procedural costs, original	\$171,215	\$279,406	\$387,598	\$495,789	\$605,030
<i>BT procedural costs, revised to account for additional 7.2%</i>					
- at original fee	\$202,727	\$330,876	\$459,025	\$587,174	\$713,936
- at revised fee of \$770.85	\$134,067	\$218,815	\$303,562	\$388,309	\$472,140
<b><i>Very high uptake scenario</i></b>					
BT procedural costs, original	\$212,181	\$361,338	\$510,494	\$659,651	\$806,707
<i>BT procedural costs, revised to account for additional 7.2%</i>					
- at original fee	\$249,995	\$425,412	\$600,829	\$776,246	\$951,914
- at revised fee of \$770.85	\$165,327	\$281,333	\$397,340	\$513,346	\$629,520

#### **14. Key issues from ESC for MSAC**

ESC noted that the patient population are those with persistent (uncontrolled) asthma despite treatment with, and adherence to, optimised asthma therapy (OAT), defined as maximal inhaled therapy which includes high-dose inhaled corticosteroid (ICS) combined with a long-acting beta agonist, unless contraindicated or not tolerated.

ESC noted that there is uncertainty with the clinical claim for superior safety of BT compared with maintenance with oral corticosteroids (MOCS) or Omalizumab (OM). ESC considered that BT is associated with an increase in respiratory adverse events peri-procedure and an increased frequency of unscheduled physician office visits and hospitalisations for respiratory adverse events. ESC discussed that post-treatment, BT was associated with a decrease in frequency of respiratory AE and a decrease in unscheduled office visits, emergency department visits and hospitalisations. Overall, ESC agreed that most adverse events experienced by subjects receiving BT were mild to moderate in severity. ESC was concerned,

however, that the use of a sham control may favour BT as the sham procedure could have a worse safety profile than a 'no intervention' control group.

ESC noted that there is no evidence comparing the safety of BT versus MOCS, but agreed that the adverse side effects of long-term exposure to oral corticosteroids are well documented. ESC also acknowledged that there was no direct safety comparison of BT and OM. ESC discussed that this could be attributed to the different nature of the treatments (i.e. a 'one-off' treatment compared to ongoing therapy), the different approaches used to express safety outcomes, and the different durations of randomised treatment follow-up in the trials.

ESC noted that the clinical efficacy claim for BT plus ongoing OAT compared to OAT alone for the treatment of uncontrolled severe asthma is one of superiority, and non-inferior safety in the longer term. ESC noted that the clinical claim is based on two randomised controlled trials (AIR2 and RISA) of BT in patients with uncontrolled severe asthma, with post-treatment follow-up periods of one year. ESC further noted that a five-year follow-up extension study provides evidence for long-term efficacy and safety in BT subjects.

ESC noted that the AIR2 study constituted the pivotal evidence for BT but questioned the reliability of the findings of this trial due to the type of statistical analysis used (Bayesian statistics). ESC noted that the RISA study was small (17 in each arm) and provided supporting information. The population showed more frequent symptoms and poorer lung function.

ESC noted that the evidence appraisal underwent both Bayesian and Frequentist statistical approaches. ESC considered the Bayesian approach to be better than the Frequentist approach, although ESC acknowledged that the Frequentist approach is more widely available. ESC noted that the Frequentist approach is a pre-specified approach, unlike the Bayesian.

ESC noted that in AIR2, statistical significance (using a Bayesian analysis) was not demonstrated for the primary outcome, change from baseline in Asthma Quality of Life Questionnaire (AQLQ), but was achieved in the per-protocol analysis (but not when analysed using a Frequentist approach). ESC was concerned that large changes from baseline in AQLQ were observed in both the BT and sham bronchoscopy groups. ESC discussed the degree to which benefit can be ascribed to the action of the thermoplasty procedure itself and whether improved asthma management may be responsible for a large degree of improvement in AQLQ and/or the Hawthorne effect.

ESC noted that BT was shown to reduce emergency visits for the entire study period and post-treatment period. ESC noted that this statistical significance was demonstrated by Bayesian analysis and maintained in a Frequentist analysis. ESC also noted that BT was shown to reduce hospitalisation and doctor office visits. ESC noted that this statistical significance was also observed by Bayesian analysis but this significance was lost using Frequentist methods.

ESC was concerned that there were no randomised controlled trial evidence with which to compare the relative efficacy of BT and MOCS, as add-on therapy to OAT, for the management of uncontrolled severe asthma. ESC noted that this assumes equivalent efficacy between BT and MOCS without justification. ESC agreed BT could not be confirmed as non-inferior to OM.

ESC noted that no direct trials of BT versus OM were identified. ESC discussed that this is likely due to the different populations and nature of treatments (ie a ‘one-off’ treatment compared to ongoing therapy’) and agreed that the indirect comparison of BT versus IM could not be valid due to substantial differences in the trial populations.

ESC discussed that BT catheters are not reusable. ESC was concerned that the total cost of catheters per patient is significant (a total of approximately \$9,000 for the three procedures).

The Applicant revised the cost of the catheters in their pre-ESC response to be \$2,750 each (noting that three catheters are required for the full course of treatment).

ESC noted that a modelled cost-utility analysis versus OAT alone and OAT+MOCS is presented as the base case economic evaluation. ESC also noted that a cost-minimisation analysis was also presented as a secondary analysis. ESC agreed that the economic evaluation was appropriate.

ESC noted that there was uncertainty around the utility weights used through the modelling. In particular, ESC questioned how missed data were handled in the calculation of the utility weights from the AQLQ data and how the utility weights associated with exacerbation events were applied. ESC was concerned these issues would have a notable impact on the economic model once addressed. For example, the latter issue could increase the incremental cost-effectiveness ratio (ICER) markedly. This concern was addressed by the Applicant’s preMSAC response which suggested that changes to the original model would be unwarranted.

ESC was also concerned that asthma-related mortality was incorrectly applied in the model. ESC noted that an elevated mortality rate was applied to the model, thereby overstating the value for money offered by BT. ESC noted that these should only be applied to those who are hospitalised. ESC noted that this was accentuated by applying a mortality risk to all patients with an exacerbation requiring an emergency department visit. ESC further discussed that revisiting the mortality rate, and applying a revised rate only to those patients who are hospitalised, has a marked impact on the results of the model. That is, likely overstating the value for money offered by BT and likely increasing the ICER for BT. The Applicant’s preMSAC response claimed that the estimate used in the Critique is incorrect and should be increased to 1.8% of hospitalisations. However, the severe asthma population from which this rate is derived would include those very severe patients who fall outside the eligible BT population. Therefore 1.8% is likely to be an overestimate, and the true mortality rate in the patient population of interest is likely to fall between 0.8% and 1.8%. The two estimates, therefore, should be viewed as a range and the results treated accordingly.

ESC was primarily concerned that there is considerable uncertainty in the anticipated caseload capacity that underpins the financial estimates. ESC was also concerned that the number of patients that access BT on the MBS may reach or even exceed the ‘very high uptake’ scenario presented in the assessment report. Similarly, ESC was concerned about the uncertainties around the number of associated consultations required prior to BT and following each BT procedure. ESC noted that the base case economic model captured four consultations; however, a total of six consultations may actually be required for the full course of treatment. ESC noted that this may impact the total cost to the MBS. ESC also questioned the number (or proportion) of procedures which would require the presence of an anaesthetist – something that could also impact the total cost to the MBS.

ESC discussed whether all patients would persist with the full course of three BT procedures in clinical practice or perhaps receive one or two procedures only. ESC considered whether these patients would derive partial benefit (or no benefit at all) and questioned the impact this would have on the MBS.

ESC considered the potential shift from public to private care if this procedure is funded and raised concern about the uncertainty around out of pocket costs. ESC also discussed that MBS funding could trigger reprioritisation of this service within treatment centres, allowing for a gradual increase in caseload capacity exceeding that presented in the submission. ESC was concerned that the assessment did not address whether the treatment effect is reduced in patients that have an extended delay between procedures.

ESC noted that the wording of the proposed MBS item descriptor is unclear and may lead to usage outside the intended population. The policy area was concerned with the wording of the descriptor, however, ESC advised that this could be rectified in the implementation stage. ESC was also concerned that the restriction of the proposed service to patients who fit the criteria would rely on specific training of, and implementation by, the physicians administering the service. ESC noted that the proposed item descriptor specifies a maximum of three claims per patient per lifetime, irrespective of the time elapsed between procedures. ESC questioned how this can be managed in practice.

#### **15. Other significant factors**

Nil.

#### **16. Applicant's comments on MSAC's Public Summary Document**

Boston Scientific are disappointed with MSAC's decision not to recommend bronchial thermoplasty for listing on the Medicare Benefits Schedule at this time. Randomised controlled trials with duration of treatment effect for at least 5 years have shown a reduction in the rate of severe exacerbations, emergency department visits, and days lost from work. Evidence based best practice treatment guidelines have been updated to reflect developments in clinical data and clinical experience, namely the Global Initiative for Asthma (GINA) and British Thoracic Society (BTS) Guidelines. Further, the American College of Chest Physicians, INTERASTHMA Global Asthma Association, Asthma and Allergy Foundation of America, and the American College of Allergy, Asthma, and Immunology endorse bronchial thermoplasty in carefully selected patients.

We are concerned MSAC considered the clinical management algorithm to be uncertain despite it being developed in consultation with the PASC. Also, we are concerned MSAC did not accept the Bayesian statistics in the AIR2 trial despite advice from ESC which considered the Bayesian approach to be superior to the alternative Frequentist approach. Over 4000 patients globally have benefited through treatment with bronchial thermoplasty therapy. The clinical literature supports bronchial thermoplasty as a therapeutic consideration for some carefully chosen patients in Australia who, despite optimal medical treatment, have persistent burden of disease, asthma exacerbations, emergency department visits or hospitalisations. Boston Scientific will seek to work with all stakeholders to ensure a reapplication for the proposed service provides a solution to the unmet clinical need for patients who remain symptomatic despite maximal medical treatment.

#### **17. Further information on MSAC**

MSAC Terms of Reference and other information are available on the MSAC Website at:  
[www.msac.gov.au](http://www.msac.gov.au).