Evidence Summary: Inhaled Corticosteroid and Long-Acting Beta$_2$-Agonist Controller Therapy vs. the Same Inhaled Corticosteroid Dose and Short-Acting Beta$_2$-Agonist for Quick-Relief Therapy in Individuals Ages 12 Years and Older with Persistent Asthma

For this comparator, the Agency for Healthcare Research and Quality (AHRQ) systematic review report rated the strength of evidence based on two randomized controlled trials by Scicchitano et al. (2004) and Rabe et al. (2006).[2,3] However, the opinion of the Expert Panel is that the comparator in these studies was a higher dose of an inhaled corticosteroid controller therapy instead of the same dose as reported previously in the AHRQ systematic review report. For this reason, the Expert Panel included these two randomized controlled trials (RCTs) in the evidence summary that follows. The AHRQ systematic review report identified a third RCT (Sovani et al. 2008)[4] that it did not consider when it rated the strength of evidence, most likely because the study had a high risk of bias and the sample was very small (N = 71).

Evidence Summary: Inhaled Corticosteroid and Long-Acting Beta$_2$-Agonist Controller Therapy vs. a Higher Inhaled Corticosteroid Dose and Short-Acting Beta$_2$-Agonist for Quick-Relief Therapy in Individuals Ages 12 Years and Older with Persistent Asthma[a]

Outcomes	Number of participants (number of studies)	Certainty of evidence (GRADE)	Relative effect (95% CI)	Anticipated absolute effects (95% CI)	
				Risk with ICS controller and SABA quick-relief therapy vs. higher ICS dose and/or N	Risk difference or mean difference for ICS-LABA as controller and reliever therapy
EXACERBATIONS (*CRITICAL* OUTCOME)					
Composite outcome made up of need for systemic corticosteroids, hospitalizations, and ED visits[b,c] Follow-up: 52 weeks	3,741 total (2 RCTs)[3,5]	High	RR: 0.62 (0.53 to 0.71)	388/1869 (20.8%)388/1869 (20.8%)	**Favors intervention** 239/1,872 (12.8%), 79 fewer per 1,000 (from 98 fewer to 60 fewer)

Outcomes	Number of participants (number of studies)	Certainty of evidence (GRADE)	Relative effect (95% CI)	Anticipated absolute effects (95% CI)	
				Risk with ICS controller and SABA quick-relief therapy vs. higher ICS dose and/or N	Risk difference or mean difference for ICS-LABA as controller and reliever therapy
ASTHMA CONTROL (*CRITICAL* OUTCOME)					
Not reported					
QUALITY OF LIFE (*CRITICAL* OUTCOME)					
Not reported					
ASTHMA SYMPTOMS (*CRITICAL* OUTCOME)					
Nonvalidated scales[d] Follow-up: 24 to 52 weeks	(3 RCTs)[2,3,5]	—	—	**Favors intervention** Based on results from multiple nonvalidated symptom measures	

Abbreviations: CI, confidence interval; GRADE, Grading of Recommendations Assessment, Development and Evaluation; ED, emergency department; ICS, inhaled corticosteroid; LABA, long-acting beta$_2$-agonist; RCT, randomized controlled trial; RR, relative risk; SABA, short-acting beta$_2$-agonist.

Footnotes, including GRADE explanations:

a. The Expert Panel reviewed Scicchitano et al. (2004) and Rabe et al. (2006) and concluded that the comparator was a higher dose of ICS controller therapy instead of the same dose, as reported in the Agency for Healthcare Research and Quality (AHRQ) systematic review report.[2,3]

b. No studies provided data on individual exacerbation outcomes (exacerbations requiring systemic corticosteroids, asthma-related hospitalizations, or asthma-related ED visits). Three studies (O'Byrne et al. 2005, Scicchitano et al. 2004, and Rabe et al. 2006)[2,3,5] provided data on the composite outcome of exacerbations requiring systemic corticosteroids, hospitalizations, ED visits, or peak expiratory flow less than 70%. For this outcome, the calculated pooled RR was 0.60 (95% CI, 0.53 to 0.68).

c. O'Byrne et al. (2005) enrolled individuals with asthma ages 4–80 years (mean age 35.5 years).[5] The Expert Panel did not rate this outcome down for indirectness.

d. The AHRQ systematic review report only evaluated asthma control outcomes measured with validated scales. None of the studies collected data on the asthma control outcome using validated scales. While developing the guidelines, the Expert Panel reviewed three RCTs[2,3,5] that measured asthma symptoms using various nonvalidated symptom scales; the results of these RCTs favored the intervention.

Evidence Summary: Inhaled Corticosteroid and Long-Acting Beta$_2$-Agonist Controller and Reliever Therapy vs. Inhaled Corticosteroid Controller at a Higher Comparative Inhaled Corticosteroid dose and Short-Acting Beta$_2$-Agonist Quick Relief in Children Ages 4–11 Years with Persistent Asthma[a]

Outcomes	Number of participants (number of studies)	Certainty of evidence (GRADE)	Relative effect (95% CI)	Anticipated absolute effects (95% CI)	
				Risk with ICS controller and SABA quick-relief therapy (higher ICS dose) and/or N	Risk difference or mean difference for ICS-LABA controller and reliever therapy
EXACERBATIONS (*CRITICAL* OUTCOME)					
Composite outcome measure composed of need for systemic corticosteroids, hospitalizations, ED visits, or increases in ICS or other medication dose[b] Follow-up: 12 months	224 (1 RCT)[6]	Moderate[c]	RR: 0.43 (0.21 to 0.87)	21/106 (19.8%)	**Favors intervention** 10/118 (8.5%), 113 fewer per 1,000 (from 157 fewer to 26 fewer)
ASTHMA CONTROL (*CRITICAL* OUTCOME)					
Not reported					
QUALITY OF LIFE (*CRITICAL* OUTCOME)					
Not reported					
ASTHMA SYMPTOMS (IMPORTANT OUTCOME)					
Nonvalidated scales[d] Follow-up: 12 months	(1 RCT)[6]	—	—	**Favors intervention** Of nonvalidated symptom measures, only night-time awakenings were different between groups	

Abbreviations: CI, confidence interval; ED, emergency department; GRADE, Grading of Recommendations Assessment, Development and Evaluation; ICS, inhaled corticosteroid; LABA, long-acting beta$_2$-agonist; RCT, randomized controlled trial; RR, relative risk; SABA, short-acting beta$_2$-agonist.

Footnotes, including GRADE explanations:

a. Only 1 RCT (Bisgaard et al. 2006) provided data on this intervention and comparator in this age group.[6] This a priori subgroup analysis was published separately from the full study.[5]

b. No studies provided data on individual exacerbation outcomes (exacerbations requiring systemic corticosteroids, asthma-related hospitalizations, or asthma-related ED visits). Bisgaard et al. (2006)[6] provided data on a composite exacerbation outcome (exacerbations requiring systemic corticosteroids, hospitalizations, ED visits, increase in ICS or other medication doses, or peak expiratory flow less than 70%). The RR for this composite outcome was 0.55 (95% CI, 0.32 to 0.94). This study also provided data on the mild exacerbation outcome, for which the risk ratio was 0.86 (95% CI, 0.72 to 1.04).[6]

c. The Agency for Healthcare Research and Quality (AHRQ) systematic review report rated this outcome down for indirectness because Bisgaard et al. (2006) used a daily dose lower than what *Expert Panel Report 3: Guidelines for the Diagnosis and Management of Asthma* considered to be a low dose for this age group.[6]

d. The AHRQ systematic review report only evaluated asthma control outcomes measured with validated scales. No studies collected data on the asthma control outcome using validated scales. While developing the guidelines, the Expert Panel reviewed studies that collected data on asthma symptoms using various nonvalidated symptom scales. In one of these studies,[6] rates of asthma-related nighttime awakenings differed between groups and favored the intervention.

Harms:

Two studies reported data on the intervention's impact on growth in children ages 4–11 years, and the results of both favored single maintenance and reliever therapy (SMART) over daily higher-dose inhaled corticosteroid therapy. Bisgaard et al. (2006) reported an adjusted mean difference in growth of 1.0 cm between children with asthma treated with budesonide-formoterol SMART vs. those treated with a fixed higher dose of budesonide and an as-needed short-acting beta$_2$-agonist (SABA; 95% CI, 0.3 to 1.7; *P* = 0.0054).[6] O'Byrne et al. (2005) also found a mean difference in growth of 1.0 cm between children treated with budesonide-formoterol SMART and those treated with a fixed, higher dose of budesonide plus as-needed SABA (95% CI, 0.3 to 1.7; P = 0.0054).[5] Neither study found differences in growth between children with asthma treated with SMART and those treated with daily budesonide-formoterol and as-needed SABA for relief therapy. The 11 studies with data on serious adverse events found no differences in rates of these effects between groups.[2,3,5,7-14]

New evidence

Yes.[15]

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Evidence to Decision Table XIX — Inhaled Corticosteroids and Long-Acting Beta$_2$-Agonists for Controller and Reliever Therapy vs. Inhaled Corticosteroids and Long-Acting Beta$_2$-Agonists for Controller Therapy in Individuals with Persistent Asthma

Background

In *Expert Panel Report 3: Guidelines for the Diagnosis and Management of Asthma*, published in 2007, scheduled, daily ICS dosing was the preferred pharmacologic controller therapy for persistent asthma in individuals of all ages.[1] The report suggested that intermittent ICS dosing schedules may be useful in some settings, but the evidence at that time was insufficient to support a recommendation for intermittent ICS dosing.[1] In 2015, the National Heart, Lung, and Blood Advisory Council Working Group determined that a sufficient number of studies had been published on intermittent ICS dosing to warrant a systematic literature review. This table addresses comparisons of ICS with LABA as both controller and reliever therapy versus ICS with LABA used as controller therapy with SABA as quick relief therapy in individuals ages 5 years and older with persistent asthma.

Desirable effects: How substantial are the desirable anticipated effects?

JUDGMENT	RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS
Large	Five RCTs found a 32% reduction in exacerbations (standard composite outcome) in comparison with the same ICS dose plus LABA for controller therapy with SABA for quick-relief therapy in individuals ages 12 years and older. One RCT with moderate certainty of evidence found a 72% reduction in individuals ages 4–11 years. The reduction in exacerbations (25%) was smaller in 2 RCTs than with a higher ICS dose plus LABA with SABA for quick-relief therapy in individuals ages 12 years and older. These studies found no differences in asthma control or quality of life. The results of 1 new study not included in the AHRQ systematic review report (Pilcher et al. 2017) that used the same dose ICS in individuals ages 12 years and older were consistent with the results of the RCTs included in the AHRQ systematic review report.	

Undesirable effects: How substantial are the undesirable anticipated effects?		
JUDGMENT	**RESEARCH EVIDENCE**	**ADDITIONAL CONSIDERATIONS**
Trivial	Growth data showed no differences between groups in undesirable anticipated effects or serious adverse events.	

Certainty of evidence: What is the overall certainty of the evidence of effects?		
JUDGMENT	**RESEARCH EVIDENCE**	**ADDITIONAL CONSIDERATIONS**
High	The certainty of evidence is high for the intervention in individuals ages 12 years and older in comparison with either the same ICS dose or a higher ICS dose in ICS-LABA. The certainty of evidence is moderate for children ages 4–11 years in comparison with the same ICS dose in ICS-LABA.	

Values: Is there important uncertainty about or variability in how much people value the main outcomes?		
JUDGMENT	**RESEARCH EVIDENCE**	**ADDITIONAL CONSIDERATIONS**
No important uncertainty or variability	There is no important uncertainty or variability in how much people value the main outcomes.	

Balance of effects: Does the balance between desirable and undesirable effects favor the intervention or the comparison?		
JUDGMENT	**RESEARCH EVIDENCE**	**ADDITIONAL CONSIDERATIONS**
Favors the intervention	There is substantial benefit in the form of a reduction in exacerbations and trivial undesirable effects for individuals ages 12 years and older. The results from 1 study are consistent with the studies in ages 12 years and older for the comparison with the same ICS dose in ICS-LABA in children ages 4–11 years. The effect size for exacerbations is smaller in the comparison with a higher ICS dose in ICS-LABA, and the data show no difference in asthma control or quality of life in the comparison with a higher ICS dose in ICS-LABA.	

Acceptability: Is the intervention acceptable to key stakeholders?		
JUDGMENT	**RESEARCH EVIDENCE**	**ADDITIONAL CONSIDERATIONS**
Yes		Use of a single inhaler for both controller and reliever therapy is likely to be acceptable to individuals with asthma and providers. No regulatory barriers (e.g., black box warnings) to the use of a single inhaler exist (although as-needed use is not an approved indication for ICS-LABA).

Feasibility: Is the intervention feasible to implement?		
JUDGMENT	**RESEARCH EVIDENCE**	**ADDITIONAL CONSIDERATIONS**
Yes		Cost could be a consideration for some individuals with asthma if ICS-LABA is substantially more expensive than SABA because of limited or lack of health insurance coverage of this therapy.

Equity: What would the impact be on health equity?		
JUDGMENT	**RESEARCH EVIDENCE**	**ADDITIONAL CONSIDERATIONS**
Probably increased	Exacerbations are more common in ethnic minority populations and individuals with lower socioeconomic status. Therefore, reductions in exacerbations by an intervention might disproportionately affect such individuals. In contrast, members of these populations might have less access to care, which could limit the benefits of the intervention.	

Abbreviations: AHRQ, Agency for Healthcare Research and Quality, ICS, inhaled corticosteroids; LABA, long-acting beta$_2$-agonist; RCT, randomized controlled trial; SABA, short-acting beta$_2$-agonist.

Evidence Summary: Inhaled Corticosteroid and Long-Acting Beta$_2$-Agonist for Controller and Reliever Therapy vs. the Same Inhaled Corticosteroid Dose and Long-Acting Beta$_2$-Agonist for Controller Therapy in Children Ages 4–11 Years with Persistent Asthma[a]

Outcomes	Number of participants (number of studies)	Certainty of evidence (GRADE)	Relative effect (95% CI)	Anticipated absolute effects (95% CI)	
				Risk with ICS-LABA controller and SABA quick relief therapy (same ICS dose) and/or N	Risk difference or mean difference with ICS-LABA controller and reliever therapy
EXACERBATIONS (*CRITICAL* OUTCOME)					
Composite outcome comprising need for hospitalization, systemic corticosteroids, ED visits, or increased doses of ICS or other medications[b] Follow-up: 52 weeks	235[c] (1 RCT)[2]	Moderate[d]	RR: 0.28 (0.14 to 0.53)	36/117 (30.8%)	**Favors intervention** 10/118 (8.5%), 222 fewer per 1,000 (from 265 fewer to 145 fewer)
ASTHMA CONTROL (*CRITICAL* OUTCOME)					
Not reported					
QUALITY OF LIFE (*CRITICAL* OUTCOME)					
Not reported					

Abbreviations: CI, confidence interval; ED, emergency department; GRADE, Grading of Recommendations Assessment, Development, and Evaluation; ICS, inhaled corticosteroid; LABA, long-acting beta$_2$-agonist; RCT, randomized controlled trial; RR, relative risk; SABA, short-acting beta$_2$-agonist.

Footnotes, including GRADE explanations:

a. Only 1 RCT provided data on this intervention and comparator.[2] This a priori subgroup analysis was published in a separate publication from the full study.[3]

b. No studies provided data on individual exacerbation outcomes (exacerbations requiring systemic corticosteroids, asthma-related hospitalizations, or asthma-related ED visits). Bisgaard et al. (2006)[2] also provided data on a composite exacerbation outcome (exacerbations requiring hospitalization, systemic corticosteroids, ED visits, increased doses of ICS or other medications, or peak expiratory flow less than 70%). The risk ratio was 0.38 (95% CI, 0.23 to 0.63). This study also provided data on the mild exacerbation outcome, for which the risk ratio was 0.75 (0.64 to 0.88).[2]

c. While developing the clinical guidelines, the Expert Panel reviewed the Bisgaard et al. (2006) study, and the opinion of the Expert Panel was that the RCT's sample size for the two relevant treatment groups was 235.[2]

d. The Agency for Healthcare Research and Quality systematic review report rated this outcome down for indirectness because the RCT used a lower dose than that approved in the package insert. The dose considered in the 2007 *Expert Panel Report 3: Guidelines for the Diagnosis and Management of Asthma* was also a low dose for this age group.[2]

Evidence Summary: Inhaled Corticosteroid and Long-Acting Beta$_2$-Agonist for Controller and Reliever Therapy vs. the Same Inhaled Corticosteroid Dose and Long-Acting Beta$_2$-Agonist for Controller Therapy and Short-Acting Beta$_2$-Agonist for Quick-Relief Therapy in Individuals Ages 12 Years and Older with Persistent Asthma[a]

Outcomes	Number of participants (number of studies)	Certainty of evidence (GRADE)	Relative effect (95% CI)	Anticipated absolute effects (95% CI)	
				Risk with ICS-LABA controller and SABA quick-relief therapy (same ICS dose) and/or N	Risk difference or mean difference with ICS-LABA controller and reliever therapy
EXACERBATIONS (*CRITICAL* OUTCOME)					
Need for systemic corticosteroids Follow-up: 48 to 52 weeks	3,792 (2 RCTs)[4,5]	High	RR: 0.70 (0.57 to 0.86)	311/1,891 (16.4%)	**Favors intervention** 219/1,901 (11.5%), 49 fewer per 1,000 (from 71 fewer to 23 fewer)
Requiring hospitalization Follow-up: 24 to 52 weeks	2,394[a] (2 RCTs)[4,6]	Moderate[b]	RR: 0.39 (0.18 to 0.85)	35/1,194 (2.9%)	**Favors intervention** 13/1,200 (1.1%), 18 fewer per 1,000 (from 24 fewer to 4 fewer)
Requiring ED visit Follow-up: 52 weeks	2,091 (1 RCT)[4]	High	RR: 0.74 (0.59 to 0.93)	151/1,042 (14.5%)	**Favors intervention** 112/1,049 (10.7%), 38 fewer per 1,000 (from 59 fewer to 10 fewer)
Composite outcome of need for systemic corticosteroid treatment, hospitalization, or ED visit[c,d] Follow-up: 24 to 52 weeks	8,483 (5 RCTs)[4-8]	High	RR: 0.68 (0.58 to 0.80)	843/4,257 (19.8%)	**Favors intervention** 572/4,226 (13.5%), 63 per 1,000 (from 83 fewer to 40 fewer)

Outcomes	Number of participants (number of studies)	Certainty of evidence (GRADE)	Relative effect (95% CI)	Anticipated absolute effects (95% CI)	
				Risk with ICS-LABA controller and SABA quick-relief therapy (same ICS dose) and/or N	Risk difference or mean difference with ICS-LABA controller and reliever therapy
ASTHMA CONTROL (*CRITICAL* OUTCOME)					
ACQ-5 responder (score reduction of ≥0.5)[e] Follow-up: 12 months	2,091 (1 RCT)[4]	High	RR: 1.14 (1.05 to 1.24)	511/1,042 (49.0%)	**Favors intervention** 587/1,049 (56.0%), 69 more per 1,000 (from 25 more to 118 more)
QUALITY OF LIFE (*CRITICAL* OUTCOME)					
Not reported					

Abbreviations: ACQ-5, five-item Asthma Control Questionnaire; CI, confidence interval; ED, emergency department; GRADE, Grading of Recommendations Assessment, Development, and Evaluation; ICS, inhaled corticosteroid; LABA, long-acting beta$_2$-agonist; RCT, randomized controlled trial; RR, relative risk; SABA, short-acting beta$_2$-agonist.

Footnotes, including GRADE explanations:

a. The Expert Panel concluded that the total sample size from two RCTs for this outcome was 2,394.[4,6]

b. The Agency for Healthcare Research and Quality (AHRQ) systematic review report rated this outcome down for inconsistency because the point estimates differed between the two studies.

c. Data from five RCTs on the composite exacerbation outcome (need for hospitalization or ED visit) resulted in a pooled RR of 0.69 (95% CI, 0.63 to 0.76).[4-8] Data from one RCT on another composite exacerbation outcome (need for systemic corticosteroid treatment, hospitalization, ED visit, or unscheduled visit) showed an RR of 0.79 (95% CI, 0.65 to 0.95).[8] Data from three RCTs on mild exacerbations resulted in a pooled RR of 0.94 (95% CI, 0.81 to 1.09).[4,5,7] Another RCT also found no exacerbations requiring intubation.[5]

d. The AHRQ systematic review report includes an additional RCT, O'Byrne et al. (2005), only in a sensitivity analysis for the main composite exacerbation outcome because this RCT enrolled individuals with asthma ages 4–80 years old. The sensitivity analysis that includes this study yielded a pooled RR of 0.65 (95% CI, 0.55 to 0.77).[3]

e. Data from three RCTs on ACQ-5 scores resulted in a pooled mean difference of 0.16 less (95% CI, from 0.39 less to 0.06 more).[4,7,9] Data from one RCT on the Asthma Control Test were inconclusive or insufficient.

Evidence Summary: Inhaled Corticosteroid and Long-Acting Beta$_2$-Agonist for Controller and Reliever Therapy vs. a Higher Inhaled Corticosteroid Dose and Long-Acting Beta$_2$-Agonist for Controller Therapy and Short-Acting Beta$_2$-Agonist for Quick-Relief Therapy in Individuals Ages 12 Years and Older with Persistent Asthma

Outcomes	Number of participants (number of studies)	Certainty of evidence (GRADE)	Relative effect (95% CI)	Anticipated absolute effects (95% CI)	
				Risk with ICS-LABA controller and SABA quick-relief therapy (higher ICS dose) and/or N	Risk difference or mean difference with ICS-LABA controller and reliever therapy
EXACERBATIONS (*CRITICAL* OUTCOME)					
Need for systemic corticosteroids[a] Follow-up: 24 weeks	2,304 (1 RCT)[10]	Moderate[b]	RR: 0.82 (0.62 to 1.07)		**No difference**
Composite outcome of need for systemic corticosteroid treatment, hospitalization, or ED visit[c] Follow-up: 24 weeks	6,742 (2 RCTs)[9,10]	High	RR: 0.75 (0.59 to 0.96)	394/3,371 (11.7%)	**Favors intervention** 296/3371 (8.8%), 29 fewer per 1,000 (from 48 fewer to 5 fewer)
ASTHMA CONTROL (*CRITICAL* OUTCOME)					
ACQ-5 (MID for ages ≥18 years: 0.5 points) Follow-up: 24 weeks	6,559 (2 RCTs)[9,10]	High	–	**No difference** MD: 0.02 lower (from 0.07 lower to 0.04 higher)[10] MD 0.02 lower (from 0.08 lower to 0.05 higher)[9] MD 0.03 higher (from 0.03 lower to 0.09 higher)[9]	

Outcomes	Number of participants (number of studies)	Certainty of evidence (GRADE)	Relative effect (95% CI)	Anticipated absolute effects (95% CI)	
				Risk with ICS-LABA controller and SABA quick-relief therapy (higher ICS dose) and/or N	Risk difference or mean difference with ICS-LABA controller and reliever therapy
QUALITY OF LIFE (*CRITICAL* OUTCOME)					
AQLQ score of 1 for severe to 7 for no impairment (MID: 0.5 points) Follow-up: 24 weeks	4,270 (1 RCT)[9]	High	–	**No difference** - MD: 0.01 higher (from 0.07 lower to 0.08 higher) MD 0.02 lower (from 0.09 lower to 0.06 higher)[9]	

Abbreviations: ACQ-5, Asthma Control Questionnaire 5; AQLQ, Asthma Quality of Life Questionnaire; CI, confidence interval; ED, emergency department; GRADE, Grading of Recommendations Assessment, Development, and Evaluation; ICS, inhaled corticosteroid; LABA, long-acting beta$_2$-agonist; MD, mean difference; MID, minimally important difference; RCT, randomized controlled trial; RR, relative risk.

Footnotes, including GRADE explanations:

a. The Expert Panel could not locate raw data for this result from one RCT.[10]

b. The Expert Panel rated this outcome down for imprecision because the confidence interval overlapped with the null effect and indicated both benefit and harm.

c. Data from two RCTs[9,10] were also available on another composite exacerbation outcome (exacerbations requiring hospitalizations or ED visits); these data are not shown in this table. The results show a pooled RR of 0.76 (95% CI, 0.46 to 1.25). One three-arm RCT[9] also provided data on the mild exacerbation outcome. The two separate comparisons had an RR of 0.97 in the ICS-LABA controller and reliever therapy group (95% CI, 0.91 to 1.04) and 1.04 in the ICS-LABA controller and SABA quick-relief group (95% CI, 0.97 to 1.11).

Harms:

Two studies had data on growth results in children ages 4–11 years; both favored single maintenance and reliever therapy (SMART) over daily higher-dose inhaled corticosteroid therapy. Bisgaard et al. (2006) found an adjusted mean difference in growth of 1.0 cm between individuals with asthma receiving budesonide-formoterol (SMART) vs. those receiving a fixed higher dose of budesonide and as-needed SABA (95% CI, 0.3 to 1.7; p = 0.0054).[2] O'Byrne et al. (2005) also found a mean difference in growth of 1.0 cm between children treated with budesonide-formoterol (SMART) vs. those treated with a fixed higher dose of budesonide plus as-needed SABA (95% CI, 0.3 to 1.7; *P* = 0.0054).[3] Neither study found differences in growth between patients treated with SMART and those treated with daily budesonide-formoterol and as-needed SABA for reliever therapy. The 11 studies with data on serious adverse events found no differences in this outcome between groups.[3,4,7,8,10-16]

New evidence

Yes.[17]

References

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Evidence to Decision Table XX — Long-Acting Muscarinic Antagonists vs. Long-Acting Beta$_2$-Agonists as Add-on to Inhaled Corticosteroid Controller Therapy in Individuals Ages 12 Years and Older with Uncontrolled Persistent Asthma

Background

LAMAs are part of a pharmacologic class of long-acting bronchodilators. *Expert Panel Report 3: Guidelines for the Diagnosis and Management of Asthma* did not address the role of LAMAs in asthma treatment. Since that report's publication in 2007, several trials have investigated the use of LAMAs as a controller therapy for asthma. Only studies in individuals with asthma who were older than 12 years were included in the AHRQ systematic review report and in this table. In February 2017, the FDA approved tiotropium bromide for the long-term, once-daily maintenance (controller) treatment of asthma in individuals ages 6 years and older.[1] Most of the studies described in this table used tiotropium bromide as the intervention.

Desirable effects: How substantial are the desirable anticipated effects?

JUDGMENT	RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS
Trivial	The Expert Panel was unable to find any data or information on desirable effects for any of the *critical* or *important* outcomes.	

Undesirable effects: How substantial are the undesirable anticipated effects?

JUDGMENT	RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS
Small	The efficacy trials suggested similar rates of undesirable effects in participants assigned to ICS+LABA or to ICS+LAMA. However, the findings in the BELT study indicate a 2.6 higher rate of asthma-related hospitalizations in the ICS+LAMA group than in the ICS+LABA group.[2] Also, the number of hospitalizations (3.6 per 100 persons) in the ICS+LAMA group in BELT was higher than that in the FDA-required safety studies in the ICS+LABA group (0.6 per 100 persons). Two asthma-related deaths occurred in the BELT study (2 of 1,070 participants). Both deaths occurred in the ICS+LAMA group (2/532, 0.38%). Also, the proportion of asthma-related deaths in the ICS+LAMA group was 38 times higher than that in the ICS+LABA group in the FDA-required safety studies.	

Certainty of evidence: What is the overall certainty of the evidence of effects?		
JUDGMENT	**RESEARCH EVIDENCE**	**ADDITIONAL CONSIDERATIONS**
Moderate		

Values: Is there important uncertainty about or variability in how much people value the main outcomes?		
JUDGMENT	**RESEARCH EVIDENCE**	**ADDITIONAL CONSIDERATIONS**
Probably no important uncertainty or variability	There is probably no uncertainty or variability in how much individuals with asthma value the main outcomes.	

Balance of effects: Does the balance between desirable and undesirable effects favor the intervention or the comparison?		
JUDGMENT	**RESEARCH EVIDENCE**	**ADDITIONAL CONSIDERATIONS**
Probably favors the comparison	The Expert Panel was unable to find any data or information to suggest desirable effects on the *critical* or *important* outcomes. However, a small concern is raised by the undesirable effects in Blacks treated with ICS+LAMA therapy in comparison with Blacks treated with ICS+LABA therapy.	

Acceptability: Is the intervention acceptable to key stakeholders?		
JUDGMENT	**RESEARCH EVIDENCE**	**ADDITIONAL CONSIDERATIONS**
No	Given the absence of desirable effects and the small concern about undesirable effects, the intervention is likely not acceptable.	

Feasibility: Is the intervention feasible to implement?		
JUDGMENT	**RESEARCH EVIDENCE**	**ADDITIONAL CONSIDERATIONS**
Yes	Although the intervention is technically feasible, the Expert Panel was unable to find any data or information to show that its desirable effects outweigh its undesirable effects.	

Equity: What would the impact be on health equity?		
JUDGMENT	**RESEARCH EVIDENCE**	**ADDITIONAL CONSIDERATIONS**
Probably reduced	A concern is that the intervention could have a negative impact on health equity because of the potential for undesirable effects in Blacks treated with ICS+LAMA therapy.	

Abbreviations: AHRQ, Agency for Healthcare Research and Quality; BELT, Blacks and Exacerbations on LABA v. Tiotropium; FDA, U.S. Food and Drug Administration; ICS, inhaled corticosteroid; LABA, long-acting beta$_2$-agonist; LAMA, long-acting muscarinic antagonist.

Evidence Summary: Long-Acting Muscarinic Antagonist vs. Long-Acting Beta$_2$-Agonist as Add-on to Inhaled Corticosteroid Controller Therapy in Individuals Ages 12 Years and Older with Uncontrolled Persistent Asthma

Outcomes	Number of participants (number of studies)	Certainty of evidence (GRADE)	Relative effect (95% CI)	Anticipated absolute effects (95% CI)	
				Risk with LABA as add-on to ICS controller therapy and/or N	Risk difference or mean differences with LAMA as add-on to ICS controller therapy
EXACERBATIONS[a] (*CRITICAL* OUTCOME)					
Need for treatment with systemic corticosteroids Follow-up: 2.1 to 24 weeks	2,574 (5 RCTs)[3-6]	Moderate[b]	RR: 0.87 (0.53 to 1.42)	5.4% (56/1041)	4.9% (75/1,533) 7 fewer per 1,000 (from 25 fewer to 23 more)
ASTHMA CONTROL[c] (*CRITICAL* OUTCOME)					
Use of responder definition in ACQ-7.[d] ≥0.5 decrease in score Follow-up: 24 weeks	1,577 (2 RCTs)[4]	High	RR: 1.03 (0.96 to 1.11)	**No difference**	
ACQ-7 score of 0 for no impairment to 7 for maximum impairment (MID: 0.5 points) Follow-up: 24 weeks	1,577 (2 RCTs)[4]	High		**No difference** MD: 0.02 points higher (from 0.04 lower to 0.08 higher)	

Outcomes	Number of participants (number of studies)	Certainty of evidence (GRADE)	Relative effect (95% CI)	Anticipated absolute effects (95% CI)	
				Risk with LABA as add-on to ICS controller therapy and/or N	Risk difference or mean differences with LAMA as add-on to ICS controller therapy
QUALITY OF LIFE (*CRITICAL* OUTCOME)					
AQLQ score of 1 for no impairment to 7 for maximum (MID in ages ≥18 years: 0.5 points) Follow-up: 14 to 24 weeks	1,982 (4 RCTs)[3,4,6]	High		**No difference** MD: 0.06 points higher (from 0.15 lower to 0.03 higher)	
IMPORTANT OUTCOMES					
Rescue medication use (MID: −0.81 puffs/day) Follow-up: 2.1 to 78 weeks	2,450 (6 RCTs)[2-5,7,8]	Low[e]		**No difference** MD: 0.61 more puffs (from 0.12 lower to 1.35 higher)	
All-cause mortality Follow-up: 2.1 to 78 weeks	3,572 (4 RCTs)[2,4,5]	Low[f]	OR: 7.50 (0.78 to 72.27)	0.0% (0/1,135)	0.2% (3/1,835)

Abbreviations: ACQ-7, seven-item Asthma Control Questionnaire; AQLQ, Asthma Quality of Life Questionnaire; CI, confidence interval; GRADE, Grading of Recommendations Assessment, Development, and Evaluation; ICS, inhaled corticosteroid; LABA, long-acting beta$_2$-agonist; LAMA, long-acting muscarinic antagonist; MD, mean difference; MID, minimally important difference; OR, odds ratio; RCT, randomized controlled trial; RR, relative risk.

Footnotes, including GRADE explanations:

a. In one RCT with a crossover design[6] (N = 210) and low certainty of evidence due to imprecision, the RR for exacerbations requiring oral corticosteroids or increases in ICS dose or other asthma medication (14-week follow-up) was 0.60 (95% CI, 0.15 to 2.42).

b. The Expert Panel rated this outcome down for inconsistency.

c. One RCT (N = 1,577) provided additional data on asthma worsening, defined as progressive worsening of asthma symptoms, compared with day-to-day symptoms or a decrease in morning peak expiratory flow of at least 30% for 2 or more days. The RR for asthma worsening was 1.00 (95% CI, 0.84 to 1.20).[4]

d. In one RCT (N = 126) that also provided data on six-item Asthma Control Questionnaire scores, the mean difference was 0.03 (95% CI, 0.0 to 0.6).[6]

e. The Expert Panel rated this outcome down twice for imprecision because the confidence interval was very wide and the boundaries of the confidence interval were consistent with both benefit and harm.

f. The Expert Panel rated this outcome down twice for imprecision because the confidence interval was very wide.

Harms:
Five efficacy trials compared inhaled corticosteroid and long-acting muscarinic antagonist (ICS+LAMA) therapy with ICS and long-acting beta$_2$-agonist (ICS+LABA) therapy. Three placebo-controlled trials, including two crossover trials, found no differences in rates of serious adverse events (SAEs).[1]

The authors of two articles[7,8] reported findings in participants ages 18 to 60 years after 6 months of treatment in a four-arm, parallel-group, unmasked, active-comparator trial. The studies included 72 participants treated with ICS+LAMA, 68 with ICS+LABA (formoterol), 81 treated with montelukast and ICS, and 76 with doxofylline and ICS. The results were limited to 297 of 362 participants who completed the 6-month study. The results showed no SAEs (defined by the authors as hospitalizations for asthma), but some adverse events (AEs) did occur. The number of AEs was similar in each of the four groups: 10 in the ICS+LAMA group (dry mouth in five individuals), six in the ICS+LABA group (oral candidiasis in two individuals), seven in the montelukast and ICS group (headache in four individuals), and eight in the doxofylline and ICS group (nausea, palpitations, and insomnia in two individuals each). It was unclear whether some individuals with asthma experienced more than one AE, and the study reports did not document the number of unique individuals who had one or more AEs. The 2015 report appears to provide follow-up findings to those reported in 2014. The earlier report presented data on a more limited set of outcomes after 123 participants had completed a 90-day follow-up period. The 2014 report did not present findings about SAEs or AEs.

The authors of a report on the Blacks and Exacerbations on LABA v. Tiotropium (BELT) study included Blacks ages 18 to 75 years in the United States who were followed for up to 18 months (depending on the date of enrollment) in a two-arm, parallel-group, unmasked, active-comparator trial (N = 532 treated with ICS+LAMA and N = 538 treated with ICS+LABA).[2] This was a real-world effectiveness trial, not a blinded study. Members of each group received two inhalers, one for each medicine. Participants in the ICS+LAMA group were asked to take two inhalers (ICS and LAMA) in the morning and one (ICS) at night. Participants in the ICS+LABA group took two inhalers twice per day. The proportion of individuals with asthma who had all-cause AEs or SAEs did not differ significantly between the two groups (ICS+LAMA, 3%; ICS+LABA 2%, *P* = 0.16). However, 19 asthma-related hospitalizations occurred in the ICS+LAMA group; the rate was 10 in the ICS+LABA group (*P* = 0.09). The adjusted rates of asthma-related hospitalizations were higher in the ICS+LAMA group (risk ratio, 2.6; 95% CI 1.14 to 5.91; *P* = 0.02). Three all-cause deaths occurred in the ICS+LAMA group (one attributed to lack of adherence to asthma study medicines, one attributed to an asthma attack in a participant who was adherent to asthma study medicines, and one attributed to heart failure) and no deaths in the ICS+LABA group (*P* = 0.12). Two (2/532, 0.38%) asthma-related deaths occurred in the ICS+LAMA group and none (0/538, 0.0%) in the ICS+LABA group (*P* = 0.25).

According to a 2019 Centers for Disease Control and Prevention report, Blacks have a twofold higher risk of asthma-related deaths than Whites; the rates are 2.2 asthma-related deaths per 100,000 population (0.002%) in non-Hispanic Blacks and 1.0 per 100,000 population in non-Hispanic Whites (0.001%).[9] Additional data on rates of asthma-related deaths come from three 6-month, randomized, double-blind, active-controlled, clinical safety trials[10] required by the U.S. Food and Drug Administration (FDA) in 35,089 individuals ages 12 years and older with asthma. Two asthma-related deaths (2/36,010, 0.006%) occurred: both deaths occurred in the ICS+LABA group (2/18,004 [0.01%]). The proportion of asthma-related deaths in the ICS+LAMA group in the BELT study was 38 times higher than that in the ICS+LABA group in the FDA-required safety studies. No asthma-related deaths [0/17,552, 0.0%] occurred in the ICS-only group. In these three studies, 115 asthma-related hospitalizations occurred in the ICS+LABA group and 105 asthma-related hospitalizations occurred in the ICS-only group. The number of hospitalizations in the ICS+LAMA group in the BELT study (3.6 per 100 persons) was higher than that in the FDA-required safety studies in the ICS+LABA group (0.6 per 100 persons).

The frequency of SAEs in the efficacy trials did not differ by treatment. However, the Expert Panel was particularly concerned about the findings in the real-world effectiveness trial, which could have more closely represented what might occur in clinical practice. In conclusion, AEs were more common with LAMA than with LABA therapy, but this difference was not statistically significant.

New evidence
No.

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Evidence to Decision Table XXI — Long-Acting Muscarinic Antagonists vs. Placebo as Add-on to Inhaled Corticosteroid Controller Therapy in Individuals Ages 12 Years and Older with Uncontrolled Persistent Asthma

Background

LAMAs are a pharmacologic class of long-acting bronchodilators. *Expert Panel Report 3: Guidelines for the Diagnosis and Management of Asthma* did not address the role of LAMAs in asthma treatment. Since that report's publication in 2007, several trials have investigated the use of LAMA as a controller therapy for asthma. In February 2017, the FDA approved tiotropium bromide for the long-term, once-daily maintenance (controller) treatment of asthma in individuals ages 6 years and older.[1]

Desirable effects: How substantial are the desirable anticipated effects?

JUDGMENT	RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS
Small	LAMA as an add-on to ICS controller therapy provides a small benefit in reducing exacerbations in comparison with placebo (24 fewer per 1,000; 95% CI; 38 fewer to 6 fewer per 1,000). The evidence shows no difference in effects on asthma control or quality of life. The Expert Panel concluded that the desirable effects of add-on LAMA therapy are small.	The judgment about the size of the desirable effects is subjective because of the absence of established definitions of a "trivial," "small," or "moderate" reduction in numbers of exacerbations and "MIDs" for many of the outcome measures.

Undesirable effects: How substantial are the undesirable anticipated effects?

JUDGMENT	RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS
Trivial	The evidence shows no differences in rates of serious adverse events among 3,065 participants enrolled in 6 efficacy trials that compared ICS+LAMA with ICS+placebo. Also, no deaths occurred in these 6 efficacy trials. Importantly, the efficacy trials excluded participants with a history of glaucoma or urinary retention. The Expert Panel concluded that the undesirable effects were trivial.	The Expert Panel concluded that the harms identified in the BELT study[2] were not applicable to this key question because BELT compared ICS+LAMA to ICS+LABA therapy, and this study compared ICS+LAMA with ICS+placebo.

Certainty of evidence: What is the overall certainty of the evidence of effects?

JUDGMENT	RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS
Moderate		

Values: Is there important uncertainty about or variability in how much people value the main outcomes?		
JUDGMENT	**RESEARCH EVIDENCE**	**ADDITIONAL CONSIDERATIONS**
Probably no important uncertainty or variability	There is probably no uncertainty or variability in how much people value the main outcomes. However, because the addition of a LAMA reduces rates of exacerbations but does not affect asthma control or quality of life, if an individual with asthma places more value on asthma control or quality of life than on reductions in exacerbations, the addition of a LAMA is not likely to achieve the individual's goal.	MIDs for asthma control and asthma quality of life measures are available in the published literature, but no standard exists for assessing the MID for exacerbations.

Balance of effects: Does the balance between desirable and undesirable effects favor the intervention or the comparison?		
JUDGMENT	**RESEARCH EVIDENCE**	**ADDITIONAL CONSIDERATIONS**
Probably favors the intervention	The difference in desirable outcomes was small, and there was a trivial concern about undesirable effects related to the addition of LAMA to ICS vs. the addition of a placebo to ICS. The small effect on desirable outcomes was driven entirely by a reduction in the number of exacerbations, and the intervention had no effect on asthma control or asthma quality of life.	

Acceptability: Is the intervention acceptable to key stakeholders?		
JUDGMENT	**RESEARCH EVIDENCE**	**ADDITIONAL CONSIDERATIONS**
Probably yes	The limited evidence of benefit could reduce the intervention's acceptability to individuals with asthma and other stakeholders who place less value on reductions in exacerbations than on asthma control or quality of life.	

Feasibility: Is the intervention feasible to implement?		
JUDGMENT	**RESEARCH EVIDENCE**	**ADDITIONAL CONSIDERATIONS**
Yes	The Expert Panel was unable to find any data or information suggesting that implementation is not feasible.	

Equity: What would the impact be on health equity?		
JUDGMENT	**RESEARCH EVIDENCE**	**ADDITIONAL CONSIDERATIONS**
Probably no impact	The Expert Panel was unable to find any data or information indicating that this intervention could affect health equity.	

Abbreviations: CI, confidence interval; FDA, U.S. Food and Drug Administration; ICS, inhaled corticosteroid; LABA, long-acting beta$_2$-agonist; LAMA, long-acting muscarinic antagonist; MID, minimally important difference.

Evidence Summary: Long-Acting Muscarinic Antagonist vs. Placebo as Add-on to Inhaled Corticosteroid Controller Therapy in Individuals Ages 12 Years and Older with Uncontrolled Persistent Asthma

Outcomes	Number of participants (number of studies)	Certainty of evidence (GRADE)	Relative effect (95% CI)	Anticipated absolute effects (95% CI)	
				Risk with placebo and/or N	Risk difference or mean difference for LAMA as Add-on to ICS controller therapy
EXACERBATIONS (*CRITICAL* OUTCOME)					
Need for treatment with systemic corticosteroids Follow-up: 2 weeks (15 days) to 48 weeks	3,036 (5 RCTs)[3-7]	Moderate[a]	RR: 0.67 (0.48 to 0.92)	7.4% (74/1,006)	**Favors intervention** 4.2% (86/2,030), 24 fewer per 1,000 (from 38 fewer to 6 fewer)
Need for ED visits, outpatient visits, or hospitalizations				Not reported[b]	
ASTHMA CONTROL (*CRITICAL* OUTCOME)					
Defined by respondents on ACQ-7[d] (MID: decrease in score by ≥0.5 points) Follow-up: 2 weeks (15 days) to 48 weeks	2,680 (5 RCTs)[4-8]	Moderate[c]	RR: 1.08 (0.96 to 1.21)	61.0% (527/864)	**No difference** 67.0% (1,217/1,816), 49 more per 1,000 (from 24 fewer to 128 more)
QUALITY OF LIFE (*CRITICAL* OUTCOME)					
AQLQ scores of 1 for severe to 7 for no impairment (MID for ages ≥18 years: 0.5 points) Follow-up: 24 weeks	1,461 (2 RCTs)[3,5]	High	-	**No difference** Trial 1 (Kerstjens et al. 2015), MD: 0.07 (from 0.06 lower to 0.20 higher) Trial 2 (Kerstjens et al. 2015), MD: 0.11 (from 0.03 lower to 0.25 higher)	

Outcomes	Number of participants (number of studies)	Certainty of evidence (GRADE)	Relative effect (95% CI)	Anticipated absolute effects (95% CI)	
				Risk with placebo and/or N	Risk difference or mean difference for LAMA as Add-on to ICS controller therapy
IMPORTANT OUTCOMES					
Rescue medication use, measured by difference in number of mean puffs in 24 hours Follow-up: 2 to 52 weeks	3,104 (6 RCTs)[4-8]	High[d]	–	N = 2,110	**No difference** N = 994, MD: 0.08 puffs/day fewer (from 0.23 fewer to 0.07 more)
Mortality Follow-up: 2 to 52 weeks	3,065 (6 RCTs)[4-8]	High[e]		0% (no deaths)	0% (no deaths)

Abbreviations: ACQ-7, 7-item Asthma Control Questionnaire; AQLQ, Asthma Quality of Life Questionnaire; CI, confidence interval; ED, emergency department; GRADE, Grading of Recommendations Assessment, Development, and Evaluation; ICS, inhaled corticosteroid; LAMA, long-acting muscarinic antagonist; MD, mean difference; MID, minimally important difference; RCT, randomized controlled trial.

Footnotes, including GRADE explanations:

a. The Expert Panel rated this outcome down for imprecision because the confidence intervals crossed the threshold for clinical significance and would have resulted in different conclusions based on the extremes of the confidence interval, which included both potential benefit and harm.

b. Additional data on the asthma worsening outcome were also available from 3 RCTs (total N = 2,420).[4,5,7] This outcome was defined as a progressive increase in asthma symptoms compared with day-to-day symptoms or a decrease in morning peak expiratory flow of at least 30% for 2 or more days. In the intervention arm, 22.2% (356/1,604) of individuals had worsening asthma symptoms, as did 27.3% (223/816) of individuals in the placebo arm. The pooled risk ratio was 0.81 (0.68 to 0.97). In absolute terms, this result translated to 52 fewer asthma worsening outcomes per 1,000 (95% CI, from 87 fewer to 8 fewer).

c. The Agency for Healthcare Research and Quality (AHRQ) systematic review report rated this outcome down for inconsistency.

d. The Expert Panel rated this outcome up from the rating in the AHRQ systematic review report (which rated the evidence for this outcome as moderate).

e. Certainty of evidence was not assessed for this outcome in the AHRQ systematic review report.

Harms:
The six studies[4-8] in 3,065 participants that compared the efficacy of long-acting muscarinic antagonists with placebo added to inhaled corticosteroid therapy found a low rate of serious adverse events and no differences in serious adverse event rates between groups. No deaths occurred in these six trials.

New evidence
No.

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Evidence to Decision Table XXII — Long-Acting Muscarinic Antagonists vs. Montelukast as Add-on to Inhaled Corticosteroid Controller Therapy in Individuals Ages 12 Years and Older with Uncontrolled Persistent Asthma

Background

LAMAs are a pharmacologic class of long-acting bronchodilators. *Expert Panel Report 3: Guidelines for the Diagnosis and Management of Asthma* did not address the role of LAMAs in asthma treatment. Since that report's publication in 2007, several trials have investigated the use of LAMA as a controller therapy for asthma. In February 2017, the FDA approved tiotropium bromide for the long-term, once-daily maintenance (controller) treatment of asthma in individuals ages 6 years and older.[1] Most of the studies described in this table used tiotropium bromide as the intervention.

Desirable effects: How substantial are the desirable anticipated effects?

JUDGMENT	RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS
Trivial	The Expert Panel was unable to find any data or information on *critical* outcomes (exacerbations, asthma control, or asthma quality of life) or information on desirable effects on the outcome of rescue medication use.	

Undesirable effects: How substantial are the undesirable anticipated effects?

JUDGMENT	RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS
Trivial	The rate of undesirable effects was similar in one study that compared the addition of montelukast with LAMA as add-on therapy to ICS.	The Expert Panel concluded that the harms identified in the BELT study[2] were not applicable to this key question because BELT compared ICS+LAMA with ICS+LABA. In addition, this study compared ICS+LAMA with ICS+montelukast.

Certainty of evidence: What is the overall certainty of the evidence of effects?

JUDGMENT	RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS
Very low		

Values: Is there important uncertainty about or variability in how much people value the main outcomes?		
JUDGMENT	**RESEARCH EVIDENCE**	**ADDITIONAL CONSIDERATIONS**
Probably no important uncertainty or variability	The Expert Panel concluded that there was probably no important uncertainty or variability in how much people value the main outcomes.	

Balance of effects: Does the balance between desirable and undesirable effects favor the intervention or the comparison?		
JUDGMENT	**RESEARCH EVIDENCE**	**ADDITIONAL CONSIDERATIONS**
Does not favor either the intervention or the comparator	The Expert Panel was unable to find any data or information to suggest beneficial effects on critical outcomes, and the effect on 1 noncritical outcome was inconclusive.	

Acceptability: Is the intervention acceptable to key stakeholders?		
JUDGMENT	**RESEARCH EVIDENCE**	**ADDITIONAL CONSIDERATIONS**
Don't know	Evidence was insufficient to allow a determination of the intervention's acceptability.	

Feasibility: Is the intervention feasible to implement?		
JUDGMENT	**RESEARCH EVIDENCE**	**ADDITIONAL CONSIDERATIONS**
Probably yes	Although the intervention is technically feasible, the Expert Panel was unable to find any data or information showing that it is effective.	

Equity: What would the impact be on health equity?		
JUDGMENT	**RESEARCH EVIDENCE**	**ADDITIONAL CONSIDERATIONS**
Probably no impact	The intervention is unlikely to have an impact on health equity.	

Abbreviations: BELT, Blacks and Exacerbations on LABA vs. Tiotropium; CI, confidence interval; FDA, U.S. Food and Drug Administration; ICS, inhaled corticosteroid; LABA, long-acting beta$_2$-agonist; LAMA, long-acting muscarinic antagonist.

Evidence Summary: Long-Acting Muscarinic Antagonist vs. Montelukast as Add-on to Inhaled Corticosteroid Controller Therapy in Individuals Ages 12 Years and Older with Uncontrolled Persistent Asthma

Outcomes	Number of participants (number of studies)	Certainty of evidence (GRADE)	Relative effect (95% CI)	Anticipated absolute effects (95% CI)	
				Risk with montelukast as add-on to ICS controller therapy and/or N	Risk difference or mean difference for LAMA as an add-on to ICS controller therapy
EXACERBATIONS (*CRITICAL* OUTCOME)					
Need for treatment with systemic corticosteroids	Not reported				
Need for oral corticosteroids or other asthma medication	Not reported				
ASTHMA CONTROL (*CRITICAL* OUTCOME)					
AQLQ scores of 1 for severe to 7 for no impairment (MID for ages ≥18 years: 0.5 points)	Not reported				
QUALITY OF LIFE (*CRITICAL* OUTCOME)					
AQLQ scores of 1 for severe to 7 for no impairment (MID for ages ≥18 years: 0.5 points)	Not reported				

Outcomes	Number of participants (number of studies)	Certainty of evidence (GRADE)	Relative effect (95% CI)	Anticipated absolute effects (95% CI)	
				Risk with montelukast as add-on to ICS controller therapy and/or N	Risk difference or mean difference for LAMA as an add-on to ICS controller therapy
RESCUE MEDICATION USE (IMPORTANT OUTCOME)					
Number of puffs/day MID: –0.81puffs/day Follow-up: 12.9 to 25.7 weeks	153 (1 RCT)[3,4]	Low[a,b]		MD: 1.19 puffs/day more (from 0.88 more to 1.50 more per day)[4,c]	

Abbreviations: ACQ-7, 7-item Asthma Control Questionnaire; AQLQ, Asthma Quality of Life Questionnaire; CI, confidence interval; GRADE, Grading of Recommendations Assessment, Development, and Evaluation; ICS, inhaled corticosteroids; LAMA, long-acting muscarinic antagonist; MD, mean difference; MID, minimally important difference.

Footnotes, including GRADE explanations:

a. The Expert Panel rated this outcome down for risk of bias because of a lack of blinding of individuals with asthma, study personnel, and outcome assessors.

b. The Expert Panel rated this outcome down for inconsistency because the confidence intervals were consistent with both benefit and harm.

c. Two papers[3,4] reported findings in participants ages 18–60 years after 6 months of treatment in a four-arm, parallel-group, unmasked, active-comparator trial. The studies included 72 participants treated with ICS+LAMA, 68 with ICS+LABA (formoterol), 81 treated with montelukast and ICS, and 76 with doxofylline and ICS. These results were limited to 297 of 362 participants who completed the 6-month study. The 2015 report appears to describe an extension of the findings reported in 2014. The 2014 report presented a more limited set of outcomes after 123 participants had completed a 90-day follow-up period. No data were reported for any of the *critical* patient-*important* outcomes.

Harms:
With respect to harms, the rate of undesirable effects appeared to be similar in the one study that directly compared montelukast vs. LAMA as add-on therapy to ICS. Specifically, no author-defined serious adverse events occurred in the study (hospitalizations for asthma), but the numbers of adverse events (AEs) overall were similar across the four groups: 10 in the ICS+LAMA group (dry mouth was the most common AE and occurred in 5 individuals with asthma), 6 in the ICS+LABA group (oral candidiasis was the most common AE and occurred in 2 individuals with asthma), 7 in the montelukast+ICS group (headache was the most common AE and occurred in 4 individuals with asthma), and 8 in the doxofylline+ICS group (nausea, palpitations, and insomnia were the most common AEs and occurred in 2 individuals with asthma for each). Whether some individuals with asthma reported more than one AE was unclear, and the number of unique individuals with asthma who had one or more AEs in this study was not reported.

New evidence
No.

References

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Evidence to Decision Table XXIII — Long-Acting Muscarinic Antagonist as Add-on to Inhaled Corticosteroid Controller Therapy vs. Doubled Dose of Inhaled Corticosteroid in Individuals Ages 12 Years and Older with Uncontrolled Persistent Asthma

Background

LAMAs are a pharmacologic class of long-acting bronchodilators. *Expert Panel Report 3: Guidelines for the Diagnosis and Management of Asthma* did not address the role of LAMAs in asthma treatment. Since that report's publication in 2007, several trials have investigated the use of LAMA as a controller therapy for asthma. In February 2017, the FDA approved tiotropium bromide for the long-term, once-daily maintenance (controller) treatment of asthma in individuals ages 6 years and older.[1] Most of the studies described in this table used tiotropium bromide as the intervention.

Desirable effects: How substantial are the desirable anticipated effects?

JUDGMENT	RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS
Trivial	In a study comparing a doubled ICS dose with the addition of LAMA to ICS, differences in rates of exacerbations, asthma control, or quality of life were not statistically significant.	An earlier study also suggested that doubling the ICS dose does not reduce rates of asthma exacerbations,[2] so the lack of difference in desirable effects between ICS+LAMA and double-dose ICS treatment indicates a lack of benefit for ICS+LAMA (rather than a similar level of desirable effect).

Undesirable effects: How substantial are the undesirable anticipated effects?

JUDGMENT	RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS
Trivial	A small study that compared the addition of a LAMA to an ICS with double-dose ICS treatment found no difference in the number of SAEs, and no deaths occurred. The study excluded individuals with significant illnesses or lung diseases, other than asthma.	The Expert Panel concluded that the harms identified in the BELT study[3] were not applicable to this key question because BELT compared ICS+LAMA to ICS+LABA, and this study compared ICS+LAMA with a double dose of ICS.

Certainty of evidence: What is the overall certainty of the evidence of effects?

JUDGMENT	RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS
Low		

Values: Is there important uncertainty about or variability in how much people value the main outcomes?		
JUDGMENT	**RESEARCH EVIDENCE**	**ADDITIONAL CONSIDERATIONS**
Probably no important uncertainty or variability	There is probably no important uncertainty or variability in how much people value the main outcomes, and informed individuals with asthma would make similar decisions.	The asthma control and asthma quality of life measures have established MIDs, but the measure of exacerbations does not. Although percentages of control days increased and symptom scores improved, these measures were not validated, and the magnitude of the difference was of uncertain significance.

Balance of effects: Does the balance between desirable and undesirable effects favor the intervention or the comparison?		
JUDGMENT	**RESEARCH EVIDENCE**	**ADDITIONAL CONSIDERATIONS**
Does not favor either the intervention or the comparison	There is no difference in desirable or undesirable effects related to the addition of LAMA to ICS therapy and double-dose ICS therapy.	

Acceptability: Is the intervention acceptable to key stakeholders?		
JUDGMENT	**RESEARCH EVIDENCE**	**ADDITIONAL CONSIDERATIONS**
No	The Expert Panel was unable to find any evidence suggesting that the benefits outweigh the harms and costs.	

Feasibility: Is the intervention feasible to implement?		
JUDGMENT	**RESEARCH EVIDENCE**	**ADDITIONAL CONSIDERATIONS**
Yes	The Expert Panel was unable to find any evidence that this intervention is effective, but it is simple to implement.	

Equity: What would the impact be on health equity?		
JUDGMENT	**RESEARCH EVIDENCE**	**ADDITIONAL CONSIDERATIONS**
Probably no impact	The Expert Panel was unable to find any evidence showing that the intervention would affect health equity.	

Abbreviations: BELT, Blacks and Exacerbations on LABA vs. Tiotropium; CI, confidence interval; FDA, U.S. Food and Drug Administration; ICS, inhaled corticosteroid; LABA, long-acting beta$_2$-agonist; LAMA, long-acting muscarinic antagonist; MID, minimally important difference; SAE, serious adverse effect.

Evidence Summary: Long-Acting Muscarinic Antagonist as Add-on to Inhaled Corticosteroid Controller Therapy vs. Doubled Dose of Inhaled Corticosteroid in Individuals Ages 12 Years and Older with Uncontrolled Persistent Asthma

Outcomes	Number of participants (number of studies)	Certainty of evidence (GRADE)	Relative effect (95% CI)	Anticipated absolute effects (95% CI)	
				Risk with doubled ICS dose and/or N	Risk difference or mean difference for LAMA as add-on to ICS controller therapy
EXACERBATIONS (*CRITICAL* OUTCOME)					
Need for treatment with systemic corticosteroids Follow-up: 14 weeks	210 (1 crossover RCT)[4]	Low[a]	RR: 0.48 (0.12 to 1.84)	**No difference** Unclear from AHRQ report; absolute effects could not be calculated.	
Need for oral corticosteroids or increase in ICS or other asthma medication dose Follow-up: 14 weeks	210 (1 crossover RCT)[4]	Low[a]	RR: 0.32 (0.09 to 1.13)	**No difference** Unclear from AHRQ report; absolute effects could not be calculated.	
ASTHMA CONTROL (*CRITICAL* OUTCOME)					
ACT-6 score of 0 for no impairment to 7 for maximum impairment (MID: 0.5 points) Follow-up: 2 weeks (15 days) to 48 weeks	127 (1 crossover RCT)[4]	Moderate[b]		**No difference** MD: 0.15 lower (from 0.45 lower to 0.15 higher)	
QUALITY OF LIFE (*CRITICAL* OUTCOME)					
AQLQ scores of 1 for severe to 7 for no impairment (MID for ages ≥18 years: 0.5 points) Follow-up: 24 weeks	122 (1 crossover RCT)[4]	Moderate[b]		**No difference** MD 0.04 higher (from 0.32 lower to 0.4 higher)	

Abbreviations: ACT-6, six-item Asthma Control Test; AHRQ, Agency for Healthcare Research and Quality; AQLQ, Asthma Quality of Life Questionnaire; CI, confidence interval; GRADE, Grading of Recommendations Assessment, Development, and Evaluation; ICS, inhaled corticosteroid; LAMA, long-acting muscarinic antagonist; MD, mean difference; MID, minimally important difference; RCT, randomized controlled trial; RR, relative risk.

Footnotes, including GRADE explanations:

a. The Expert Panel rated this outcome down twice for imprecision because the confidence interval was very wide.

b. The Expert Panel rated this outcome down because of concerns about the crossover trial's design and because of attrition bias—data were only available on asthma control and quality of life for a subset of participants.

Harms:

In one crossover randomized controlled trial in which participants were assigned to add-on long-acting muscarinic antagonist therapy, a doubled ICS dose, or a long-acting $beta_2$-agonist, the incidence of serious adverse events (SAEs) was similar in each group.[4] Three individuals with asthma treated with ICS+LAMA had an SAE (two hospitalizations for pneumonia and one for a fractured radius), and four participants treated with a doubled ICS dose had an SAE (one hospitalization for spinal stenosis surgery, one for atypical chest pain, one for transient global amnesia, and one for pneumonia). No deaths occurred in either group.

New evidence

No.

References

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Evidence to Decision Table XXIV — Long-Acting Muscarinic Antagonist as Add-On to Inhaled Corticosteroid with Long-Acting $Beta_2$-Agonist vs. Inhaled Corticosteroid with Long-Acting $Beta_2$-Agonist Alone in Individuals Ages 12 Years and Older with Uncontrolled Persistent Asthma

Background

LAMAs are a pharmacologic class of long-acting bronchodilators. *Expert Panel Report 3: Guidelines for the Diagnosis and Management of Asthma* did not address the role of LAMAs in asthma treatment. Since that report's publication in 2007, several trials have investigated the use of LAMA as a controller therapy for asthma. In February 2017, the FDA approved tiotropium bromide for the long-term, once-daily maintenance (controller) treatment of asthma in individuals ages 6 years and older.[1] Most of the studies described in this table used tiotropium bromide as the intervention.

Desirable effects: How substantial are the desirable anticipated effects?

JUDGMENT	RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS
Small	The effects on asthma control and quality of life were small, and the intervention had no effect on exacerbations.	

Undesirable effects: How substantial are the undesirable anticipated effects?

JUDGMENT	RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS
Trivial	Studies suggest that the rates of undesirable effects are similar for ICS+ LABA+LAMA compared to ICS+LABA.	

Certainty of evidence: What is the overall certainty of the evidence of effects?

JUDGMENT	RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS
Moderate		

Values: Is there important uncertainty about or variability in how much people value the main outcomes?

JUDGMENT	RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS
Probably no important uncertainty or variability	There is probably no uncertainty or variability in how much individuals with asthma value the main outcomes.	

Balance of effects: Does the balance between desirable and undesirable effects favor the intervention or the comparison?		
JUDGMENT	**RESEARCH EVIDENCE**	**ADDITIONAL CONSIDERATIONS**
Probably favors the intervention	The desirable effects on the *critical* outcomes (quality of life and asthma control) were small, and the undesirable effects were trivial.	The serious adverse events in the Wechsler et al. (2015) study[2] in Black individuals with asthma assigned to ICS+LAMA vs. ICS+LABA may not be relevant to individuals with asthma treated with LAMA added to ICS+LABA. The Expert Panel therefore did not consider the harms in this study when it addressed this key question.

Acceptability: Is the intervention acceptable to key stakeholders?		
JUDGMENT	**RESEARCH EVIDENCE**	**ADDITIONAL CONSIDERATIONS**
Probably yes	The intervention is probably acceptable; however, the limited evidence of benefit may reduce the intervention's acceptability to individuals with asthma and other stakeholders who place less value on asthma control and quality of life than on reductions in exacerbations.	

Feasibility: Is the intervention feasible to implement?		
JUDGMENT	**RESEARCH EVIDENCE**	**ADDITIONAL CONSIDERATIONS**
Yes	The Expert Panel was unable to find any data or information suggesting that implementation is not feasible.	

Equity: What would the impact be on health equity?		
JUDGMENT	**RESEARCH EVIDENCE**	**ADDITIONAL CONSIDERATIONS**
Probably increased	The desirable effects outweigh the undesirable effects. Because asthma disproportionately affects disadvantaged populations, the Expert Panel believes that this intervention is likely to increase health equity.	

Abbreviations: FDA, U.S. Food and Drug Administration; ICS, inhaled corticosteroid; LABA, long-acting beta$_2$-agonist; LAMA, long-acting muscarinic antagonist.

Evidence Summary: Inhaled Corticosteroid and Long-Acting Beta$_2$-Agonist Controller Therapy vs. the Same Inhaled Corticosteroid Dose and Short-Acting Beta$_2$-Agonist for Quick-Relief Therapy in Individuals Ages 12 Years and Older with Persistent Asthma

Outcomes	Number of participants (number of studies)	Certainty of evidence (GRADE)	Relative effect (95% CI)	Anticipated absolute effects (95% CI)	
				Risk with ICS-LABA and/or N	Risk difference or mean difference for LAMA as add-on to ICS-LABA
EXACERBATIONS (*CRITICAL* OUTCOME)					
Need for treatment with systemic corticosteroids Follow-up: 12 to 48 weeks	1,299 (3 RCTs)[3,4]	Moderate[a]	RR: 0.84 (0.57 to 1.22)	25.5% 150/589	**No difference** 17.6% (125/710) 41 fewer per 1,000 (from 110 fewer to 56 more)
Need for hospitalization	907 (2 RCTs)[4]	Moderate[a]		**No difference**[b] Kerstjens et al. (2012) Trials 1 and 2, 2012 RR in Trials 1 and 2: 0.80 (0.42 to 1.52)	
ASTHMA CONTROL[c] (*CRITICAL* OUTCOME)					
As defined by responders on ACQ-7 Follow-up: 12 to 48 weeks	1,299 (3 RCTs)[3,4]	Moderate[d]		**Favors intervention** Hamelmann et al. 2017 RR: 1.01 (0.89 to 1.14)[3] Kerstjens et al. (2012) Trial 1 & 2, 2012 RR for Trials 1 and 2: 1.28 (1.13 to 1.46)[4]	
ACQ-7 scores of 1 for severe to 7 for no impairment (MID for ages ≥18 years: 0.5 points) Follow-up: 12 to 48 weeks	1,301 (3 RCTs)[3,4]	Moderate	–	**No difference** MD: 0.07 lower (from 0.31 lower to 0.17 higher)	

Outcomes	Number of participants (number of studies)	Certainty of evidence (GRADE)	Relative effect (95% CI)	Anticipated absolute effects (95% CI)	
				Risk with ICS-LABA and/ or N	Risk difference or mean difference for LAMA as add-on to ICS-LABA
QUALITY OF LIFE (*CRITICAL* OUTCOME)					
AQLQ score Follow-up: 48 weeks	907 (2 RCTs)[4]	High		**No difference** Kerstjens et al. (2012) Trial 1, 2012, MD: 0.04 (from 0.13 lower to 0.20 higher) Kerstjens et al. (2012) Trial 2, 2012, MD: 0.14 (from 0.03 lower to 0.31 higher)	
AQLQ score (for responders; MID: 0.5 points) Follow-up: 48 weeks	907 (2 RCTs)[4]	High	RR: 1.62 (1.34 to 1.96)	**Favors intervention**	
IMPORTANT OUTCOMES					
Rescue medication use, difference in mean puffs in 24 hours Follow-up: 12 to 48 weeks	1,292 (3 RCTs)[3,4]	Moderate[d]	–	**No difference** MD: 0.10 less (from 0.37 less to 0.18 more)	
Mortality Follow-up: 12 to 48 weeks	1,299 (3 RCTs)[3,4]	Very low[a,e]	–	0% (no deaths)	**No difference** 0% (no deaths)

Abbreviations: ACQ-7, seven-item Asthma Control Questionnaire; AQLQ, Asthma Quality of Life Questionnaire; CI, confidence interval; GRADE, Grading of Recommendations Assessment, Development, and Evaluation; ICS, inhaled corticosteroid; LABA, long-acting beta$_2$-agonist; LAMA, long-acting muscarinic antagonist; MD, mean difference; MID, minimally important difference; RCT, randomized controlled trial; RR, relative risk.

Footnotes, including GRADE explanations:

a. The Expert Panel rated this outcome down for imprecision because the confidence interval included both benefit and harm.

b. Raw data from two RCTs for this outcome show 16 hospitalizations (16/453) in the add-on LAMA arm and 20 hospitalizations (20/454) in the comparator arm (RR: 0.80; 95% CI, 0.42 to 1.52).

c. Additional data on the asthma worsening outcome are available from 3 RCTs (total N = 1,299).[3,4] This outcome was defined as a progressive increase in severity of asthma symptoms in comparison with day-to-day symptoms or a decrease in morning peak expiratory flow of at least 30% for 2 or more days. The pooled RR was 0.78 (95% CI, 0.72 to 0.86).

d. The Expert Panel rated this outcome down for the inconsistencies among the three studies (one study had a narrow confidence interval suggesting no benefit, whereas the findings from the other two trials suggested a benefit).

e. Certainty of evidence was not assessed for this outcome in the Agency for Healthcare Research and Quality systematic review report. The trials were underpowered to detect differences in mortality rates.

Harms:

Only one placebo-controlled clinical trial[3] examined add-on long-acting muscarinic antagonists (LAMAs) in adolescents. This study included 398 participants ages 12–17 years and compared the addition of tiotropium 5 mcg/day or 2.5 mcg/day via a Respimat device to an inhaled corticosteroid (with or without other controllers) vs. placebo added to ICS treatment (with or without other controllers) for 12 weeks. In this study, by Hamelmann,[3] serious adverse events (SAEs) were uncommon, and their rates were similar in the three groups: 3 (2.2%) with tiotropium 5 mcg/day, 2 (1.6%) with tiotropium 2.5 mcg/day, and 2 (1.4%) with placebo.

A single report included two placebo-controlled trials (N = 459 in Trial 1, N = 453 in Trial 2) in adults.[4] These trials randomized adults treated with ICS+LABA to add-on LAMA (tiotropium via Respimat 5 mcg/day) or placebo for 48 weeks. The incidence of author-defined SAEs was higher in these adult studies[4] than in the study by Hamelmann et al. (2017)[3] in adolescents, but the incidence of SAEs was similar in the tiotropium and placebo groups in the two adult studies. In Trial 1 in adults, SAEs occurred in 18/237 (7.6%) participants in the tiotropium Respimat group and in 15/222 (6.8%) participants in the placebo group. The rates in Trial 2 were 19/219 participants (8.7%) in the tiotropium Respimat group and 25/234 (10.7%) in the placebo group in the second trial (Kerstjens et al. 2012).[4]

New evidence

No.

References

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Evidence to Decision Table XXV — Long-Acting Muscarinic Antagonist as Add-on to Inhaled Corticosteroid with Long-Acting Beta$_2$-Agonist vs. Double Dose of Inhaled Corticosteroid-Long-Acting Beta$_2$-Agonist in Individuals Ages 12 Years and Older with Uncontrolled Persistent Asthma

Background

LAMAs are a pharmacologic class of long-acting bronchodilators. *Expert Panel Report 3: Guidelines for the Diagnosis and Management of Asthma* did not address the role of LAMAs in asthma treatment. Since that report's publication in 2007, several trials have investigated the use of LAMA as a controller therapy for asthma. In February 2017, the FDA approved tiotropium bromide for the long-term, once-daily maintenance (controller) treatment of asthma in individuals ages 6 years and older.[1] Most of the studies described in this table used tiotropium bromide as the intervention.

Desirable effects: How substantial are the desirable anticipated effects?

JUDGMENT	RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS
Don't know	One nonblinded study (N = 94) (Wang et al. 2015) compared ICS+ LABA+tiotropium (N = 33), LABA+double-dose ICS (N = 30), and ICS+LABA+montelukast (N = 31). The Expert Panel reviewed results from the first 2 arms (ICS+LABA+tiotropium and LABA+double-dose ICS) for this question. Data on *critical* outcomes were insufficient to assess desirable effects. The certainty of evidence was very low for 1 *critical* outcome, asthma control. No data were reported on the other two *critical* outcomes, asthma quality of life and exacerbations.	

Undesirable effects: How substantial are the undesirable anticipated effects?

JUDGMENT	RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS
Don't know	Two participants developed pneumonia in the doubled ICS dose group, but the other 2 groups had no other adverse events. These data were insufficient to address undesirable effects.	

Certainty of evidence: What is the overall certainty of the evidence of effects?

JUDGMENT	RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS
Very low		

Values: Is there important uncertainty about or variability in how much people value the main outcomes?		
JUDGMENT	**RESEARCH EVIDENCE**	**ADDITIONAL CONSIDERATIONS**
Probably no important uncertainty or variability	There is no uncertainty or variability in how much individuals with asthma value the main outcomes.	

Balance of effects: Does the balance between desirable and undesirable effects favor the intervention or the comparison?		
JUDGMENT	**RESEARCH EVIDENCE**	**ADDITIONAL CONSIDERATIONS**
Don't know	The data are insufficient to make a judgment about the balance of desirable and undesirable effects.	

Acceptability: Is the intervention acceptable to key stakeholders?		
JUDGMENT	**RESEARCH EVIDENCE**	**ADDITIONAL CONSIDERATIONS**
Probably no	The data are insufficient to make a judgment about acceptability.	

Feasibility: Is the intervention feasible to implement?		
JUDGMENT	**RESEARCH EVIDENCE**	**ADDITIONAL CONSIDERATIONS**
Probably yes	Implementing inhaler therapy is feasible.	

Equity: What would the impact be on health equity?		
JUDGMENT	**RESEARCH EVIDENCE**	**ADDITIONAL CONSIDERATIONS**
Don't know	The data are insufficient to make a judgment about the potential impact on health equity.	

Abbreviations: FDA, U.S. Food and Drug Administration; ICS, inhaled corticosteroid; LABA, long-acting beta$_2$-agonist; LAMA, long-acting muscarinic antagonist.

Evidence Summary: Long-Acting Muscarinic Antagonist as Add-on to Inhaled Corticosteroid with Long-Acting Beta$_2$-Agonist vs. Double Dose of Inhaled Corticosteroid with Long-Acting Beta$_2$-Agonist in Individuals Ages 12 Years and Older with Uncontrolled Persistent Asthma

Outcomes	Number of participants (number of studies)	Certainty of evidence (GRADE)	Relative effect (95% CI)	Anticipated absolute effects (95% CI)	
				Risk with ICS-LABA and/or N	Risk difference or mean difference for LAMA as add-on to double ICS dose plus LABA
EXACERBATIONS (*CRITICAL* OUTCOME)					
Need for treatment with systemic corticosteroids				Not reported	
Exacerbations requiring hospitalization				Not reported	
ASTHMA CONTROL (*CRITICAL* OUTCOME)					
Based on ACT composite scores Follow-up: 12 weeks	63 (1 RCT)[2]	Very low[a,b]		**No difference** MD: 0.61 less (from 4.82 less to 3.6 more) improvement in the add-on LAMA group	
QUALITY OF LIFE (*CRITICAL* OUTCOME)					
Not reported					

Abbreviations: ACT, Asthma Control Test; CI, confidence interval; GRADE, Grading of Recommendations Assessment, Development, and Evaluation; ICS, inhaled corticosteroid; LABA, long-acting beta$_2$-agonist; LAMA, long-acting muscarinic antagonist; MD, mean difference; RCT, randomized controlled trial.

Footnotes, including GRADE explanations:

a. The Expert Panel rated this outcome down twice for imprecision because the confidence interval was very wide and the boundaries of the confidence intervals showed both benefit and harm.

b. The Expert Panel rated this outcome down for risk of bias because this study was not blinded and the result for patient-reported outcomes was susceptible to bias.

Harms:

In the randomized controlled trial reported by Wang 2015 et al. (2015),[2] 94 adults treated with inhaled corticosteroid (ICS)+long-acting beta$_2$-agonist (LABA) therapy were randomized to one of the following groups:

1. Add-on inhaled long-acting muscarinic antagonist (tiotropium bromide 18 mcg/day)
2. Add-on montelukast (10 mg/day)
3. Doubled ICS dose (fluticasone 500 mcg twice per day) and continued LABA therapy

The authors reported a higher risk of pneumonia in Group 3 (2/30 patients, 6.7%) than in the other groups, but they did not specify the number of patients with pneumonia in the other two groups. Furthermore, no patients stopped taking their treatment because of adverse events, but the authors provided no additional information.

New evidence

No.

References

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Evidence to Decision Table XXVI — Subcutaneous Immunotherapy vs. No Subcutaneous Immunotherapy, Placebo, or Standard or Usual Care in Individuals with Allergic Asthma

Background

Immunotherapy for allergic asthma is the therapeutic administration of exogenous aeroallergens to which a person has demonstrable sensitization. Immunotherapy can be administered subcutaneously (SCIT) or sublingually (SLIT) in both children of certain ages and adults with a history of worsening symptoms on exposure to the allergens to which they are sensitized according to test results. Thus, in addition to a clinical history confirming sensitization before consideration of SCIT or SLIT, the characteristics of the individual's allergic sensitization must be demonstrated by immediate hypersensitivity skin testing or in vitro antigen-specific IgE antibody testing. This evaluation needs to be performed by trained health care professionals who are skilled in both testing and interpretation techniques. The need for evaluation by a specialist may limit access to SCIT or SLIT, depending on local availability of testing and the individual's health insurance coverage. The verification code for this document is 914260

SCIT should be administered under direct clinical supervision because of the potential risk that the individual could develop local (injection site) and systemic reactions. Systemic reactions can include a range of anaphylactic symptoms involving the skin (urticaria), respiratory tract (rhinitis and asthma), gastrointestinal tract (nausea, diarrhea, and vomiting), and the cardiovascular system (hypotension and arrhythmias). Although rare, death after injections has been reported. Those preparing and administering SCIT, from the build-up to the maintenance phase, must have direct clinical supervision. Equipment and personnel should be available to treat serious anaphylactic reactions. intervention.

Desirable effects: How substantial are the desirable anticipated effects?

JUDGMENT	RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS
Small	For exacerbations requiring corticosteroids, the data favor SCIT. For exacerbations leading to ED visits and hospitalizations, the data show no differences. No study reports provided data on asthma symptom control using the ACT, ACQ, or P-ACT scores. Therefore, the Expert Panel evaluated studies that assessed asthma symptoms (as surrogate outcomes) using nonvalidated outcome measures. In 26/44 studies (59%), significant differences favored active treatment compared with placebo injections. Data on quality of life also favored SCIT.	Immunotherapy for asthma can reduce the symptoms of comorbid conditions, such as allergic rhinitis and allergic conjunctivitis, as an additional desirable benefit.

Undesirable effects: How substantial are the undesirable anticipated effects?		
JUDGMENT	**RESEARCH EVIDENCE**	**ADDITIONAL CONSIDERATIONS**
Varies	Local reactions reported in RCTs were frequent and consisted of itching, pain, paresthesia, heat, erythema, and induration at the injection site in 6–33% of individuals and 7–11% of SCIT doses administered. Systemic allergic reactions occurred in 0–44% of individuals treated with SCIT and in up to 12% of injections administered. Reactions included pruritus, urticaria, atopic dermatitis and other forms of eczema, rhinitis, conjunctivitis, nasal congestion, nasal obstruction, cough, asthma, bronchospasm, wheezing, dyspnea, abdominal pain, diarrhea, and hypotension. Most systemic allergic reactions were mild. Only a small number were consistent with anaphylaxis and required treatment with injectable epinephrine. Bronchoconstriction occurred in 9% of individuals treated with SCIT. Rates of systemic allergic reactions consistent with anaphylaxis differed greatly. The RCTs were not powered to assess such effects. Poorly controlled asthma is a major risk factor for fatal allergic reactions from SCIT. None of the study reports provided data on SCIT administered in the home setting.	The estimated incidence of fatal and near-fatal anaphylactic reactions ranges from 1 in 20,000[1] to 1 in 200,000[2] injections. The incidence of fatal anaphylactic reactions ranges from 1 in every 2,000,000 to 9,000,000 injections (low level of confidence, imprecise evidence). Approximately 15% of serious systemic reactions occur after individuals leave the office following 30 minutes of observation.

Certainty of evidence: What is the overall certainty of the evidence of effects?		
JUDGMENT	**RESEARCH EVIDENCE**	**ADDITIONAL CONSIDERATIONS**
Low	The three *critical* outcomes are exacerbations, quality of life, and asthma control. Two RCTs provided data on exacerbations (requiring a hospitalization or ED visit), and 4 RCTs provided data for quality of life. The certainty of evidence was low for both of those outcomes. None of the studies used validated tools to measure asthma control. Therefore, the evaluation included studies with data collected using nonvalidated tools on asthma symptoms (as surrogate outcomes).	

Values: Is there important uncertainty about or variability in how much people value the main outcomes?		
JUDGMENT	**RESEARCH EVIDENCE**	**ADDITIONAL CONSIDERATIONS**
Important uncertainty or variability	Informed individuals with asthma may make different decisions about SCIT in light of the small benefits for critical outcomes, the variable adverse effects, and the treatment's burdensome nature for some. Individuals with asthma may weigh these outcomes differently. The only outcome for which data are available is patient satisfaction.[3,4] These findings target allergic rhinitis with or without concomitant asthma and include individuals with asthma treated with SCIT or SLIT.	

Balance of effects: Does the balance between desirable and undesirable effects favor the intervention or the comparison?		
JUDGMENT	**RESEARCH EVIDENCE**	**ADDITIONAL CONSIDERATIONS**
Probably favors the intervention	Low certainty of evidence supports the efficacy of SCIT at an acceptable risk level for three *critical* outcomes (exacerbations, asthma control, and quality of life). Symptoms were used as surrogate measures of asthma control. The variability, quantity, and nature of adverse outcomes decreased the Expert Panel's confidence in the intervention's superiority.	

Acceptability: Is the intervention acceptable to key stakeholders?		
JUDGMENT	**RESEARCH EVIDENCE**	**ADDITIONAL CONSIDERATIONS**
Varies	The acceptability of SCIT to clinicians will likely vary by the availability of appropriately trained clinical staff to administer injections, monitor safety, and provide appropriate therapy for adverse reactions. Acceptability to patients appears to be independent of disease severity.[3] Individuals with asthma in focus groups list cost, time, and pain as their top criteria for choosing a treatment. Lack of insurance or distance from an allergist will also affect acceptability of SCIT to individuals with asthma.	

Feasibility: Is the intervention feasible to implement?		
JUDGMENT	**RESEARCH EVIDENCE**	**ADDITIONAL CONSIDERATIONS**
Probably yes	The intervention is feasible in areas with access to an allergist.	

Equity: What would the impact be on health equity?		
JUDGMENT	**RESEARCH EVIDENCE**	**ADDITIONAL CONSIDERATIONS**
Probably reduced	SCIT's costs and variable access may contribute to health inequity for individuals who lack access to allergists because their health insurance policies do not cover SCIT or because of scarcity of allergists in their geographic regions.	

Abbreviations: ACQ, Asthma Control Questionnaire; ACT, Asthma Control Test; ED, emergency department; ICS, inhaled corticosteroid; IgE, immunoglobulin E; P-ACT, Pediatric-Asthma Control Test; RCT, randomized controlled trial; SCIT, subcutaneous immunotherapy; SLIT, sublingual immunotherapy.

Evidence Summary: Subcutaneous Immunotherapy vs. No Subcutaneous Immunotherapy, Placebo, or Standard or Usual Care in Individuals with Allergic Asthma

Outcomes	Number of participants (number of studies)	Certainty of evidence (GRADE)	Relative effect (95% CI)	Narrative summary of results
EXACERBATIONS (*CRITICAL* OUTCOME)				
ED visits and hospitalizations[a] Follow-up: 24 to 120 weeks	161 (2 RCTs)[5,6]	Low[b,c]	—	**No difference** Tsai et al. (2010),[6] in an RCT in children (mean age 9 years), compared SCIT with a control group and found no differences in numbers of ED visits or hospitalizations (MD: –0.19). Adkinson et al. (1997), in another RCT[5] in children (mean age 8 years), compared SCIT with placebo and also showed no differences in numbers of ED visits (MD: 0.03; 95% CI –0.08 to 0.15) or hospitalizations (MD: 0.01; 95% CI –0.24 to 0.27).
Requiring corticosteroids[d] Follow-up: 96 to 144 weeks	95 (2 RCTs)[7,8]	—	—	**Favors intervention** One RCT (Zielen et al. 2010)[8] in individuals with well-controlled asthma found low exacerbation rates in groups treated with either subcutaneous mite allergoid immunotherapy (SCIT) plus fluticasone propionate (FP) or FP therapy alone for 2 years, but the report did not provide data on comparisons between groups. Another RCT, (Pifferi et al. 2002)[7] did not provide data on asthma severity or control. The SCIT group had a statistically significant greater reduction in exacerbations (8 ± 1.8 to 1 ± 0.5 per year) than the control group (8.5 ± 1.7 to 4.25 ± 0.25 per year; *P* <0.01).
ASTHMA CONTROL (*CRITICAL* OUTCOME)				
Not reported				

Outcomes	Number of participants (number of studies)	Certainty of evidence (GRADE)	Relative effect (95% CI)	Narrative summary of results
QUALITY OF LIFE (*CRITICAL* OUTCOME)				
AQLQ scores of 1 for severe to 7 for no impairment (MID: 0.5 points) Follow-up: 32 to 54 weeks	194 (4 RCTs)[9-12]	Low[c,e]	—	**Favors intervention** Two studies found statistically significant improvements in quality-of-life scores (by 6 points and 4 points).[9,10] Two studies did not show improvements in quality of life.[11,12]
Asthma symptoms measured with nonvalidated tools[f]	1,914 (44 RCTs) [5,9,10,13-51]	Low[c,e]	—	**Favors intervention** 26/44 (59%) studies that used nonvalidated tools to measure reductions in symptoms (surrogate measures of asthma control) found significant improvements favoring the active treatment over placebo injections.
Reductions in use of quick-relief medications (mean number of puffs/week)[g] Follow-up: 52 weeks	31 (1 RCT)[40]	Low[h]	—	**Insufficient evidence** One small study found that the mean number of puffs of SABA per week decreased from 27 to 14 (MD: 13 fewer puffs) in the SCIT arm and from 52 to 46 in the control arm (MD: 6 fewer puffs). The MD for use of quick-relief medication between the two arms was 7 puffs/week.

Outcomes	Number of participants (number of studies)	Certainty of evidence (GRADE)	Relative effect (95% CI)	Narrative summary of results
IMPORTANT OUTCOMES				
Use of long-term control medication Follow-up: 32 to 144 weeks	404 (6 RCTs)[5,10,12,29,40,52]	Low[e,i]	—	**Favors intervention** Most studies found reductions in long-term medication use, defined as reductions in ICS use or ICS discontinuation. Results were as follows: Adults: • Statistically significant increase in number of weeks free from ICS use compared with placebo in adults ($P \leqslant 0.001$)[10] Children: • Higher rate of ICS discontinuation than with placebo (28% vs 0%; $P = 0.002$)[52] • Significant decrease in number of days of ICS use in the SCIT arm but no significant difference between arms in ages 5.4–14 years[5] Adults and children: • Olsen et al. (1997)[40] reported a significant reduction in ICS dose used in the SCIT arm (38%) and a nonsignificant change in the control arm. • Hui et al. (2014)[29] reported a significantly greater reduction in ICS dose used in the SCIT than in the control group. • Lozano et al. (2014)[12] reported a significant reduction in the need for any long-term control medication in the SCIT group (decrease from 17 to 8 of 21) but not in the control group (increase from 11 to 13 of 20).

Outcomes	Number of participants (number of studies)	Certainty of evidence (GRADE)	Relative effect (95% CI)	Narrative summary of results
IMPORTANT OUTCOMES				
Reductions in systemic corticosteroid use Follow-up: 120 to 144 weeks	150 (2 RCTs)[5,7]	Low[c,j]	—	**Favors intervention** Pifferi et al. (2002)[7] found a reduction in annual days of corticosteroid use (from 22 to 1 day per year; MD: –21) in the SCIT arm and a decrease from 25 to 12 days per year (MD: –13) in the control arm in a mixed-age population. Adkinson et al. (1997)[5] in children (average age 9 years), found no difference in corticosteroid use in the SCIT and control arms (–1.9 vs. –1.7 days in the previous 60 days).
Anaphylaxis[k] Follow-up: 7 to 104 weeks	245 (5 RCTs)[8,22,52-54]	Low[e,l]	—	6 cases, all in the SCIT group
Anaphylaxis Follow-up: Not reported	792 (3 observational studies, case series, and case reports)[55-57]	—	—	55 likely cases
Mortality Follow-up: Not reported	145 (1 case report, 1 case series)[58,59]	—	—	1 possible death

Abbreviations: AQLQ, Asthma Quality of Life Questionnaire; CI, confidence interval; ED, emergency department; FP, fluticasone propionate; GRADE, Grading of Recommendations Assessment, Development, and Evaluation; ICS, inhaled corticosteroids; MD, mean difference; RCT, randomized controlled trial; RR, relative risk; SABA, short-acting beta$_2$-agonist; SCIT, subcutaneous immunotherapy.

Footnotes, including GRADE explanations:

a. Two studies evaluated the outcome of number of clinic visits and office visits, but whether these were unscheduled visits or well visits is not clear. Study 1, which compared SCIT with placebo, found increased numbers of clinic visits (MD: 4.8). The second study compared SCIT with placebo and found no difference in numbers of office visits (MD: 0.03; 95% CI, −0.07 to 0.14).

b. The Agency for Healthcare Research and Quality (AHRQ) systematic review report rated this outcome down for risk of bias because one study had unclear sequence generation, allocation concealment, and blinding.

c. The AHRQ systematic review report rated this outcome down for imprecision.

d. The AHRQ systematic review did not rate the strength of evidence for exacerbations requiring corticosteroids. The Expert Panel reviewed the exacerbation data from appendix Table D7 in that report to help provide information on this critical outcome.

e. The AHRQ systematic review rated this outcome down for risk of bias, most commonly due to concerns regarding sequence generation, allocation concealment, and/or blinding in several studies.

f. The AHRQ systematic review report only evaluated the effect of immunotherapy on asthma control in studies that used a validated tool, including the Asthma Control Test, Asthma Control Questionnaire, and Patient Asthma Concerns Tool. No published studies used any of these tools to evaluate asthma control. The Expert Panel considered data from studies that used other means of evaluating symptoms (e.g., symptom diaries) as surrogate measures. In these studies, the comparator was placebo injection, and the studies used the same symptom measure for the intervention and placebo groups.[60-62]

g. Despite the low certainty of evidence, the Expert Panel reviewed the study, but it was not confident in the results from this one small study (N = 31) to adequately inform this outcome.

h. The Expert Panel rated this outcome down twice for imprecision due to small sample size (N = 31).

i. The Expert Panel rated this outcome down for inconsistency because although these studies had data on ICS use, the metrics (e.g., dose in micrograms, rates of discontinuation, or number of weeks free of use) they used varied. The approach to ICS dose adjustment also varied by study and did not appear to follow strict protocols. One study also compared SCIT to a variety of regimens (e.g., leukotriene receptor antagonists and long-acting $beta_2$-agonists) in addition to ICS treatment.

j. The Expert Panel rated this outcome down for inconsistency because the two studies had different results.

k. Among the five RCTs included in the AHRQ systematic review report, one RCT compared modified SCIT with unmodified SCIT.[54] One case of anaphylaxis occurred in this RCT.

l. The Expert Panel rated this outcome down for imprecision because of the small number of events but did not rate the outcome down for indirectness or inconsistency (a deviation from the evidence report).

Harms:

Rates of systemic allergic reactions in randomized controlled trials (RCTs) ranged from 0 to 44% of individuals with asthma (or 11.7% of total injections). Types of reactions (when reported) were pruritis, urticaria, atopic dermatitis and other forms of eczema, rhinitis, conjunctivitis, nasal congestion or obstruction, coughing, bronchospasm, wheezing, dyspnea, abdominal pain, diarrhea, and hypotension. In observational studies, rates ranged from 0.6% of individuals with asthma and 0.1% of injections to 23.9% of individuals with asthma. Reported systemic reactions consisted of urticaria, flushing, nasal congestion, nasal itching, wheezing, chest tightness, bronchospasm, vasculitis, and anaphylaxis. A full description is available on pages 23–25 of the AHRQ evidence report.

Rates of local reactions in RCTs ranged from 6.3 to 33.3% of individuals in the subcutaneous immunotherapy (SCIT) arm and 0 to 12.5% of individuals in the placebo arm. Local reactions consisted of itching, pain, paresthesia, heat, erythema, and induration at the injection site. Calculated risk differences ranged from −0.317 to 0.4 (a range of 32 additional cases of local reactions in the placebo group to 40 additional cases per 100 people treated with SCIT). In observational studies, rates ranged from 5.6 to 27.3% of individuals and 6.5 to 10.7% of SCIT doses administered. Local reactions consisted of swelling or urticarial plaques at the injection site. A full description is available on pages 22–23 of the AHRQ evidence report.

The only reported death that was potentially related with SCIT was in one case report of a 17-year-old girl with moderate persistent asthma. She had been treated with SCIT for 4 years but stopped the treatment because of a skin reaction. Twelve hours after starting a new regimen, she complained of abdominal pain, vomiting, and diarrhea without fever. She developed respiratory failure 2 days later and was admitted to an intensive care unit. The young woman had high creatine phosphokinase and troponin levels, leukopenia, thrombocytopenia, and bilateral interstitial markings on a chest radiograph. On the fourth day, she developed hypoxic coma, was intubated and placed on mechanical ventilation, and subsequently developed shock and acute renal impairment. On the fifth day, she developed multiorgan failure and died. The authors suggested that the cause was an immunological mechanism secondary to manipulation or the way the dose was escalated, and they considered the attribution of causality to SCIT to be probable. Using the World Health Organization criteria for assessing case reports, the Evidence-Based Practice Center that conducted the systematic review agreed that SCIT might have caused this death (causality) because the event was related to the intervention but not to the dose.

New evidence

Yes.[63,64]

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Evidence to Decision Table XXVII — Sublingual Immunotherapy vs. No Sublingual Immunotherapy, Placebo, or Standard or Usual Care in Individuals with Allergic Asthma

Background

Immunotherapy for allergic asthma is the therapeutic administration of exogenous aeroallergens to which a person has demonstrable sensitization. Immunotherapy can be administered subcutaneously (SCIT) or sublingually (SLIT) in both children of certain ages and adults with a history of worsening symptoms on exposure to the allergens to which they are sensitized according to test results. Thus, in addition to a clinical history confirming sensitization before consideration of SCIT or SLIT, the characteristics of the individual's allergic sensitization must be demonstrated by immediate hypersensitivity skin testing or in vitro antigen-specific IgE antibody testing. This evaluation needs to be performed by trained health care professionals who are skilled in both testing and test result interpretation. The need for evaluation by a specialist may limit access to SCIT or SLIT, depending on local availability of testing and the individual's health insurance coverage.

SLIT can be administered at home and consists of exposure to the allergen via an aqueous solution or tablet formulation placed under the tongue. SLIT therapy requires the first dose to be administered in the clinician's office followed by a 30-minute wait. If no problems develop, the individual may continue taking the medication at home, thereby eliminating the commute to the clinic and the clinic visit time that are required for SCIT. Patients should ideally have prescriptions for injectable epinephrine. Currently, only tablet formulations for ragweed, grass, and dust mites have FDA approval and are available to treat allergic rhinitis with and without conjunctivitis. No SLIT formulations, either tablet or liquid, are approved specifically for asthma treatment. The potentially less severe side effect profile of SLIT is an advantage, although local oral irritation and itching may impair adherence to this therapy.

Desirable effects: How substantial are the desirable anticipated effects?		
JUDGMENT	**RESEARCH EVIDENCE**	**ADDITIONAL CONSIDERATIONS**
Trivial	No studies provided data on asthma exacerbations leading to ED visits, clinic visits, or hospitalizations. However, studies do provide data on exacerbations (variously defined in the studies), and these data favor SLIT. For asthma control and quality of life, the studies show no difference with SLIT. Three studies provide information on exacerbations. ▪ In their study, Virchow et al. (2016) used SLIT tablets, and they reported data on time to first exacerbation. They did not report data on numbers of exacerbations. ▪ de Blay et al. (2014) used SLIT tablets (low overall risk of bias; N = 604) in their study, but did not provide raw data or rates. This report stated that the study did not find a statistically significant reduction in the number of asthma exacerbations. ▪ The Gomez et al. (2005) study, which used the aqueous form of SLIT (medium overall risk of bias, concerns about allocation concealment and blinding of outcome assessors; N = 60), found 71 exacerbations in 30 individuals in the SLIT group and 123 exacerbations in 30 individuals in the placebo group.	SLIT may reduce the symptoms of comorbid conditions (allergic rhinitis or allergic conjunctivitis).

Undesirable effects: How substantial are the undesirable anticipated effects?		
JUDGMENT	**RESEARCH EVIDENCE**	**ADDITIONAL CONSIDERATIONS**
Small	Local reactions were frequent—they occurred in up to 80% of individuals. However, reactions were also common in those treated with placebo. Systemic reactions were frequent, anaphylaxis rates could not be determined, and no deaths were reported.	–

Certainty of evidence: What is the overall certainty of the evidence of effects?		
JUDGMENT	**RESEARCH EVIDENCE**	**ADDITIONAL CONSIDERATIONS**
Moderate		–

Values: Is there important uncertainty about or variability in how much people value the main outcomes?		
JUDGMENT	**RESEARCH EVIDENCE**	**ADDITIONAL CONSIDERATIONS**
Important uncertainty or variability	Informed patients may make different decisions about SLIT. There is important uncertainty, given the heterogeneous group of studies that used tablet as well as liquid formulations and mono- vs. multiple-allergen therapy, the trivial benefits, the variable adverse effects, and the treatment that may be considered burdensome by some individuals. Therefore, individuals with asthma may weigh the outcomes differently.	Individuals with comorbid conditions (allergic rhinitis or allergic conjunctivitis) may place a higher value on the outcome. In addition, the adherence to the dosing schedule by the individuals has an effect on the main outcomes.

Balance of effects: Does the balance between desirable and undesirable effects favor the intervention or the comparison?		
JUDGMENT	**RESEARCH EVIDENCE**	**ADDITIONAL CONSIDERATIONS**
Does not favor either the intervention or the comparison	The desirable effects are trivial, and the undesirable effects are very small.	

Acceptability: Is the intervention acceptable to key stakeholders?		
JUDGMENT	**RESEARCH EVIDENCE**	**ADDITIONAL CONSIDERATIONS**
Probably yes	The intervention is probably acceptable to primary care providers and individuals with asthma. Whether it is acceptable to insurance companies is unknown.	

Feasibility: Is the intervention feasible to implement?		
JUDGMENT	**RESEARCH EVIDENCE**	**ADDITIONAL CONSIDERATIONS**
Varies	Primary care physicians would not prescribe SLIT because the liquid formulations do not have FDA approval. Individuals with asthma would need to visit an allergist to receive SLIT. Access to an allergist might be limited for individuals with asthma in rural areas.	

Equity: What would the impact be on health equity?		
JUDGMENT	**RESEARCH EVIDENCE**	**ADDITIONAL CONSIDERATIONS**
Probably reduced	The costs of and variable access to SLIT may contribute to health inequities for individuals with asthma.	

Abbreviations: ED, emergency department; FDA, U.S. Food and Drug Administration; RCT, randomized controlled trial; SCIT, subcutaneous immunotherapy; SLIT, sublingual immunotherapy.

Evidence Summary: Sublingual Immunotherapy vs. No Sublingual Immunotherapy or Placebo or Standard Care/Usual Care in Individuals with Allergic Asthma

Outcomes	Number of participants (number of studies)	Certainty of evidence (GRADE)	Relative effect (95% CI)	Narrative summary of results
EXACERBATIONS (*CRITICAL* OUTCOME)				
ED visits, clinic visits, and hospitalizations	No studies	—	—	Not reported
Varies across 3 studies	1,873 (3 RCTs)[1-3]	—	—	**Favors intervention** Virchow et al. (2016)[3] used SLIT tablets and provided data on time to first exacerbation but not numbers of exacerbations. Time to first moderate exacerbation favored the intervention, but time to first severe exacerbation did not. A second RCT report, by de Blay et al. (2014),[1] also used SLIT tablets, but the authors did not provide raw data or rates. They said only that the study did not show a statistically significant decrease in rates of asthma exacerbations. A third RCT led by Gomez et al. (2004)[2] that used aqueous SLIT found 71 exacerbations in 30 individuals in the SLIT group and 123 exacerbations in 30 individuals in the placebo group.

Outcomes	Number of participants (number of studies)	Certainty of evidence (GRADE)	Relative effect (95% CI)	Narrative summary of results
ASTHMA CONTROL (*CRITICAL* OUTCOME)				
ACQ (3 studies) and ACT (1 study) Follow-up: 52 to 156 weeks	1,193 (4 RCTs)[1,3-5]	Moderate[a]	—	**No difference** In the Virchow et al. (2016)[3] study, which administered SLIT tablets, a higher proportion of individuals in the SLIT arm had an ACQ score <0.75 (achievement of the MID could not be determined). In another RCT, led by de Blay et al. (2014),[1] that also administered SLIT tablets, the score in the SLIT arm decreased by 0.41 points, and this difference was consistent with the lack of a score change in the placebo arm (MID not met). A third RCT, led by Devillier et al. (2016)[4] found no statistically significant improvement with aqueous SLIT (no raw data provided). In an RCT led by Marogna et al. (2013)[5] in which participants took SLIT tablets for dust mite allergies or an active comparator (ICS or ICS-montelukast) for 3 years, the results showed significant differences in ACT scores between the SLIT and comparator groups (24 points with SLIT and 18 points with the comparator).
QUALITY OF LIFE (*CRITICAL* OUTCOME)				
AQLQ Follow-up: 52 weeks	1,120 (3 RCTs)[1,3,4]	High	—	**No difference** The 3 RCTs that compared SLIT with placebo did not find statistically significant improvements in quality of life.
IMPORTANT OUTCOMES				
Reduced systemic corticosteroid use Follow-up: 24 weeks	110 (1 RCT)[6]	Moderate[b]	—	**No difference** One study in children (24 weeks) found no difference in corticosteroid use (tablets/day) between the SLIT and comparator arms.

Outcomes	Number of participants (number of studies)	Certainty of evidence (GRADE)	Relative effect (95% CI)	Narrative summary of results
IMPORTANT OUTCOMES				
Reduced use of quick-relief medication (mean number of puffs/week) Follow up: 12 to 24 weeks	298 (5 RCTs)[2,5-8]	Moderate[c,d]	—	**Favors intervention** Two studies measured the number of SABA doses used during 3-month pollen seasons each year for 3 years or 5 years. In a 3-year study led by Marogna et al. (2009)[8] that used aqueous SLIT, the MD was 16.1 fewer SABA doses in the SLIT arm and 3.6 fewer doses in the montelukast arm. In a second, 3-year study led by Marogna et al. (2013)[5] that used SLIT tablets, the MD for SABA doses was 10.1 fewer doses with SLIT than the comparator arms: 0.7 fewer doses for placebo, 2.9 fewer doses for corticosteroids, and 4.5 fewer doses for corticosteroids plus montelukast. A third RCT by the same author[7] used aqueous SLIT and measured the number of doses of SABA used during 3-month pollen seasons each year for 5 years. The results showed an MD of 17.9 fewer doses in the SLIT group and 9.4 fewer doses in the control group, which was treated with inhaled budesonide. Niu et al. (2006)[6] studied aqueous SLIT in children and did not find a significant change in SABA use. Another aqueous SLIT study by Gomez et al. (2005)[2] found a 50% reduction in SABA doses in the treatment group and a 21% reduction in the placebo group.
Use of long-term control medication Follow up: 32 to 56 weeks	1,409 (4 RCTs)[1,4,6,9]	Moderate[e]	—	**Favors intervention** 4 RCTs found statistically significant reductions in ICS use with SLIT in comparison with controls.

Outcomes	Number of participants (number of studies)	Certainty of evidence (GRADE)	Relative effect (95% CI)	Narrative summary of results
IMPORTANT OUTCOMES				
Anaphylaxis	1,772 (6 RCTs)[1,3,9-12]	Low[f,g]	RR: 1.00 (95% CI, 0.06 to 15.96)	0 cases
Anaphylaxis	3 (3 case reports)[13-15]	—	—	2 certain cases[13,14] and 1 likely case;[15] 1 case required discontinuation of therapy, 1 individual received a modified dosing protocol, and the outcome for the last case is unclear.
Death	4,231 (3 RCTs)[3,4,16]	Low[f,g]	—	0 cases

Abbreviations: ACQ, Asthma Control Questionnaire; ACT, Asthma Control Test; AQLQ, Asthma Quality of Life Questionnaire; ED, emergency department; GRADE, Grading of Recommendations Assessment, Development, and Evaluation; ICS, inhaled corticosteroid; MD, mean difference; RCT, randomized controlled trial; RR, relative risk; SABA, short-acting beta$_2$-agonist; SLIT, sublingual immunotherapy.

Footnotes, including GRADE explanations:

a. The Expert Panel rated this outcome down for inconsistency and imprecision; only one of the four studies showed a clinically meaningful improvement.

b. The Agency for Healthcare Research and Quality (AHRQ) systematic review report rated this outcome down for risk of bias because of the small study in children that had a medium risk of bias.

c. The AHRQ evidence report rated this outcome down for risk of bias.

d. The Expert Panel noted that the results were inconsistent because of one study that found no reduction, but the panel did not rate this outcome down for inconsistency.

e. The AHRQ evidence report rated this outcome down for risk of bias.

f. The AHRQ evidence report rated this outcome down for medium risk of bias.

g. The AHRQ evidence report rated this outcome down for imprecision because of the lack of anaphylaxis events or deaths.

Harms:
No adverse events were reported.

New evidence
No.

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Evidence to Decision Table XXVIII — Bronchial Thermoplasty and Standard Care vs. Standard Care (with or without a Sham Procedure) for Adults with Asthma

Background

BT has FDA approval for the treatment of adults with severe persistent asthma. BT procedures are similar in several countries and in settings similar to those in most bronchoscopy centers. The standard care provided during the studies was a continuation of maintenance treatments (e.g., ICS with or without oral corticosteroids or LABA) at study entry. Individuals with asthma in the AIR study received prednisone 50 mg on the day of and the day after each BT procedure, followed by maintenance therapy for 2 months, and then LABA withdrawal for ≥2 weeks. If symptoms emerged, the LABA treatment was resumed, and additional attempts were made to withdraw this medication at 6 months and 12 months.[1] In the RISA study, individuals with asthma in both groups received prednisone 50 mg per day for 5 days starting 3 days before each BT procedure (or after a comparable clinic visit for the control group). The corticosteroid dose was stable for the first 22 weeks, and attempts were then made to reduce the oral corticosteroid and ICS doses gradually over the remaining 30 weeks.[2] The AIR 2 study report did not describe a protocol for changing maintenance medications during the follow-up period.[3]

Desirable effects: How substantial are the desirable anticipated effects?

JUDGMENT	RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS
Small	The desirable anticipated effects are small for BT in comparison with standard of care with or without a sham procedure. The durability of the beneficial effects is not known because of a lack of long-term follow-up beyond 5 years.	

Undesirable effects: How substantial are the undesirable anticipated effects?

JUDGMENT	RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS
Moderate	The undesirable effects are moderate. Significant adverse effects occur in the short term. Long-term consequences are largely unknown. The adverse effects are variable, but some case studies have documented what could be new-onset bronchiectasis and vascular pseudoaneurysm.	During the treatment period, more severe exacerbations occurred in the BT plus standard care arm than in the sham plus standard care arm. Undesirable effects during the 3-year follow-up period were similar in the BT and standard care arms in RISA (N = 32). For this study, 5-year follow-up data were only reported for the BT group.

Certainty of evidence: What is the overall certainty of the evidence of effects?		
JUDGMENT	**RESEARCH EVIDENCE**	**ADDITIONAL CONSIDERATIONS**
Low		

Values: Is there important uncertainty about or variability in how much people value the main outcomes?		
JUDGMENT	**RESEARCH EVIDENCE**	**ADDITIONAL CONSIDERATIONS**
Important uncertainty or variability	Individuals with asthma may make different decisions in light of the harms (short-term worsening of symptoms and unknown long-term adverse effects), burden, cost, and small benefits (improvement in quality of life, reduction in number of exacerbations).	Long-term adverse effects and which individuals with asthma may benefit the most from the therapy are unclear.

Balance of effects: Does the balance between desirable and undesirable effects favor the intervention or the comparison?		
JUDGMENT	**RESEARCH EVIDENCE**	**ADDITIONAL CONSIDERATIONS**
Probably favors the intervention	In two RCTs with low certainty of evidence, BT reduced the number of exacerbations leading to ED visits and exacerbations requiring oral or parenteral corticosteroid treatment, or doubled ICS doses. Two RCTs with low certainty of evidence found that BT improves quality of life in comparison with standard of care or sham BT. One RCT with low certainty of evidence showed that BT improves asthma control in comparison with standard of care. Two RCTs with low certainty of evidence found that BT reduces rescue medication use in comparison with standard of care or sham BT.	The balance of effects favors BT only in individuals with severe recalcitrant asthma that does not respond to other treatments. BT has not been tested in children. Subgroups that might benefit from BT have not been identified.

Acceptability: Is the intervention acceptable to key stakeholders?		
JUDGMENT	**RESEARCH EVIDENCE**	**ADDITIONAL CONSIDERATIONS**
Varies	Health care systems would need to establish centers that have the technology and highly trained personnel, all of which would incur a significant cost.	

Feasibility: Is the intervention feasible to implement?		
JUDGMENT	**RESEARCH EVIDENCE**	**ADDITIONAL CONSIDERATIONS**
Probably yes	Individuals with asthma who are potential candidates for this procedure should be referred to specialty centers that provide BT and have the needed expertise. Logistical and geographic hurdles may exist even if the procedure's costs are covered by health insurers.	

Equity: What would the impact be on health equity?		
JUDGMENT	**RESEARCH EVIDENCE**	**ADDITIONAL CONSIDERATIONS**
Probably reduced	Equity is likely to be affected because health care disparities are likely to limit access to the expensive technologies required to provide BT. Individuals with asthma who do not have health care insurance are less likely to undergo the intervention.	

Abbreviations: AIR, Asthma Intervention Research; BT, bronchial thermoplasty; ED, emergency department; FDA, U.S. Food and Drug Administration; ICS, inhaled corticosteroid; LABA, long-acting beta$_2$-agonist; RISA, Research in Severe Asthma.

Evidence Summary: Bronchial Thermoplasty and Standard Care vs. Sham Procedure and Standard Care for Adults with Severe Asthma

Outcomes	Number of participants (number of studies)	Certainty of evidence (GRADE)	Relative effect (95% CI)	Anticipated absolute effects (95% CI)	
				Risk with sham procedure and standard care and/or N	Risk difference or mean difference for BT vs. standard care
EXACERBATIONS					
Need for systemic corticosteroids or doubling of ICS dose (number of participants and number of exacerbations per participant year)[a] Follow-up: 52 weeks	288 (1 RCT)[3]	Low[b,c]	RR: 0.66 (0.47 to 0.93)	N = 98 Rate: 0.70 (0.12)	**Favors intervention** MD: 0.22 lower (might not be clinically meaningful) Credible interval: from 0.031 lower to 0.520 higher
Need for ED visit (exacerbations per participant per year) Follow-up: 52 weeks	288 (1 RCT)[3]	Low[b,d]	—	N = 98 Rate: 0.43	**Favors intervention** MD: 0.36 lower Credible interval: from 0.111 lower to 0.832 higher
Need for hospitalization (number of participants)[a] Follow-up: 52 weeks	288 (1 RCT)[3]	Low[b,e]	RR: 0.64 (0.18 to 2.35)	4/98 (4.1%)	**No difference** 15 fewer per 1,000 (from 33 fewer to 55 more)
ASTHMA CONTROL					
ACQ (MID for ages ≥18 years: 0.5) Follow-up: 52 weeks	288 (1 RCT)[3]	Low[b,c]	—	N = 98 Mean change from baseline: −0.77 (1.08)	**No difference** MD: 0.05 lower (from 0.30 lower to 0.20 higher)

Outcomes	Number of participants (number of studies)	Certainty of evidence (GRADE)	Relative effect (95% CI)	Anticipated absolute effects (95% CI)	
				Risk with sham procedure and standard care and/or N	Risk difference or mean difference for BT vs. standard care
QUALITY OF LIFE					
AQLQ scores of 1 for severe to 7 for no impairment (MID: 0.5; number of responders and continuous score)[f] Follow-up: 52 weeks	288 (1 RCT)[3]	Very low[b,c,g]	RR: 1.23 (1.04 to 1.45)	63/98 responders (64.3%) Mean change from baseline: 1.16 (1.23)	**No difference** 148 more per 1,000 (from 26 more to 289 more) MD: 0.19 points higher (from 0.10 lower to 0.48 higher)
OTHER OUTCOMES					
Rescue medication use: number of puffs/week (MID for ages ≥18 years: −5.67 puffs/week)[h] Follow-up: 52 weeks	288 (1 RCT)[3]	Low[b,c]	—	N = 98 Mean change from baseline: −4.3	**No difference** MD: 1.7 fewer puffs/week (from 5.56 lower to 2.16 higher)

Abbreviations: ACQ, Asthma Control Questionnaire; AQLQ, Asthma Quality of Life Questionnaire; BT, bronchial thermoplasty; CI, confidence interval; ED, emergency department; GRADE, Grading of Recommendations Assessment, Development, and Evaluation; ICS, inhaled corticosteroid; MD, mean difference; MID, minimally important difference; RCT, randomized controlled trial; RR, relative risk.

Footnotes, including GRADE explanations:

a. One RCT (Castro et al. 2010, N = 288)[3] also found exacerbations during the treatment period.

b. The Expert Panel rated this outcome down for risk of bias because the Castro et al. (2010)[3] study had medium overall risk of bias as a result of unclear allocation concealment and funding from the manufacturer.

c. The Agency for Healthcare Research and Quality (AHRQ) systematic review report rated this outcome down for imprecision because the credible interval for the continuous measure crossed the null value.

d. The Expert Panel rated this outcome down due to the wide credible interval.

e. The AHRQ systematic review report rated this outcome down for imprecision because the confidence interval was wide and showed both benefit and harm.

f. Based on a per-protocol analysis from one RCT (Castro et al., 2010),[3] the mean difference in AQLQ scores was 0.24 (credible interval, 0.009 to 0.478).

g. The AHRQ evidence report rated this outcome down for possible selective outcome reporting because the AQLQ responder analysis was not prespecified.

h. One RCT (Castro et al., 2010, N = 288)[3] also provided data on rescue medication use outcome, which it measured as proportion of days of use. The mean difference was 2.1% less (95% CI, 10.86% less to 6.66% more).

Evidence Summary: Bronchial Thermoplasty and Standard Care vs. Standard Care Alone for Moderate to Severe Asthma in Adults

Outcomes	Number of participants (number of studies)	Certainty of evidence (GRADE)	Relative effect (95% CI)	Anticipated absolute effects (95% CI)	
				Risk with standard care alone and/or N	Risk difference or mean difference with BT and standard care
EXACERBATIONS					
Need for treatment with oral corticosteroids or decrease in morning PEF by >30% (exacerbations per participant per week)[a] Follow-up: 52 weeks	112 (1 RCT)[1]	Very low[b,c,d]	—	N = 56 Mean change from baseline: −0.03	**No difference** MD: 0.03 lower (from 0.12 lower to 0.06 lower)
Mild exacerbations (exacerbations per participant per week) Follow-up: 52 weeks	112 (1 RCT)[1]	Low[b,d]	—	N = 56 Mean change from baseline: 0.03	**No difference** MD: 0.20 lower (from 0.34 lower to 0.06 lower)
Need for hospitalization (number of participants) Follow-up: 52 weeks	144 (2 RCTs)[1,2]	Low[b,c]	—	RISA trial[2]: 4 hospitalizations; AIR trial[1]: 3 hospitalizations in 2 individuals with asthma	**No difference** RISA trial: 5 hospitalizations (P = 0.32) AIR trial: 3 hospitalizations in 3 individuals with asthma
ASTHMA CONTROL					
ACQ (MID for ages ≥18 years: 0.5) Follow-up: 52 weeks	144 (2 RCTs)[1,2]	Low[b,e]	—	N = 73	**Favors intervention** RISA trial[2]: MD: 0.77 lower (from 1.33 lower to 0.21 lower) AIR trial[1]: MD: 0.71 lower (from 1.05 lower to 0.37 lower)

Outcomes	Number of participants (number of studies)	Certainty of evidence (GRADE)	Relative effect (95% CI)	Anticipated absolute effects (95% CI)	
				Risk with standard care alone and/or N	Risk difference or mean difference with BT and standard care
QUALITY OF LIFE					
AQLQ scores of 1 for severe to 7 for no impairment (MID: 0.5) Follow-up: 52 weeks	144 (2 RCTs)[1,2]	Low[b,e]	—	N = 73	**Favors intervention** RISA trial[2]: MD: 1.11 higher (from 0.55 higher to 1.67 higher) AIR trial[1]: MD: 0.7 higher (from 0.28 higher to 1.12 higher)
OTHER OUTCOMES					
Rescue medication use: number of puffs/week (MID for ages ≥18 years: −5.67 puffs/week)[f] Follow-up: 52 weeks	144 (2 RCTs)[1,2]	Low[b,e]	—	N = 73	**Favors intervention** RISA trial[2]: MD: 19.49 lower (35.5 lower to 3.41 lower) AIR trial[1]: MD: 7.8 lower (14.78 lower to 0.82 lower)

Abbreviations: AIR, Asthma Intervention Research; ACQ, Asthma Control Questionnaire; AQLQ, Asthma Quality of Life Questionnaire; BT, bronchial thermoplasty; CI, confidence interval; GRADE, Grading of Recommendations Assessment, Development and Evaluation; MD, mean difference; MID, minimally important difference; PEF, peak expiratory flow; RCT, randomized controlled trial; RISA, Research in Severe Asthma.

Footnotes, including GRADE explanations:

a. The Expert Panel supplemented the information on adverse events reported in the publication on the AIR 2 trial,[3] which compared BT and standard of care to a sham bronchoscopic procedure and standard of care, with data from a presentation to the U.S. Food and Drug Administration's Anesthesiology and Respiratory Therapy Devices Panel on October 28, 2009.[4]

b. The Agency for Healthcare Research and Quality (AHRQ) systematic review report rated this outcome down for risk of bias mainly because the Cox 2007[1] and Pavord 2007[2] studies were unblinded and, to a lesser degree, because of the lack of clarity on the funder's role.

c. The AHRQ evidence report rated this outcome down for imprecision.

d. The AHRQ evidence report rated this outcome down for indirectness because the study measured the outcome while participants were not taking a long-acting $beta_2$-agonist.

e. The AHRQ evidence report rated this outcome down for imprecision because the 95% CI overlapped with the minimally important difference.

f. One RCT (Pavord et al., 2007, N = 32)[2] found no difference in overall reductions in both oral (P = 0.12) and inhaled corticosteroid doses (P = 0.59).

Harms:
The Research in Severe Asthma (RISA) and Asthma Intervention Research (AIR) 2 studies[2,3] found increased rates of bronchial irritation, chest discomfort, cough, discolored sputum, dyspnea, night awakenings, and wheezing during the 12-week treatment period. These studies followed 162 of 190 individuals with asthma treated with bronchial thermoplasty (BT) from the RISA trial[5] for up to 5 years after treatment. The results showed ongoing or new dyspnea (9.5% of participants), chest discomfort (4.8–8.3%), bronchial irritation (2.4%), wheezing (4.8–8.3%), and coughing (4.8%) at the end of the 5-year study period.

Hospitalizations (during and immediately after the treatment period) were more frequent in all three studies in individuals with asthma who underwent BT. In the AIR 2 study, 16 of 190 individuals who underwent BT were hospitalized, as were 2 of 98 individuals in the control group during the treatment period.[a] The treatment period involved three BT procedures performed 3 weeks apart. Asthma hospitalizations for 10 of the 16 individuals in the BT group and for both individuals in the control group were for worsening asthma. In the AIR study,[1] 4 of 15 individuals experienced 7 hospitalizations in the 12 months after the end of the treatment period, whereas none of 17 individuals in the standard-of-care arm were hospitalized. Other reasons for hospitalization of individuals in the BT arms of the three studies were segmental atelectasis, lower respiratory tract infections, low forced expiratory volume in 1 second, hemoptysis, and an aspirated prosthetic tooth.

Additional Data on Adverse Events During the Treatment Period for Bronchial Thermoplasty and Standard of Care vs. Sham Treatment and Standard of Care

Certainty Assessment							Number of patients		Effect		Certainty
Number of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	BT + SOC	Sham + SOC	Relative (95% CI)	Absolute (95% CI)	
EXACERBATIONS: SEVERE EXACERBATIONS DURING TREATMENT PERIOD (UP TO 6 WEEKS)											
1 (N = 288)[3]	RCT	Serious[a]	Not serious	Not serious	Not serious	None	52/190 (27.4%)	6/98 (6.1%)	RR: 4.47 (1.99 to 10.04)	**Favors sham treatment** 212 more per 1,000 (from 61 more to 553 more)	Moderate
EXACERBATIONS											
1 (N = 288)[3]	RCT	Serious[a]	Not serious	Not serious	Serious[b]	None	16/190 (8.4%)	2/98 (2.0%)	RR: 4.13 (0.97 to 17.58)	**May favor sham treatment** 64 more per 1,000 (from 1 fewer to 338 more)	Low

Abbreviations: BT, bronchial thermoplasty; CI, confidence interval; RCT, randomized controlled trial; RR, relative risk; SOC, standard of care.

Footnotes, including GRADE explanations:

a. The Expert Panel rated this outcome down for risk of bias because the Castro et al. (2010)[3] study had a medium risk of bias due to unclear allocation concealment and funding from the manufacturer.

b. The Agency for Healthcare Research and Quality systematic review report rated this outcome down for imprecision because the confidence interval crossed the null value.

New evidence
Yes.[6-10]