Supplementary Online Content

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eFigure 14. Metaregression for Association of Change in FEV_1 (L) With Duration of Study Follow-up (LAMA vs Placebo as Add-on to ICS)

eFigure 15. Metaregression for Association of Change in FEV_1 (L) With Duration of Study Follow-up (LAMA vs LABA as Add-on to ICS)

eFigure 16. Metaregression for Association of Rescue Medication Use (Puffs/24 h) With Duration of Study Follow-up (LAMA vs Placebo as Add-on to ICS)

eFigure 17. Metaregression for Association of Rescue Medication Use (Puffs/24 h) With Duration of Study Follow-up (LAMA vs LABA as Add-on to ICS)

This supplementary material has been provided by the authors to give readers additional information about their work.

eAppendix A. Search strategies

Medline, Cochrane Central and Cochrane Database of Systematic Reviews- via Ovid

1. Asthma.mp or Asthma/
2. Wheez$.mp.
3. Bronchial spasm/ or bronchospas$.mp.
4. Bronchoconstriction/ or bronchoconstrict$.mp.
5. Bronchial hyperreactivity/
6. Reactive airway disease.mp.
7. 1 or 2 or 3 or 4 or 5 or 6
8. Long acting muscarinic antagonist.mp.
9. Tiotropium bromide/ or tiotropium.mp.
10. Aclidinium.mp.
11. Glycopyrronium.mp. or glycopyrrolate/ or glycopyrrolate.mp.
12. Umeclidinium.mp.
13. 9 or 10 or 11 or 12
14. 8 or 13
15. 7 and 14
16. Limit 15 to humans

Embase

1. 'asthma'/de OR asthma
2. 'wheezing'/de OR wheezing
3. 'wheeze'/de OR wheeze
4. 'bronchospasm'/de OR 'bronchospasm'
5. 'bronchoconstriction'/de OR 'bronchoconstriction'
6. 'bronchial hyperreactivity'/de OR
7. 'reactive airway disease'
8. #1 OR #2 OR #3 OR #4 OR #5 OR #6 OR #7
9. 'long acting muscarinic antagonist'
10. 'tiotropium'/exp/dd_ih
11. 'aclidinium'/exp/dd_ih
12. 'glycopyrronium'/exp/dd_ih
13. "glycopyrrolaye'/exp/dd_ih
14. 'umeclidinium'/exp/dd_ih
15. #9 OR #10 OR #11 OR #12 OR #13 OR #14
16. #8 AND #15

eAppendix B. Strength of Evidence

Strength of evidence was based on the five following domains:

- Risk of bias: The overall pattern within the 7 risk of bias domains was considered along with how much the individual study contributed to the overall analysis sample size.
- Consistency: Consistency refers to the degree of similarity in the direction of effects (do all studies show the same effect, e.g. all superior or all null) and the magnitude of effect (the degree to which point estimates are similar) across studies within an evidence base. The magnitude of effect is often evaluated quantitatively using test for the presence (e.g., Cochran's Q tes) or the magnitude of heterogeneit (e.g., I^2 statistic).
- Directness: Directness of evidence expresses how closely available evidence measures an outcome of interest, both in the directness of the outcome and the comparison. This represents a slingle link between an intervention and the outcome. Comparisons are considered direct when the studies compare interventions specifically with each other.
- Precision: Precision is the degree of certainty surrounding an estimate of effect with respect to an outcome. A precise body of evidence should enable decisionmakers to draw conclusions about whether one treatment is superior, inferior, or equivalent to another. For continuous outcomes, we used the minimally important difference (where available) for each outcome and whether confidence intervals crossed that threshold. For dichotomous outcomes, we used a relative risk increase or reuction of 0.25 from the point estimate. If the confidence interval crossed these thresholds, the outcome was comparison/outcome was considered imprecise.
- Publication bias: Publication bias occurs when a decision is made to publish or report research findings based on their direction or magnitude of effect. Visual evaluations of funnel plots and tests for plot asymmetry were considered. Significant evaluations and tests were deemed to have positive publication bias.

Using evaluations of the 5 domains above, strength of evidence for each comparison and outcome was defined as:

- High: We are very confident that the estimate of effect lies close to the true effect for this outcome. The body of evidence has few or no deficiencies. We believe that the findings are stable, i.e., another study would not change the conclusions.
- Moderate: We are moderately confident that the estimate of effect lies close to the true effect for this outcome. The body of evidence has some deficiencies. We believe the findings are likely to be stable, but some doubt remains.
- Low: We have limited confidence that the estimate of effect lies close to the true effect for this outcome. The body of evidence has major or numerous deficiencies (or both). We believe that additional evidence is needed before concluding either that the findings are stable or that the estimate of effect is close to the true effect.
- Insufficient: We have no evidence, we are unable to estimate an effect, or we have no confidence in the estimate of the effect for this outcome. No evidence is available of the body of evidence has unacceptable deficiencies, precluding reaching a conclusion.

The strength of evidence was downgraded when one or more of the five domains above were noted.

eTable 1. Study and population baseline characteristics for LAMA vs. placebo as add-on to ICS RCTs

Study, Year	Duration of follow-up	Study population	Intervention Comparisons	Age (y) [mean (SD)]	Males [No., (%)]	Duration of asthma (y) [mean (SD)]	FEV1 (L) [mean (SD)]	FEV1 % predicted [mean (SD)]	Rescue inhaler use (puffs/d) [mean (SD)]	ICS dose during study (μg/d) [mean (SD)]
Peters, 2010[13]	14w	≥18 years of age with moderately severe asthma not well controlled on a ICS alone. Tiotropium or salmeterol were added on to run-in dose of beclomethasone 80μg BID	Tiotropium 18μg daily (Handihaler) n=210	42.2 (12.3)	69 (32.9)	26.1 (14.1)	2.31 (0.77)	71.5 (14.9)	1.71 (2.09)	NR
			Doubling ICS dose to 160μg BID (MDI) n=210							
Bateman, 2011[1]	16w	18-65 years of age with moderate persistent asthma (GINA step 3) not controlled on ICS alone (400-1000μg/d budesonide or equivalent). Randomized therapy added on to ICS continued at prestudy dose	Tiotropium 5μg daily (Respimat) n=128	43.5 (12.6)	46 (35.9)	18.1 (12.1)	2.3 (0.77)	74.1 (16.1)	NR	NR
			Placebo n=126	44.0 (11.9)	51 (40.5)	17.3 (12.2)	2.4 (0.8)	75.3 (19.0)	NR	NR
Kerstjens, 2015[2] Study 1	24w	18-75 year of age with moderate persistent asthma according to GINA guidelines despite treatment with stable medium dose ICS (400-800μg/d budesonide or equivalent) alone or in fixed combination with LABA, symptomatic with ACQ-7 ≥1.5. Randomized therapy was added to prestudy stable maintenance ICS dose[a]	Tiotropium 5μg daily (Respimat) n=264	44.4 (12.6)	110 (41.7)	22.9 (14.7)	2.2 (0.6)	72.2 (8.2)	NR	666.4 (216.2)[b]
			Tiotropium 2.5μg daily (Respimat) n=262	43.7 (13.1)	106 (40.5)	22.2 (14.1)	2.2 (0.7)	73.1 (8.6)	NR	649.8 (196.2)[b]
			Placebo n=269	42.5 (13.1)	103 (38.3)	20.2 (13.4)	2.3 (0.7)	73.0 (8.2)	NR	661.5 (209.5)[b]

eTable 1. Study and population baseline characteristics for LAMA vs. placebo as add-on to ICS RCTs (Continued)

Study, Year	Duration of follow-up	Study population	Intervention Comparisons	Age (y) [mean (SD)]	Males [No., (%)]	Duration of asthma (y) [mean (SD)]	FEV1 (L) [mean (SD)]	FEV1 % predicted [mean (SD)]	Rescue inhaler use (puffs/d) [mean (SD)]	ICS dose during study (μg/d) [mean (SD)]
Kerstjens, 2015[2] Study 2	24w	18-75 year of age with moderate persistent asthma according to GINA guidelines despite treatment with stable medium dose ICS (400-800μg/d budesonide or equivalent) alone or in fixed combination with LABA, symptomatic with ACQ-7 ≥1.5. Randomized therapy was added to prestudy stable maintenance ICS dose[c]	Tiotropium 5μg daily (Respimat) n=253	44.3 (12.7)	107 (42.3)	23.1 (15.3)	2.3 (0.6)	72.2 (8.3)	NR	661.3 (216.1)[b]
			Tiotropium 2.5μg daily (Respimat) n=257	43.0 (12.6)	97 (37.7)	21.9 (14.5)	2.3 (0.7)	72.5 (8.0)	NR	662.1 (229.5)[b]
			Placebo n=254	43.0 (13.0)	109 (42.9)	22.0 (13.9)	2.3 (0.7)	73.0 (8.4)	NR	675.6 (225.4)[b]
Lee, 2015[3]	15d	18 years of age and older with symptomatic asthma despite ICS treatment, alone or in combination with LABA or leukotriene modifier	Umeclidinium/fluticasone 15.6/100μg daily (DPI) n=62	47.5 (13.8)	112 (31)	<1y=2% 1-4y=13% 5-9y=17% ≥10=69%	1.85 (0.53)	62.3 (10.3)	NR	NR
			Umeclidinium/fluticasone 31.25/100μg daily (DPI) n=60							
			Umeclidinium/fluticasone 62.5/100μg daily (DPI) n=63							
			Umeclidinium/fluticasone 125/100μg daily (DPI) n=58							
			Umeclidinium/fluticasone 250/100μg daily (DPI) n=55							
			Fluticasone 100μg daily (DPI) n=64							

eTable 1. Study and population baseline characteristics for LAMA vs. placebo as add-on to ICS RCTs (Continued)

Study, Year	Duration of follow-up	Study population	Intervention Comparisons	Age (y) [mean (SD)]	Males [No., (%)]	Duration of asthma (y) [mean (SD)]	FEV1 (L) [mean (SD)]	FEV1 % predicted [mean (SD)]	Rescue inhaler use (puffs/d) [mean (SD)]	ICS dose during study (μg/d) [mean (SD)]
Ohta, 2015[4]	52w	18-75 years of age with moderate-severe asthma according to GINA guidelines despite receiving stable medium-dose ICS (400-800μg/d of budesonide or equivalent) alone or fixed combination with LABA, symptomatic with ACQ-7 ≥1.5. Randomized therapy was added to continued background ICS dose with or without LABA[d]	Tiotropium 2.5μg daily (Respimat) n=114	44.7 (12.1)	53 (36.8)	21.0 (0.8 to 57.8)[e]	NR	NR	NR	673.2 (247.4)[b,f]
			Tiotropium 5μg daily (Respimat) n=114	42.6 (12.8)	48 (42.1)	21.0 (0.3 to 54.0)[e]	NR	NR	NR	658.9 (220.5)[b,f]
			Placebo N=57	47.8 (13.0)	19 (33.3)	26.8 (0.8 to 63.0)[e]	NR	NR	NR	644.2 (220.9)[b,f]
Hammelmann, 2016[6]	48w	12-17 years of age with moderate symptomatic asthma with an ACQ ≥1.5 receiving maintenance therapy with ICS with or without LABA or LTRA. Randomized therapy was added on to maintenance ICS dose with or without LTRA[g]	Tiotropium 5μg daily (Respimat) n=134	14.5 (1.6)	89 (66.4)	8.2 (4.2)	2.6 (0.6)	77.3 (8.6)	NR	536 (256)[b,f]
			Tiotropium 2.5μg daily (Respimat) n=125	14.2 (1.8)	81 (64.8)	7.7 (4.0)	2.5 (0.6)	78.1 (7.9)	NR	557 (346)[b,f]
			Placebo n=138	14.2 (1.7)	88 (63.8)	7.7 (4.2)	2.6 (0.6)	77.6 (7.5)	NR	527 (275)[b,f]
Paggiaro, 2016[5]	12w	18-75 years of age with mild symptomatic asthma with an ACQ ≥1.5 despite receiving maintenance therapy with low-moderate ICS (200-400μg/d budesonide or equivalent) that is GINA step 2. Randomized therapy was added on to continued low-medium ICS dose	Tiotropium 5μg daily (Respimat) n=155	41.9 (13.0)	59 (38.1)	15.2 (10.2)	2.3 (0.6)	74.9 (8.1)	NR	376.9 (59.7)[b,f]
			Tiotropium 2.5μg daily (Respimat) n=154	43.8 (14.0)	72 (46.8)	17.1 (13.0)	2.3 (0.7)	73.2 (8.6)	NR	384.4 (93.4)[b,f]
			Placebo n=155	42.8 (12.1)	52 (33.5)	16.2 (12.3)	2.2 (0.6)	73.7 (8.5)	NR	383.0 (77.1)[b,f]

ACQ=Asthma Control Questionnaire; BID=twice daily; d=day(s); DPI=dry powder inhaler; FEV1=forced expiratory volume in one second; GINA=Global Initiative for Asthma; ICS=inhaled corticosteroid; L=liter; LABA=long-acting ß-agonist; LTRA=leukotriene receptor antagonist; MDI=metered dose inhaler; n=patient sample size; NR=not reported; RCT=randomized controlled trial; SD=standard deviation; w=weeks; y=years

[a]Concurrent therapy during the study with leukotriene modifiers was 11.7% in the tiotropium 5μg daily arm, 8.8% in the tiotropium 2.5μg daily arm, 10.9% in the salmeterol 50μg BID arm and 10.8% in the placebo arm

[b]Data at baseline, randomized treatments were add-on to continued use of ICS

[c]Concurrent therapy during the study with leukotriene modifiers was 7.1% in the tiotropium 5μg daily arm, 9.7% in the tiotropium 2.5μg daily arm, 8.3% in the salmeterol 50μg BID arm and 7.5% in the placebo arm

[d]Concurrent therapies during the study in the tiotropium 2.5μg daily arm included LABAs (54.4%), leukotriene modifiers (31.6%) and methylxanthines (22.8%). Concurrent therapies during the study in the tiotropium 5μg daily arm included LABAs (57.0%), leukotriene modifiers (25.4%) and methylxanthines (16.7%). Concurrent therapies during the study in the placebo arm included LABAs (61.4%), leukotriene modifiers (24.6%) and methylxanthines (17.5%).

[e]Data reported as median (range)

[f]Budesonide equipotent dose in μg

[g]Concurrent therapy during the study with leukotriene modifiers was 11.2% in the tiotropium 5μg daily arm, 6.4% in the tiotropium 2.5μg daily arm and 10.1% in the placebo arm

eTable 2. Study and population baseline characteristics overview for LAMA vs. other controller as add-on to ICS RCTs

Study, Year	Duration of follow-up	Study population	Intervention Comparisons	Age (y) [mean (SD)]	Males [No., (%)]	Duration of asthma (yr) [mean (SD)]	FEV_1 (L) [mean (SD)]	FEV_1 % predicted [mean (SD)]	Rescue inhaler use (puffs/d) [mean (SD)]	ICS dose during study (μg/d) [mean (SD)]
Peters, 2010[13]	14w	≥18 years of age with moderately severe asthma not well controlled on ICS alone. Tiotropium or salmeterol were added on to run-in dose of beclomethasone 80μg BID	Tiotropium 18μg daily (Handihaler) n=210	42.2 (12.3)	69 (32.9)	26.1 (14.1)	2.31 (0.77)	71.5 (14.9)	1.71 (2.09)	NR
			Salmeterol 50μg BID (DPI) n=210		69 (32.9)					NR
Bateman, 2011[1]	16w	18-65 years of age with moderate persistent asthma (GINA step 3) not controlled on ICS alone (400-1000μg/d budesonide or equivalent). Randomized therapy added on to ICS continued at prestudy dose	Tiotropium 5μg daily (Respimat) n=128	43.5 (12.6)	46 (35.9)	18.1 (12.1)	2.3 (0.77)	74.1 (16.1)	NR	NR
			Salmeterol 50μg BID (MDI) n=134	42.3 (13.4)	97 (38.1)	15.4 (10.7)	2.4 (0.8)	75.6 (17.6)	NR	NR
Rajanandh, 2014[7]	90d	18-60 years of age with uncontrolled, mild to moderate persistent asthma according to the GINA guidelines[a]	Tiotropium 18μg daily (HandiHaler) + budesonide 400μg daily n=31	40.4 (13.6)	20 (64.5)	5.4 (2.7)	NR	66.9 (1.7)	NR	NR
			Formoterol 6μg BID + budesonide 400μg daily n=32	37.2 (14.9)	18 (56.3)	5.6 (2.7)	NR	66.6 (2.0)	NR	NR
			Doxofylline 400mg daily + budesonide 400μg daily n=30	37.1 (18.8)	11 (36.7)	5.2 (2.7)	NR	66.8 (1.5)	NR	NR
			Montelukast 10mg daily + budesonide 400μg daily n=30	39.3 (17.0)	12 (40.0)	5.6 (3.0)	NR	67.2 (1.4)	NR	NR

eTable 2. Study and population baseline characteristics overview for LAMA vs. other controller as add-on to ICS RCTs (Continued)

Study, Year	Duration of follow-up	Study population	Intervention Comparisons	Age (y) [mean (SD)]	Males [No., (%)]	Duration of asthma (yr) [mean (SD)]	FEV_1 (L) [mean (SD)]	FEV_1 % predicted [mean (SD)]	Rescue inhaler use (puffs/d) [mean (SD)]	ICS dose during study (μg/d) [mean (SD)]
Kerstjens, 2015[2] Study 1	24w	18-75 year of age with moderate persistent asthma according to GINA guidelines despite treatment with stable medium dose ICS (400-800μg/d budesonide or equivalent) alone or in fixed combination with LABA, symptomatic with ACQ-7 ≥1.5. Randomized therapy was added to prestudy stable maintenance ICS dose[b]	Tiotropium 5μg daily (Respimat) n=264	44.4 (12.6)	110 (41.7)	22.9 (14.7)	2.2 (0.6)	72.2 (8.2)	NR	666.4 (216.2)[c]
			Tiotropium 2.5μg daily (Respimat) n=262	43.7 (13.1)	106 (40.5)	22.2 (14.1)	2.2 (0.7)	73.1 (8.6)	NR	649.8 (196.2)[c]
			Salmeterol 50μg BID (MDI) n=275	42.6 (12.6)	116 (42.2)	21.4 (14.5)	2.3 (0.6)	72.8 (8.5)	NR	656.7 (193.1)[c]
Kerstjens, 2015[2] Study 2	24w	18-75 year of age with moderate persistent asthma according to GINA guidelines despite treatment with stable medium dose ICS (400-800μg/d budesonide or equivalent) alone or in fixed combination with LABA, symptomatic with ACQ-7 ≥1.5. Randomized therapy was added to prestudy stable maintenance ICS dose[d]	Tiotropium 5μg daily (Respimat) n=253	44.3 (12.7)	107 (42.3)	23.1 (15.3)	2.3 (0.6)	72.2 (8.3)	NR	661.3 (216.1)[c]
			Tiotropium 2.5μg daily (Respimat) n=257	43.0 (12.6)	97 (37.7)	21.9 (14.5)	2.3 (0.7)	72.5 (8.0)	NR	662.1 (229.5)[c]
			Salmeterol 50μg BID (MDI) n=266	41.5 (13.1)	113 (42.5)	20.4 (14.1)	2.4 (0.7)	73.1 (8.1)	NR	644.7 (217.2)[c]

eTable 2. Study and population baseline characteristics overview for LAMA vs. other controller as add-on to ICS RCTs (Continued)

Study, Year	Duration of follow-up	Study population	Intervention Comparisons	Age (y) [mean (SD)]	Males [No., (%)]	Duration of asthma (yr) [mean (SD)]	FEV_1 (L) [mean (SD)]	FEV_1 % predicted [mean (SD)]	Rescue inhaler use (puffs/d) [mean (SD)]	ICS dose during study (μg/d) [mean (SD)]
Lee, 2015[3]	15d	18 years of age and older with symptomatic asthma despite ICS treatment, alone or in combination with LABA or leukotriene modifier	Umeclidinium/fluticasone 15.6/100μg daily (DPI) n=62	47.5 (13.8)	112 (31)	<1y=2% 1-4y=13% 5-9y=17% ≥10=69%	1.85 (0.53)	62.3 (10.3)	NR	NR
			Umeclidinium/fluticasone 31.25/100μg daily (DPI) n=60							
			Umeclidinium/fluticasone 62.5/100μg daily (DPI) n=63							
			Umeclidinium/fluticasone 125/100μg daily (DPI) n=58							
			Umeclidinium/fluticasone 250/100μg daily (DPI) n=55							
			Vilanterol/fluticasone 125/100μg daily (DPI) n=59							

eTable 2. Study and population baseline characteristics overview for LAMA vs. other controller as add-on to ICS RCTs (Continued)

Study, Year	Duration of follow-up	Study population	Intervention Comparisons	Age (y) [mean (SD)]	Males [No., (%)]	Duration of asthma (yr) [mean (SD)]	FEV_1 (L) [mean (SD)]	FEV_1 % predicted [mean (SD)]	Rescue inhaler use (puffs/d) [mean (SD)]	ICS dose during study (μg/d) [mean (SD)]
Rajanandh, 2015[8]	180d	18-60 years of age with uncontrolled, mild-moderate persistent asthma according to GINA guidelines[a]	Tiotropium 18μg daily (Handihaler) + budesonide 400μg daily n=72	37.4 (13.6)	38 (52.8)	5.8 (8.7)	NR	66.1 (6.4)	4.4 (1.1)	NR
			Formoterol 6μg BID + budesonide 400μg daily n=68	38.4 (14.9)	38 (55.4)	6.6 (6.7)	NR	66.2 (8.3)	4.4 (1.1)	NR
			Montelukast 10mg daily + budesonide 400μg daily n=81	36.3 (17.0)	36 (44.4)	5.9 (8.0)	NR	67.2 (6.5)	4.5 (1.2)	NR
			Doxofylline 400mg daily + budesonide 400μg daily n=76	38.3 (18.8)	41 (53.9)	6.2 (9.7)	NR	66.3 (7.0)	4.5 (1.1)	NR
Wechsler, 2015[9]	18m	18-75 years of age with asthma currently on or eligible for step 3 or 4 combination ICS/LABA according to the NHLBI guidelines. Randomized therapy was added to continued baseline ICS dose	Tiotropium 18μg daily (HandiHaler) n=532	45.2 (12.6)	127 (23.9)	23.3 (15.8)	2.1 (0.7)	78.6 (17.6)	3.4 (3.5)	NR[f]
			LABA BID[e] n=538	45.1 (12.6)	130 (24.2)	25.6 (16.0)	2.1 (0.6)	78.7 (18.6)	3.5 (3.7)	NR[f]

Abbreviations: ACQ=Asthma Control Questionnaire; BID=twice daily; d=day; DPI=dry powder inhaler; FEV1=forced expiratory volume in one second; GINA=Global Initiative for Asthma; ICS=inhaled corticosteroid; L=liter; LABA=long-acting β_2-agonist; =months; MDI=metered dose inhaler; n=patient sample size; NHLBI=National Heart, Lung, and Blood Institute; NR=not reported; RCT=randomized controlled trial; SD=standard deviation; μg=microgram; w=week; y=year

[a]Confirmed through author correspondence

[b]Concurrent therapy during the study with leukotriene modifiers was 11.7% in the tiotropium 5μg daily arm, 8.8% in the tiotropium 2.5μg daily arm, 10.9% in the salmeterol 50μg BID arm and 10.8% in the placebo arm

[c]Data at baseline, randomized treatments were add-on to continued use of ICS
[d]Concurrent therapy during the study with leukotriene modifiers was 7.1% in the tiotropium 5μg daily arm, 9.7% in the tiotropium 2.5μg daily arm, 8.3% in the salmeterol 50μg BID arm and 7.5% in the placebo arm
[e]Either salmeterol 50μg or formoterol 9μg BID, based on baseline usage of LABA. 116/538 (21.6%) for formoterol & 422/538 (78.4%) for salmeterol
[f]Mean/median ICS dose was not reported, although patients continued baseline ICS dose. Of those taking an ICS without LABA at baseline (28%), 88% were taking low-dose ICS <500μg. Of those taking ICS+LABA, 70% were using a single inhaler to delivery both medications. Approximately half were taking fluticasone/salmeterol 250/50μg

eTable 3. Study and population baseline characteristics for LAMA added to ICS and LABA vs. ICS and LABA RCTs

Study, Year	Duration of follow-up	Study population	Intervention Comparisons	Age (y) [mean (SD)]	Males [No., (%)]	Duration of asthma (y) [mean (SD)]	FEV1 (L) [mean (SD)]	FEV1 % predicted [mean (SD)]	Rescue inhaler use (puffs/d) [mean (SD)]	ICS dose during study (μg/d) [mean (SD)]
Kerstjens, 2012[10] Study 1	48w	18-75 years of age with severe persistent, symptomatic asthma & ACQ-7 ≥1.5 despite daily ICS (≥800μg budesonide or equivalent per day) and LABA therapy. Randomized therapy added on to pretrial maintenance high-dose ICS and LABA. Other maintenance medications allowed to continue at stable doses[a]	Tiotropium 5μg daily (Respimat) n=237	52.9 (12.4)	91 (38.4)	31 (6 to 70)[b]	1.60 (0.55)	54.6 (12.2)	2.8 (NR)	800 (800-1600)[c,d,e]
			Placebo n=222	53.9 (12.8)	79 (35.6)	28 (6 to 68)[b]	1.56 (0.54)	54.6 (12.2)	3.3 (NR)	
Kerstjens, 2012[10] Study 2	48w	18-75 years of age with severe persistent, symptomatic asthma & ACQ-7 ≥1.5 despite daily ICS (≥800μg budesonide or equivalent per day) and LABA therapy. Randomized therapy added on to pretrial maintenance high-dose ICS and LABA; Other maintenance medications allowed to continue at stable doses.[f]	Tiotropium 5μg daily (Respimat) n=219	51.4 (12.5)	92 (42.0)	26 (5 to 72)[b]	1.66 (0.57)	55.1 (12.8)	3.4 (NR)	800 (800-1600) [c,d,e]
			Placebo n=234	53.6 (11.7)	99 (42.3)	28 (5 to 69)[b]	1.60 (0.51)	55.0 (12.6)	3.3 (NR)	
Wang, 2015[11]	12w	Adults with moderate persistent asthma according to GINA guidelines, uncontrolled on salmeterol/ fluticasone 50/250μg BID with daily symptoms and use of SABA. Tiotropium was added on to continued salmeterol/fluticasone 50/250μg BID	Tiotropium 18μg daily (HandiHaler) n=33	36.7 (5.79)[g]	18 (54.5)	NR	NR	NR	NR	500[h]
			Increase salmeterol /fluticasone to 50/500μg BID (DPI) n=30	35.3 (5.89)[g]	16 (53.3)	NR	NR	NR	NR	1000[h]

eTable 3. Study and population baseline characteristics for LAMA added to ICS and LABA vs. ICS and LABA RCTs (Continued)

Study, Year	Duration of follow-up	Study population	Intervention Comparisons	Age (y) [mean (SD)]	Males [No., (%)]	Duration of asthma (y) [mean (SD)]	FEV1 (L) [mean (SD)]	FEV1 % predicted [mean (SD)]	Rescue inhaler use (puffs/d) [mean (SD)]	ICS dose during study (μg/d) [mean (SD)]
Hamelmann, 2017[12]	12w	12-17 years of age with severe persistent asthma according to GINA guidelines despite high-dose ICS (>400μg/d in 12-14y, >800-1600μg/d of budesonide equivalent if >14y) with another controller OR medium dose ICS (200-400μg/d budesonide equivalent in 12-14y, 400-800μg/d in >14y) with two other controllers; Symptomatic with ACQ-7 ≥1.5. Randomized therapies were added on to ICS and other controllers used prior to the study[i]	Tiotropium 5μg daily (Respimat) n=130	14.3 (1.6)	83 (63.8)	7.3 (4.0)	2.6 (0.7)	79.4 (12.3)	NR	776.7 (381.2)[d,e]
			Tiotropium 2.5μg daily (Respimat) n=127	14.4 (1.8)	80 (63.0)	8.0 (3.9)	2.5 (0.6)	79.8 (9.9)	NR	727.8 (343.6) [d,e]
			Placebo n=135	14.1 (1.7)	79 (58.5)	8.0 (3.7)	2.5 (0.6)	79.4 (12.2)	NR	736.6 (347.9) [d,e]

Abbreviations: ACQ=Asthma Control Questionnaire; BID=twice daily; d=day; DPI=dry powder inhaler; FEV1=forced expiratory volume in one second; GINA=Global Initiative for Asthma; ICS=inhaled corticosteroid; L=liter; LABA=long-acting β_2-agonist; LAMA=long-acting muscarinic antagonist; n=patient sample size; NR=not reported; RCT=randomized controlled trial; SABA=short-acting β-agonist; SD=standard deviation; μg=microgram; w=week; y=year

[a]Concurrent therapies during the study in the tiotropium arm included leukotriene modifiers (25.3%), theophylline (18.6%), omalizumab (2.5%), systemic steroids (6.8%) and antihistamines (20.3%). Concurrent therapies during the study in the placebo arm included leukotriene modifiers (27.5%), theophylline (21.2%), omalizumab (4.5%), systemic steroids (5.0%) and antihistamines (16.2%)

[b]Data reported as median (range)

[c]Data reported as median (interquartile range)

[d]Data at baseline, randomized treatments were added on to continued use of ICS

[e]Budesonide equipotent dose in μg

[f]Concurrent therapies during the study in the tiotropium arm included leukotriene modifiers (16.4%), theophylline (14.2%), omalizumab (2.7%), systemic steroids (3.7%) and antihistamines (14.2%). Concurrent therapies during the study in the placebo arm included leukotriene modifiers (19.7%), theophylline (12.8%), omalizumab (6.0%), systemic steroids (5.6%) and antihistamines (8.1%)

[g]Data reported as mean (standard error)

[h]ICS dose assumed due to fixed dosing with add-on therapy (tiotropium arm) or increased dose (salmeterol/fluticasone arm) used in trial

[i]Concurrent therapies during the treatment period in the tiotropium 5μg arm were systemic corticosteroids (3%), short acting anticholinergic (0.8%), long-acting β_2-agonists (82.3%), theophylline (6.2%) and leukotriene modifiers (78.5%). In this arm, 33.1% of patients were on 2 controllers while 66.9% were on three controllers. Concurrent therapies during the treatment period in the tiotropium 2.5μg arm were systemic corticosteroids (0.8%), long-acting β_2-agonists (79.5%), theophylline (4.7%) and leukotriene modifiers (81.9%). In this arm, 33.9% of patients were on 2 controllers while 66.1% were on three controllers. Concurrent therapies during the treatment period in the placebo arm were systemic corticosteroids (1.5%), long-acting β_2-agonists (85.9%), theophylline (5.2%) and leukotriene modifiers (80.7%). In this arm, 28.2% of patients were on 2 controllers while 71.9% were on three controllers

eTable 4. Subgroup analysis for tiotropium dose

Outcome	Reference No. for Included Studies	No. of Participants[a]		Results	
		LAMA Group	Control Group	Absolute Risk Difference, % (95% CI)[b]	Effect Size (95% CI)[c]
Tiotropium vs. placebo (base case analysis)					
Exacerbation requiring systemic corticosteroid	1-3,6,7	86/2030	74/1006	-1.8 (-3.8 to 0.3)	RR 0.67 (0.48 to 0.92)
Asthma worsening[d]	2,5,6	356/1604	223/816	-4.8 (-10.4 to 0.8)	RR 0.81 (0.68 to 0.97)
ACQ-7 score[e]	2,5,6	1527	777	NA	MD -0.10 (-0.28 to 0.07)
ACQ-7 responder[f]	2,4-6	1217/1816	527/864	5.2 (-2.2 to 12.6)	RR 1.08 (0.96 to 1.21)
FEV1 peak, L	2,5,6	1527	783	NA	MD 0.18 (0.13 to 0.24)
FEV1 trough, L	1-6	2154	1019	NA	MD 0.13 (0.10 to 0.17)
FEV1 AUC, L	2,5,6	1527	783	NA	MD 0.18 (0.13 to 0.23)
FVC peak, L	2,6	1224	629	NA	MD 0.11 (0.05 to 0.18)
FVC trough, L	1,2,4,6	1580	810	NA	MD 0.08 (0.04 to 0.13)
FVC AUC, L	2,6	1230	629	NA	MD 0.11 (0.05 to 0.17)
Rescue medication use, puffs/24 hours	1-6	2110	994	NA	MD -0.08 (-0.23 to 0.07)
Tiotropium 2.5µg vs. placebo					
Exacerbation requiring systemic corticosteroid	2,5,6	33/798	56/816	-1.9 (-8.9 to 5.2)	RR 0.63 (0.20 to 2.04)
Asthma worsening[d]	2,5,6	170/798	186/806	-4.1 (-17.7 to 9.6)	RR 0.82 (0.49 to 1.38)
ACQ-7 score[e]	2,5,6	761	777	NA	MD -0.12 (-0.35 to 0.11)
ACQ-7 responder[f]	2,4-6	603/903	527/864	5.4 (-1.0 to 11.7)	RR 1.08 (0.98 to 1.20)
FEV1 peak, L	2,5,6	763	783	NA	MD 0.20 (0.13 to 0.27)
FEV1 trough, L	2,4-6	877	839	NA	MD 0.12 (0.03 to 0.21)
FEV1 AUC, L	2,5,6	763	783	NA	MD 0.19 (0.12 to 0.25)
FVC peak, L	2,6	612	629	NA	MD 0.13 (0.03 to 0.24)
FVC trough, L	2,4,6	726	685	NA	MD 0.07 (-0.04 to 0.18)
FVC AUC, L	2,6	612	629	NA	MD 0.13 (0.04 to 0.21)
Rescue medication use, puffs/24 hours	2,4-6	848	805	NA	MD -0.09 (-0.34 to 0.16)
Tiotropium 5µg vs. placebo					
Exacerbation requiring systemic corticosteroid	1,2,5,6	50/806	73/942	-2.5 (-4.6 to -0.4)	RR 0.69 (0.32 to 1.47)
Asthma worsening[d]	2,5,6	186/806	223/816	-4.5 (-7.4 to -1.6)	RR 0.85 (0.63 to 1.15)
ACQ-7 score[e]	2,5,6	766	777	NA	MD -0.09 (-0.23 to 0.06)
ACQ-7 responder[f]	2,4-6	614/913	527/864	5.4 (-3.4 to 14.1)	RR 1.08 (0.95 to 1.24)
FEV1 peak, L	2,5,6	764	783	NA	MD 0.17 (0.13 to 0.21)
FEV1 trough, L	1,2,4-6	1006	964	NA	MD 0.13 (0.12 to 0.15)
FEV1 AUC, L	2,5,6	764	783	NA	MD 0.17 (0.12 to 0.21)
FVC peak, L	2,6	613	629	NA	MD 0.09 (0.06 to 0.12)
FVC trough, L	1,2,4,6	854	810	NA	MD 0.08 (0.05 to 0.12)
FVC AUC, L	2,6	618	629	NA	MD 0.09 (0.05 to 0.13)
Rescue medication use, puffs/24 hours	1,2,4-6	978	930	NA	MD -0.03 (-0.22 to 0.16)
Tiotropium 2.5µg vs. 5µg					
Exacerbation requiring systemic corticosteroid	2,5,6	33/798	34/806	1.2 (-5.8 to 8.1)	RR 1.70 (0.11 to 25.55)
Asthma worsening[d]	2,5,6	170/798	186/806	0.9 (-14.8 to 16.6)	RR 1.08 (0.45 to 2.57)
ACQ-7 score[e]	2,5,6	761	766	NA	MD -0.03 (-0.16 to 0.10)

eTable 4. Subgroup analysis for tiotropium dose (Continued)

Outcome	Reference No. for Included Studies	No. of Participants		Results	
		LAMA Group	Control Group	Absolute Risk Difference, % (95% CI)[b]	Effect Size (95% CI
ACQ-7 responder[f]	2,4-6	603/903	614/913	-0.5 (-5.7 to 4.7)	RR 0.99 (0.92 to 1.07)
FEV1 peak, L	2,5,6	763	764	NA	MD 0.03 (-0.01 to 0.07)
FEV1 trough, L	2,4-6	877	878	NA	MD -0.01 (-0.08 to 0.06)
FEV1 AUC, L	2,5,6	763	764	NA	MD 0.02 (-0.02 to 0.07)
FVC peak, L	2,6	612	612	NA	MD 0.04 (-0.04 to 0.12)
FVC trough, L	2,4,6	726	726	NA	MD -0.01 (-0.13 to 0.11)
FVC AUC, L	2,6	612	618	NA	MD 0.03 (-0.02 to 0.08)
Rescue medication use, puffs/24 hours	2,4-6	848	850	NA	MD -0.08 (-0.37 to 0.20)

Abbreviations: ACQ=Asthma Control Questionnaire; AUC=area under curve; CI=confidence interval; FVC=forced vital capacity; FEV1=forced expiratory volume in one second; MD=mean difference; RD=risk difference; RR=relative risk

[a] Data are presented as number of participants with an event over the total number of participants in the group.

[b] Data are presented as absolute risk differences (risk in LAMA group minus risk in Control group) between groups.

[c] For continuous outcomes, the mean difference (MD) value represents the difference in change scores (change from baseline) between the LAMA and Control groups.

[d]Asthma worsening was defined by studies as a progressive increase in asthma symptoms compared to day-to-day symptoms or a decrease in morning peak expiratory flow (PEF) ≥30% for 2 or more days.

[e] ACQ (range 0 [worse] to 6 [better control]) is a patient self-administered tool for assessing overall asthma control. The minimal important difference is a 0.5 point change.[14]

[f] ACQ responder was defined as an individual who had their score improve by at least 0.5 of greater.[15]

eTable 5. Sensitivity Analyses Removing Studies with High Risk of Bias

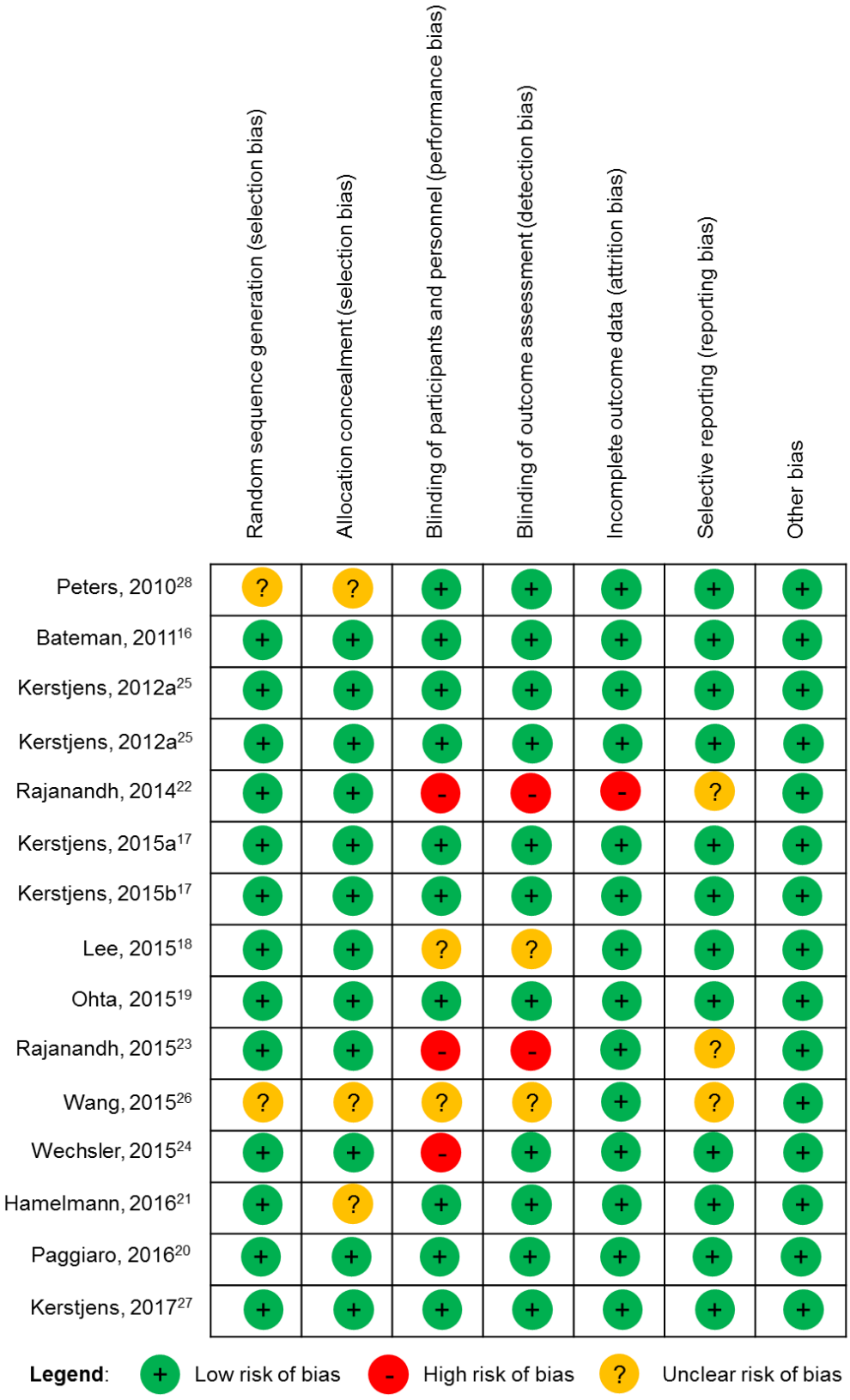
Outcome	Reference No. for Included Studies	Basecase Analyses Results Effect Size (95% CI)[a]	Low Risk of Bias Analyses Results Effect Size (95% CI)[b]
LAMA vs. LABA as add-on to ICS			
Death			
All-cause	2,3,9	OR 7.50 (0.78 to 72.27) RD 0.1 (-0.3 to 0.6)	No deaths occurred
Asthma-specific	2,3,9	OR 7.49 (0.47 to 119.86) RD 0.1 (-0.2 to 0.4)	No deaths occurred
Spirometry			
FEV1 trough, L	1-3,9,13	MD 0.02 (-0.02 to 0.07)	MD 0.03 (-0.03 to 0.08)
FEV1 % predicted	7-9	MD -4.54 (-12.69 to 3.61)	NA (All-studies had a high risk of bias)
Asthma-related QOL			
AQLQ score	2,9,13	MD -0.06 (-0.15 to 0.03)	MD -0.07 (-0.16 to 0.02)
Health Resource Utilization			
Rescue medication use, puffs/24h	1-3,7-9	MD 0.63 (-0.11 to 1.36)	MD 0.23 (-0.05 to 0.51)

Abbreviations: ACQ-5, 5-item Asthma Control Questionnaire; CI, confidence interval; ER, emergency room; FEV1, forced expiratory volume in one second; ICS, inhaled corticosteroid; LABA, long-acting beta agonist; MD, mean difference; OR, odds ratio; RD, risk difference; RR, risk ratio

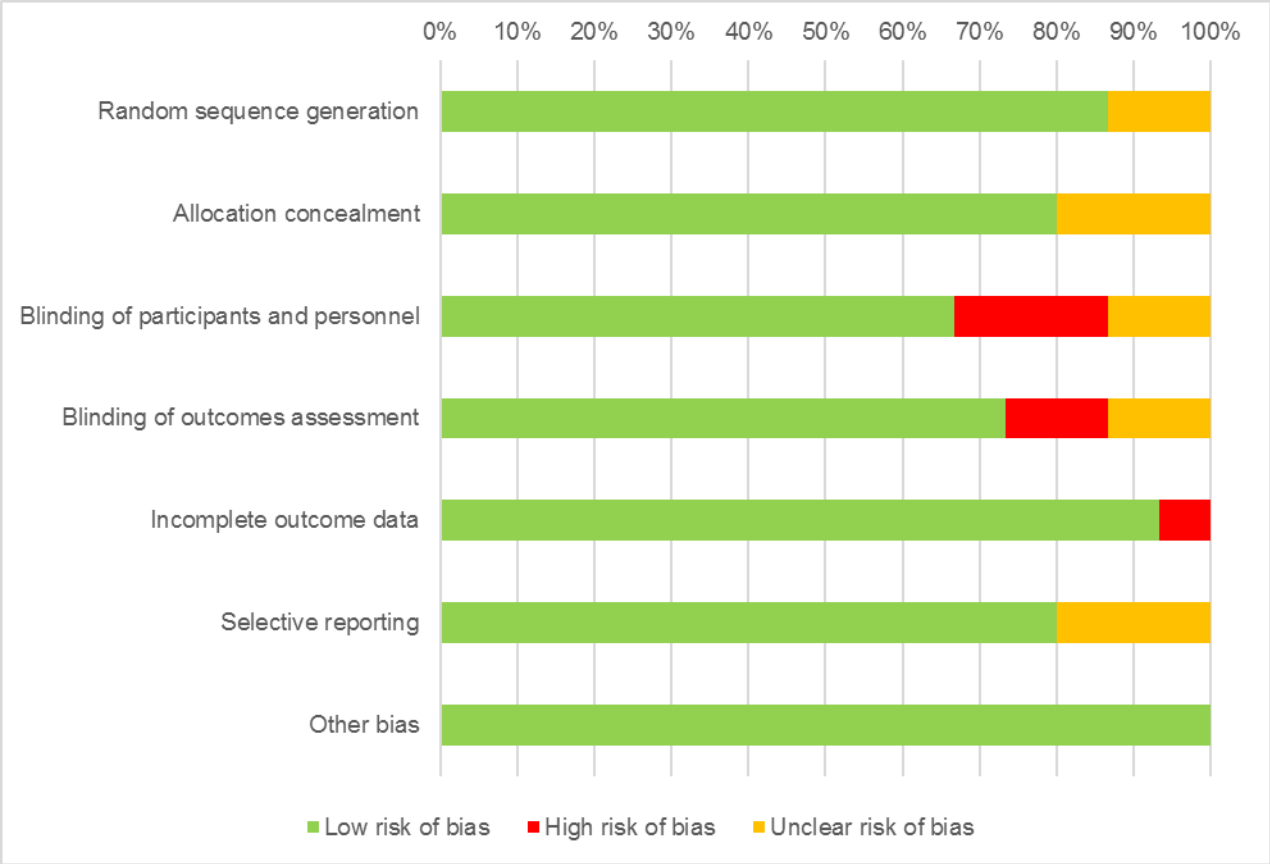
[a] Risk difference data are presented as absolute risk differences (risk in LAMA group minus risk in Control group) between groups.

[b] For continuous outcomes, the mean difference (MD) value represents the difference in change scores (change from baseline) between the LAMA and Control groups.

eFigure 1. Assessment of Risk of Bias Using Cochrane Collaboration Tool



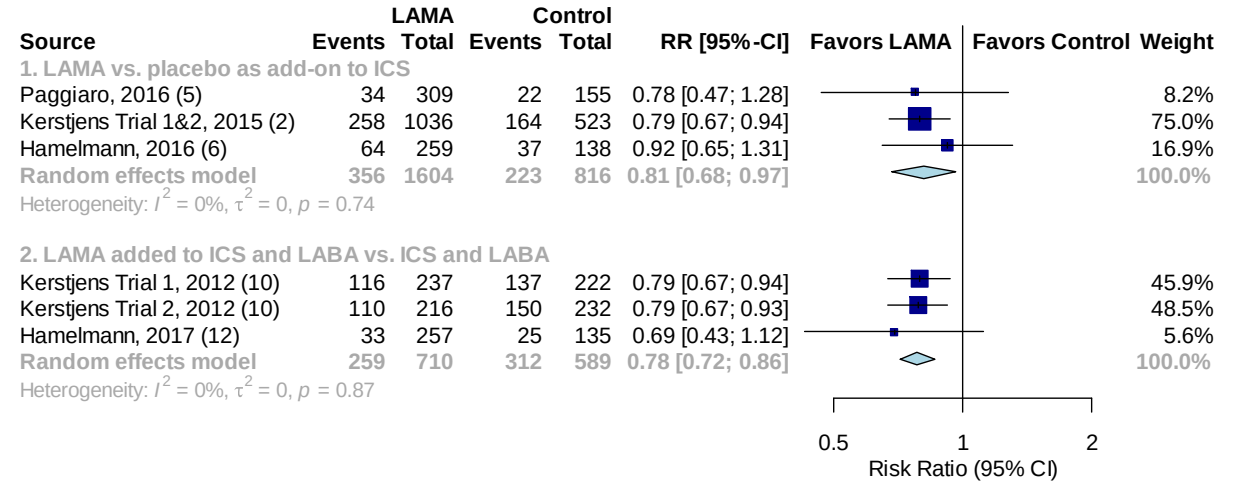
eFigure 2. Summative Assessment of Risk of Bias (No. Studies = 15)



eFigure 3. Asthma worsening

Box sizes are proportional to study weight (box center positioned at point estimate of effect). Horizontal lines indicate 95% CIs. The I^2 value indicates the percentage of variability across the pooled estimates attributable to statistical heterogeneity (range 0-100%), and the p-value is a test of heterogeneity across all studies (p value < 0.10 indicates likely variation across pooled estimates related to statistical heterogeneity). Asthma worsening was defined by studies as a progressive increase in asthma symptoms compared to day-to-day symptoms or a decrease in morning peak expiratory flow (PEF) ≥30% for 2 or more days. The term "Events" refers to the number of participants in each arm who experienced an event.

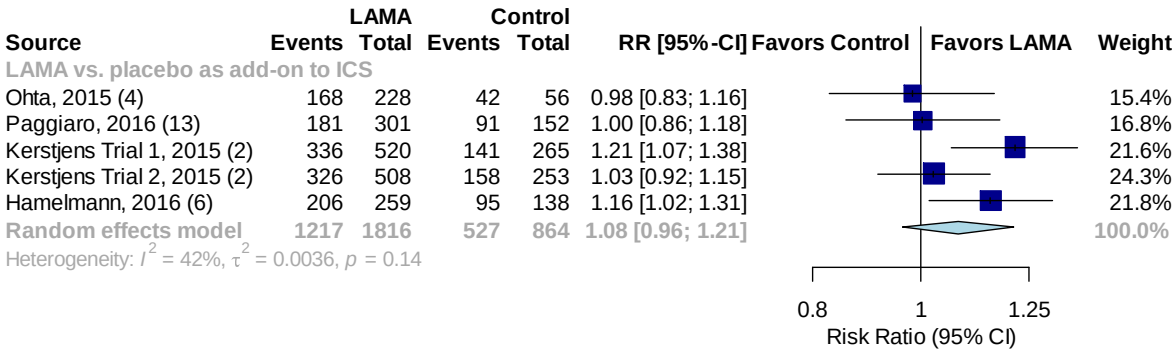
Abbreviations: CI, confidence interval; ICS, inhaled corticosteroid; LABA, long-acting beta agonist; LAMA, long-acting muscarinic antagonist; RR, risk ratio



eFigure 4. ACQ-7 responder

Box sizes are proportional to study weight (box center positioned at point estimate of effect). Horizontal lines indicate 95% CIs. The I^2 value indicates the percentage of variability across the pooled estimates attributable to statistical heterogeneity (range 0-100%), and the p-value is a test of heterogeneity across all studies (p value < 0.10 indicates likely variation across pooled estimates related to statistical heterogeneity). ACQ responder was defined as an individual who had their score improve by at least 0.5 of greater.[15] The term "Events" refers to the number of participants in each arm who experienced an event.

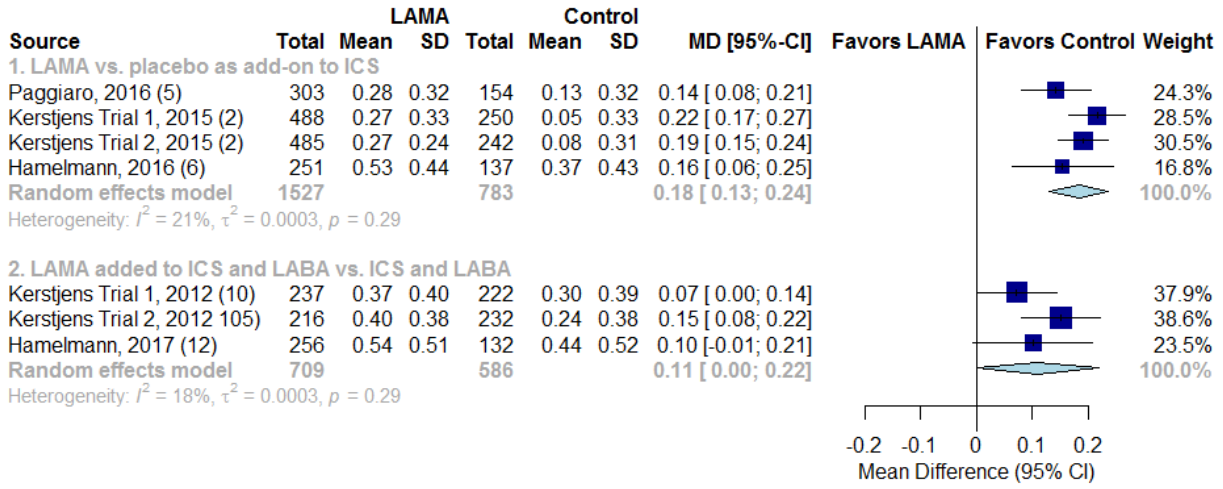
Abbreviations: ACQ, asthma control questionnaire; CI, confidence interval; ICS, inhaled corticosteroid; LAMA, long-acting muscarinic antagonist; RR, risk ratio



eFigure 5. FEV1 peak (L)

Box sizes are proportional to study weight (box center positioned at point estimate of effect). The mean value represents the mean change from baseline (change score) for each study group and the mean difference (MD) value represents the difference in change scores (change from baseline) between the LAMA and Control groups. Horizontal lines indicate 95% CIs. The I^2 value indicates the percentage of variability across the pooled estimates attributable to statistical heterogeneity (range 0-100%), and the p-value is a test of heterogeneity across all studies (p value < 0.10 indicates likely variation across pooled estimates related to statistical heterogeneity). A minimally important change in FEV1 was defined as an increase or decrease of 0.2 liters or more.[15]

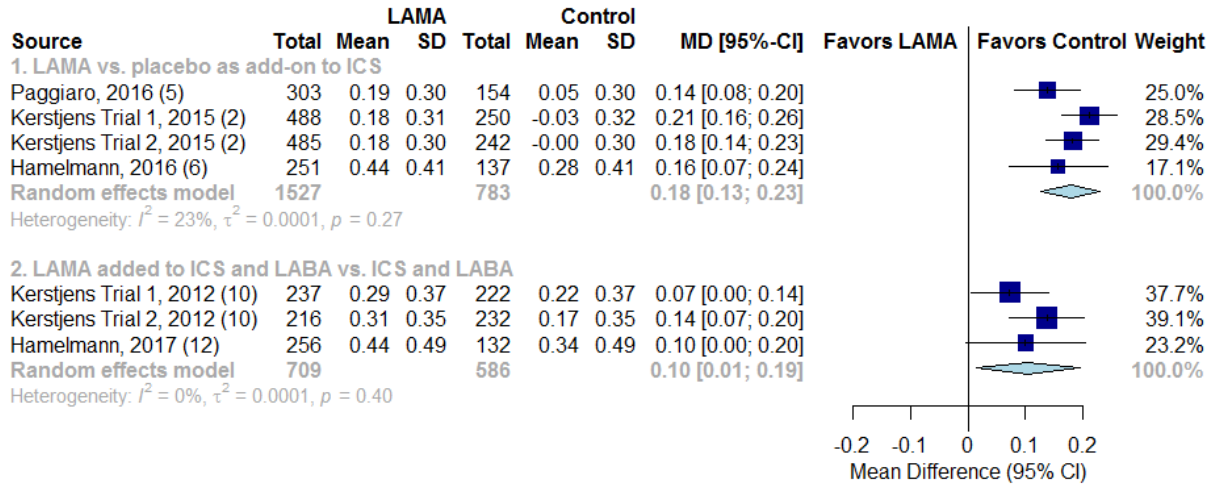
Abbreviations: CI, confidence interval; FEV1, forced expiratory volume in 1 second; ICS, inhaled corticosteroid; LABA, long-acting beta-agonist; LAMA, long-acting muscarinic antagonist; MD, mean difference; SD, standard deviation



eFigure 6. FEV1 AUC (L)

Box sizes are proportional to study weight (box center positioned at point estimate of effect). The mean value represents the mean change from baseline (change score) for each study group and the mean difference (MD) value represents the difference in change scores (change from baseline) between the LAMA and Control groups. Horizontal lines indicate 95% CIs. The I^2 value indicates the percentage of variability across the pooled estimates attributable to statistical heterogeneity (range 0-100%), and the p-value is a test of heterogeneity across all studies (p value < 0.10 indicates likely variation across pooled estimates related to statistical heterogeneity). A minimally important change in FEV1 was defined as an increase or decrease of 0.2 liters or more.[15]

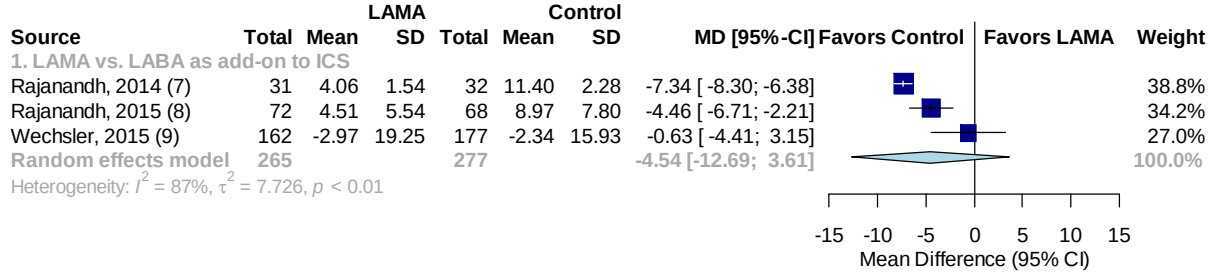
Abbreviations: AUC, area under the curve; CI, confidence interval; FEV1, forced expiratory volume in 1 second; ICS, inhaled corticosteroid; LABA, long-acting beta-agonist; LAMA, long-acting muscarinic antagonist; MD, mean difference; SD, standard deviation



eFigure 7. FEV1 % predicted

Box sizes are proportional to study weight (box center positioned at point estimate of effect). The mean value represents the mean change from baseline (change score) for each study group and the mean difference (MD) value represents the difference in change scores (change from baseline) between the LAMA and Control groups. Horizontal lines indicate 95% CIs. The I^2 value indicates the percentage of variability across the pooled estimates attributable to statistical heterogeneity (range 0-100%), and the p-value is a test of heterogeneity across all studies (p value < 0.10 indicates likely variation across pooled estimates related to statistical heterogeneity).

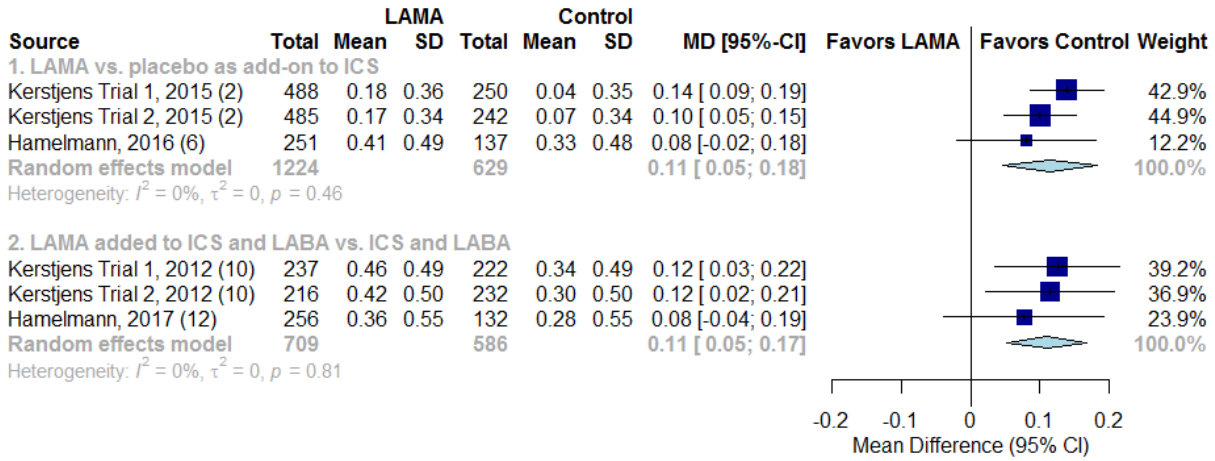
Abbreviations: CI, confidence interval; FEV1, forced expiratory volume in 1 second; ICS, inhaled corticosteroid; LABA, long-acting beta-agonist; LAMA, long-acting muscarinic antagonist; MD, mean difference; SD, standard deviation



eFigure 8. FVC peak (L)

Box sizes are proportional to study weight (box center positioned at point estimate of effect). The mean value represents the mean change from baseline (change score) for each study group and the mean difference (MD) value represents the difference in change scores (change from baseline) between the LAMA and Control groups. Horizontal lines indicate 95% CIs. The I^2 value indicates the percentage of variability across the pooled estimates attributable to statistical heterogeneity (range 0-100%), and the p-value is a test of heterogeneity across all studies (p value < 0.10 indicates likely variation across pooled estimates related to statistical heterogeneity). A minimally important change in FVC was defined as an increase or decrease of 0.2 liters or more.[15]

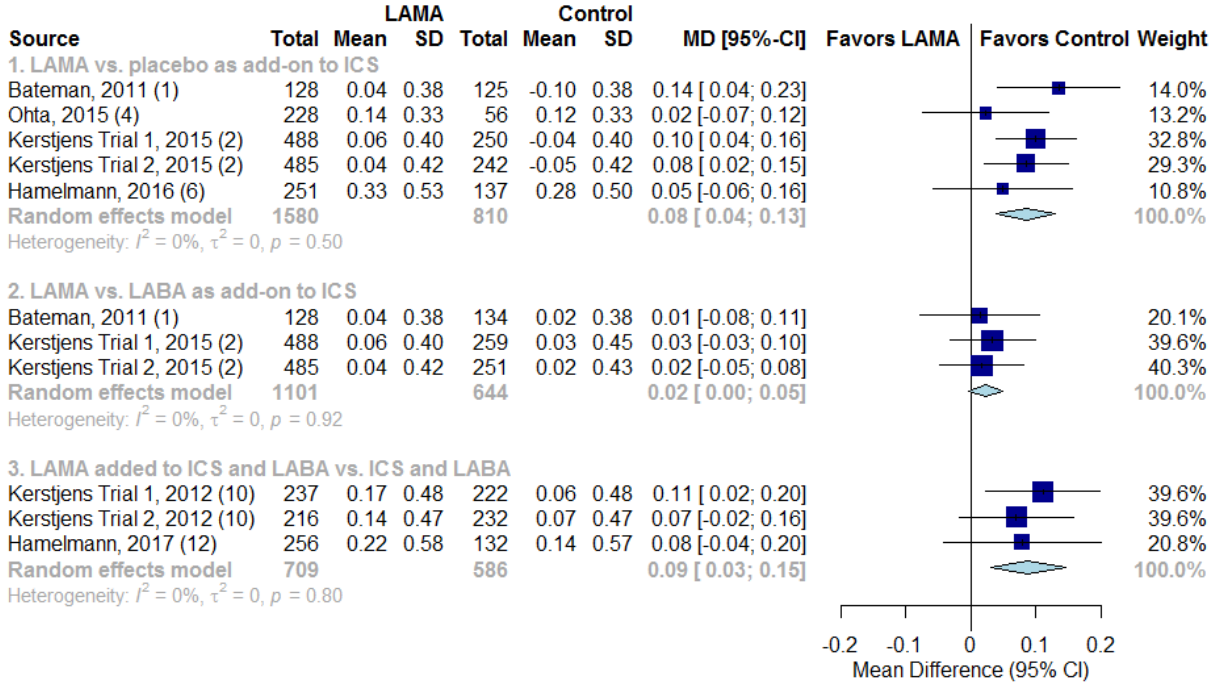
Abbreviations: CI, confidence interval; FVC, forced vital capacity; ICS, inhaled corticosteroid; LABA, long-acting beta-agonist; LAMA, long-acting muscarinic antagonist; MD, mean difference; SD, standard deviation



eFigure 9. FVC trough (L)

Box sizes are proportional to study weight (box center positioned at point estimate of effect). The mean value represents the mean change from baseline (change score) for each study group and the mean difference (MD) value represents the difference in change scores (change from baseline) between the LAMA and Control groups. Horizontal lines indicate 95% CIs. The I^2 value indicates the percentage of variability across the pooled estimates attributable to statistical heterogeneity (range 0-100%), and the p-value is a test of heterogeneity across all studies (p value < 0.10 indicates likely variation across pooled estimates related to statistical heterogeneity). A minimally important change in FVC was defined as an increase or decrease of 0.2 liters or more.[15]

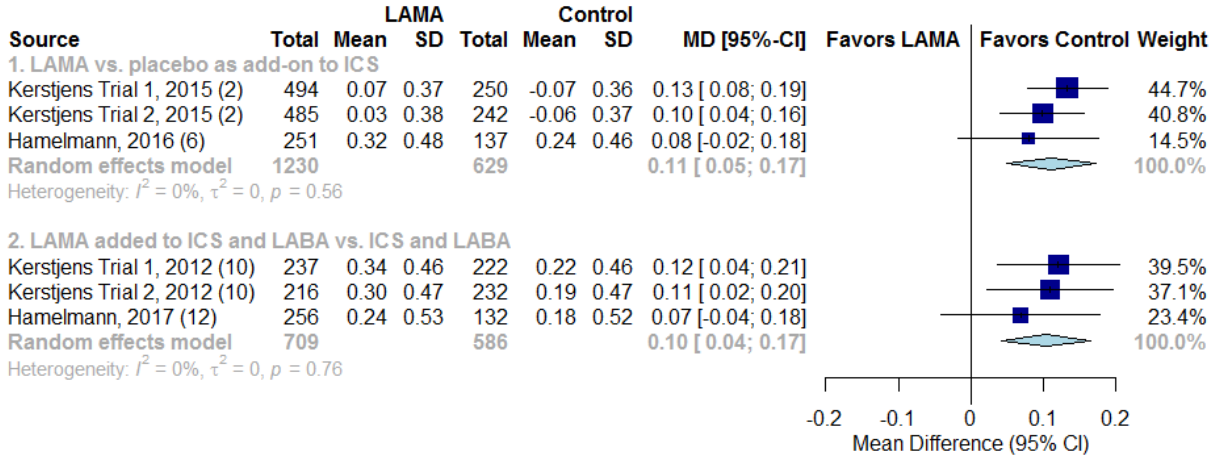
Abbreviations: CI, confidence interval; FVC, forced vital capacity; ICS, inhaled corticosteroid; LABA, long-acting beta-agonist; LAMA, long-acting muscarinic antagonist; MD, mean difference; SD, standard deviation



eFigure 10. FVC AUC (L)

Box sizes are proportional to study weight (box center positioned at point estimate of effect). The mean value represents the mean change from baseline (change score) for each study group and the mean difference (MD) value represents the difference in change scores (change from baseline) between the LAMA and Control groups. Horizontal lines indicate 95% CIs. The I^2 value indicates the percentage of variability across the pooled estimates attributable to statistical heterogeneity (range 0-100%), and the p-value is a test of heterogeneity across all studies (p value < 0.10 indicates likely variation across pooled estimates related to statistical heterogeneity). A minimally important change in FVC was defined as an increase or decrease of 0.2 liters or more.[15]

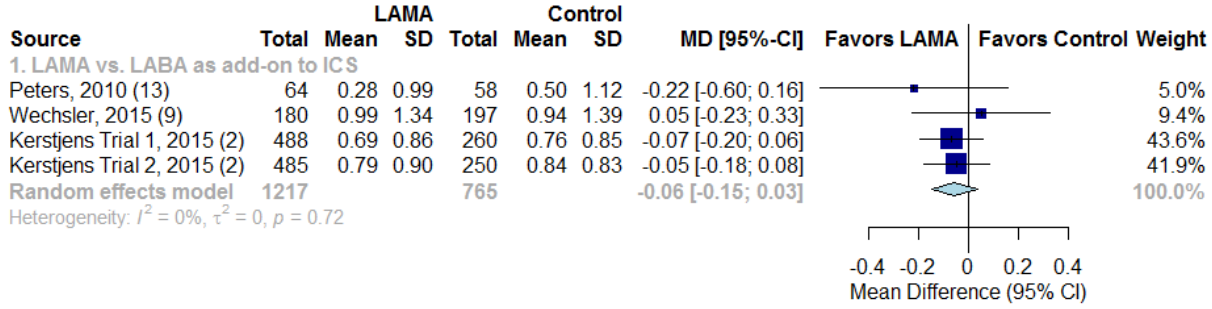
Abbreviations: AUC, area under the curve; CI, confidence interval; FVC, forced vital capacity; ICS, inhaled corticosteroid; LABA, long-acting beta-agonist; LAMA, long-acting muscarinic antagonist; MD, mean difference; SD, standard deviation



eFigure 11. AQLQ score

Box sizes are proportional to study weight (box center positioned at point estimate of effect). The mean value represents the mean change from baseline (change score) for each study group and the mean difference (MD) value represents the difference in change scores (change from baseline) between the LAMA and Control groups. Horizontal lines indicate 95% CIs. The I^2 value indicates the percentage of variability across the pooled estimates attributable to statistical heterogeneity (range 0-100%), and the p-value is a test of heterogeneity across all studies (p value < 0.10 indicates likely variation across pooled estimates related to statistical heterogeneity). AQLQ (range 1 [severe impairment] to 7 [no impairment] is an asthma-specific quality of life tool. The minimal important difference is a 0.5 point change.[16,17]

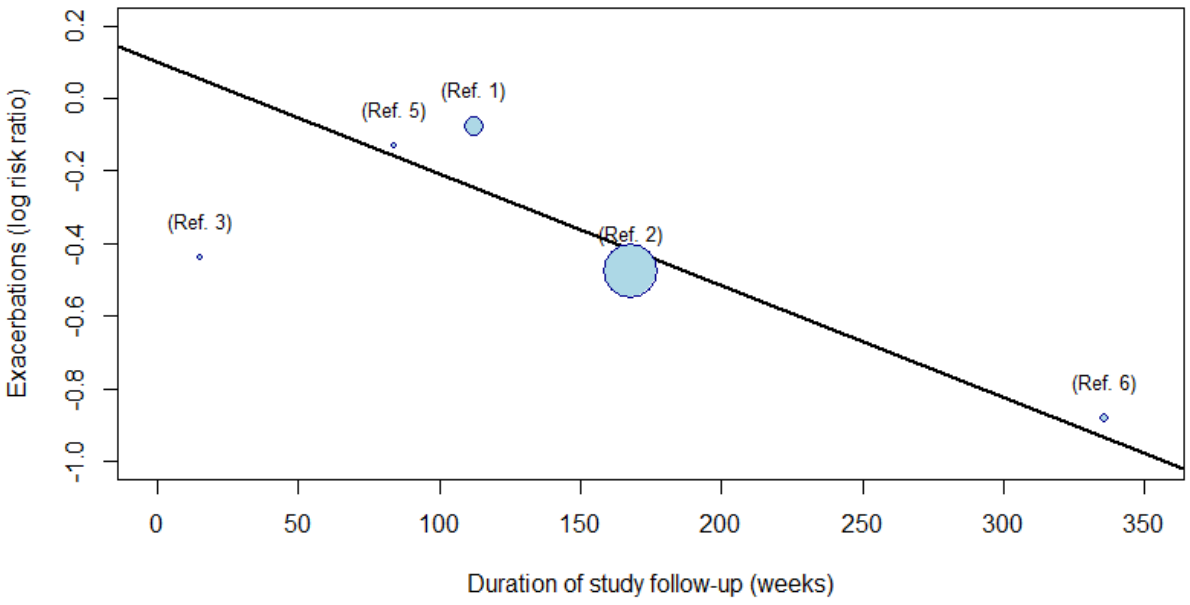
Abbreviations: AQLQ, Asthma Quality of Life Questionnaire; CI, confidence interval; ICS, inhaled corticosteroid; LABA, long-acting beta-agonist; LAMA, long-acting muscarinic antagonist; MD, mean difference; SD, standard deviation



eFigure 12. Metaregression for Association of Exacerbation Risk with Duration of Study (n=5) Follow-up (LAMA vs. Placebo as add-on to ICS)

This is a scatter plot with the log risk ratio of exacerbations for each study on the y-axis and the duration of study follow-up (weeks) on the x-axis. Each blue bubble represents a study in the analysis with the size of the bubble being inversely proportional to the variance of the estimated treatment effect. For this analysis, duration of study follow-up was not associated with a change in exacerbation risk (p=0.06).

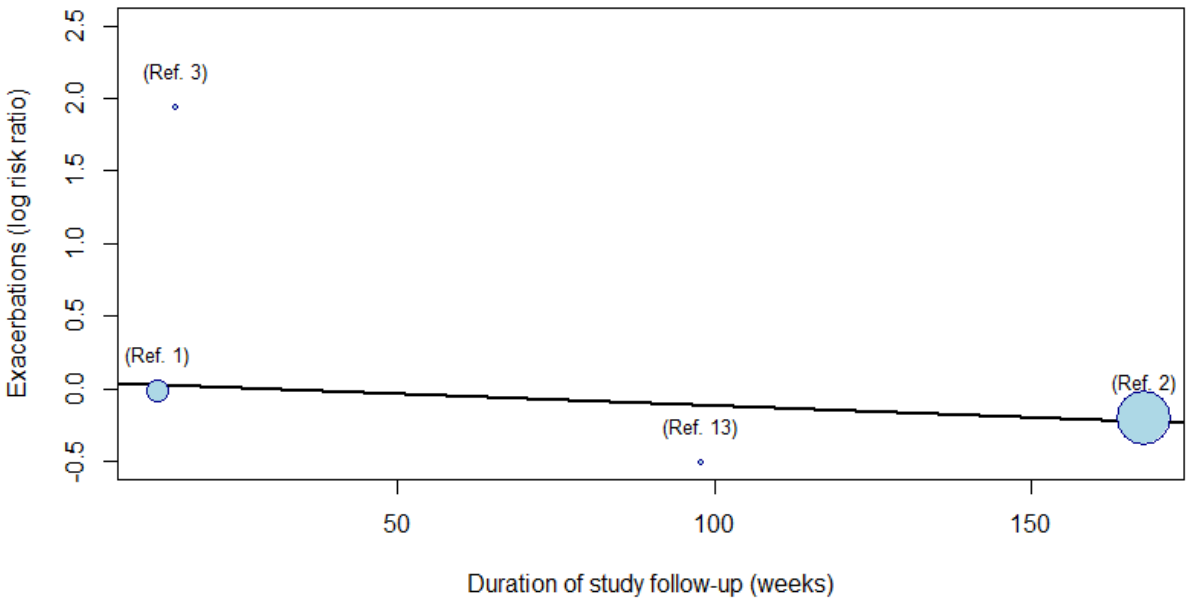
Abbreviations: ICS, inhaled corticosteroid; LAMA, long-acting muscarinic antagonist



eFigure 13. Metaregression for Association of Exacerbation Risk with Duration of Study (n=4) Follow-up (LAMA vs. LABA as add-on to ICS)

This is a scatter plot with the log risk ratio of exacerbations for each study on the y-axis and the duration of study follow-up (weeks) on the x-axis. Each blue bubble represents a study in the analysis with the size of the bubble being inversely proportional to the variance of the estimated treatment effect. For this analysis, duration of study follow-up was not associated with a change in exacerbation risk (p=0.56).

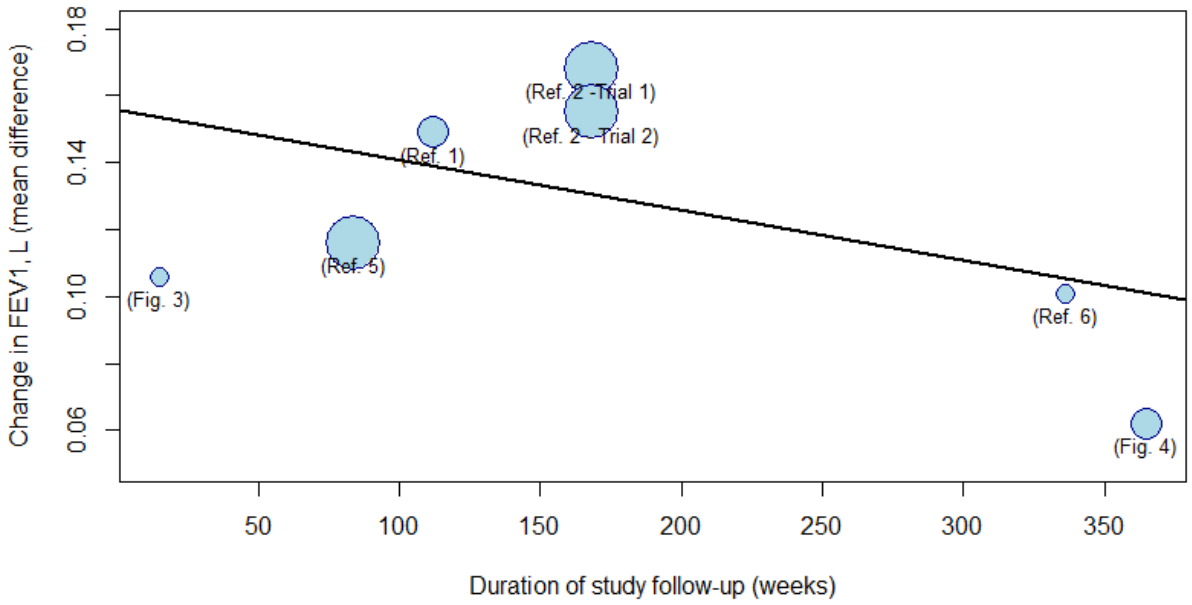
Abbreviations: ICS, inhaled corticosteroid; LAMA, long-acting muscarinic antagonist



eFigure 14. Metaregression for Association of Change in FEV1 (L) with Duration of Study (n=7) Follow-up (LAMA vs. Placebo as add-on to ICS)

This is a scatter plot with the change in FEV1 (L) for each study on the y-axis and the duration of study follow-up (weeks) on the x-axis. Each blue bubble represents a study in the analysis with the size of the bubble being inversely proportional to the variance of the estimated treatment effect. The mean difference (MD) value represents the difference in change scores (change from baseline) between the LAMA and Control groups. For this analysis, duration of study follow-up was not associated with a change in exacerbation risk (p=0.32).

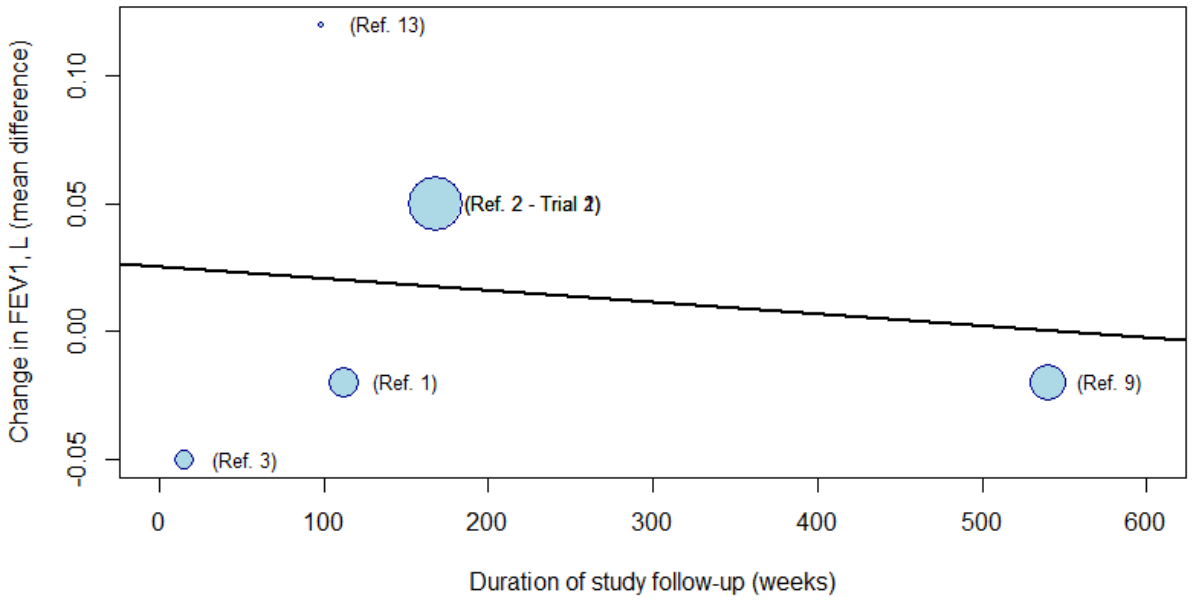
Abbreviations: FEV1, forced expiratory volume in 1 second; ICS, inhaled corticosteroid; L, liters; LAMA, long-acting muscarinic antagonist



eFigure 15. Metaregression for Association of Change in FEV1 (L) with Duration of Study (n=6) Follow-up (LAMA vs. LABA as add-on to ICS)

This is a scatter plot with the change in FEV1 (L) for each study on the y-axis and the duration of study follow-up (weeks) on the x-axis. Each blue bubble represents a study in the analysis with the size of the bubble being inversely proportional to the variance of the estimated treatment effect. The mean difference (MD) value represents the difference in change scores (change from baseline) between the LAMA and Control groups. For this analysis, duration of study follow-up was not associated with a change in exacerbation risk (p=0.73).

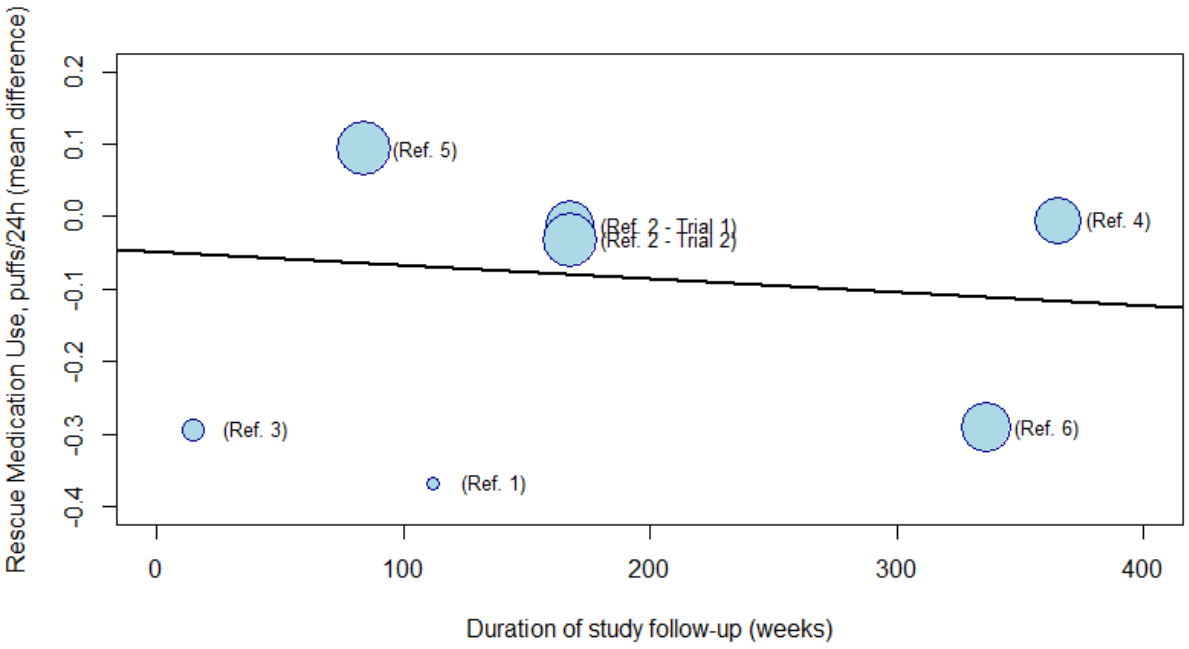
Abbreviations: FEV1, forced expiratory volume in 1 second; ICS, inhaled corticosteroid; L, liters; LAMA, long-acting muscarinic antagonist



eFigure 16. Metaregression for Association of Rescue Medication Use (puffs/24h) with Duration of Study (n=7) Follow-up (LAMA vs. Placebo as add-on to ICS)

This is a scatter plot with the change in rescue medication use (puffs/24h) for each study on the y-axis and the duration of study follow-up (weeks) on the x-axis. Each blue bubble represents a study in the analysis with the size of the bubble being inversely proportional to the variance of the estimated treatment effect. The mean difference (MD) value represents the difference in change scores (change from baseline) between the LAMA and Control groups. For this analysis, duration of study follow-up was not associated with a change in exacerbation risk (p=0.34).

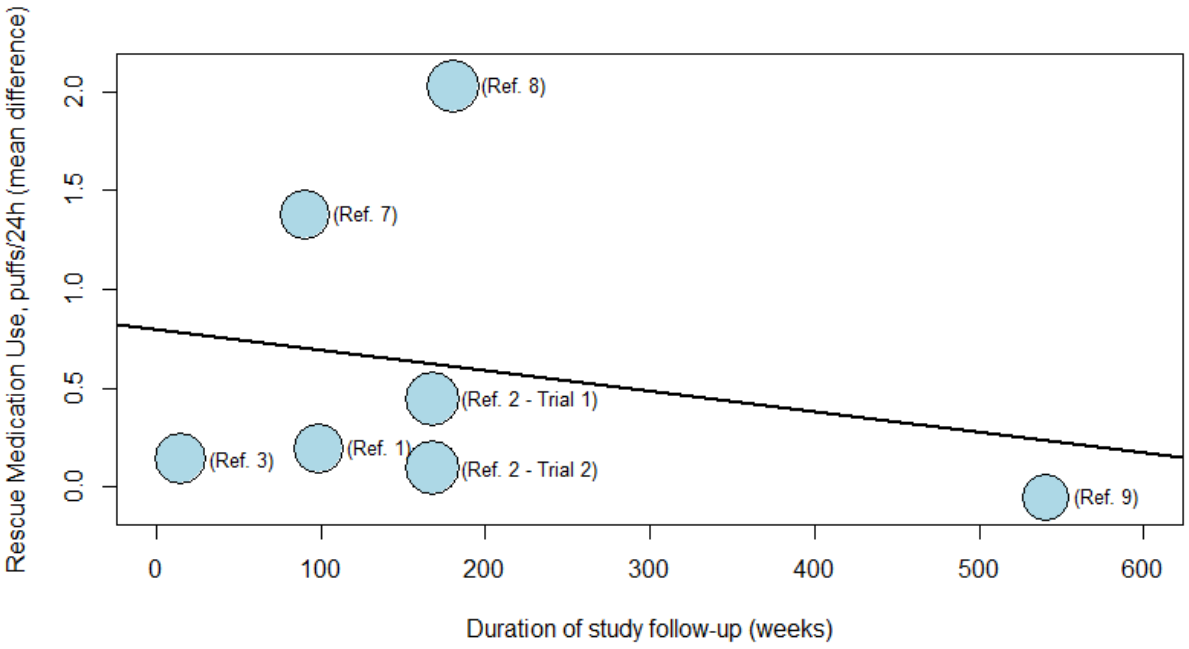
Abbreviations: h, hours; ICS, inhaled corticosteroid; LAMA, long-acting muscarinic antagonist



eFigure 17. Metaregression for Association of Rescue Medication Use (puffs/24h) with Duration of Study (n=7) Follow-up (LAMA vs. LABA as add-on to ICS)

This is a scatter plot with the change in rescue medication use (puffs/24h) for each study on the y-axis and the duration of study follow-up (weeks) on the x-axis. Each blue bubble represents a study in the analysis with the size of the bubble being inversely proportional to the variance of the estimated treatment effect. The mean difference (MD) value represents the difference in change scores (change from baseline) between the LAMA and Control groups. For this analysis, duration of study follow-up was not associated with a change in exacerbation risk (p=0.67).

Abbreviations: h, hours; ICS, inhaled corticosteroid; LAMA, long-acting muscarinic antagonist



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