Supplemental Online Content

Kim LHY, Saleh C, Whalen-Browne A, O'Byrne PM, Chu DK. Triple vs dual inhaler therapy and asthma outcomes in moderate-to-severe asthma: a systematic review and meta-analysis. *JAMA*. doi:10.1001/jama.2021.7872

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

eMethods 1. Search Strategies – Inception to Dec 8th, 2020 for all databases

MEDLINE and HEALTHSTAR	
Database: OVID Medline Epub Ahead of Print, In-Process & Other Non-Indexed Citations, Ovid MEDLINE(R) Daily and Ovid MEDLINE(R) 1946 to Present	
Search Strategy:	
1	exp Asthma/ or asthma.mp. (178618)
2	wheez$.mp. (14006)
3	exp Bronchial Spasm/ (4314)
4	bronchospas$.mp. (5504)
5	exp Bronchoconstriction/ (4157)
6	reactive airway disease.mp. (338)
7	bronchoconstrict$.mp. (11556)
8	1 or 2 or 3 or 4 or 5 or 6 or 7 (192730)
9	long acting muscarinic antagonist.mp. (531)
10	tiotropium.mp. or exp Tiotropium Bromide/ (1843)
11	aclidinium.mp. (230)
12	exp Glycopyrrolate/ or glycopyrronium.mp. (1222)
13	glycopyrrolate.mp. (1478)
14	umeclidinium.mp. (243)
15	9 or 10 or 11 or 12 or 13 or 14 (3743)
16	8 and 15 (588)
EMBASE	
Database: Embase <1974 to 2020 December 07>	
Search Strategy:	
1	exp asthma/ or asthma.mp. (297062)
2	wheezing.mp. or exp wheezing/ (32407)
3	wheeze.mp. or exp wheezing/ (29987)
4	bronchospasm.mp. or exp bronchospasm/ (28076)
5	exp bronchoconstriction/ or bronchoconstriction.mp. (30966)
6	bronchial hyperreactivity.mp. or exp bronchus hyperreactivity/ (13713)
7	reactive airway disease.mp. (548)
8	1 or 2 or 3 or 4 or 5 or 6 or 7 (331501)
9	long acting muscarinic antagonist.mp. (1128)
10	tiotropium.mp. or exp tiotropium bromide/ (6575)
11	aclidinium.mp. or exp aclidinium bromide/ (827)
12	glycopyrronium.mp. or exp glycopyrronium/ (7417)
13	glycopyrrolate.mp. (1420)
14	exp umeclidinium/ or umeclidinium.mp. (843)
15	9 or 10 or 11 or 12 or 13 or 14 (14297)
16	8 and 15 (2868)
Cochrane Central Register of Controlled Trials (CENTRAL)	
1	asthma (9244)
2	MeSH descriptor: [Asthma] explode all trees (11669)
3	Wheez* (1066)
4	bronchial spasm (62)
5	MeSH descriptor: [bronchial spasm] explode all trees (391)
6	bronchospas*(443)
7	bronchoconstriction (274)
8	MeSH descriptor: [Bronchoconstriction] explode all trees (561)
9	bronchoconstrict* (289)
10	bronchial hyperreactivity (137)
11	MeSH descriptor: [bronchial hyperreactivity] explode all trees (578)
12	reactive airway disease (108)

13	#1 or #2 or #3 or #4 or #5 or #6 or #7 or #8 or #10 or #11 or #12 (10064)
14	long acting muscarinic antagonist (202)
15	MeSH descriptor: [muscarinic antagonists] explode all trees (896)
16	tiotropium bromide (592)
17	MeSH descriptor: [tiotropium bromide] explode all trees (685)
18	tiotropium (914)
19	aclidinium (102)
20	glycopyrronium (363)
21	glycopyrrolate (410)
22	MeSH descriptor: [glycopyrrolate] explode all trees (475)
23	umeclidinium (193)
24	#16 or #17 or #18 or #19 or #20 or #21 or #22 or #23 (1665)
25	#14 or #15 or #24 (2537)
26	#13 or #25 (9)

WHO International Clinical Trials Registry Platform (ICTRP)

long acting muscarinic antagonist OR tiotropium bromide OR tiotropium OR aclidinium OR glycopyrronium OR glycopyrrolate OR umeclidinium

FDA and EMA

- Tiotropium/Tiotropium bromide
  - FDA: Spiriva (NDA #021395)
    - Spiriva Respimat (NDA #207070)
    - Spiriva Respimat (metered) (NDA #021936)
  - EMA: Eklira Genuair (MA #EU/1/12/778/001-3)
    - Bretaris Genuair (MA #EU/1/12/781/001-3)
    - Brimica Genuair (MA #EU/1/14/963/001-3)
    - Duaklir Genuair (MA #EU/1/14/964/001-3)
- Aclidinium/aclidinium bromide
  - FDA: Tudorza Pressair (NDA #202450)
  - EMA: Eklira Genuair (MA #EU/1/12/778/001-3)
    - Bretaris Genuair (MA #EU/1/12/781/001-3)
    - Brimica Genuair (MA #EU/1/14/963/001-3)
    - Duaklir Genuair (MA #EU/1/14/964/001-3)
- Glycopyrronium/Glycopyrrolate
  - FDA: Seebri (NDA #207923)
    - Lonhala Magnair Kit (NDA #208437)
  - EMA: Tovanor Breezhaler (MA #EU/1/12/790/001-8)
    - Seebri Breezhaler (MA #EU/1/12/788/001-8)
    - Enurev Breezhaler (MA #EU/1/12/789/001-8)
    - Bevespo Aerosphere (MA #EU/1/18/1339/001-2)
    - Trimbow (MA #EU/1/17/1208/001-5)
    - Uluna Breezhaler (MA #EU/1/14/917/001-8)
    - Xoterna Breezhaler (MA #EU/1/13/863/001-8)
    - Ultibrow Breezhaler (MA #EU/1/13/862/001-8)
    - Trydonis (MA #EU/1/18/1274/001-5)
- Umeclidinium
  - FDA: Incruse Ellipta (NDA #205382)
    - Trelegy Ellipta (NDA #209482)
  - EMA: Incruse Ellipta (MA #EU/1/14/922/001-3)
    - Rolufta Ellipta (MA #EU/1/17/1174/001-3)
    - Laventair Ellipta (MA #EU/1/14/899/001-3)
    - Anoro Ellipta (MA #EU/1/14/898/001-3)
    - Trelegy Ellipta (MA #EU/1/17/1236/001-3)
    - Tembyric Ellipta (MA #EU/1/19/1378/001-3)
    - Elebrato Ellipta (MA #EU/1/17/1237/001-3)

eMethods 2. Additional Methods Details

For dichotomous outcomes, we calculated the risk ratio (RR) with 95% confidence interval (CI). Outcomes that could occur more than once per patient (eg. exacerbations) were pooled as incidence rate ratios (IRR) with 95%CI. For time-to-event outcomes, we extracted patient-level time-to-event data by digitizing Kaplan-Meier curves[1], validating proportional hazards assumptions, fitting shared frailty Cox regression models with study as random effects, and reporting hazard ratio (HR) with 95% CI. We also verified each extracted studies' HR matched its reported one. We compared these results to meta-analysis of HRs reported in aggregate form. For rare dichotomous outcomes (mortality, serious cardiovascular events), we pooled risk differences with sensitivity analyses using Bayesian random effects meta-analyses of risk ratios with noninformative priors for treatment effects and Turner priors[2] for between-study heterogeneity. For continuous outcomes, we calculated the mean difference with 95% CI and if different scales were used between studies, we converted all scales to have the same directionality and then pooled effects as standardized mean difference (SMD) using hedges' g. If the standard deviations for change from baseline estimates for continuous outcomes were not available, then we used 1) mean of correlation coefficient calculated from the included studies[3] and 2) imputed correlation coefficient of 0.7 as it is a more realistic assumption and the results were robust to sensitivity analysis with a more conservative assumption of correlation coefficient of 0.5. All analyses were completed by complete case scenario according to the assigned groups and the total number of randomized patients for each outcome is reported throughout the main text. To facilitate interpretability, we then converted these pooled SMDs to the most familiar scale (eg. ACQ-7) using the median SD across included studies[4]. For each continuous outcome, we also present relative and absolute treatment effects according to the probability of achieving the minimal important difference (MID), calculated using the median and standard deviation of the control group and the pooled mean difference to estimate the mean in the treatment group[4]. Minimally important difference for ACQ score and AQLQ score have been both reported to be 0.5. Crossover trials were accounted for as parallel group studies and according to Cochrane guidance, used the first period to reduce the risk of carryover effects when the periods were clearly specified or estimated as such, as a conservative approach[3]. Severe asthma exacerbation was defined by a need for systemic steroids for ≥3 days, hospitalization, intensive care admission or intubation, or emergency department visits. Asthma worsening was defined as a progressive increase in one or more asthma symptoms or a decline in lung function (i.e. ≥30% decrease in peak expiratory flow) for two or more consecutive days that does not meet definition of severe asthma exacerbation.

GRADE assessments of certainty were determined through consideration of study design (RCTs start at high certainty) and five domains: risk of bias, inconsistency, indirectness, imprecision and publication bias. The RCTs were downgraded for any serious concerns per domain and the rationales for downgrading were presented in the Summary of Findings table (eTable 1).

Trial Sequential Analysis (TSA) was completed using TSA Viewer 0.9.5.9 Beta (Copenhagen: Copenhagen Trial Unit, Centre for Clinical Intervention Research, Rigshospitalet, 2016), Lan-DeMets implementation of the O'Brien-Fleming monitoring boundaries[5], adjustment for heterogeneity, and information size set to a two-sided alpha of 0.05, beta 0.80, 10-30% relative risk reduction and the baseline control-group event rate for each outcome.

Minimally Clinically Important Difference for ACQ-5, -6, -7 and ACT		
Scale	**Notes**	**MCID**
ACQ-7	Consists of six disease-related items and an assessment of lung function with FEV_1	Scores range between 0 (totally controlled) and 6 (severely uncontrolled) MCID: 0.5
ACQ-6	Omits FEV_1 assessment	
ACQ-5	Omits bronchodilator use and FEV_1 assessment	
ACT	Comprises 5 items pertaining to symptoms and daily functioning, ranging from a score of 5 to 25	A score >19 indicates well-controlled asthma MCID: for adults, 3 points for children, 2 points

Definitions of Adverse Events by FDA

Serious Adverse Events	An adverse event or suspected adverse reaction is considered "serious" if, in the view of either the investigator or sponsor, it results in any of the following outcomes: Death, a life-threatening adverse event, inpatient hospitalization or prolongation of existing hospitalization, a persistent or significant incapacity or substantial disruption of the ability to conduct normal life functions, or a congenital anomaly/birth defect. Important medical events that may not result in death, be life-threatening, or require hospitalization may be considered serious when, based upon appropriate medical judgment, they may jeopardize the patient or subject and may require medical or surgical intervention to prevent one of the outcomes listed in this definition.
Non-serious Adverse Events	Any untoward medical occurrence associated with the use of a drug in humans, whether or not considered drug related.

Pre-specified subgroup included stratification by study risk of bias, design (parallel vs cross-over), history of previous exacerbation (≥1 vs. <1 in the past year), population age, dose and type of triple therapy, and comparator dose and type. Tests for interaction were done in RevMan version 5.3, which tests mean effects between subgroups[6]. Sensitivity analyses to test the robustness of the findings included 1) worst-case or various plausible scenarios for missing participants, 2) reweighing trials using fixed-effect analysis, 3) excluding unpublished trials, 4) excluding cross-over trials, 5) analyzing different doses of the intervention independently rather than collapsing them as Cochrane guidance suggests to[3] 6) using the more conservative Knapp-Hartung-Sidik-Jonkman random effects meta-analytic method[7], and 7) using different correlation coefficients (0.5 and 0.7) and averaged SD for change from baseline continuous outcomes.

To account for double zeros in the mortality dataset, we analyzed using a Bayesian approach to pool relative risks, or a frequentist approach to pool risk differences[3]. In addition to the standard frequentist approach, we synthesized the available evidence with a Bayesian approach using hybrid Metropolis-Hastings and Gibbs sampling, a 10,000 sample burn-in, 40,000 Markov chain Monte-Carlo (MCMC) samples and noninformative (mean 0, variance 5) priors for the mean effect, and Turner[6] priors for estimates of heterogeneity, to inform mean posterior estimates of effect and 95% credible intervals (CrIs). Model convergence was confirmed in all cases with good mixing in visual inspection of trace plots, autocorrelation plots, histograms, and kernel density estimates in all scenarios. Parameters were blocked, leading to acceptance of approximately 50% and efficiency >1% in all cases.

eMethods 3. PRISMA Checklist.

Section/topic	#	Checklist item	Reported on page #
TITLE			
Title	1	Identify the report as a systematic review, meta-analysis, or both.	1
ABSTRACT			
Structured summary	2	Provide a structured summary including, as applicable: background; objectives; data sources; study eligibility criteria, participants, and interventions; study appraisal and synthesis methods; results; limitations; conclusions and implications of key findings; systematic review registration number.	3-4
INTRODUCTION			
Rationale	3	Describe the rationale for the review in the context of what is already known.	5-6
Objectives	4	Provide an explicit statement of questions being addressed with reference to participants, interventions, comparisons, outcomes, and study design (PICOS).	6
METHODS			
Protocol and registration	5	Indicate if a review protocol exists, if and where it can be accessed (e.g., Web address), and, if available, provide registration information including registration number.	7
Eligibility criteria	6	Specify study characteristics (e.g., PICOS, length of follow-up) and report characteristics (e.g., years considered, language, publication status) used as criteria for eligibility, giving rationale.	7
Information sources	7	Describe all information sources (e.g., databases with dates of coverage, contact with study authors to identify additional studies) in the search and date last searched.	7
Search	8	Present full electronic search strategy for at least one database, including any limits used, such that it could be repeated.	eMethods 1
Study selection	9	State the process for selecting studies (i.e., screening, eligibility, included in systematic review, and, if applicable, included in the meta-analysis).	7
Data collection process	10	Describe method of data extraction from reports (e.g., piloted forms, independently, in duplicate) and any processes for obtaining and confirming data from investigators.	8-9
Data items	11	List and define all variables for which data were sought (e.g., PICOS, funding sources) and any assumptions and simplifications made.	8-9
Risk of bias in individual studies	12	Describe methods used for assessing risk of bias of individual studies (including specification of whether this was done at the study or outcome level), and how this information is to be used in any data synthesis.	10

Summary measures	13	State the principal summary measures (e.g., risk ratio, difference in means).	11, eMethods 2
Synthesis of results	14	Describe the methods of handling data and combining results of studies, if done, including measures of consistency (e.g., I^2) for each meta-analysis.	9-13, eMethods 2

Section/topic	#	Checklist item	Reported on page #
Risk of bias across studies	15	Specify any assessment of risk of bias that may affect the cumulative evidence (e.g., publication bias, selective reporting within studies).	10-11, eFigure 1
Additional analyses	16	Describe methods of additional analyses (e.g., sensitivity or subgroup analyses, meta-regression), if done, indicating which were pre-specified.	9-13, eMethods 2
RESULTS			
Study selection	17	Give numbers of studies screened, assessed for eligibility, and included in the review, with reasons for exclusions at each stage, ideally with a flow diagram.	14, Fig 1
Study characteristics	18	For each study, present characteristics for which data were extracted (e.g., study size, PICOS, follow-up period) and provide the citations.	14-15, Table 1
Risk of bias within studies	19	Present data on risk of bias of each study and, if available, any outcome level assessment (see item 12).	15, eFigure 1
Results of individual studies	20	For all outcomes considered (benefits or harms), present, for each study: (a) simple summary data for each intervention group (b) effect estimates and confidence intervals, ideally with a forest plot.	15-18, Fig2-4, eTable 1, eFigure 3-7
Synthesis of results	21	Present results of each meta-analysis done, including confidence intervals and measures of consistency.	15-18, Fig2-3, eTable 1, eFigure 3-7
Risk of bias across studies	22	Present results of any assessment of risk of bias across studies (see Item 15).	eTable 1
Additional analysis	23	Give results of additional analyses, if done (e.g., sensitivity or subgroup analyses, meta-regression [see Item 16]).	18-19, eTable 3
DISCUSSION			
Summary of evidence	24	Summarize the main findings including the strength of evidence for each main outcome; consider their relevance to key groups (e.g., healthcare providers, users, and policy makers).	20
Limitations	25	Discuss limitations at study and outcome level (e.g., risk of bias), and at review-level (e.g., incomplete retrieval of identified research, reporting bias).	23

Conclusions	26	Provide a general interpretation of the results in the context of other evidence, and implications for future research.	24
FUNDING			
Funding	27	Describe sources of funding for the systematic review and other support (e.g., supply of data); role of funders for the systematic review.	1, 25

eTable 1. Summary of findings:

Triple therapy (ICS/LABA/LAMA) compared to dual therapy (ICS/LABA) for asthma

Outcome № of participants (studies)	Relative effect (95% CI)	Anticipated absolute effects (95% CI)			Certainty	What happens (Standardized GRADE terminology[8])
		Dual Therapy	Triple Therapy	**Difference**		
Severe exacerbations (RR) № of participants: 9701 (9 RCTs)	**RR 0.83** (0.77 to 0.90)	**Study population, history of exacerbation**			⨁⨁⨁⨁ HIGH	Triple therapy (ICS/LABA/LAMA) reduces severe exacerbations. Risk for future exacerbation leads to important changes in anticipated absolute effects.
		30.0%	**24.6%** (22.5 to 26.7)	**5.4% fewer** (7.5 to 3.3 fewer)		
		Study population no history of exacerbation				
		2.7%	**2.2%** (2 to 2.4)	**0.5% fewer** (0.7 to 0.3 fewer)		
		Cohorts (US database), no exacerbation[9]				
		11.0%	**9.0%** (8.3 to 9.8)	**2.0% fewer** (2.8 to 1.2 fewer)		
Severe exacerbation rate (IRR) № of participants: 10048 (7 RCTs)	**Rate ratio 0.85** (0.78 to 0.92)	**GINA 3[9] [c]**			⨁⨁⨁⨁ HIGH	Triple therapy (ICS/LABA/LAMA) reduces severe exacerbation rate. Risk for future exacerbation, including severity of asthma, leads to important changes in anticipated absolute effects.
		14.3%	**12.2%** (11.2 to 13.2)	**2.1% fewer** (3.1 to 1.1 fewer)		
		GINA 4[9] [d]				
		15.3%	**13.0%** (11.9 to 14.1)	**2.3% fewer** (3.4 to 1.2 fewer)		
		GINA 5[9] [e]				
		45.5%	**38.7%** (35.5 to 41.9)	**6.8% fewer** (10 to 3.6 fewer)		
Severe exacerbation time-to-event (HR) № of participants: 8583 (6 RCTs)	**HR 0.84** (0.77 to 0.92)	**Low risk for future exacerbation**			⨁⨁⨁⨁ HIGH	Triple therapy (ICS/LABA/LAMA) improves severe exacerbation time-to-event. Risk for future exacerbation leads to important changes in anticipated absolute effects.
		10.0%	**8.5%** (7.7 to 9.2)	**1.5% fewer** (2.3 to 0.8 fewer)		
		High risk for future exacerbation				
		30.0%	**25.9%** (23.1 to 27.6)	**4.1% fewer** (6.9 to 2.4 fewer)		
Asthma control assessed with: ACQ (lower better; MID 0.5) № of participants: 10967 (14 RCTs)	**RR to achieve MID 1.04** (1.01 to 1.06)	The mean asthma control was **1.46** (median of mean change from baseline -0.72 SD 0.66) MID: 62.9%	- **65.2%** (63.7 to 66.6)	MD **0.04 better** (0.01 to 0.07 better) **2.2% more** (0.7 to 3.7 more)	⨁⨁⨁⨁ HIGH	Triple therapy (ICS/LABA/LAMA) results in a slight improvement in asthma control which may be clinically unimportant.
Quality of life assessed with: AQLQ (higher better; MID 0.5) № of participants: 4825 (6 RCTs)	**RR to achieve MID 1.03** (0.98 to 1.09)	The mean quality of life was **5.50** (median of mean change from baseline 0.66 SD 1.01) MID: 56.2%	- **58.2%** (55.1 to 61.3)	MD **0.05 better** (0.03 worse to 0.13 better) **2.0% more** (1.2 fewer to 5.0 more)	⨁⨁⨁◯ MODERATE [a]	Triple therapy (ICS/LABA/LAMA) likely results in little to no difference in quality of life.
Lung function assessed with: FEV_1 (litres, MID 0.1-0.2L) № of participants: 11990 (18 RCTs)	**RR increase ≥ 0.2L 1.27** (1.22 to 1.32)	The mean lung function was **1.70 L** (median of mean change from baseline 0.10L SD 0.32L) ≥ 0.2L: 37.4%	- **47.4%** (45.7 to 49.3)	MD **0.08 litres greater** (0.07 to 0.10 greater) **10.0% more** (8.3 to 11.9 more)	⨁⨁⨁⨁ HIGH	Triple therapy (ICS/LABA/LAMA) results in a slight increase in lung function.
Treatment-related adverse events № of participants: 7024 (8 RCTs)	**RR 1.18** (0.96 to 1.46)	5.3%	**6.3%** (5.1 to 7.8)	**1.0% more** (0.2 fewer to 2.4 more)	⨁⨁⨁◯ MODERATE [b]	Triple therapy (ICS/LABA/LAMA) likely results in little to no difference in treatment-related adverse events. Similar findings for any adverse event, Serious Adverse Events, pulmonary infectious adverse events, eye-related adverse events, and arrhythmia. Triple therapy slightly increases dry mouth/dysphonia (3.0% vs. 1.8%; RR 1.65 [95%CI 1.14-2.38], high certainty).

eTable 1. Summary of findings:

Triple therapy (ICS/LABA/LAMA) compared to dual therapy (ICS/LABA) for asthma

Outcome № of participants (studies)	Relative effect (95% CI)	Anticipated absolute effects (95% CI)			Certainty	What happens (Standardized GRADE terminology[8])
		Dual Therapy	Triple Therapy	**Difference**		
All cause mortality № of participants: 9761 (9 RCTs)	**RD 0.02%** (-0.16% to 0.21%)	0.12%	**0.14%** (0% to 0.33%)	**0.02% more** (0.16% fewer to 0.21% more)	⨁⨁⨁⨁ HIGH	Triple therapy (ICS/LABA/LAMA) results in little to no difference in all-cause mortality.

The risk in the intervention group (and its 95% confidence interval) is based on the assumed risk in the comparison group and the **relative effect** of the intervention (and its 95% CI).

GINA: Global Initiative for Asthma; **CI:** Confidence interval; **RR:** Risk ratio; **HR:** Hazard Ratio; **MD:** Mean difference. Click here for an online-interactive Summary of Findings (gradepro.org), https://bit.ly/JAMATripleTherapy

GRADE Working Group grades of evidence

GRADE domains considered in rating the certainty of evidence: Risk of bias, inconsistency, indirectness, imprecision, publication bias, residual confounding, effect magnitude, and dose-response relationship. Serious concerns in the first five domains lead to rating down the certainty of the evidence. Explanations for rating down are detailed in the footnotes. If the evidence is rated as high certainty there are no serious concerns with any of the domains.

High certainty: We are very confident that the true effect lies close to that of the estimate of the effect

Moderate certainty: We are moderately confident in the effect estimate: The true effect is likely to be close to the estimate of the effect, but there is a possibility that it is not

Low certainty: Our confidence in the effect estimate is limited: The true effect may be substantially different from the estimate of the effect

Very low certainty: We have very little confidence in the effect estimate: The true effect is likely to be substantially different from the estimate of effect

a. Could be imprecise due to CIs crossing zero, but not so imprecise that it crosses the MID of 0.5 on either side of the mean effect. Nevertheless, we conservatively rated down for imprecision.

b. Could be imprecise due to CIs crossing zero, but the upper and lower 95%CI bounds of absolute effects are likely clinically unimportant. Nevertheless, we conservatively rated down for imprecision.

c. **GINA 3:** Patients controlled on low dose ICS-LABA maintenance and reliever therapy, daily low dose ICS-LABA maintenance plus as-needed SABA, or low dose ICS-leukotriene receptor antagonist

d. **GINA 4:** Patients controlled on medium dose ICS-LABA as maintenance and reliever therapy, medium dose ICS-LABA maintenance plus as-needed SABA, or high dose ICS-LABA

e. **GINA 5:** Patients not controlled despite GINA step 4 therapy

ACQ: ACQ-7 is a 7-item list that contains 5 symptoms-based questions, rescue bronchodilator use, and FEV_1 assessment with each item scored on a 7-point scale (0=no impairment to 6=maximum impairment)[18]. ACQ-6 contains all items of ACQ-7 except FEV_1 assessment[18,23]. ACQ-5 only contains 5 symptoms-based questions[23]. The questions are equally weighted and ACQ score is the mean of the included questions ranging from 0 [totally controlled] to 6 [severely uncontrolled][18]. MCID for a change in ACQ is 0.5 for all three questionnaires[18].

ACT: ACT is a 5-item list with each item scored on a 5-point scale (for symptoms and activity-related rating: 1=all the time to 5=not at all; for asthma control rating: 1=not controlled at all to 5=completely controlled)[19]. The total score ranges from 5 (poor control of asthma) to 25 (complete control of asthma)[19]. MCID for a change in ACT is 3[19].

AQLQ and mini-AQLQ: AQLQ score is a 32-item list with each item scored on a 7-point scare (1=severely impaired to 7=not impaired at all)[20]. Mini-AQLQ is a shorter 15-item list version of AQLQ[21]. The higher score on both questionnaires correlates with better quality of life[21,24]. The MCID for a change in both AQLQ and mini-AQLQ is 0.5[24]

eTable 2. Inclusion/Exclusion criteria

Author, year (#)	Inclusion criteria	Exclusion criteria
Hamelmann, 2017	Aged 12–17 years Asthma for >=3 months Symptomatic asthma with ACQ-7 >= 1.5 Receipt of high-dose ICS >=1+ controllers or medium-dose ICS + >=2+ controllers for >= 4 weeks prior Prebronchodilator FEV1 60–90% predicted FEV1 reversibility >=12% and >=200 mL after salbutamol Variability of absolute FEV1 from screening to randomisation within ±30% Never smoked or stopped smoking >=1 year before enrolment	Any significant disease other than asthma
Hoshino, 2018	Asthma for >= 3 months Symptomatic at the time of screening Receiving ICS + LABA for 4 or more weeks prior to the screening FEV1 > 60% of the predicted Never smoked or < 5 pack-years and stopped >= 1 year prior	COPD or any respiratory disease other than asthma Glaucoma Prostatic hyperplasia Respiratory tract infection in the 2 weeks prior to screening
Ishiura, 2019	Documented asthma and COPD (proven airway hyperresponsiveness and incomplete reversible airway obstruction) Receiving ICS+LABA	Not Reported
Ishiura, 2020	Documented asthma and COPD (proven airway hyperresponsiveness and incomplete reversible airway obstruction) Receiving ICS+LABA	oral steroid therapy for at least 8 weeks prior to participation. Unstable moderate to severe sympotoms
Jabbal, 2017	Aged >=18 years Persistent asthma Minimum FEV1 of >50% predicted Mannitol responsive Receiving an ICS or ICS + LABA	Not Reported
Jabbal, 2020	Aged 18-65 years Persistent asthma Current smoking Receipt of at least 400ug per day of ICS (as HFA-budesonide equivalent dose)	History of COPD or asthma-COPD overlap Asthma exacerbations requiring systemic steroids within 1 month or requiring hospital admission within 3 months
Kerstjens, 2011		
Kerstjens, 2012 #1	Aged 18-75 years Asthma for >= 5 years, diagnosed before 40 years Symptomatic asthma with ACQ-7 >=1.5	COPD or other serious coexisting illnesses Concurrent use of anticholinergic bronchodilators

Author, year (#)	Inclusion criteria	Exclusion criteria
	Postbronchodilator FEV1 =< 80% predicted and =<70% FVC after salbutamol Receiving ICS + LABA >= 1 asthma exacerbation treated with systemic steroids in the previous year Never smoked or < 10 pack-year history and stopped >= 1 year prior	
Kerstjens, 2012 #2	Aged 18-75 years Asthma for >= 5 years, diagnosed before 40 years Symptomatic asthma with ACQ-7 >=1.5 Postbronchodilator FEV1 =< 80% predicted and =<70% FVC after salbutamol Receiving ICS + LABA >= 1 asthma exacerbation treated with systemic steroids in the previous year Never smoked or < 10 pack-year history and stopped >= 1 year prior	COPD or other serious coexisting illnesses Concurrent use of anticholinergic bronchodilators
Kerstjens, 2020	Aged 18-75 years Asthma for >= 1 year Receipt of medium- or high-dose ICS + LABA for >= 3 months prior, stable for >=1 month Symptomatic asthma with ACQ-7 >=1.5 Postbronchodilator FEV1 =< 80% predicted and =<70% FVC after salbutamol Receiving ICS + LABA >= 1 asthma exacerbation treated with systemic steroids in the previous year Prebronchodilator FEV1 < 80% predicted and =<70% FVC	Asthma exacerbation requiring hospitalization, ED visit, or systemic steroids in the last 6 weeks History of intubation for asthma Condition likely to be worsened by ICS administration or at risk participating in study Receipt of a LAMA for asthma within the past 3 months Narrow angle glaucoma Symptomatic prostatic hypertrophy unless stable on treatment Bladder-neck obstruction RTI or asthma worsening within 4 weeks prior Any chronic condition affecting upper respiratory tract which may interfere History of chronic lung disease other than asthma Type 1 diabetes or uncontrolled type II diabetes Significant health condition that might compromise patient safety, compliance, evaluation, or completion of the study Lactose hypersensitivity History of alcohol or other substance use History of non-compliance to medications or unwilling to complete a patient diary Patients who do not maintain regular day/night, waking/sleeping cycles smoking tobacco products within 6 months before screening or a smoking history of greater than 10 pack-years, a chronic lung disease other than asthma, or an asthma exacerbation requiring systemic corticosteroids, hospitalisation, or emergency room visit within 6 weeks of screening
Lee, 2020	Aged >= 18 years Asthma for at least 1 year Pre-bronchodilator morning FEV1 of >=30% to <85% predicted Change in FEV1 of >=12% and >=200mL after albuterol or salbutamol Symptomatic with ACQ-6 ≥1.5	Asthma exacerbation within the 6 weeks prior to visit 1 Diagnosis of COPD or other concurrent respiratory disorder Pneumonia or pneumonia risk factors at screening Clinically significant medical condition including liver disease, cardiac disease, cancer, ECG abnormality

Author, year (#)	Inclusion criteria	Exclusion criteria
	Documented health-care contact or documented temporary change in asthma therapy for acute asthma symptoms within 1 year before screening Receiving daily ICS + LABA for at least 12 consecutive weeks before pre-screening, at a stable dose for at least 6 weeks prior to pre-screening with an ICS dose of >250ug/d of fluticasone propionate or equivalent	Medical condition that could be impacted by a muscarinic antagonist Drug or alcohol misuse Current smokers or former smokers with >=10 pack-years Pregnant or lactating women, or those planning on becoming pregnant Patients at risk of non-compliance or unable to comply or those with conditions
Singh, 2014	Aged ≥18 years Uncontrolled asthma Receiving stable medium doses of ICS+LABA for at least 4 weeks prior Prebronchodilator FEV1 ≥40% and <80% of predicted value Change in FEV ≥12% and ≥200mL with salbutamol Symptomatic with ACQ ≥1.5 Co-operative attitude and ability to be trained to correctly use the pMDI	Inability to carry out PFTs or comply with study procedure or intake History of near-fatal asthma, ICU admission for asthma, or frequent exacerbations Asthma exacerbation requiring hospitalization, ED visit, or systemic steroids in the last 4 weeks Lower RTI in the last 4 weeks On therapy for GERD and/or with history of GERD causing asthma symptoms History of seasonal worsening of asthma and cannot complete study outside of allergen season Any other significant lung disease including COPD, cystic fibrosis, bronchiectasis, alpha-1 antitrypsin deficiency Current smoking or ex-smoking with >= 10 pack-years and stopped =< 1 year prior Change in dose, schedule, formulation of ICS + LABA in 4 weeks prior Current or prior treatment with LAMA Current treatment with anti-IgE antibodies Pregnant or lactating women Women of child-bearing potential not using highly effective contraception Receipt of an investigational drug within 2 months prior Clinically significant cardiovascular disease or abnormal ECG Narrow-angle glaucoma, Prostatic hypertrophy, Bladder neck obstruction Other severe acute or chronic medical or psychiatric condition or laboratory abnormality that may increase risk Receipt of a live-attenuated virus vaccination within 2 weeks Lack of mental or legal capacity History of alcohol or drug misuse disorder Intolerance, hypersensitivity or contraindication to beta-agonists, ICS, anticholinergics, or propellant gases/excipients Major surgery within 3 months or planned during trial Current treatment with non-potassium sparing diuretics Current treatment with monoamine oxidase inhibitors or tricyclic antidepressants Receipt of any therapy that could interfere with the study drugs
NCT03358147, 2017	Aged 12-80 years Documented physician diagnosis of asthma Receiving ICS + LABA for >= 4 weeks	Oral steroids within 4 weeks prior Current smoking, former smoking with >10 pack-years, or stopped <6 months ago History of life-threatening asthma exacerbation

Author, year (#)	Inclusion criteria	Exclusion criteria
	Prebronchodilator FEV1 40-85% predicted for those aged 18-80 years, and 40-90% for those aged 12-17 years Acceptable spirometry performance	Treatment for lower RTI or asthma exacerbation within 4 weeks Hospitalization for asthma within 3 months History of or current clinically significant disease Cancer not in remission for >= 5 years Treatment with another investigational study drug within 30 days or 5 half lives Previously randomized in any PT001 study
Ohta, 2015	Aged 18-75 years Asthma for >= 12 weeks, diagnosed before 40 years Change in FEV1 of more than 12% and over 200 mL after salbutamol 400 µg Receiving stable medium dose ICS +/- LABA, for >=4 weeks prior to screening Symptomatic asthma with ACQ-7 score >= 1.5 Prebronchodilator FEV1 >= 60% and =< 90% of predicted normal Never smoked or <10 pack-year history and stopped smoking >= 1 year prior	COPD or other significant unstable concomitant disease On any investigational drug, non-topical beta-blockers or other asthma therapies within 4 weeks prior to enrolment/screening On anti-immunoglobulin E antibodies within 6 months of enrolment/screening Asthma exacerbation or RTI within 4 weeks prior to enrolment/screening Participating in another trial Narrow-angle glaucoma Micturition disorder because of prostatic hyperplasia Failed to complete >=80% of their electronic diary during the run-in period
Szefler, 2017	Aged 6 to 11 years Asthma for at least 6-months Symptomatic with ACQ-IA 38 >= 1.5 Receiving stable high dose ICS + >=1+ controllers or at a stable medium dose ICS + >=2+ controllers >= 4 weeks before screening Prebronchodilator FEV1 of 60% to 90% of predicted FEV1 reversibility of >= 12% after 200-mg salbutamol (albuterol) dose Variability of absolute FEV1 values from screening to randomization +/-30%	Significant disease other than asthma
Virchow, 2019 (TRIMARAN)	Aged 18–75 years Asthma for at least 1 year, diagnosed before age 40 years Prebronchodilator FEV1 < 80% predicted Change in FEV1 of more than 12% and over 200 mL after salbutamol 400 µg Symptomatic with ACQ-7 ≥1.5 At least one exacerbation requiring systemic corticosteroids, ED visit, or admission to hospital in the previous 12 months Receiving a stable dose of an ICS + LABA for at least 4 weeks before study entry (Medium dose of inhaled corticosteroid)	History of near fatal asthma or admission to ICU for asthma Severe exacerbation in the 4 weeks before study entry or during run-in period Any other substantial lung disease that could interfere with study assessments Current smokers or former smokers with >=10 pack-years or who stopped <1 year before screening Current treatment with monoclonal antibodies or other biological drugs Clinically significant cardiovascular conditions or laboratory abnormalities Unstable concurrent disease that could affect efficacy or safety
Virchow, 2019 (TRIGGER)	Aged 18–75 years Asthma for at least 1 year, diagnosed before age 40 years Prebronchodilator FEV1 < 80% predicted Change in FEV1 of more than 12% and over 200 mL after salbutamol 400 µg Symptomatic with ACQ-7 ≥1.5	History of near fatal asthma or admission to ICU for asthma Severe exacerbation in the 4 weeks before study entry or during run-in period Any other substantial lung disease that could interfere with study assessments Current smokers or former smokers with >=10 pack-years or who stopped <1 year before screening Current treatment with monoclonal antibodies or other biological drugs

Author, year (#)	Inclusion criteria	Exclusion criteria
	At least one exacerbation requiring systemic corticosteroids, ED visit, or admission to hospital in the previous 12 months Receiving a stable dose of an ICS + LABA for at least 4 weeks before study entry (High dose of inhaled corticosteroid)	Clinically significant cardiovascular conditions or laboratory abnormalities Unstable concurrent disease that could affect efficacy or safety
Wang, 2015	Moderate asthma with daily symptoms, exacerbations that may affect activity and sleep, nocturnal symptoms more than once a week, daily use of inhaled SABA, FEV1 or PEF 60%-80% predicted, and PEF or FEV1 variability >30% ACT score 12-20	Not Reported
Watz, 2020	Aged 18-75 years Documented physician diagnosis of asthma for >= 12 months Receiving ICS + LABA for >= 3 month and at a stable medium or high dose of ICS for at least 1 month Prebronchodilator FEV1 < 80 % predicted Change in FEV1 of ≥ 12 % and 200 mL after salbutamol or albuterol	Smoked or inhaled tobacco products within the 6-month period prior Asthma exacerbation requiring systemic steroids or hospitalization or ED visit within 6 weeks Narrow-angle glaucoma Symptomatic benign prostatic hyperplasia (BPH) Bladder-neck obstruction Severe renal impairment or urinary retention Respiratory tract infection or asthma worsening within 4 weeks prior Any chronic conditions affecting the upper respiratory tract or chronic lung disease other than asthma Type I diabetes or uncontrolled Type II diabetes Clinically significant ECG abnormality History of hypersensitivity or intolerance to any of the study drugs Narcolepsy and/or insomnia Maintenance Immunotherapy (desensitization) for allergies for less than 3 months Maintenance Immunotherapy for more than 3 months prior, expected to change throughout the course of the study Pregnant or nursing (lactating) women Women of child-bearing potential not using highly effective contraception Having discontinued LAMA therapy in the past for any safety, tolerability or perceived lack of efficacy reason Paradoxical bronchospasm in response to inhaled medicines Clinically relevant bronchoconstriction with forced expiratory maneuvers Potassium level below the laboratory limit of normal
Zhang, 2018	Aged >18 years Asthma Pre-bronchodilator FEV1 < 60% predicted	Critical disease other than asthma Pregnant or lactating women Use of receptor antagonists Lung diseases in addition to asthma or pulmonary lobectomy Contraindications to salmeterol or tiotropium bromide

eTable 3. Subgroup and Sensitivity Analyses

	Severe exacerbations	FEV1	Asthma Control Score	Asthma-related Quality of Life
Subgroup analyses				
Risk of Bias subgroup analysis				
High	N/A	MD 0.09 (0.04 to 0.14)	SMD 0.09 (-0.40 to 0.59)	SMD 0.31 (-0.20 to 0.83)
Low	RR 0.83 (0.77 to 0.90)	MD 0.08 (0.07 to 0.10)	SMD -0.07 (-0.10 to -0.03)	SMD 0.05 (-0.03 to 0.13)
Interaction	N/A	0.80	0.53	0.32
Previous exacerbations subgroup analysis				
<1 exacerbation in the previous year	RR 0.65 (0.29 to 1.47)	MD 0.08 (0.06 to 0.10)	SMD -0.05 (-0.10 to 0.00)	SMD 0.07 (-0.07 to 0.20)
≥1 exacerbation in the previous year	RR 0.84 (0.77 to 0.91)	MD 0.08 (0.06 to 0.10)	SMD -0.08 (-0.13 to -0.02)	SMD 0.05 (-0.06 to 0.16)
Interaction	0.52	0.88	0.55	0.83
Type-2 asthma status subgroup analysis				
$T2_{Low}$	0.85 (0.76 to 0.95)	MD 0.09 (0.06 to 0.12)	N/A	N/A
$T2_{High}$	0.86 (0.74 to 1.01)	MD 0.08 (0.01 to 0.09)		
Interaction	0.88	0.09		
Types of LAMA subgroup analysis				
Tiotropium	RR 0.82 (0.68 to 1.00)	MD 0.08 (0.06 to 0.11)	SMD -0.04 (-0.16 to 0.08)	SMD 0.14 (0.02 to 0.27)
Glycopyrronium	RR 0.82 (0.75 to 0.89)	MD 0.07 (0.04 to 0.10)	SMD -0.05 (-0.10 to 0.00)	SMD -0.00 (-0.07 to 0.07)
Umeclidinium	RR 0.93 (0.72 to 1.21)	MD 0.08 (0.07 to 0.09)	SMD -0.10 (-0.17 – 0.04)	N/A
Interaction	0.65	0.52	0.42	0.05
Credibility	N/A			Low
Age subgroup analysis				
Age <18	RR 0.72 (0.31 to 1.66)	MD 0.06 (-0.01 to 0.12)	SMD 0.08 (-0.06 to 0.23)	NA
Age ≥18 *	RR 0.83 (0.76 to 0.91)	MD 0.08 (0.07 to 0.10)	SMD -0.08 (-0.12 to -0.04)	
Interaction	0.72	0.48	0.04	
Credibility	N/A	N/A	Low	N/A
FEV1 subgroup analysis				
FEV1 ≥ 80%	RR 0.91 (0.72 to 1.15)	MD 0.06 (0.00 to 0.11)	SMD -0.09 (-0.16 to 0.03)	N/A
FEV1 <80%	RR 0.80 (0.74 to 0.87)	MD 0.09 (0.07 to 0.10)	SMD -0.06 (-0.11 to 0.01)	
Not reported	N/A	MD 0.03 (-0.03 to 0.09)	SMD -0.01 (-0.13 to 0.11)	
Interaction	0.42	0.17	0.46	

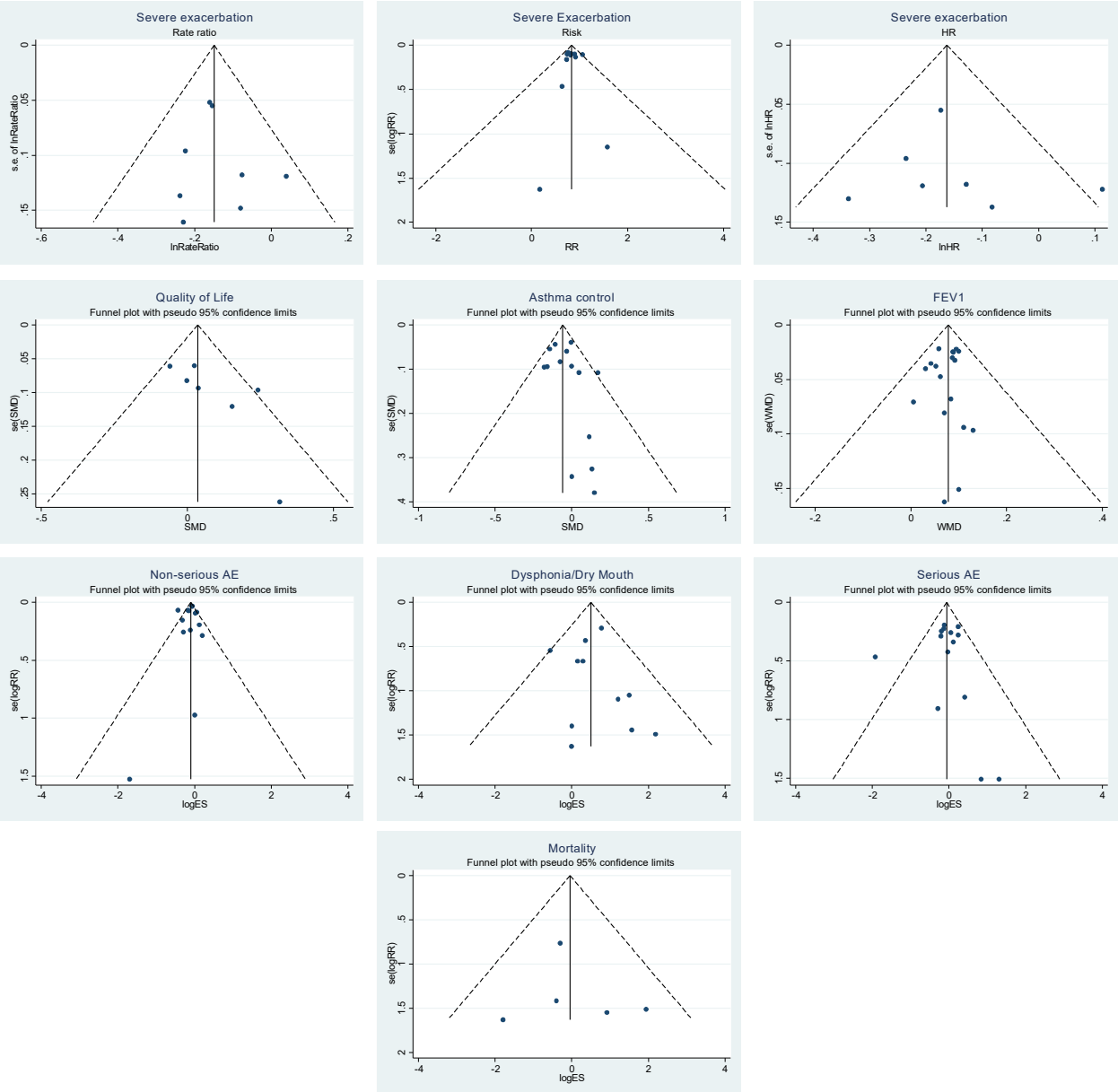
	Severe exacerbations	FEV1	Asthma Control Score	Asthma-related Quality of Life
Smoking history subgroup analysis				
Non-smoker (No current smoker included & minimal (<20%) prior smokers included)	RR 0.84 (0.73 to 0.97)	MD 0.08 (0.07 to 010)	SMD -0.07 (-0.11 to -0.03)	N/A
Smoking history (≥20% prior smokers included)	RR 0.85 (0.77 to 0.91)	MD 0.08 (0.05 to 0.11)	SMD 0.07 (-0.39 to 0.53)	
Not reported	N/A	MD 0.04 (-0.03 to 0.11)	SMD 0.10 (-0.31 to 0.52)	
Interaction	0.92	0.47	0.61	
Dose of ICS subgroup analysis				
Medium and High	RR 0.83 (0.77 to 0.95)	MD 0.08 (0.05 to 0.11)	SMD -0.04 (-0.16 to 0.07)	SMD 0.07 (-0.03 to 0.16)
Medium only	RR 0.79 (0.72 to 0.87)	MD 0.08 (0.06 to 0.10)	SMD -0.04 (-0.09 to 0.02)	SMD 0.06 (-0.14 to 0.25)
High only	RR 1.06 (0.87 to 1.30)	MD 0.13 (-0.06 to 0.32)	SMD 0.08 (-0.26 to 0.42)	N/A
Interaction	0.03	0.86	0.80	0.94
Credibility	Low	N/A		
Types of ICS subgroup analysis				
Budesonide	RR 0.83 (0.68 to 1.00)	MD 0.09 (0.06 to 0.12)	SMD -0.04 (-0.14 to 0.06)	SMD 0.15 (0.04 to 0.26)
Fluticasone	RR 0.93 (0.72 to 1.21)	MD 0.08 (0.06 to 0.09)	SMD -0.12 (-0.18 to 0.06)	N/A
Beclomethasone	RR 0.75 (0.67 to 0.85)	MD 0.06 (0.03 to 0.09)	SMD -0.06 (-0.13 to 0.02)	
Mometasone	RR 0.92 (0.80 to 1.05)	MD 0.09 (0.05 to 0.13)	SMD -0.02 (-0.13 to 0.10)	SMD -0.01 (-0.10 to 0.09)
Interaction	0.15	0.75	0.26	0.10
* NCT03358147, 2017 considered as age ≥18 as median age was 47.7				
Sensitivity analyses				
Worse case scenario	RR 0.83 (0.74 to 0.92)	N/A		
Exclude unpublished studies	N/A	MD 0.08 (0.06 to 0.10)	SMD -0.05 (-0.09 to -0.01)	SMD 0.06 (-0.03 to 0.14)
Exclude high risk of bias (Approach 1: Cochrane RoB 2)	N/A	MD 0.08 (0.07 to 0.10)	SMD -0.07 (-0.10 to -0.03)	SMD 0.05 (-0.03 to 0.13)
Exclude high risk of bias (Approach 2: Dechartes et. al. with the focus on the randomization process [sequence generation and allocation concealment] and blinding)	N/A	MD 0.08 (0.07 to 0.10)	SMD -0.07 (-0.10 to -0.03)	SMD 0.05 (-0.03 to 0.13)

Sensitivity analyses				
	Severe exacerbations	**FEV1**	**Asthma Control Score**	**Asthma-related Quality of Life**
Fixed effect analyses	RR 0.82 (0.75 to 0.89)	MD 0.08 (0.06 to 0.09)	SMD -0.05 (-0.09 to -0.01)	SMD 0.04 (-0.02 to 0.09)
Exclude crossover trials	N/A	MD 0.08 (0.06 to 0.10)	SMD -0.05 (-0.09 to -0.01)	SMD 0.05 (-0.05 to 0.15)
Exclude asthma-COPD overlap trials	N/A	N/A	SMD -0.05 (-0.09 to -0.01)	N/A
Hartung-Knapp-Sidik-Jonkman random effects	RR 0.83 (0.76 to 0.91)	MD 0.08 (0.07-0.09)	SMD -0.05 (-0.09 to -0.01)	SMD 0.05 (-0.05 to 0.15)
Correlation coefficient of 0.5	N/A	MD 0.08 (0.06 to 0.09)	SMD -0.05 (-0.09 to -0.01)	SMD 0.02 (-0.03 to 0.07)
Correlation coefficient of 0.7	N/A	MD 0.07 (0.05 to 0.08)	SMD -0.05 (-0.09 to -0.01)	SMD 0.09 (-0.02 to 0.20)
Excluding estimated value for CAPTAIN 2020	RR 0.80 (0.74 to 0.87)	N/A	N/A	N/A
	Mortality	**Cardiac serious adverse events**		
Accounting for no events in both groups using Bayesian meta-analysis (non-informative effect priors, Turner priors for heterogeneity),	1.03 (95% Credible Interval 0.35 to 2.47)	0.78 (95% Credible Interval 0.40 to 1.34)	N/A	N/A
Accounting for no events in both groups using Bayesian meta-analysis (non-informative effect priors, Turner priors for heterogeneity) only studies with 24-52 wk follow up	0.96 (95% Credible Interval 0.24 to 2.63)	N/A	N/A	N/A
Frequentist risk difference	0.02% (95%CI -0.16% to 0.21%)	0.006% (95%CI -0.2% to 0.2%)	N/A	N/A
Additional analyses, RR	**Dysphonia/Dry mouth**	**SAE**	**Non-serious AE**	**Treatment related AE**
Low risk of bias only	1.66 (1.15-2.41)	0.92 (0.73-1.16)	0.89 (0.81-0.97)	1.13 (0.95-1.34)
Published only	1.66 (1.15-2.40)	0.90 (0.70-1.17)	0.87 (0.80-0.95)	1.13 (0.95-1.34)
	Serious pulmonary infection	**Non-serious pulmonary infection**	**Eye-related AE, RD**	**Nonserious cardiac adverse event, RD**
Low risk of bias only	0.87 (0.50-1.50)	0.96 (0.83-1.12)	-0.01% (-0.21%, 0.01%)	0.01% (-0.27%, 0.29%)
Published only	0.83 (0.47-1.46)	0.97 (0.84-1.12)	-0.01% (-0.21%, 0.01%)	0.01% (-0.27%, 0.29%)
	Serious cardiovascular AE, RD	**Serious cardiovascular AE, RR**	**Mortality, RD**	**Mortality, RR**
Low risk of bias only	0.006% (-0.2%, 0.2%)	0.77 (0.38-1.55)	0.02% (-0.02%, 0.02%)	0.96 (0.33-2.75)
Published only	-0.04% (-0.3%, 0.2%)	0.75 (0.33-1.72)	0.02% (-0.02%, 0.02%)	0.96 (0.33-2.75)

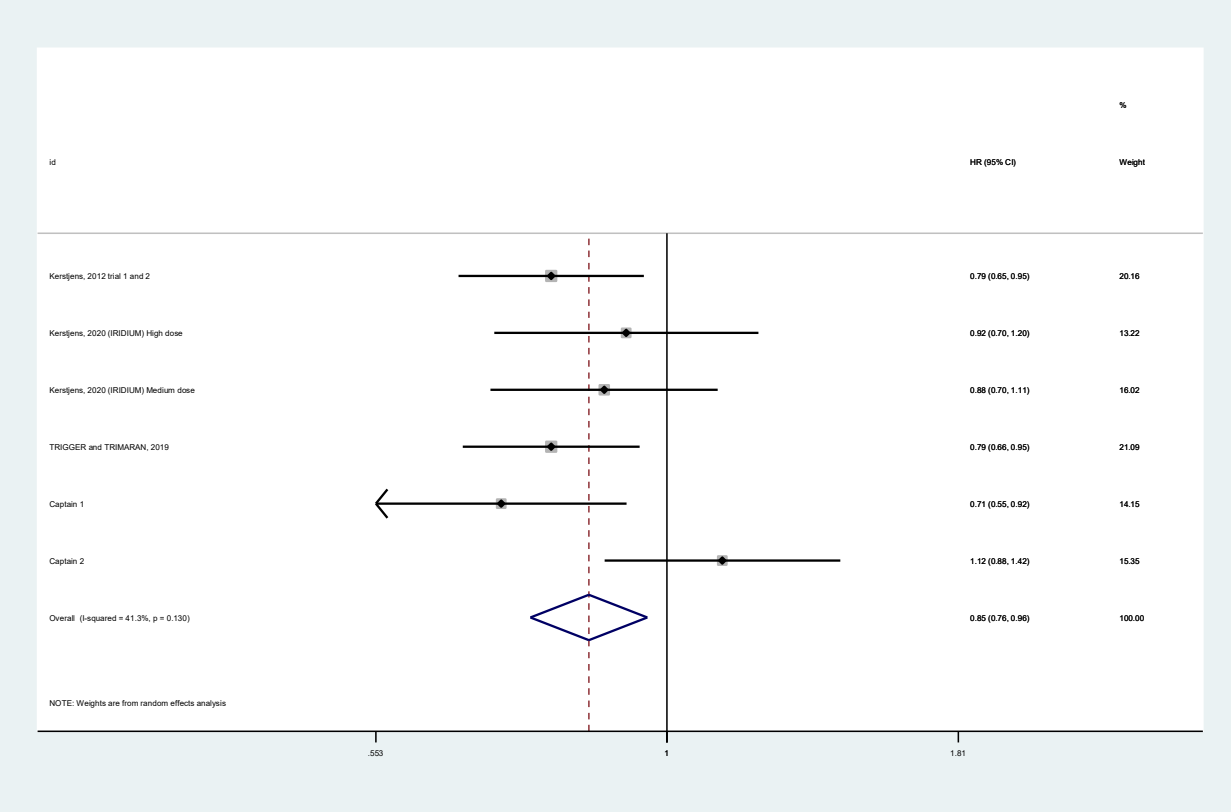
Considering Zhang 2018 (n=80), according to an alternate risk of bias approach, as high risk of bias did not change any of the estimates for outcomes it reported (FEV1, non-serious AE, dysphonia/dry mouth, cardiovascular AE)

eFigure 1 Assessment of Risk of Bias using Cochrane Collaboration Tool

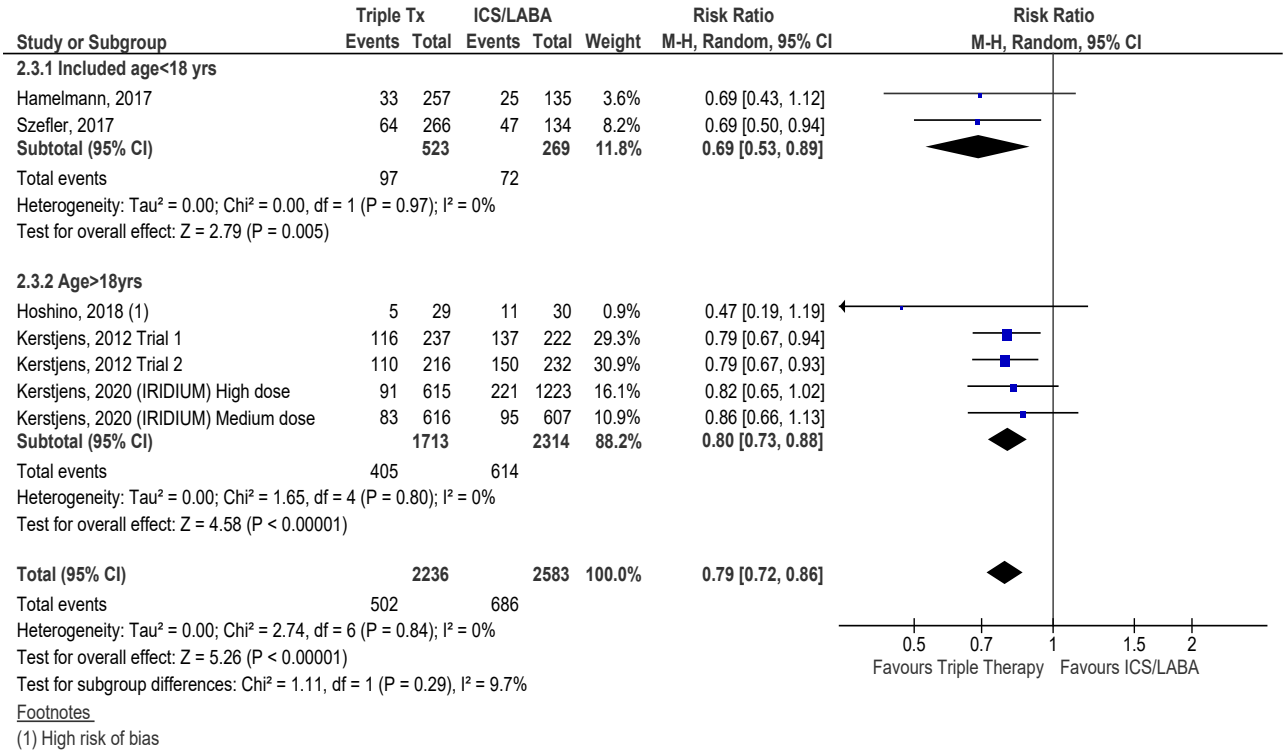
eFigure 2. Funnel plots



eFigure 3. Pooled Reported Hazard Ratios



eFigure 4. Asthma Worsening



Footnotes

(1) High risk of bias

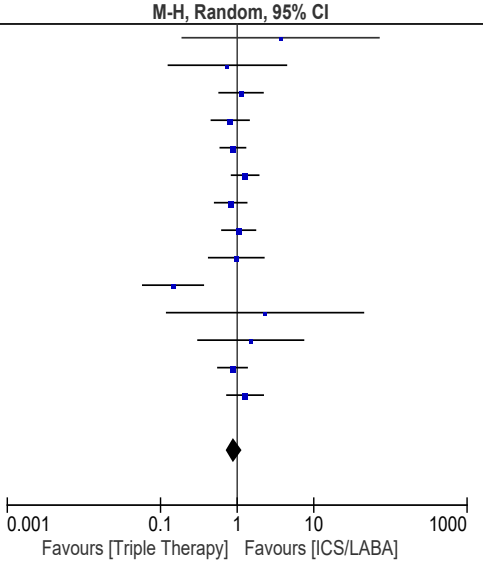
eFigure 5. Serious and Non-Serious Adverse Events

Serious Adverse Event

Study or Subgroup	Experimental Events	Experimental Total	Control Events	Control Total	Weight	Risk Ratio M-H, Random, 95% CI
Hamelmann, 2017	3	257	0	135	0.6%	3.69 [0.19, 70.92]
Kerstjens, 2011	3	207	2	103	1.6%	0.75 [0.13, 4.40]
Kerstjens, 2012 Trial 1	18	237	15	222	7.7%	1.12 [0.58, 2.18]
Kerstjens, 2012 Trial 2	19	219	25	234	9.2%	0.81 [0.46, 1.43]
Kerstjens, 2020 (IRIDIUM) High dose	46	616	52	613	13.1%	0.88 [0.60, 1.29]
Kerstjens, 2020 (IRIDIUM) Medium dose	49	617	38	608	12.4%	1.27 [0.84, 1.91]
Lee, 2020 (CAPTAIN) FF 100	41	811	25	407	10.8%	0.82 [0.51, 1.33]
Lee, 2020 (CAPTAIN) FF 200	44	812	21	406	10.3%	1.05 [0.63, 1.74]
NCT03358147 2017	24	834	7	237	5.7%	0.97 [0.43, 2.23]
Ohta, 2015	8	348	9	57	4.9%	0.15 [0.06, 0.36]
Singh, 2014	3	465	0	153	0.6%	2.31 [0.12, 44.53]
Szefler, 2017	6	267	2	134	2.0%	1.51 [0.31, 7.36]
TRIGGER, 2019	43	858	33	573	11.7%	0.87 [0.56, 1.35]
TRIMARAN, 2019	28	576	22	574	9.5%	1.27 [0.73, 2.19]
Total (95% CI)		**7124**		**4456**	**100.0%**	**0.92 [0.73, 1.16]**
Total events	335		251			

Heterogeneity: Tau² = 0.07; Chi² = 22.25, df = 13 (P = 0.05); I² = 42%

Test for overall effect: Z = 0.73 (P = 0.46)

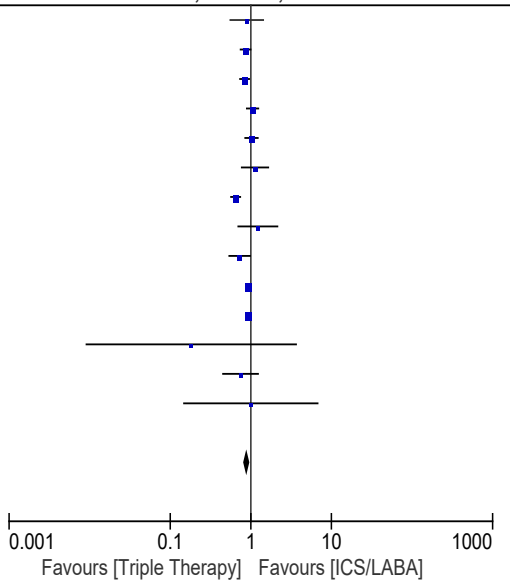


Non-Serious Adverse Event

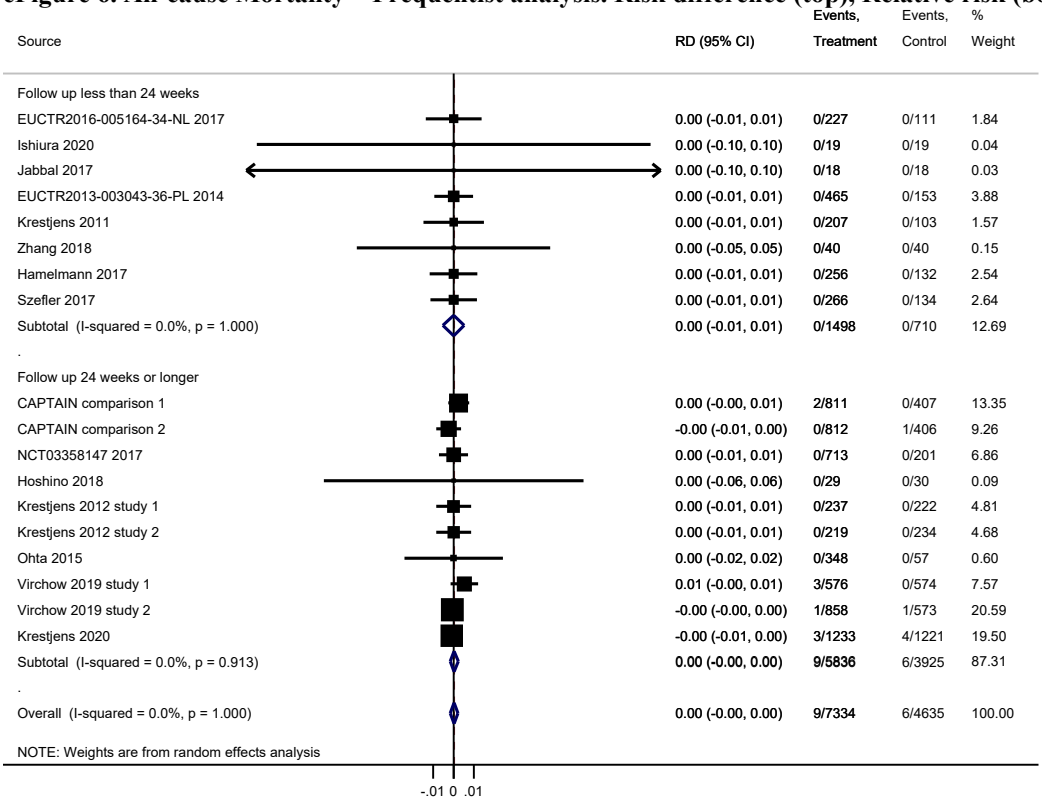
Study or Subgroup	Experimental Events	Experimental Total	Control Events	Control Total	Weight	Risk Ratio M-H, Random, 95% CI
Hamelmann, 2017	39	257	23	135	2.8%	0.89 [0.56, 1.43]
Kerstjens, 2012 Trial 1	136	237	148	222	11.0%	0.86 [0.75, 0.99]
Kerstjens, 2012 Trial 2	134	219	171	234	11.6%	0.84 [0.73, 0.95]
Lee, 2020 (CAPTAIN) FF 100	285	811	136	407	10.0%	1.05 [0.89, 1.24]
Lee, 2020 (CAPTAIN) FF 200	249	812	122	406	9.4%	1.02 [0.85, 1.22]
NCT03358147 2017	115	834	29	237	3.9%	1.13 [0.77, 1.65]
Ohta, 2015	198	348	50	57	11.5%	0.65 [0.57, 0.74]
Singh, 2014	52	465	14	153	2.1%	1.22 [0.70, 2.14]
Szefler, 2017	71	267	49	134	5.5%	0.73 [0.54, 0.98]
TRIGGER, 2019	620	858	443	573	14.8%	0.93 [0.88, 0.99]
TRIMARAN, 2019	431	576	455	574	14.7%	0.94 [0.89, 1.01]
Wang, 2015	0	33	2	30	0.1%	0.18 [0.01, 3.65]
Watz, 2020	32	227	21	111	2.5%	0.75 [0.45, 1.23]
Zhang, 2018	2	40	2	40	0.2%	1.00 [0.15, 6.76]
Total (95% CI)		**5984**		**3313**	**100.0%**	**0.89 [0.81, 0.97]**
Total events	2364		1665			

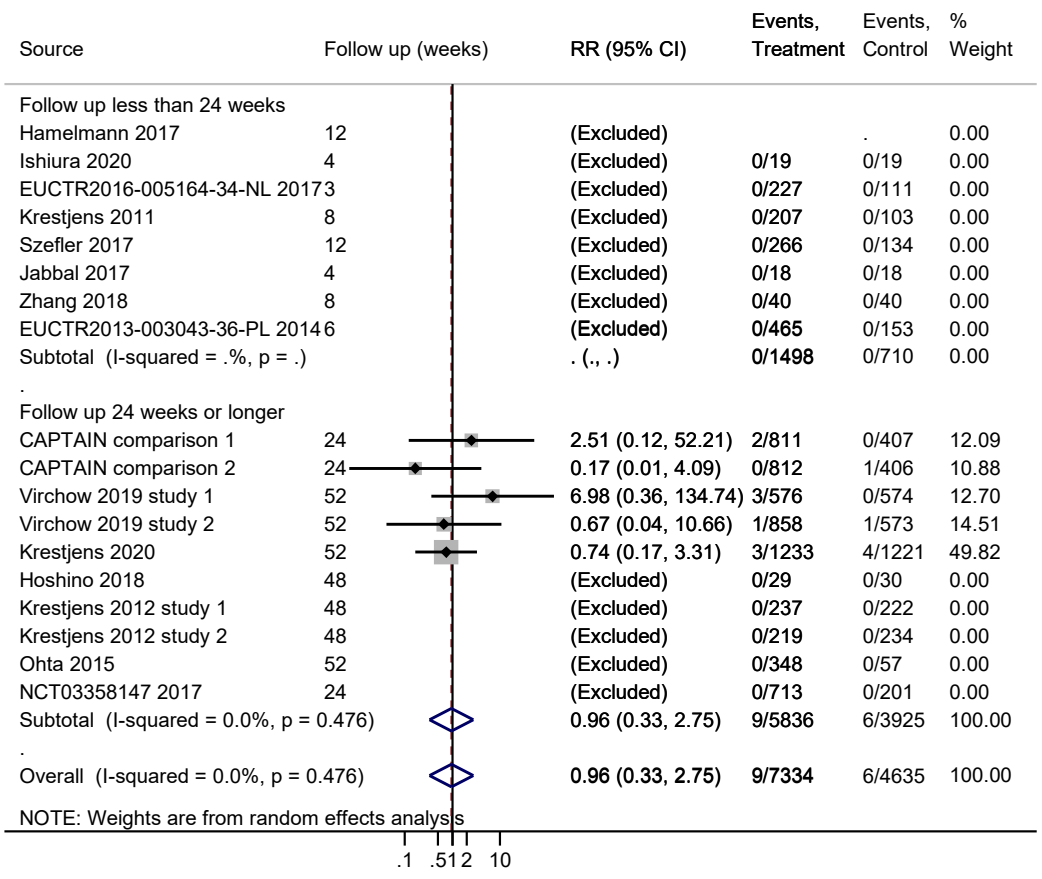
Heterogeneity: Tau² = 0.01; Chi² = 40.57, df = 13 (P = 0.0001); I² = 68%

Test for overall effect: Z = 2.71 (P = 0.007)



eFigure 6. All-cause Mortality – Frequentist analysis. Risk difference (top), Relative risk (bottom)



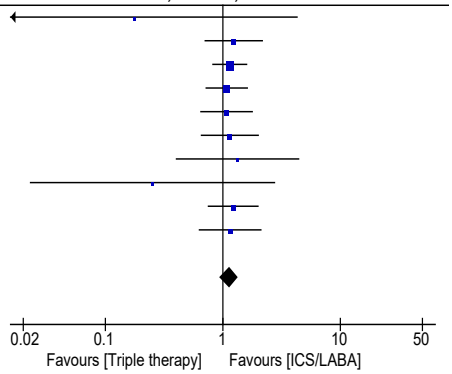


eFigure 7. Breakdown of Adverse Events

Treatment-Related Adverse Events

Study or Subgroup	Triple therapy Events	Total	ICS/LABA Events	Total	Weight	Risk Ratio M-H, Random, 95% CI
Hamelmann, 2017	0	257	1	135	0.3%	0.18 [0.01, 4.28]
Kerstjens, 2012 trial 1 and 2 pooled	26	456	21	456	9.5%	1.24 [0.71, 2.17]
Kerstjens, 2020 (IRIDIUM) High dose	51	616	89	1231	27.3%	1.15 [0.82, 1.59]
Kerstjens, 2020 (IRIDIUM) Medium dose	46	617	42	608	18.3%	1.08 [0.72, 1.61]
Lee, 2020 (CAPTAIN) FF 100	45	811	21	407	11.7%	1.08 [0.65, 1.78]
Lee, 2020 (CAPTAIN) FF 200	39	812	17	406	9.6%	1.15 [0.66, 2.00]
Ohta, 2015	16	228	3	57	2.1%	1.33 [0.40, 4.42]
Szefler, 2017	1	266	2	134	0.5%	0.25 [0.02, 2.75]
TRIGGER, 2019	44	858	24	573	12.6%	1.22 [0.75, 1.99]
TRIMARAN, 2019	22	576	19	574	8.2%	1.15 [0.63, 2.11]
Total (95% CI)		**5497**		**4581**	**100.0%**	**1.13 [0.95, 1.34]**
Total events	290		239			

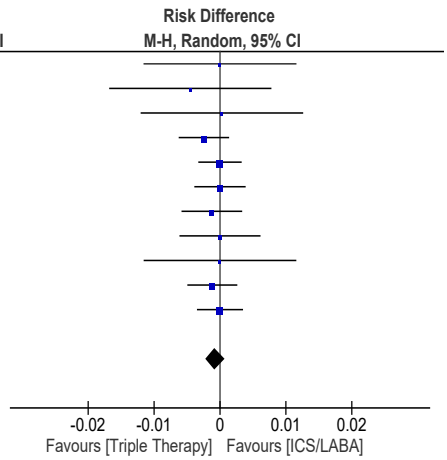
Heterogeneity: Tau² = 0.00; Chi² = 3.20, df = 9 (P = 0.96); I² = 0%
Test for overall effect: Z = 1.41 (P = 0.16)



Serious Eye-Related Adverse Events

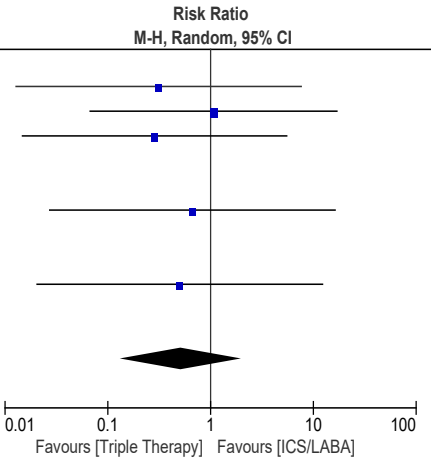
Study or Subgroup	Triple Therapy Events	Total	ICS/LABA Events	Total	Weight	Risk Difference M-H, Random, 95% CI
Hamelmann, 2017	0	257	0	135	1.5%	0.0000 [-0.0115, 0.0115]
Kerstjens, 2012 Trial 1	0	237	1	222	1.3%	-0.0045 [-0.0167, 0.0077]
Kerstjens, 2012 Trial 2	1	219	1	234	1.3%	0.0003 [-0.0119, 0.0125]
Kerstjens, 2020 (IRIDIUM) High dose	0	616	3	1231	14.3%	-0.0024 [-0.0062, 0.0013]
Kerstjens, 2020 (IRIDIUM) Medium dose	0	617	0	608	19.4%	0.0000 [-0.0032, 0.0032]
Lee, 2020 (CAPTAIN) FF 100	0	407	0	811	13.7%	0.0000 [-0.0038, 0.0038]
Lee, 2020 (CAPTAIN) FF 200	0	406	1	812	9.8%	-0.0012 [-0.0057, 0.0033]
NCT03358147 2017	0	834	0	237	5.4%	0.0000 [-0.0060, 0.0060]
Szefler, 2017	0	266	0	134	1.5%	0.0000 [-0.0115, 0.0115]
TRIGGER, 2019	0	571	1	860	14.6%	-0.0012 [-0.0049, 0.0025]
TRIMARAN, 2019	0	576	0	574	17.1%	0.0000 [-0.0034, 0.0034]
Total (95% CI)		**5006**		**5858**	**100.0%**	**-0.0007 [-0.0021, 0.0007]**
Total events	1		7			

Heterogeneity: Tau² = 0.00; Chi² = 1.98, df = 10 (P = 1.00); I² = 0%
Test for overall effect: Z = 0.97 (P = 0.33)

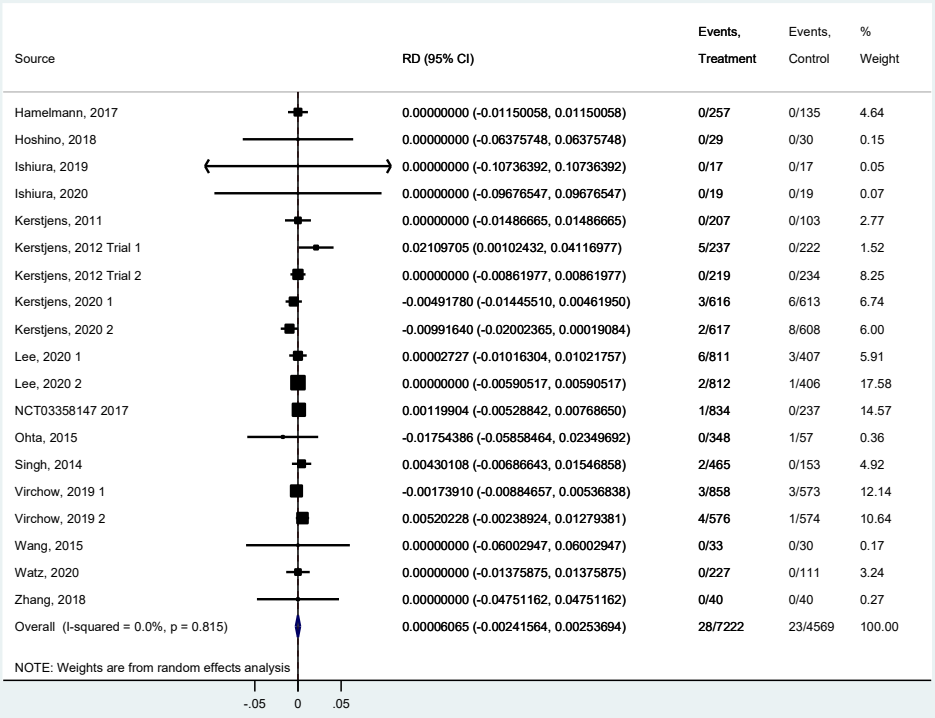


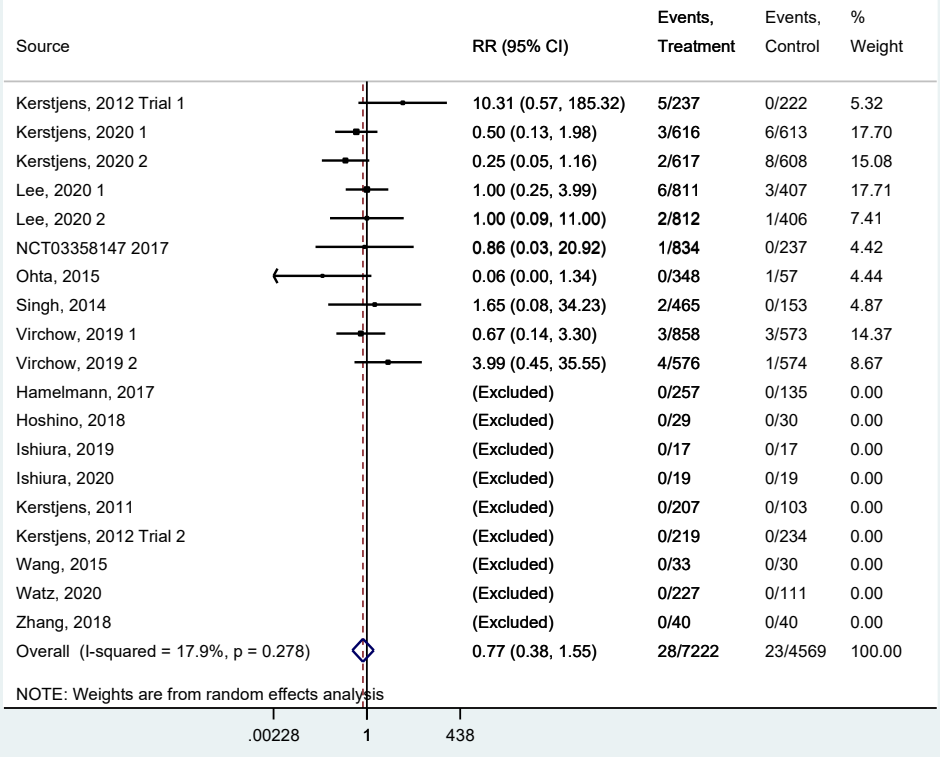
Study or Subgroup	Triple Therapy Events	Total	ICS/LABA Events	Total	Weight	Risk Ratio M-H, Random, 95% CI
Hamelmann, 2017	0	257	0	135		Not estimable
Kerstjens, 2012 Trial 1	0	237	1	222	18.2%	0.31 [0.01, 7.63]
Kerstjens, 2012 Trial 2	1	219	1	234	24.3%	1.07 [0.07, 16.98]
Kerstjens, 2020 (IRIDIUM) High dose	0	616	3	1231	21.2%	0.29 [0.01, 5.51]
Kerstjens, 2020 (IRIDIUM) Medium dose	0	617	0	608		Not estimable
Lee, 2020 (CAPTAIN) FF 100	0	407	0	811		Not estimable
Lee, 2020 (CAPTAIN) FF 200	0	406	1	812	18.2%	0.67 [0.03, 16.31]
NCT03358147 2017	0	834	0	237		Not estimable
Szefler, 2017	0	266	0	134		Not estimable
TRIGGER, 2019	0	571	1	860	18.2%	0.50 [0.02, 12.30]
TRIMARAN, 2019	0	576	0	574		Not estimable
Total (95% CI)		**5006**		**5858**	**100.0%**	**0.52 [0.13, 2.02]**
Total events	1		7			

Heterogeneity: Tau² = 0.00; Chi² = 0.55, df = 4 (P = 0.97); I² = 0%
Test for overall effect: Z = 0.95 (P = 0.34)



Serious Cardiovascular Adverse Events (eg. Arrythmia, myocardial infarction)

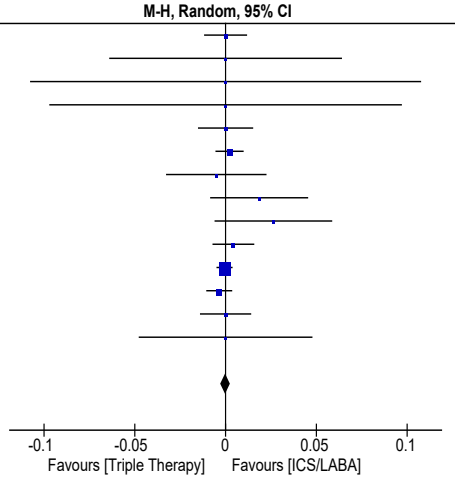




Non-Serious Cardiac Adverse Events (eg. ECG abnormalities, Arrythmia)

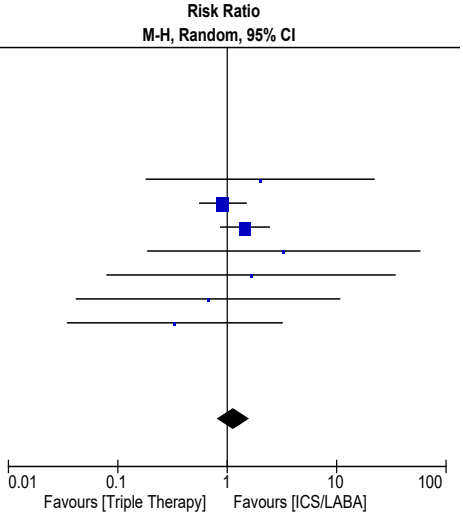
Study or Subgroup	Triple Therapy Events	Triple Therapy Total	ICS/LABA Events	ICS/LABA Total	Weight	Risk Difference M-H, Random, 95% CI
Hamelmann, 2017	0	257	0	135	5.9%	0.0000 [-0.0115, 0.0115]
Hoshino, 2018	0	29	0	30	0.2%	0.0000 [-0.0638, 0.0638]
Ishiura, 2019	0	17	0	17	0.1%	0.0000 [-0.1074, 0.1074]
Ishiura, 2020	0	19	0	19	0.1%	0.0000 [-0.0968, 0.0968]
Kerstjens, 2011	0	207	0	103	3.5%	0.0000 [-0.0149, 0.0149]
Kerstjens, 2012 trial 1 and 2 pooled	2	456	1	456	14.1%	0.0022 [-0.0052, 0.0096]
Lee, 2020 (CAPTAIN) FF 100	22	407	48	811	1.0%	-0.0051 [-0.0325, 0.0222]
Lee, 2020 (CAPTAIN) FF 200	24	406	33	812	1.1%	0.0185 [-0.0082, 0.0451]
Ohta, 2015	6	228	0	57	0.8%	0.0263 [-0.0058, 0.0584]
Singh, 2014	2	465	0	153	6.2%	0.0043 [-0.0069, 0.0155]
TRIGGER, 2019	1	858	1	573	45.9%	-0.0006 [-0.0047, 0.0035]
TRIMARAN, 2019	1	576	3	574	16.7%	-0.0035 [-0.0103, 0.0033]
Watz, 2020	0	227	0	111	4.1%	0.0000 [-0.0138, 0.0138]
Zhang, 2018	0	40	0	40	0.3%	0.0000 [-0.0475, 0.0475]
Total (95% CI)		**4192**		**3891**	**100.0%**	**0.0001 [-0.0027, 0.0029]**
Total events	58		86			

Heterogeneity: Tau² = 0.00; Chi² = 9.46, df = 13 (P = 0.74); I² = 0%
Test for overall effect: Z = 0.05 (P = 0.96)



Study or Subgroup	Triple Therapy Events	Triple Therapy Total	ICS/LABA Events	ICS/LABA Total	Weight	Risk Ratio M-H, Random, 95% CI
Hamelmann, 2017	0	257	0	135		Not estimable
Hoshino, 2018	0	29	0	30		Not estimable
Ishiura, 2019	0	17	0	17		Not estimable
Ishiura, 2020	0	19	0	19		Not estimable
Kerstjens, 2011	0	207	0	103		Not estimable
Kerstjens, 2012 trial 1 and 2 pooled	2	456	1	456	2.0%	2.00 [0.18, 21.98]
Lee, 2020 (CAPTAIN) FF 100	22	407	48	811	47.8%	0.91 [0.56, 1.49]
Lee, 2020 (CAPTAIN) FF 200	24	406	33	812	43.8%	1.45 [0.87, 2.43]
Ohta, 2015	6	228	0	57	1.4%	3.29 [0.19, 57.61]
Singh, 2014	2	465	0	153	1.3%	1.65 [0.08, 34.23]
TRIGGER, 2019	1	858	1	573	1.5%	0.67 [0.04, 10.66]
TRIMARAN, 2019	1	576	3	574	2.2%	0.33 [0.03, 3.18]
Watz, 2020	0	227	0	111		Not estimable
Zhang, 2018	0	40	0	40		Not estimable
Total (95% CI)		**4192**		**3891**	**100.0%**	**1.14 [0.81, 1.59]**
Total events	58		86			

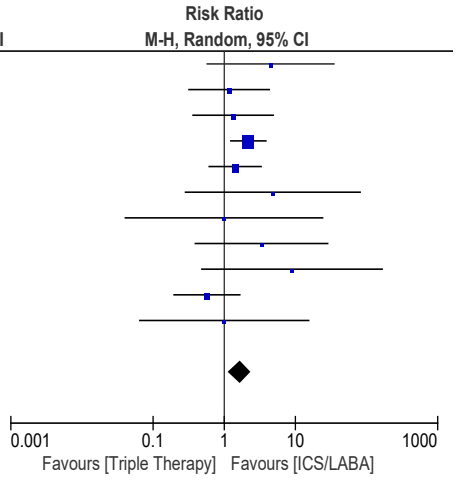
Heterogeneity: Tau² = 0.00; Chi² = 3.74, df = 6 (P = 0.71); I² = 0%
Test for overall effect: Z = 0.73 (P = 0.46)



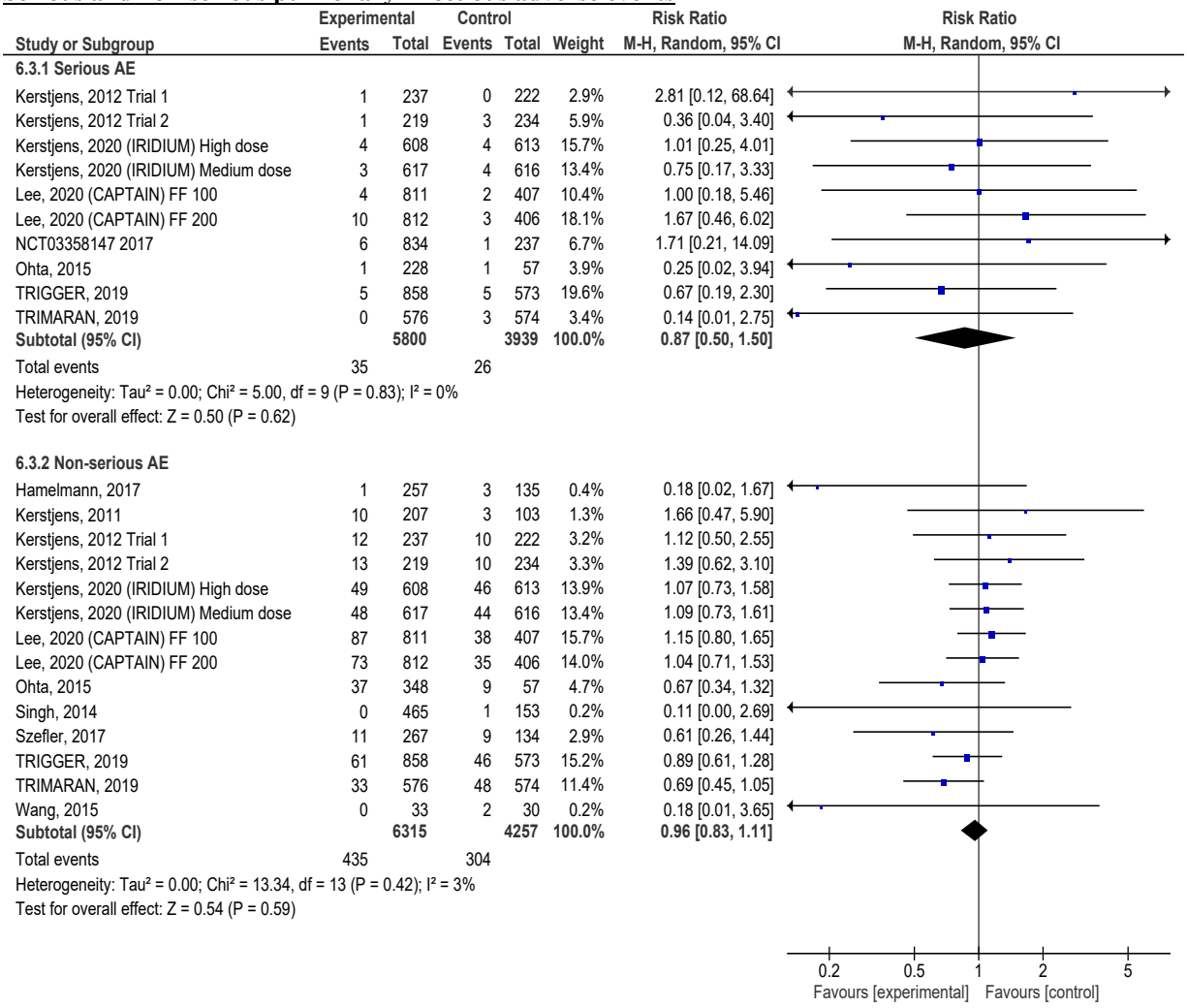
Non-Serious Dry Mouth and Dysphonia

Study or Subgroup	Triple Therapy Events	Triple Therapy Total	ICS/LABA Events	ICS/LABA Total	Weight	Risk Ratio M-H, Random, 95% CI
Kerstjens, 2011	9	207	1	103	3.2%	4.48 [0.58, 34.87]
Kerstjens, 2012 Trial 1	5	237	4	222	7.9%	1.17 [0.32, 4.30]
Kerstjens, 2012 Trial 2	5	219	4	234	7.9%	1.34 [0.36, 4.91]
Kerstjens, 2020 (IRIDIUM) High dose	24	616	22	1231	41.1%	2.18 [1.23, 3.86]
Kerstjens, 2020 (IRIDIUM) Medium dose	13	617	9	608	18.9%	1.42 [0.61, 3.31]
Ohta, 2015	9	228	0	57	1.7%	4.81 [0.28, 81.48]
Singh, 2014	1	465	0	153	1.3%	0.99 [0.04, 24.21]
TRIGGER, 2019	5	858	1	573	2.9%	3.34 [0.39, 28.51]
TRIMARAN, 2019	4	576	0	574	1.6%	8.97 [0.48, 166.20]
Watz, 2020	7	227	6	111	11.8%	0.57 [0.20, 1.66]
Zhang, 2018	1	40	1	40	1.8%	1.00 [0.06, 15.44]
Total (95% CI)		**4290**		**3906**	**100.0%**	**1.65 [1.14, 2.38]**
Total events	83		48			

Heterogeneity: Tau² = 0.00; Chi² = 8.71, df = 10 (P = 0.56); I² = 0%
Test for overall effect: Z = 2.68 (P = 0.007)

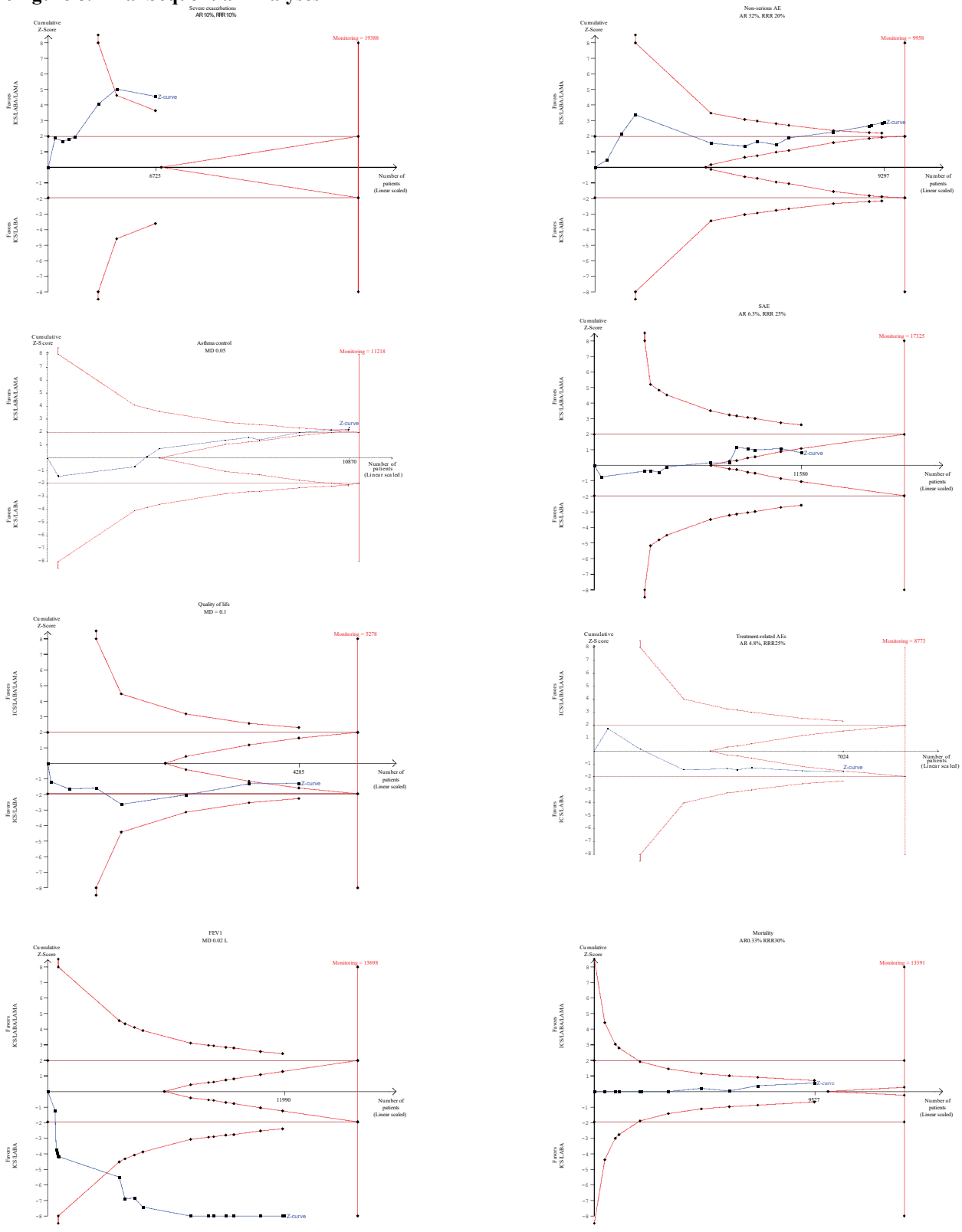


Serious and non-serious pulmonary infectious adverse events



Study or Subgroup	Experimental Events	Experimental Total	Control Events	Control Total	Weight	Risk Ratio M-H, Random, 95% CI
6.3.1 Serious AE						
Kerstjens, 2012 Trial 1	1	237	0	222	2.9%	2.81 [0.12, 68.64]
Kerstjens, 2012 Trial 2	1	219	3	234	5.9%	0.36 [0.04, 3.40]
Kerstjens, 2020 (IRIDIUM) High dose	4	608	4	613	15.7%	1.01 [0.25, 4.01]
Kerstjens, 2020 (IRIDIUM) Medium dose	3	617	4	616	13.4%	0.75 [0.17, 3.33]
Lee, 2020 (CAPTAIN) FF 100	4	811	2	407	10.4%	1.00 [0.18, 5.46]
Lee, 2020 (CAPTAIN) FF 200	10	812	3	406	18.1%	1.67 [0.46, 6.02]
NCT03358147 2017	6	834	1	237	6.7%	1.71 [0.21, 14.09]
Ohta, 2015	1	228	1	57	3.9%	0.25 [0.02, 3.94]
TRIGGER, 2019	5	858	5	573	19.6%	0.67 [0.19, 2.30]
TRIMARAN, 2019	0	576	3	574	3.4%	0.14 [0.01, 2.75]
Subtotal (95% CI)		**5800**		**3939**	**100.0%**	**0.87 [0.50, 1.50]**
Total events	35		26			
Heterogeneity: Tau² = 0.00; Chi² = 5.00, df = 9 (P = 0.83); I² = 0%						
Test for overall effect: Z = 0.50 (P = 0.62)						
6.3.2 Non-serious AE						
Hamelmann, 2017	1	257	3	135	0.4%	0.18 [0.02, 1.67]
Kerstjens, 2011	10	207	3	103	1.3%	1.66 [0.47, 5.90]
Kerstjens, 2012 Trial 1	12	237	10	222	3.2%	1.12 [0.50, 2.55]
Kerstjens, 2012 Trial 2	13	219	10	234	3.3%	1.39 [0.62, 3.10]
Kerstjens, 2020 (IRIDIUM) High dose	49	608	46	613	13.9%	1.07 [0.73, 1.58]
Kerstjens, 2020 (IRIDIUM) Medium dose	48	617	44	616	13.4%	1.09 [0.73, 1.61]
Lee, 2020 (CAPTAIN) FF 100	87	811	38	407	15.7%	1.15 [0.80, 1.65]
Lee, 2020 (CAPTAIN) FF 200	73	812	35	406	14.0%	1.04 [0.71, 1.53]
Ohta, 2015	37	348	9	57	4.7%	0.67 [0.34, 1.32]
Singh, 2014	0	465	1	153	0.2%	0.11 [0.00, 2.69]
Szefler, 2017	11	267	9	134	2.9%	0.61 [0.26, 1.44]
TRIGGER, 2019	61	858	46	573	15.2%	0.89 [0.61, 1.28]
TRIMARAN, 2019	33	576	48	574	11.4%	0.69 [0.45, 1.05]
Wang, 2015	0	33	2	30	0.2%	0.18 [0.01, 3.65]
Subtotal (95% CI)		**6315**		**4257**	**100.0%**	**0.96 [0.83, 1.11]**
Total events	435		304			
Heterogeneity: Tau² = 0.00; Chi² = 13.34, df = 13 (P = 0.42); I² = 3%						
Test for overall effect: Z = 0.54 (P = 0.59)						

eFigure 8. Trial Sequential Analyses



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